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Association between Blood Pressure and Serum Thyroid-Stimulating Hormone Concentration within the Reference Range: A Population-Based Study

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Context: The association between thyroid function and blood pressure is insufficiently studied.

Objective: The objective of the investigation was to study the association between TSH within the reference range and blood pressure.

Design and Setting: This was a cross-sectional, population-based study.

Subjects: A total of 30,728 individuals without previously known thyroid disease were studied.

Main Outcome Measures: The main outcome measures were mean systolic and diastolic blood pressure and pulse pressure and odds ratio for hypertension (>140/90 mm Hg or current or previous use of antihypertensive medication), according to categories of TSH.

Results: Within the reference range of TSH (0.50–3.5 mU/liter), there was a linear increase in blood pressure with increasing TSH. The average increase in systolic blood pressure was 2.0 mm Hg [95% confidence interval (CI) 1.4–2.6 mm Hg] per milliunit per liter increase in TSH among men, and 1.8 mm Hg (95% CI 1.4–2.3 mm Hg) in women. The corresponding increase in diastolic blood pressure was 1.6 mm Hg (95% CI 1.2–2.0 mm Hg) in men and 1.1 mm Hg (95% CI 0.8–1.3 mm Hg) in women. Comparing TSH of 3.0–3.5 mU/liter (upper part of the reference) with TSH of 0.50–0.99 mU/liter (lower part of the reference), the odds ratio for hypertension was 1.98 (95% CI 1.56–2.53) in men and 1.23 (95% CI 1.04–1.46) in women.

Conclusion: Within the reference range of TSH, we found a linear positive association between TSH and systolic and diastolic blood pressure that may have long-term implications for cardiovascular health. **(*J Clin Endocrinol Metab* 92: 841–845, 2007)**

THYROID HORMONES INFLUENCE the cardiovascular system (1), and thyroid dysfunction may increase the risk of cardiovascular disease (2). Previous studies have shown that both hypo- and hyperthyroid disease may increase the risk of hypertension (2–5) and that hypertension related to hypothyroidism may be reversed after T_4 treatment (6–8). Subclinical hypothyroid function, characterized by thyroid hormones within the reference range combined with elevated TSH, has been associated with higher diastolic blood pressure (9), and after T_4 treatment, it has been demonstrated that diastolic (10) and mean arterial pressure (11) may be reduced. However, others have failed to demonstrate any association between blood pressure and subclinical hypo- (12) or hyperthyroidism (13).

In people with no apparent thyroid dysfunction, one study showed lower thyroid function among people with hypertension (14). Consistent with this finding, the results of two recent population-based studies (13, 15) indicate a positive association between TSH within the reference range and systolic and diastolic blood pressure.

The association between TSH within the reference range and blood pressure is insufficiently studied. In a study of more than 30,000 individuals, we therefore examined whether concentrations of TSH within the reference range are related to systolic and diastolic blood pressure, pulse pressure, and the prevalence of hypertension.

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Abbreviations: BMI, Body mass index; CI, confidence interval.

Subjects and Methods

Between 1995 and 1997, all inhabitants 20 yr of age or older in Nord-Trøndelag County in Norway were invited to participate in the Nord-Trøndelag Health Study (HUNT). A total of 92,936 individuals were eligible to participate, and 66,140 (71.2%) attended. The study has been described in detail elsewhere (16). Briefly, the participants were asked to complete a self-administered questionnaire, which included eight thyroid-specific questions (17). By self-report, information on health and lifestyle factors was also collected as well as history of diabetes mellitus, angina pectoris, myocardial infarction, and stroke and information on the use of antihypertensive medication.

Blood pressure was measured by specially trained nurses or technicians using a Dinamap 845XT (Critikon, Tampa, FL) based on oscillometry. Cuff size was adjusted after measuring the arm circumference. After 2 min rest, the blood pressure was automatically measured three times at 1-min intervals. In this study, we used the mean value of the second and third measurement of systolic and diastolic blood pressure. Pulse pressure was calculated as the difference between systolic and diastolic blood pressure.

A nonfasting venous blood sample was drawn from each individual. Analysis of serum TSH was carried out in subsamples of the population, including all women older than 40 yr of age and 50% of men older than 40 yr of age. In addition, TSH was measured in 5% random samples of men and women 20–40 yr of age. In total, 34,851 individuals from these samples were selected for TSH analysis.

Nord-Trøndelag County is located in the middle part of Norway and is characterized by a stable and homogenous population (16). The prevalence of thyroid disease has been previously estimated (17). Briefly, 0.6% of men and 2.5% of women had hyperthyroidism, whereas 0.9% of

men and 4.8% of women had hypothyroidism, based on self-report. Among people older than 40 yr of age, 19.6% reported current or previous use of antihypertensive medication. The Norwegian population is generally considered to have sufficient iodine intake (18).

