Original Investigation | LESS IS MORE

Thyroid Function Within the Normal Range and Risk of Coronary Heart Disease
An Individual Participant Data Analysis of 14 Cohorts

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IMPORTANCE Some experts suggest that serum thyrotropin levels in the upper part of the current reference range should be considered abnormal, an approach that would reclassify many individuals as having mild hypothyroidism. Health hazards associated with such thyrotropin levels are poorly documented, but conflicting evidence suggests that thyrotropin levels in the upper part of the reference range may be associated with an increased risk of coronary heart disease (CHD).

OBJECTIVE To assess the association between differences in thyroid function within the reference range and CHD risk.

DESIGN, SETTING, AND PARTICIPANTS Individual participant data analysis of 14 cohorts with baseline examinations between July 1972 and April 2002 and with median follow-up ranging from 3.3 to 20.0 years. Participants included 55 412 individuals with serum thyrotropin levels of 0.45 to 4.49 mIU/L and no previously known thyroid or cardiovascular disease at baseline.

EXPOSURES Thyroid function as expressed by serum thyrotropin levels at baseline.

MAIN OUTCOMES AND MEASURES Hazard ratios (HRs) of CHD mortality and CHD events according to thyrotropin levels after adjustment for age, sex, and smoking status.

RESULTS Among 55 412 individuals, 1813 people (3.3%) died of CHD during 643 183 person-years of follow-up. In 10 cohorts with information on both nonfatal and fatal CHD events, 4666 of 48 875 individuals (9.5%) experienced a first-time CHD event during 533 408 person-years of follow-up. For each 1-mIU/L higher thyrotropin level, the HR was 0.97 (95% CI, 0.90-1.04) for CHD mortality and 1.00 (95% CI, 0.97-1.03) for a first-time CHD event. Similarly, in analyses by categories of thyrotropin, the HRs of CHD mortality (0.94 [95% CI, 0.74-1.20]) and CHD events (0.97 [95% CI, 0.83-1.13]) were similar among participants with the highest (3.50-4.49 mIU/L) compared with the lowest (0.45-1.49 mIU/L) thyrotropin levels. Subgroup analyses by sex and age group yielded similar results.

CONCLUSIONS AND RELEVANCE Thyrotropin levels within the reference range are not associated with risk of CHD events or CHD mortality. This finding suggests that differences in thyroid function within the population reference range do not influence the risk of CHD. Increased CHD risk does not appear to be a reason for lowering the upper thyrotropin reference limit.

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Hypothyroidism has been associated with atherosclerosis,[1] and evidence from large observational studies suggests that individuals with hypothyroidism may be at increased risk of coronary heart disease (CHD) events and CHD mortality.[2] Among people with apparently normal thyroid function, thyrotropin levels in the upper part of the reference range may indicate an early stage of hypothyroidism.[3-6] In addition, such thyrotropin levels have been associated with an adverse cardiovascular risk profile that includes high levels of non-high-density lipoprotein cholesterol, triglycerides, blood pressure, and body mass index, as well as low levels of high-density lipoprotein cholesterol.[7-11] Therefore, it seems plausible that differences in thyroid function within the population reference range may be differentially associated with CHD risk. In support of this hypothesis, the results of one cohort study suggested that thyrotropin levels within the reference range may be positively associated with CHD mortality in women, but not in men.[12,13] In contrast, the results of other studies do not suggest any association between thyrotropin levels within the reference range and the risk of CHD events,[14] vascular mortality,[15] or need for coronary revascularization.[16]

The definition of the clinically normal range for thyroid function is controversial. Some experts have suggested that the upper thyrotropin reference limit should be lowered from approximately 4.5 to 2.5 or 3.0 mIU/L since higher thyrotropin levels may indicate early-stage hypothyroidism.[17] Others disagree,[18-21] because many people with a healthy thyroid gland would thereby be classified with abnormal thyroid function, and there is no firm evidence that thyrotropin levels in the upper part of the reference range are associated with health consequences that would benefit from early recognition and treatment of hypothyroidism. Most research on such potential consequences has focused on CHD and its risk factors,[11] and a recent review concluded that there was good evidence for associations between higher thyrotropin levels within the reference range and cardiovascular risk factors and events.[11] However, most of this evidence comes from cross-sectional studies, which are inferior to prospective studies for causal inference. To clarify whether people with thyrotropin levels in the upper part of the reference range may be at increased risk of CHD, we performed a meta-analysis of individual participant data in 14 cohort studies included in the Thyroid Studies Collaboration consortium.[2,22,23]

