

Thyrotropin Levels and Risk of Fatal Coronary Heart Disease

The HUNT Study

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Background: Recent studies suggest that relatively low thyroid function within the clinical reference range is positively associated with risk factors for coronary heart disease (CHD), but the association with CHD mortality is not resolved.

Methods: In a Norwegian population-based cohort study, we prospectively studied the association between thyrotropin levels and fatal CHD in 17 311 women and 8002 men without known thyroid or cardiovascular disease or diabetes mellitus at baseline.

Results: During median follow-up of 8.3 years, 228 women and 182 men died of CHD. Of these, 192 women and 164 men had thyrotropin levels within the clinical reference range of 0.50 to 3.5 mIU/L. Overall, thyrotropin levels within the reference range were positively as-

sociated with CHD mortality (P for trend = .01); the trend was statistically significant in women (P for trend = .005) but not in men. Compared with women in the lower part of the reference range (thyrotropin level, 0.50-1.4 mIU/L), the hazard ratios for coronary death were 1.41 (95% confidence interval [CI], 1.02-1.96) and 1.69 (95% CI, 1.14-2.52) for women in the intermediate (thyrotropin level, 1.5-2.4 mIU/L) and higher (thyrotropin level, 2.5-3.5 mIU/L) categories, respectively.

Conclusions: Thyrotropin levels within the reference range were positively and linearly associated with CHD mortality in women. The results indicate that relatively low but clinically normal thyroid function may increase the risk of fatal CHD.

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EMERGING EVIDENCE INDICATES that levels of thyrotropin within the reference range are positively and linearly associated with systolic and diastolic blood pressure (BP),¹ body mass index,² and serum lipid concentrations with adverse effects on cardiovascular health.³ Furthermore, small studies of euthyroid patients with atherosclerosis suggest that relatively low thyroid function is associated with more severe coronary^{4,5} or carotid⁶ atherosclerosis.

Although studies indicate that there may be an increased risk of cardiovascular disease in people with evidence of hypothyroidism^{7,8} or hyperthyroidism,^{9,10} there is a lack of prospective studies that have assessed the relation of clinically normal thyroid function with coronary heart disease (CHD). We prospectively examined the association of thyrotropin levels within the reference range with CHD mortality in a Norwegian population-based cohort study of more than 25 000 participants without known thyroid disease, cardiovascular disease, or diabetes mellitus at baseline.

METHODS

STUDY POPULATION

Between 1995 and 1997, all inhabitants 20 years and older in Nord-Trøndelag County in the middle part of Norway were invited to participate in the Nord-Trøndelag Health Study (HUNT Study). Nord-Trøndelag County is characterized by a stable and homogeneous population,¹¹ and the Norwegian population is generally considered to have sufficient iodine intake.¹² A total of 92 936 individuals were eligible for the HUNT Study, and 66 140 (71.2%) participated. The study has been described in detail elsewhere.¹¹ Briefly, the participants completed a self-administered questionnaire that included questions on health and lifestyle and their medical history, including thyroid disease,¹³ diabetes mellitus, angina, myocardial infarction, and stroke. Information on the use of antihypertensive drugs was also collected.

Clinical measurements included BP, height, and weight. Blood pressure was measured automatically 3 times at 1-minute intervals using a noninvasive BP monitor based on oscillometry (Dinamap 845XT; Critikon, Tampa, Florida). The mean values of the second and third measurements of systolic and diastolic BP

were used in the analyses. Body mass index was calculated as weight in kilograms divided by height in meters squared.

A nonfasting venous blood sample was collected from each individual, and levels of total serum cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides, and creatinine were measured. Analysis of serum thyrotropin concentration was performed in subsamples of the population, including all women older than 40 years and a 50% random sample of men older than 40 years. In total, thyrotropin levels were measured in 32 819 individuals (22 692 women and 10 127 men) from these samples.

Of these 32 819 people, 25 313 (17 311 women and 8002 men) were included in the present study. The exclusion criteria were a history of thyroid disease at baseline ($n=2831$); a history of angina, myocardial infarction, stroke, or diabetes mellitus at baseline ($n=4007$); and missing information on smoking status ($n=668$). Each participant contributed person-time from the date of attendance at the baseline clinical examination (August 15, 1995, to June 18, 1997) until their date of death or the end of follow-up (December 31, 2004), whichever came first.

LABORATORY MEASUREMENTS

The serum concentration of thyrotropin was analyzed at the Hormone Laboratory, Aker University Hospital, Oslo, using a noncompetitive immunofluorometric assay (DELFLIA hTSH Ultra) (sensitivity, 0.03 mIU/L; total analytical variation, $<5\%$) from Wallac Oy, Turku, Finland. Reference ranges for thyrotropin levels from this population have been published previously.¹³ Based on these results, the reference range for thyrotropin in the present study was defined as 0.50 to 3.5 mIU/L.