Laboratory measurements

Serum concentration of TSH was analyzed at the Hormone Laboratory, Aker University Hospital, Oslo, using DELFIA hTSH Ultra (sensitivity 0.03 mU/liter and total analytical variation < 5%; Wallac Oy, Turku, Finland). Reference ranges for TSH from this population have been published previously (17). Based on these results, the reference range for TSH in the present study was defined as 0.50–3.5 mU/liter.

Statistical analyses

Among the 34,851 individuals who were selected for TSH analysis, 30,728 were included in the present study. Exclusion criteria were previously known thyroid disease (n = 2904) and missing information on TSH, blood pressure, use of antihypertensive medication, or smoking status (n = 1219). In the analyses related to systolic and diastolic blood pressure and pulse pressure, we further excluded those who reported current or previous use of antihypertensive medication (n = 5702).

The association between TSH and blood pressure was analyzed using general linear models. Within the reference range of TSH, we calculated mean systolic and diastolic blood pressure and pulse pressure for six categories of TSH (0.50–0.99, 1.00–1.4, 1.5–1.9, 2.0–2.4, 2.5–2.9, and 3.0–3.5 mU/liter). We also analyzed the association between TSH and blood pressure by calculating partial-regression coefficients, with corresponding 95% confidence intervals (CI). The partial-regression coefficients are presented as the average increase in blood pressure per milliunit per liter increase in TSH. Results from the analyses of log-transformed and nontransformed blood pressure were nearly identical, and we therefore present the nontransformed results.

We stratified the association of TSH and blood pressure by sex and age (age groups younger than 50 yr of age, 50–69 yr, and 70 yr and older). Similarly, we assessed whether the association of TSH and blood pressure differed between current smokers, former smokers, and never-smokers and between overweight and normal weight individuals, using body mass index (BMI; weight divided by the squared value of height) of 25.0 kg/m^2 as cutoff.

In a logistic regression model, we calculated odds ratios for hypertension for the six categories of TSH within the reference range, using TSH 0.50–0.99 mU/liter as reference group. Hypertension was defined as systolic blood pressure higher than 140 mm Hg and/or diastolic blood pressure higher than 90 mm Hg and/or current or previous use of antihypertensive medication.

In a separate analysis, we studied the association with blood pressure also including TSH concentrations outside the reference range. We calculated mean systolic and diastolic blood pressure and pulse pressure for five categories of TSH [less than 0.10, 0.10–0.49, 0.50–3.5 (reference range), 3.6–9.9, and 10.0 mU/liter and higher]. We compared the blood pressures for each category of TSH outside the reference range with mean blood pressures corresponding to TSH within the reference range. In a logistic regression model, we calculated odds ratios for hypertension for these categories of TSH, using TSH 0.50–3.5 mU/liter as reference group.

The data were analyzed using the Statistical Package for the Social Sciences (SPSS), version 14.0 for Windows (SPSS Inc., Chicago, IL).

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

Results

Within the reference range of TSH (0.50–3.5 mU/liter), there was a linear increase in systolic and diastolic blood pressure with increasing concentration of TSH (Figs. 1 and 2). The average increase in systolic blood pressure per milliunit per liter increase in TSH was 2.0 mm Hg (95% CI 1.4–2.6 mm Hg) in men and 1.8 mm Hg (95% CI 1.4–2.3 mm Hg) in women. Similarly, the average increase in diastolic blood pressure per milliunit per liter increase in TSH was 1.6 mm Hg (95% CI 1.2–2.0 mm Hg) in men and 1.1 mm Hg (95% CI 0.8–1.3 mm Hg) in women. In women, the average increase in pulse pressure was 0.8 mm Hg (95% CI, 0.5–1.1 mm Hg) per milliunit per liter increase in TSH, but in men, TSH was not significantly associated with pulse pressure. These results were adjusted for age and smoking status. Additional adjustment for arm circumference and the prevalence of diabetes mellitus, angina pectoris, myocardial infarction, or stroke did not substantially influence the results.