Methods

Cohorts

The Thyroid Studies Collaboration consists of cohorts with thyroid function measurements at baseline and prospective follow-up of CHD outcomes. Its original purpose was to examine CHD risk among people with subclinical thyroid dysfunction, and suitable cohorts for that purpose were identified through systematic literature searches of the MEDLINE and EMBASE databases from January 1, 1950, to June 30, 2011, as previously described.[2,22] Among 13 cohorts identified in the searches, 2 were excluded from the present study either because all participants had cardiovascular disease at baseline[24] or owing to a lack of information on cardiovascular disease and smoking habits at baseline.[15] Data from the remaining 11 cohorts[12-14,25-34] were included, as well as from 3 additional cohorts[35-37] that have recently joined the collaboration. The individual cohort studies were approved by their appropriate ethics boards, and the present study was approved by the Central Norway Regional Committee for Medical and Health Research Ethics. Participants provided written or, in one cohort,[29] oral informed consent. In some cohorts, participants received minor financial compensation to cover expenses related to participation.

Each cohort provided individual-level information on thyroid function measurements, cardiovascular risk factors, and history of thyroid and cardiovascular disease and diabetes mellitus, as well as prospectively recorded information on CHD outcomes during follow-up. From all cohorts, we included participants with thyrotropin levels within the reference range and with no previously known thyroid disease (or use of thyroid medication) or cardiovascular disease at baseline. As previously explained[2,22] and based on expert reviews[21,38] and a 2010 consensus meeting within our consortium, we applied a common thyrotropin reference range of 0.45 to 4.49 mIU/L for all cohorts except for the Whickham Survey.[31,34] In that cohort, we used a reference range of 0.5 to 5.9 mIU/L because the first-generation thyrotropin assay used in that study yields consistently higher levels than measurements of current assays.[2] Among 55 935 individuals who fulfilled the criteria for inclusion, we excluded 523 people (0.9%) without information on smoking habits or follow-up information, leaving a total of 55 412 participants for analysis.

We examined the risk of CHD mortality in all cohorts. In cohorts with information on both nonfatal and fatal CHD events, we also examined risks of a first-time CHD event (combined end point of CHD mortality, myocardial infarction, coronary artery revascularization, incident angina pectoris, or hospital diagnosis of CHD) and a first-time hard CHD event (combined end point of CHD mortality or myocardial infarction). Types of CHD event data available in each cohort are described in eTable 1 in the Supplement.

Statistical Analysis

For each cohort, we used separate Cox proportional hazard models to estimate the associations of thyrotropin levels with each CHD outcome. We then calculated pooled estimates across cohorts using random-effects models based on the variance model described by DerSimonian and Laird.[39,40] Heterogeneity across cohorts was assessed by the I^2 statistic, which describes the proportion of the total variation across studies attributable to heterogeneity rather than to chance. We adjusted for age (by using attained age as the time scale), sex, and smoking status[41] (never, former, or current smokers or, in one cohort,[29] ever- or never-smokers) at baseline as these characteristics may influence both thyroid function test results and CHD risk. We also analyzed women and men separately because in women, more often than in men, thyrotropin levels in the upper part of the reference range may indicate an early stage of hypothyroidism.[3,4,6] Some evidence suggests that the

association of hypothyroidism with CHD risk may be relatively stronger at younger ages[2]; therefore, we examined whether the associations differed by age at baseline (<65, 65-79, or ≥80 years). We analyzed thyrotropin both as a continuous variable and by categories, using equal width categories (0.45-1.49, 1.50-2.49, 2.50-3.49, and 3.50-4.49 mIU/L). For the Whickham Survey, analogous categories were considered to be 0.5 to 1.8, 1.9 to 3.2, 3.3 to 4.6, and 4.7 to 5.9 mIU/L. As reference, we used the lowest thyrotropin category, which is likely to have the lowest prevalence of preclinical autoimmune thyroid disease indicated by presence of thyroid peroxidase (TPO) antibodies.[4]

High thyrotropin levels may be more likely to indicate low thyroid function in people with TPO antibodies in serum.[5,6] Among cohorts with TPO antibody measurements at baseline, we therefore estimated the risk of CHD by combinations of thyrotropin level (0.45-2.49 or 2.50-4.49 mIU/L) and TPO antibody status (positive or negative using study-specific cutoff points as reported in eTable 1 in the Supplement).

In addition, we examined risks of CHD outcomes by free thyroxine (FT_4) levels at baseline, analyzing FT_4 both as a continuous variable and by categories. Because the different FT_4 assays are not standardized and yield different reference limits,[42] we used quartile categories based on the quartile distributions within each cohort. As reference, we used the highest quartile, which suggests relatively high thyroid function. After observing an association between FT_4 categories and CHD risk, we examined whether there was statistical evidence for a U-shaped association between FT_4 and CHD risk as expressed by the *P* value for the squared value of FT_4 levels.