Serum lipid and creatinine levels were analyzed at the Central Laboratory, Levanger Hospital, Nord-Trøndelag, using an autoanalyzer (Hitachi 911 Autoanalyzer; Hitachi, Mito, Japan), applying reagents from Boehringer Mannheim (Mannheim, Germany). Total serum and HDL cholesterol levels were measured using an enzymatic colorimetric cholesterol esterase method, and HDL cholesterol levels were measured after precipitation with phosphotungstate and magnesium ions. Triglycerides were also measured using an enzymatic colorimetric method, and serum creatinine concentration was measured using the Jaffe method. The day-to-day coefficients of variation were 1.3% to 1.9% for total serum cholesterol, 2.4% for HDL cholesterol, 0.7% to 1.3% for triglycerides, and 3.5% for creatinine.

MORTALITY END POINTS

The unique 11-digit identification number of every Norwegian citizen enabled linkage of data from the HUNT Study with the national Cause of Death Registry at Statistics Norway. The reporting of deaths by physicians and public health officers to the Cause of Death Registry is mandatory. In this study, the end point was death from CHD (*International Classification of Diseases, Ninth Revision*, codes 410-414 and *International Classification of Diseases, Tenth Revision*, codes I.20-I.25).

STATISTICAL ANALYSES

Participants were grouped into 5 categories by thyrotropin level: 3 categories of equal width within the reference range (0.50-1.4, 1.5-2.4, and 2.5-3.5 mIU/L), 1 category below the reference range (<0.50 mIU/L), and 1 category above the reference range (≥ 3.6 mIU/L). In a Cox proportional hazards model, we calculated hazard ratios (HRs) of dying of CHD in the 5 groups of thyrotropin, using the lower part of the reference range

(0.50-1.4 mIU/L) as the comparison group. We used attained age as the time variable in the regression analyses and, thus, all the results are age adjusted. We also adjusted for sex and smoking status (never, former, and current smokers, where former smokers were subdivided by years since smoking cessation). Statistical significance of trend within the reference range of thyrotropin was assessed with P values using the categories of thyrotropin within the reference range as an ordinal variable.

There seems to be a complex association between tobacco smoking and serum thyrotropin levels.¹⁴ In a separate analysis, we restricted the study population to nonsmokers (10 379 women and 4108 men) to avoid any effects of smoking on thyrotropin levels. Nonsmokers were defined as never-smokers and former smokers who had quit smoking 18 years or more ago. The 18-year cutoff point was based on previous analyses of the relation of smoking to thyroid function in the same population.¹⁴

Chronic diseases associated with fatal CHD could bias the present results because nonthyroidal illness may affect thyroid function.¹⁵ We, therefore, excluded individuals with known cardiovascular disease or diabetes mellitus at baseline. We also explored whether preclinical CHD at baseline could have affected these results by starting follow-up 2 years after baseline.

Furthermore, we explored whether the effect of thyrotropin could be mediated by conventional cardiovascular risk factors. In women with thyrotropin levels within the reference range, we, therefore, compared HRs derived from the age- and smoking-adjusted analyses with HRs derived from additional adjustment for total serum cholesterol level, HDL cholesterol level, triglycerides, systolic and diastolic BP, use of antihypertensive medication, body mass index, and serum creatinine level. In these analyses, we used thyrotropin as a continuous variable, yielding HRs per 1-mIU/L increase in thyrotropin. The data were analyzed using Stata version 9.0 (Stata Corp, College Station, Texas).

The HUNT Study is a collaborative effort of the Faculty of Medicine, Norwegian University of Science and Technology; the Norwegian Institute of Public Health; and the Nord-Trøndelag County Council. This study was approved by the regional committee for medical research ethics and by the Norwegian Data Inspectorate.

RESULTS

Characteristics of the study population are given in **Table 1**. During median follow-up of 8.3 years, 228 women (1.3%) and 182 men (2.3%) died of CHD. Of these, 192 women and 164 men had thyrotropin levels within the reference range. Thyrotropin levels within the reference range were positively associated with risk of fatal CHD (P for trend = .01 in the total population and P for trend = .007 in nonsmokers) (**Table 2**). There was some statistical evidence that associations of thyrotropin with fatal CHD differed between women and men (P for interaction = .03 in the total population and P for interaction = .16 in nonsmokers).

Thus, sex-specific analyses showed a positive association of thyrotropin level within the reference range with risk of fatal CHD in women (P for trend = .005). Compared with women in the lower part of the reference range (thyrotropin level, 0.50-1.4 mIU/L), the HRs were 1.41 (95% CI, 1.02-1.96) and 1.69 (95% CI, 1.14-2.52) for women in the intermediate (thyrotropin level, 1.5-2.4

Table 1. Characteristics of the Study Population

Characteristic	Thyrotropin, mIU/L				
	<0.50	0.50-1.4	1.5-2.4	2.5-3.5	≥3.6
Women					
Participants, No.	423	7045	6243	2174	1426
CHD deaths, No.	8	60	89	43	28
Thyrotropin, median, mIU/L	0.34	1.1	1.8	2.8	4.6
Age at baseline, mean (SD), y	60 (13)	56 (12)	58 (12)	60 (13)	61 (13)
Smoking status, %					
Never	44.7	43.2	54.5	60.0	61.2
Former	15.8	19.7	20.5	21.8	22.4
Current	39.5	37.1	25.1	18.2	16.4
Total serum cholesterol, mean (SD), mg/dL	239 (47)	242 (48)	247 (48)	250 (49)	258 (51)
HDL cholesterol, mean (SD), mg/dL	59 (15)	60 (16)	59 (16)	59 (15)	59 (16)
Triglycerides, mean (SD), mg/dL	147 (88)	142 (84)	150 (88)	153 (89)	159 (91)
Systolic blood pressure, mean (SD), mm Hg	143 (23)	139 (23)	143 (24)	146 (25)	148 (25)
Diastolic blood pressure, mean (SD), mm Hg	82 (12)	81 (12)	82 (12)	83 (13)	84 (13)
Current or previous use of antihypertensive drugs, %	19.4	14.1	16.7	18.5	17.5
BMI, mean (SD)	26.4 (4.3)	26.2 (4.2)	26.9 (4.5)	27.2 (4.6)	27.5 (4.7)
Serum creatinine, mean (SD), mg/dL	0.91 (0.15)	0.92 (0.16)	0.93 (0.13)	0.95 (0.14)	0.96 (0.14)
Men					
Participants, No.	133	3528	3048	871	422
CHD deaths, No.	0	66	70	28	18
Thyrotropin, median, mIU/L	0.39	1.1	1.8	2.8	4.5
Age at baseline, mean (SD), y	56 (12)	56 (11)	57 (12)	60 (12)	63 (13)
Smoking status, %					
Never	20.3	27.8	35.8	38.0	41.2
Former	33.8	34.0	36.8	41.7	42.2
Current	45.9	38.2	27.4	20.3	16.6
Total serum cholesterol, mean (SD), mg/dL	221 (40)	235 (40)	237 (42)	240 (42)	240 (42)
HDL cholesterol, mean (SD), mg/dL	51 (16)	50 (14)	49 (14)	48 (14)	48 (16)
Triglycerides, mean (SD), mg/dL	154 (74)	174 (109)	183 (110)	190 (119)	190 (114)
Systolic blood pressure, mean (SD), mm Hg	141 (21)	141 (19)	143 (20)	147 (21)	148 (23)
Diastolic blood pressure, mean (SD), mm Hg	83 (11)	84 (11)	86 (11)	88 (12)	87 (13)
Current or previous use of antihypertensive drugs, %	11.5	10.5	12.2	14.3	17.5
BMI, mean (SD)	26.2 (3.5)	26.4 (3.3)	26.8 (3.4)	27.1 (3.4)	27.2 (3.5)
Serum creatinine, mean (SD), mg/dL	1.04 (0.14)	1.06 (0.17)	1.08 (0.15)	1.10 (0.19)	1.13 (0.17)

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in meters squared); CHD, coronary heart disease; HDL, high-density lipoprotein.

SI conversion factors: To convert total serum and HDL cholesterol to millimoles per liter, multiply by 0.0259; creatinine to micromoles per liter, multiply by 88.4; and triglycerides to millimoles per liter, multiply by 0.0113.

mIU/L) and higher (thyrotropin level, 2.5-3.5 mIU/L) parts of the reference range, respectively. This association was essentially unchanged when the analysis was restricted to nonsmokers (Table 2). In men, thyrotropin levels within the reference range were not clearly related to fatal CHD. In nonsmoking men, there was a positive association of thyrotropin levels within the reference range with CHD mortality, but this association did not reach conventional levels of statistical significance (P for trend = .27) (Table 2).