We performed a set of sensitivity analyses to evaluate the robustness of the findings. First, because nonthyroidal illness may influence thyroid function test results,[43] we repeated the analyses after excluding the first 2 years of follow-up to reduce the influence that preclinical CHD at baseline could have on the results. Second, we repeated the analyses with statistical adjustment for body mass index at baseline (expressed by restricted cubic spline) because adiposity, in addition to being a possible mediator between thyroid function and CHD,[10] may be a common cause of high thyrotropin levels and CHD.[44] Third, we excluded participants with diabetes mellitus at baseline since diabetes may be associated with thyroid dysfunction[45,46] and silent CHD.[47] Fourth, we restricted the analyses to never-smokers to avoid residual confounding from smoking.[41] Fifth, in cohorts with information on use of thyroid medication during follow-up, we examined whether hazard ratios (HRs) for CHD outcomes changed after exclusion of participants who began therapy with thyroid medication during follow-up. Sixth, we restricted the analyses to the 11 cohorts that were identified through the systematic literature searches. Seventh, we repeated the analyses after excluding the Study of Health in Pomerania cohort, which was formerly iodine deficient and had a substantially different study-specific reference range for thyrotropin (0.25-2.12 mIU/L).[30] Eighth, we repeated the analyses after excluding the Whickham Survey[31,34] (which started follow-up in the 1970s) and the Leiden 85-Plus Study[27] (which only included participants aged 85 years). Ninth, we repeated the analysis of FT_4 and CHD risk after excluding participants with FT_4 levels outside the study-specific reference ranges reported in eTable 1 in the Supplement. Because thyroid function could influence the risk of CHD through thyroid hormone effects on blood pressure and cholesterol levels,[1] whenever associations with CHD outcomes were observed, we examined whether the HRs were altered by statistical adjustment for systolic blood pressure and total serum cholesterol levels at baseline. All analyses were performed using Stata, version 13.1 for Windows (StataCorp LP).

Results

Characteristics of the 14 cohorts are given in **Table 1** and eTable 1 in the Supplement. Baseline characteristics by thyrotropin category are given in eTable 2 in the Supplement. Among 55 412 individuals, 1813 people (3.3%) died of CHD during 643 183 person-years of follow-up. In one cohort of 763 individuals,[33] only 5 CHD deaths occurred; this cohort was excluded from further analyses. There was no association between thyrotropin levels and risk of CHD mortality. For each 1-mIU/L higher thyrotropin level at baseline, the HR for CHD mortality was 0.97 (95% CI, 0.90-1.04), with little heterogeneity across studies (I^2, 36%) (**Figure**). The association did not differ by sex or age (**Table 2**).

Ten cohorts had information on both fatal and nonfatal CHD events. Among 48 875 individuals in these cohorts, 4666 people (9.5%) experienced a first-time CHD event during 533 408 person-years of follow-up. For each 1-mIU/L higher thyrotropin level at baseline, the HR for a first-time CHD event was 1.00 (95% CI, 0.97-1.03). The association was homogeneous across studies (I^2, 0%) (Figure) and did not differ by sex or age (Table 2).

In 7 cohorts, the risk of hard CHD events (CHD mortality or myocardial infarction) could be examined, and 2488 (7.3%) of 34 256 individuals in these cohorts experienced a first-time hard CHD event during 356 400 person-years of follow-up. There was no association between thyrotropin levels and the risk of a first-time hard CHD event, and the HRs did not substantially differ from those of any CHD event (Table 2 and Figure).

The sensitivity analyses of thyrotropin levels and CHD risk yielded results similar to the main analysis (eTable 3 in the Supplement). We also examined CHD risk by categories of thyrotropin at baseline but found no associations with risk of CHD mortality or CHD events (**Table 3**).

Among cohorts with TPO antibody measurement at baseline, we examined the combined association of thyrotropin level and TPO antibody status with the risk of CHD mortality (4 cohorts), a first-time CHD event (3 cohorts), and a first-time hard CHD event (2 cohorts). There was no evidence that high (2.50-4.49 mIU/L) thyrotropin levels combined with TPO antibodies were associated with increased CHD risk compared with low (0.45-2.49 mIU/L) thyrotropin levels and no TPO antibodies (eTable 4 in the Supplement).

Table 1. Characteristics of the 14 Cohorts

Source	Description	No. of Participants	Age at Baseline, Median (Range), y	Women, %	Thyroid Medication Use During Follow-up, %	Start of Follow-up, y	Follow-up Time for CHD Mortality, Median (IQR), y	Person-years in Analysis of CHD Mortality
Europe								
Whickham Survey,[31,34] 1996, 2010	Adults living in and near Newcastle-upon-Tyne, England	1918	43 (18-92)	51.7	1.6	1972-1974	19 (18-20)	32 678
Rotterdam Study,[28,48] 2000, 2013	Adults living in Ommoord, the Netherlands	1014	66 (55-88)	61.5	NA	1989-1992	15.8 (12.4-16.9)	14 464
Leiden 85-Plus Study,[27] 2004	Adults aged 85 y living in Leiden, the Netherlands	274	85 (85-85)	67.2	1.1	1997-1999	6.5 (3.5-9.3)	1754
HUNT Study,[12,13] 2008, 2012	Adults living in Nord-Trøndelag, Norway	26 179	54 (20-98)	67.2	NA	1995-1997	12.3 (11.8-12.9)	304 733
EPIC-Norfolk Study,[25] 2010	Adults living in Norfolk, England	11 003	57 (39-78)	53.1	NA	1995-1998	13.4 (12.7-14.3)	142 111
SHIP,[30] 2010	Adults living in Western Pomerania, Germany	2738	45 (20-81)	50.0	2.8	1997-2001	10.1 (9.3-10.7)	26 715
PROSPER Trial,[36] 2012	Adults at high cardiovascular risk living in the Netherlands, Ireland, and Scotland	2586	74 (70-83)	49.5	0.3	1997-1999	3.3 (3.0-3.5)	8400
InCHIANTI,[35] 2013	Adults living in Tuscany, Italy	876	70 (21-98)	54.3	0.8	1998-2000	9.1 (8.8-9.2)	7219
United States								
Health, Aging, and Body Composition Study,[32] 2005	Adults with Medicare eligibility in 2 US communities	1531	74 (69-81)	51.7	1.6	1997	8.1 (7.6-8.3)	11 203
Cardiovascular Health Study,[26] 2006	Adults with Medicare eligibility in 4 US communities	1796	73 (66-98)	60.4	5.7	1992-1993	13.1 (7.8-18.7)	22 568
MrOS,[37] 2012	US men aged ≥65 y	937	72 (65-99)	0.0	NA	2000-2002	11.2 (9.7-11.8)	9466
Australia								
Busselton Health Study,[14] 2005	Adults living in Busselton, Western Australia	1698	48 (18-89)	48.5	0.4	1981	20 (20-20)	30 831
Asia								
Nagasaki Adult Health Study,[29] 2004	Atomic bomb survivors and their controls in Nagasaki, Japan	2099	57 (39-92)	61.3	0.0	1984-1987	13.0 (12.3-13.7)	25 613
South America								
Brazilian Thyroid Study,[33] 2010	Adults of Japanese descent living in São Paulo, Brazil	763	55 (30-92)	52.3	NA	1999-2000	7.3 (7.1-7.5)	5428

Abbreviations: CHD, coronary heart disease; EPIC-Norfolk, European Prospective Investigation of Cancer–Norfolk; HUNT, Nord-Trøndelag Health Study; InCHIANTI, Invecchiare in Chianti; IQR, interquartile range; MrOS, Osteoporotic Fractures in Men; NA, not available; PROSPER, Prospective Study of Pravastatin in the Elderly at Risk; SHIP, Study of Health in Pomerania.

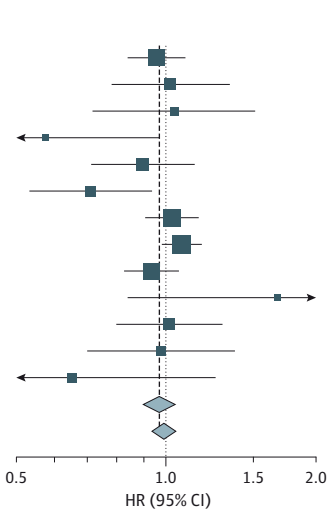
In addition, we examined associations of FT_4 levels at baseline with risk of CHD. We observed no linear associations of FT_4 levels with risk of CHD mortality (9 cohorts) or a first-time CHD event (6 cohorts) (eFigure in the Supplement), and the associations did not convincingly differ by sex or age (eTable 5 in the Supplement). In analyses by FT_4 categories, the risk of CHD mortality and CHD events did not substantially differ between participants with low (lowest quartile) and high (highest quartile) FT_4 levels (eTable 6 in the Supplement). However, the results suggested a U-shaped association between FT_4 level and CHD risk since participants with FT_4 levels in the second quartile had lower risks of CHD mortality (HR, 0.76 [95% CI, 0.57-0.99]) and CHD events (HR, 0.73 [95% CI, 0.58-0.94]) compared with participants with high (highest quartile) FT_4 levels. Nonetheless, the *P* value for squared FT_4 levels did not show statistically significant evidence of a U-shaped association of FT_4 level with CHD risk ($P = .48$ for CHD mortality and $P = .22$ for CHD events). Associations between FT_4 level and risk of hard CHD events could be examined only in 4 cohorts of elderly participants, but estimates were similar to those of any CHD event (eTable 5, eTable 6, and eFigure in the Supplement).