For the 1426 women and 422 men with thyrotropin levels higher than the reference range, HRs for fatal CHD were 1.38 (95% CI, 0.88-2.17) and 1.15 (95% CI, 0.66-1.98), respectively, compared with individuals with thyrotropin levels in the lower part of the reference range (thyrotropin level, 0.50-1.4 mIU/L). In nonsmokers (1030 women and 293 men) with thyrotropin levels higher than the reference range, the analogous HRs were 1.69 (95% CI, 1.01-2.82) and 1.57 (95% CI, 0.79-3.14), respectively. Below the reference range of thyrotropin levels,

there were too few events (8 women and 0 men) to yield any meaningful estimates.

To exclude the possible effect of preclinical CHD on the thyrotropin level, we repeated the analyses starting follow-up 2 years after baseline. The estimates, however, remained essentially unchanged: thyrotropin levels within the reference range were positively associated with fatal CHD in women (P for trend = .01). Compared with women in the lower category, the HRs for fatal CHD were 1.43 (95% CI, 1.01-2.02) and 1.61 (95% CI, 1.05-2.46) for women in the intermediate and higher categories of the reference range, respectively.

Furthermore, we explored whether serum lipid concentrations, BP, body mass index, and serum creatinine levels could mediate the association of thyrotropin with CHD mortality in women. The analysis showed that the excess mortality was attenuated by approximately one-fifth after adjustment for these factors and that serum lipid levels and BP contributed to the attenuation (Table 3).

Table 2. The HRs of Mortality From Coronary Heart Disease by Categories of Thyrotropin Concentration Within the Reference Range

Thyrotropin, mIU/L	Total Population			Nonsmokers		
	Participants, No.	Coronary Deaths, No.	HR (95% CI) ^a	Participants, No.	Coronary Deaths, No.	HR (95% CI) ^b
Women and men combined ^c						
0.50-1.4	10 573	126	1 [Reference]	5163	57	1 [Reference]
1.5-2.4	9291	159	1.25 (0.99-1.58)	5643	99	1.45 (1.05-2.02)
2.5-3.5	3045	71	1.43 (1.06-1.92)	2100	51	1.66 (1.14-2.43)
<i>P</i> value for trend		.01			.007	
Women						
0.50-1.4	7045	60	1 [Reference]	3622	36	1 [Reference]
1.5-2.4	6243	89	1.41 (1.02-1.96)	3961	64	1.54 (1.02-2.32)
2.5-3.5	2174	43	1.69 (1.14-2.52)	1555	34	1.72 (1.08-2.76)
<i>P</i> value for trend		.005			.02	
Men						
0.50-1.4	3528	66	1 [Reference]	1541	21	1 [Reference]
1.5-2.4	3048	70	1.11 (0.79-1.55)	1682	35	1.32 (0.77-2.28)
2.5-3.5	871	28	1.20 (0.76-1.88)	545	17	1.52 (0.80-2.90)
<i>P</i> value for trend		.50			.27	

Abbreviations: CI, confidence interval; HR, hazard ratio.

^aAdjusted for age and smoking status.

^bAdjusted for age.

^cAdditionally adjusted for sex.

Table 3. The HRs of CHD Mortality per 1-mIU/L Increase in Thyrotropin Concentration in Women With Thyrotropin Levels Within the Reference Range^a

Adjustment for ^b	HR (95% CI)
Age and smoking status	1.37 (1.12-1.68)
Age, smoking status, and serum creatinine level	1.37 (1.11-1.67)
Age, smoking status, and BMI	1.36 (1.11-1.67)
Age, smoking status, systolic and diastolic BP, and use of antihypertensive drugs	1.33 (1.09-1.64)
Age, smoking status, total serum cholesterol level, HDL cholesterol level, and triglycerides	1.33 (1.08-1.63)
Age, smoking status, serum creatinine level, BMI, systolic and diastolic BP, use of antihypertensive drugs, total serum cholesterol level, HDL cholesterol level, and triglycerides	1.30 (1.06-1.60)

Abbreviations: BMI, body mass index; BP, blood pressure; CHD, coronary heart disease; CI, confidence interval; HDL, high-density lipoprotein; HR, hazard ratio.

^aOf 15 295 women, 177 died of CHD. The number of participants is lower than in the main analysis owing to exclusion of individuals with missing values of serum lipids, BP, use of antihypertensive drugs, BMI, or serum creatinine.

^bAll factors are assessed as continuous variables, except for serum creatinine (in quintiles), use of antihypertensive drugs (never, previous, and current), and smoking status.

COMMENT

In this prospective mortality follow-up of more than 25 000 people from the general population, thyrotropin levels within the reference range were positively and linearly associated with fatal CHD in women. In men, there was no convincing evidence of an association.