Sensitivity analyses of FT_4 levels and CHD risk yielded results similar to the main analysis (eTable 7 and eTable 8 in the Supplement), except that when the analysis was restricted to participants with FT_4 levels within the reference range, there was statistically significant evidence to suggest a

Figure. Hazard Ratios (HRs) of Coronary Heart Disease (CHD) Mortality, a First-Time CHD Event, and a First-Time Hard CHD Event per 1-mIU/L Higher Thyrotropin Level at Baseline, Adjusted for Age, Sex, and Smoking at Baseline

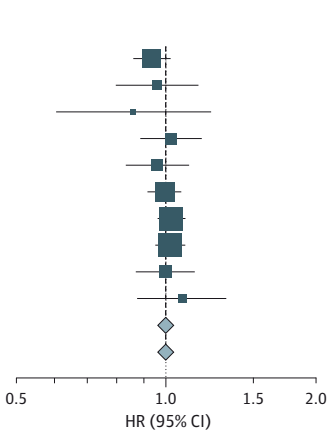
A CHD mortality

Study, y	No. of Events	No. of Participants	HR (95% CI)	Weight, % (D+L)[a]
Whickham Survey,[31,34] 1996, 2010	129	1918	0.96 (0.84-1.09)	14.38
Rotterdam Study,[28,48] 2000, 2013	68	1014	1.02 (0.78-1.34)	5.79
Nagasaki Adult Health Study,[29] 2004	29	2099	1.04 (0.71-1.51)	3.38
Leiden 85-Plus Study,[27] 2004	23	274	0.57 (0.34-0.97)	1.87
Busselton Health Study,[14] 2005	96	1698	0.90 (0.71-1.14)	7.04
Health, Aging, and Body Composition Study,[32] 2005	66	1531	0.71 (0.53-0.94)	5.39
Cardiovascular Health Study,[26] 2006	277	1796	1.03 (0.91-1.16)	15.52
HUNT Study,[12,13] 2008, 2012	612	26179	1.08 (0.98-1.18)	18.66
EPIC-Norfolk Study,[25] 2010	343	11003	0.94 (0.83-1.06)	14.91
SHIP,[30] 2010	26	2738	1.68 (0.84-3.35)	1.10
PROSPER Trial,[36] 2012	82	2586	1.01 (0.79-1.30)	6.73
MrOS,[37] 2012	37	937	0.98 (0.70-1.37)	4.03
InCHIANTI,[35] 2013	20	876	0.65 (0.33-1.26)	1.20
D+L Overall I^2 = 35.7%; P = .097			0.97 (0.90-1.04)	100.00
I-V Overall			0.99 (0.94-1.04)	



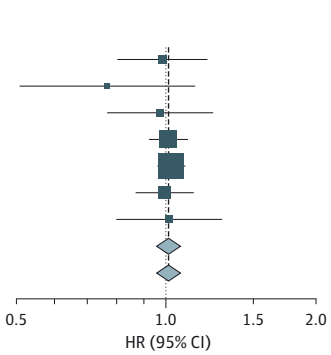
B CHD events

Study, y	No. of Events	No. of Participants	HR (95% CI)	Weight, % (D+L)[a]
Whickham Survey,[31,34] 1996, 2010	327	1918	0.94 (0.86-1.02)	14.26
Rotterdam Study,[28,48] 2000, 2013	148	1014	0.96 (0.79-1.16)	2.84
Leiden 85-Plus Study,[27] 2004	37	274	0.86 (0.60-1.23)	0.80
Busselton Health Study,[14] 2005	272	1698	1.02 (0.89-1.18)	5.17
Health, Aging, and Body Composition Study,[32] 2005	216	1531	0.96 (0.83-1.11)	4.78
Cardiovascular Health Study,[26] 2006	640	1796	0.99 (0.92-1.07)	16.15
HUNT Study,[12,13] 2008, 2012	1393	26179	1.02 (0.96-1.09)	24.46
EPIC-Norfolk Study,[25] 2010	1210	11003	1.02 (0.95-1.09)	23.40
PROSPER Trial,[36] 2012	275	2586	0.99 (0.87-1.14)	5.65
InCHIANTI,[35] 2013	148	876	1.08 (0.88-1.32)	2.49
D+L Overall I^2 = 0.0%; P = .843			1.00 (0.97-1.03)	100.00
I-V Overall			1.00 (0.97-1.03)	



C Hard CHD events

Study, y	No. of Events	No. of Participants	HR (95% CI)	Weight, % (D+L)[a]
Rotterdam Study,[28,48] 2000, 2013	120	1014	0.98 (0.80-1.21)	4.86
Leiden 85-Plus Study,[27] 2004	31	274	0.76 (0.51-1.14)	1.28
Health, Aging, and Body Composition Study,[32] 2005	75	1531	0.97 (0.76-1.24)	3.49
Cardiovascular Health Study,[26] 2006	489	1796	1.01 (0.92-1.11)	25.11
HUNT Study,[12,13] 2008, 2012	1393	26179	1.02 (0.96-1.09)	50.15
PROSPER Trial,[36] 2012	275	2586	0.99 (0.87-1.14)	11.58
InCHIANTI,[35] 2013	105	876	1.01 (0.79-1.29)	3.53
D+L Overall I^2 = 0.0%; P = .893			1.01 (0.96-1.06)	100.00
I-V Overall			1.01 (0.96-1.06)	



The squares represent HRs from each cohort, and the lines represent 95% CIs. The diamonds represent pooled HRs (with 95% CIs) from random-effects (DerSimonian and Laird[39] [D+L] Overall) and fixed-effect (inverse variance [I-V] Overall) meta-analysis. EPIC-Norfolk indicates European Prospective Investigation of Cancer–Norfolk; HUNT, Nord-Trøndelag Health Study; InCHIANTI, Invecchiare in Chianti; and PROSPER, Prospective Study of Pravastatin in the Elderly at Risk.

[a] Weights are from random-effects analysis.

U-shaped association between FT_4 and risk of CHD events (squared value of FT_4 levels, P = .02). The association of FT_4 categories with CHD risk remained essentially unchanged after adjustment for baseline levels of systolic blood pressure and total serum cholesterol levels (eTable 8 in the Supplement).

Table 2. HRs of CHD Outcomes per 1-mIU/L Higher Thyrotropin Level at Baseline, Overall, and by Sex and Age[a]

Characteristic	CHD Mortality		CHD Events		CHD Hard Events[b]	
	No. of Events/Participants	HR (95% CI)	No. of Events/Participants	HR (95% CI)	No. of Events/Participants	HR (95% CI)
Overall	1808/54 649	0.97 (0.90-1.04)	4666/48 875	1.00 (0.97-1.03)	2488/34 256	1.01 (0.96-1.06)
Sex						
Women	830/32 343	0.91 (0.79-1.04)	2063/29 687	0.98 (0.92-1.04)	1229/22 031	1.01 (0.95-1.09)
Men	978/22 306	1.01 (0.94-1.08)	2603/19 188	1.01 (0.97-1.06)	1259/12 225	1.00 (0.94-1.07)
P value for interaction		.30		.50		.78
Age at baseline, y						
<65	330/34 164	0.95 (0.84-1.07)	1550/30 277	0.95 (0.90-1.01)	558/19 307	0.96 (0.75-1.22)
65-79	1155/17 870	0.99 (0.91-1.07)	2642/16 183	1.03 (0.98-1.08)	1526/12 586	1.02 (0.97-1.08)
≥80	323/2615	1.03 (0.92-1.17)	474/2415	1.04 (0.94-1.14)	404/2363	1.03 (0.93-1.15)
P value for trend		.35		.07		.36

Abbreviations: CHD, coronary heart disease; HR, hazard ratio.

[a] Adjusted for age, sex, and smoking at baseline.

[b] Defined as CHD mortality or myocardial infarction.

Discussion

In this individual participant data analysis of 55 412 people from 14 cohorts, differences in thyrotropin levels within the reference range were not associated with risk of CHD mortality or CHD events.

Associations between thyrotropin levels within the reference range and risk of CHD have been examined in a few cohort studies,[12-16] 2 of which are included in the present individual participant data analysis.[12-14] In one of these cohorts, each 1-mIU/L higher thyrotropin level at baseline was associated with a 37% higher risk of CHD mortality in women,[12] but there was no corresponding association in men and no association of thyrotropin with risk of hospitalization for myocardial infarction.[12,13] In other cohorts, there were no associations of thyrotropin levels with risk of CHD events,[14] vascular mortality,[15] or coronary revascularizations.[16]

Compared with the previous cohort studies, a major strength of this individual participant data analysis is the large sample size, which enabled more precise risk estimates for both fatal and total CHD events. The use of individual-level data enabled similar classification of exposures and covariates across cohorts. In cohorts in which medication was recorded during follow-up, few participants initiated therapy with thyroid medication, and risk estimates for CHD were similar after exclusion of these individuals. Therefore, use of thyroid medication is not likely to have substantially influenced our results. The results of this meta-analysis strongly suggest that differences in thyrotropin levels within the population reference range are not associated with the risk of CHD and that the previously reported association between thyrotropin levels within the reference range and CHD mortality[12,13] is likely to be a chance finding. A limitation of the present study is that only one measurement of thyroid function at baseline was available, and we could not specifically examine the risk of CHD among people whose thyrotropin level remained in the upper part of the reference range over time. Also, few cohorts included measurement of TPO antibodies, so the risk of CHD among people with thyrotropin levels in the upper part of the reference range combined with the presence of TPO antibodies could not be estimated with high precision.