Previously, small cross-sectional studies have reported that low but clinically normal thyroid function is

associated with more severe coronary^{4,5} and carotid⁶ atherosclerosis and increased carotid artery intima media thickness.¹⁶ Also, recent studies show that impaired endothelial function, suggesting early-stage atherosclerosis,¹⁷ may be more prevalent in hypothyroid patients and in people with thyrotropin levels in the upper part of the reference range.¹⁸ In old age, there is some evidence that within the clinical reference range, higher levels of thyroid function may be positively associated with total mortality.⁹ However, 1 prospective study¹⁰ that specifically analyzed vascular disease mortality did not show any association with thyrotropin levels in the reference range.

In previous studies, linear and positive associations between thyrotropin levels within the reference range and BP¹ and less favorable serum lipid profiles in people with higher thyrotropin levels have been reported.³ In this study, we observed a modest attenuation of the effect of thyrotropin level on CHD mortality after adjustment for BP and serum lipids. This may indicate that the effect of thyrotropin level at least partly may be mediated by these factors.

It has been suggested that thyrotropin levels within the reference range may be positively associated with body mass index² and negatively associated with insulin sensitivity.¹⁹ Also, thyroid hormones may affect the cardiovascular system through effects on vascular smooth muscle cells, cardiac myocytes,²⁰ coronary angiogenesis,²¹ renal function,²² hemostasis,²³ oxidation of low-density lipoproteins, and homocysteine levels.⁷ In addition, thyrotropin may have cardiovascular effects that are not mediated by thyroid hormones. Thus, administration of recombinant human thyrotropin was recently associated with acute impairment of endothelial function.²⁴ It has also been suggested, but not convincingly shown, that inflammation associated with autoimmune thyroid dis-

ease could contribute to atherosclerosis in people with low thyroid function.^{25,26}

Subclinical hypothyroidism, characterized by elevated serum thyrotropin levels but thyroid hormone levels within the reference range, has been associated with CHD in some cross-sectional^{8,25} and prospective²⁷⁻²⁹ studies, although results are inconsistent.^{8,30,31} We found evidence of an increased risk of fatal CHD in nonsmoking women with thyrotropin levels higher than the reference range. However, in the baseline survey forming the basis of this cohort, participants with pathologic thyrotropin levels were recommended to consult their physician, and any subsequent management may have altered their cardiovascular risk and could have biased these risk estimates. Therefore, we focused our analysis on CHD mortality associated with thyrotropin levels within the reference range.

Previous prospective studies^{9,10,27} indicate that high levels of thyroid function may be associated with increased cardiovascular mortality. It has also been shown that high thyroid function may be associated with a higher prevalence of hypertension, impaired cardiac function,²⁰ and atrial fibrillation.^{20,32} Owing to few coronary deaths in people with thyrotropin levels below the reference range, we could not assess the association of hyperthyroid function with fatal CHD in this study.

To our knowledge, no clinical trial has tested whether thyroxine replacement could protect against CHD. However, some clinical studies of patients with subclinical hypothyroidism have shown that thyroxine treatment may improve serum lipid levels,³³⁻³⁵ BP,^{36,37} and adiposity,³⁵ as well as endothelial function^{35,38} and carotid artery intima media thickness.³⁴ A beneficial effect of thyroxine treatment on serum lipid levels has also been demonstrated in individuals with thyrotropin levels in the upper part of the reference range.³⁹

This study shows that CHD mortality increases in women with increasing levels of thyrotropin within the reference range. These results indicate that relatively low but clinically normal thyroid function may increase the risk of fatal CHD.

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Author Contributions: Dr Åsvold had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. *Study concept and design:* Åsvold, Bjørø, and Vatten. *Acquisition of data:* Bjørø and Vatten. *Analysis and interpretation of data:* Åsvold, Nilsen, Gunnell, and Vatten. *Drafting of the manuscript:* Åsvold and Vatten. *Critical revision of the manuscript for important intellectual content:* Bjørø, Nilsen, Gunnell, and Vatten. *Statistical analysis:* Åsvold and Nilsen. *Obtained funding:* Bjørø and Vatten. *Administrative, technical, and material support:* Vatten. *Study supervision:* Bjørø, Nilsen, Gunnell, and Vatten. **Financial Disclosure:** None reported.

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Correction

Incorrect Middle Initial. In the article titled "The Growing Burden of Diabetes Mellitus in the US Elderly Population," by Sloan et al, published in the January 28th issue of the *Archives* (2008;168[2]:192-199), the fourth author's middle initial in the byline on page 192 was incorrect. It should have read as follows: Alisa M. Shea, MPH.