Of the different measures of thyroid function, we emphasized serum thyrotropin levels in this study for 2 reasons. First, thyrotropin levels in the upper part of the reference range are sometimes a marker of early-stage hypothyroidism, as indicated by an increased prevalence of autoimmune thyroid disease and risk of future hypothyroidism.[3-6] Second, serum thyrotropin is considered to be the most sensitive marker for change in thyroid function since pituitary thyrotropin secretion responds to even slight changes in circulating thyroid hormone levels.[49] The discrepancy in our data between thyrotropin showing no association but FT_4 showing a possible U-shaped association with CHD risk was therefore unexpected. It has been suggested that serum thyrotropin, although a reflection of thyroid-pituitary feedback, may not reflect thyroid status in every organ.[18,50] Under this assumption, FT_4 levels that are sensed as appropriate by the pituitary gland could be inappropriate for the vascular system and lead to increased risk of CHD similar to that seen in hypothyroid[2] or hyperthyroid[22] individuals. However, there are several reasons to suspect that the association of FT_4 levels with CHD risk in our data may not be causal. First, FT_4 measurements may be affected by low albumin levels,[51] which have been associated with increased CHD risk,[52] and use of specific cardiovascular medications, such as aspirin, heparin, and furosemide.[53,54] Second, the lack of robust statistical evidence, as expressed by *P* values for the squared value of FT_4 levels, suggests that the U-shaped association of FT_4 levels with CHD risk may be a chance finding. Further study of the role of FT_4 in disease risk among people with clinically normal thyroid function is needed.

Controversy surrounds the definition of the reference range for thyrotropin,[17-21] and it has been suggested that the

Table 3. HRs of CHD Outcomes by Categories of Thyrotropin Levels at Baseline, Overall, and by Sex and Age at Baseline[a]

Thyrotropin, mIU/L[b]	CHD Mortality		CHD Events		CHD Hard Events[c]	
	No. of Events/Participants	HR (95% CI)	No. of Events/Participants	HR (95% CI)	No. of Events/Participants	HR (95% CI)
Overall						
0.45-1.49	695/23 785	1 [Reference]	1857/20 791	1 [Reference]	970/14 828	1 [Reference]
1.50-2.49	678/19 996	0.99 (0.86-1.14)	1757/18 748	1.00 (0.89-1.11)	945/13 096	1.00 (0.88-1.13)
2.50-3.49	303/7636	0.99 (0.84-1.17)	747/6702	1.01 (0.92-1.11)	414/4572	1.06 (0.94-1.21)
3.50-4.49	132/3232	0.94 (0.74-1.20)	305/2634	0.97 (0.83-1.13)	159/1760	0.95 (0.78-1.16)
Women						
0.45-1.49	309/13 689	1 [Reference]	776/12 359	1 [Reference]	456/9422	1 [Reference]
1.50-2.49	303/11 799	0.84 (0.65-1.09)	766/11 285	0.94 (0.82-1.09)	460/8346	0.91 (0.73-1.14)
2.50-3.49	143/4711	0.93 (0.74-1.17)	349/4232	0.98 (0.83-1.16)	221/3023	1.13 (0.95-1.34)
3.50-4.49	75/2144	0.88 (0.62-1.23)	172/1811	0.98 (0.80-1.19)	92/1240	0.91 (0.68-1.21)
Men						
0.45-1.49	386/10 096	1 [Reference]	1081/8432	1 [Reference]	514/5406	1 [Reference]
1.50-2.49	375/8197	1.13 (0.90-1.40)	991/7463	1.03 (0.91-1.17)	485/4750	1.03 (0.90-1.18)
2.50-3.49	160/2925	1.12 (0.92-1.35)	398/2470	1.05 (0.90-1.22)	193/1549	1.03 (0.82-1.30)
3.50-4.49	57/1088	1.02 (0.76-1.36)	133/823	1.00 (0.76-1.31)	67/520	1.03 (0.78-1.36)
Age <65 y						
0.45-1.49	161/16 000	1 [Reference]	748/13 769	1 [Reference]	294/9200	1 [Reference]
1.50-2.49	117/12 306	0.96 (0.69-1.33)	560/11 611	0.93 (0.73-1.18)	191/7358	0.96 (0.60-1.53)
2.50-3.49	39/4182	0.97 (0.68-1.38)	168/3594	0.85 (0.70-1.03)	51/2072	0.86 (0.63-1.16)
3.50-4.49	13/1676	0.83 (0.46-1.52)	74/1303	1.02 (0.78-1.34)	22/677	1.26 (0.76-2.09)
Age 65-79 y						
0.45-1.49	431/6862	1 [Reference]	958/6152	1 [Reference]	547/4777	1 [Reference]
1.50-2.49	431/6680	1.03 (0.85-1.25)	1000/6190	1.05 (0.93-1.18)	592/4808	1.02 (0.83-1.26)
2.50-3.49	210/3018	1.04 (0.85-1.26)	495/2717	1.11 (0.99-1.25)	290/2119	1.13 (0.97-1.31)
3.50-4.49	83/1310	1.00 (0.77-1.29)	189/1124	1.02 (0.81-1.29)	97/882	0.91 (0.73-1.14)
Age ≥80 y						
0.45-1.49	103/923	1 [Reference]	151/870	1 [Reference]	129/851	1 [Reference]
1.50-2.49	130/1010	1.08 (0.74-1.56)	197/947	1.18 (0.95-1.47)	162/930	1.04 (0.75-1.46)
2.50-3.49	54/436	1.03 (0.69-1.53)	84/391	1.18 (0.90-1.55)	73/381	1.17 (0.85-1.61)
3.50-4.49	36/246	1.27 (0.77-2.07)	42/207	1.26 (0.88-1.79)	40/201	1.23 (0.82-1.85)

Abbreviations: CHD, coronary heart disease; HR, hazard ratio.

[a] Adjusted for age, sex and smoking at baseline.

[b] For the Whickham Survey,[31,34] which used a first-generation thyrotropin assay, the following categories were used: 0.5 to 1.8, 1.9 to 3.2, 3.3 to 4.6, and 4.7 to 5.9 mIU/L.

[c] Defined as CHD mortality or myocardial infarction.

upper reference limit should be lowered to 2.5 to 3.0 mIU/L.[17] This approach would have a large effect on the number of people classified as having abnormal thyroid function. For example, approximately 8% to 14% of US adults without known thyroid disease would be reclassified as having abnormally high thyrotropin levels[20] that might necessitate follow-up and suggest a need for levothyroxine therapy. Unnecessary levothyroxine therapy is undesirable since many patients receive excessive levothyroxine doses (as indicated by low thyrotropin levels)[55,56] that may increase their risk of atrial fibrillation and osteoporosis.[57] A large UK study[56] of new levothyroxine users between 2001 and 2009, excluding those receiving levothyroxine in association with hyperthyroidism, pituitary disease, thyroid surgery, pregnancy, or use of thyroid-altering medication, reported an increase in the use of levothyroxine for borderline elevated thyrotropin levels, and approximately 6% had a thyrotropin level of less than 4.0 mIU/L at the initiation of levothyroxine therapy. This finding suggests that levothyroxine is being prescribed to many individuals in whom its clinical benefit is uncertain.

Knowledge about health hazards associated with thyrotropin in the upper part of the reference range is important to inform a lowering of the upper thyrotropin reference limit. Cardiovascular hazards have been suggested by cross-sectional studies[7-11] that found positive associations of thyrotropin with adverse lipid levels and higher blood pressure and body mass index. However, recent longitudinal evidence suggests that associations are very weak, if any, between thyrotropin levels within the reference range and future levels of serum lipids, blood pressure, and body mass index.[58,59] In line with those findings, the present study provides prospective evidence indicating that individuals with thyrotropin levels in the upper part of the reference range are not at increased risk of CHD. The

present results are also consistent with a previous Thyroid Studies Collaboration[2] analysis showing similar risk of CHD between people with mildly elevated serum thyrotropin levels (4.5-6.9 mIU/L) and people with thyrotropin within the reference range.

In this study, we examined associations between thyrotropin levels and future CHD among people without previously known cardiovascular disease. Our results do not inform whether thyrotropin levels measured after the clinical onset of cardiovascular disease may have prognostic value, as suggested by some evidence.[60] In addition, we did not examine whether levels of thyroid function tests within the reference ranges may be differentially associated with all-cause mortality[16,61,62] or the risk of non-CHD outcomes, such as atrial fibrillation,[62,63] heart failure,[62] fractures,[64] dementia,[62,65] chronic kidney disease[66] or cancer mortality,[61] as suggested in some prospective studies. However, except for a modestly increased risk of chronic kidney disease,[66] these studies did not show increased disease risk among people with thyrotropin levels in the upper part of the reference range and thus do not provide evidence in support of lowering the upper thyrotropin reference limit.

Conclusions

In this individual participant data analysis of 55 412 individuals from 14 cohorts, thyrotropin levels in the upper part of the reference range were not associated with an increased risk of CHD events or CHD mortality. This finding suggests that differences in thyroid function within the population reference range do not influence the risk of CHD. Increased risk of CHD does not appear to be a reason for lowering the upper thyrotropin reference limit.

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