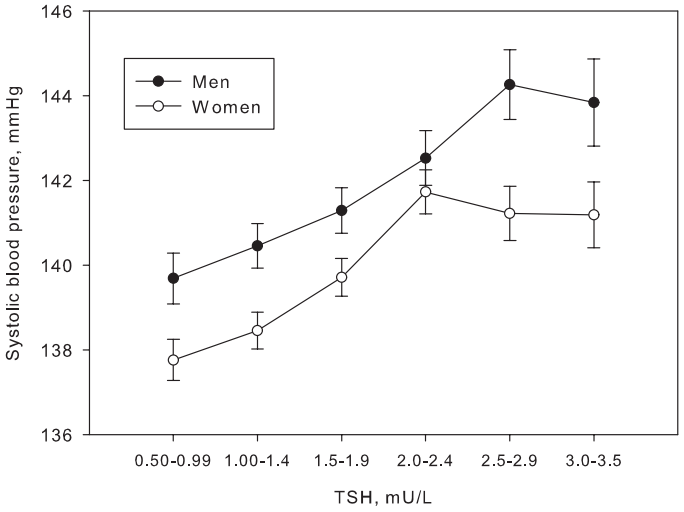

FIG. 1. Mean systolic blood pressure (with SE) by categories of TSH within the reference range (0.50–3.5 mU/liter) in men (n = 8,014) and women (n = 14,721), adjusted for age and smoking status.

Subgroup analyses showed that the association between TSH and systolic and diastolic blood pressure was consistent in all age groups, except for systolic blood pressure in men above 70 yr of age. There was a statistically significant increase in pulse pressure with increasing TSH in men 50–69

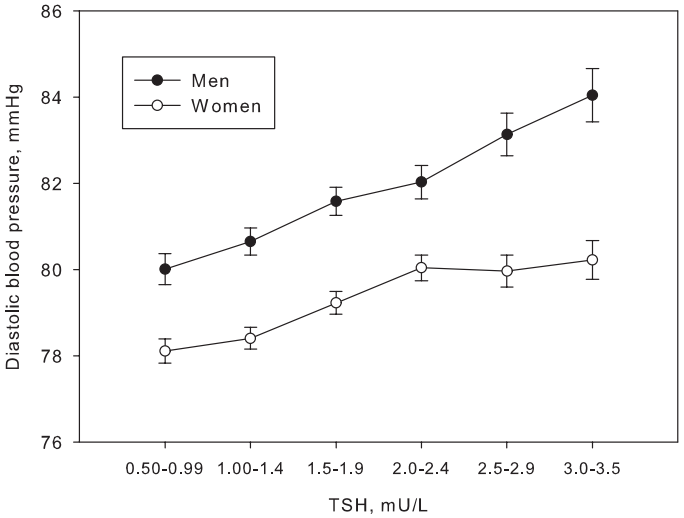

FIG. 2. Mean diastolic blood pressure (with SE) by categories of TSH within the reference range (0.50–3.5 mU/liter) in men (n = 8,014) and women (n = 14,721), adjusted for age and smoking status.

TABLE 1. Mean increase (mm Hg, with 95% CI) in systolic (SBP) and diastolic blood pressure (DBP) and pulse pressure (PP) per milliunit per liter increase in TSH within the reference range (TSH of 0.50–3.5 mU/liter) in men and women, by categories of age, smoking, and BMI, adjusted for age and smoking status

	Men				Women			
	No.	SBP	DBP	PP	No.	SBP	DBP	PP
Age								
<50 yr	2971	1.6 (0.8–2.4)	1.4 (0.8–1.9)	0.3 (−0.3 to 0.8)	5576	1.6 (1.0–2.2)	1.1 (0.7–1.5)	0.5 (0.1–1.0)
50–69 yr	3601	2.9 (1.9–3.8)	1.8 (1.3–2.4)	1.1 (0.4–1.7)	6447	2.2 (1.4–2.9)	1.1 (0.7–1.6)	1.1 (0.5–1.6)
≥70 yr	1442	0.8 (−0.9 to 2.4)	1.6 (0.7–2.4)	−0.8 (−2.0 to 0.4)	2698	1.5 (0.2–2.8)	0.9 (0.1–1.6)	0.6 (−0.3 to 1.6)
Smoking								
Never	2628	2.0 (1.0–3.0)	1.8 (1.2–2.5)	0.2 (−0.5 to 0.9)	7037	1.9 (1.2–2.6)	1.1 (0.7–1.5)	0.8 (0.3–1.3)
Former	2882	1.6 (0.5–2.6)	1.1 (0.5–1.7)	0.5 (−0.3 to 1.2)	3141	2.3 (1.4–3.3)	1.1 (0.5–1.6)	1.3 (0.6–1.9)
Current	2504	2.5 (1.4–3.7)	2.1 (1.4–2.8)	0.5 (−0.3 to 1.3)	4543	1.4 (0.5–2.2)	1.0 (0.5–1.5)	0.4 (−0.2 to 1.0)
BMI								
<25.0 kg/m^2	2649	2.0 (0.9–3.1)	1.6 (1.0–2.2)	0.4 (−0.4 to 1.1)	6200	1.0 (0.4–1.7)	0.7 (0.3–1.1)	0.4 (−0.1 to 0.8)
≥25.0 kg/m^2	5324	1.9 (1.1–2.6)	1.5 (1.0–1.9)	0.4 (−0.1 to 0.9)	8401	2.0 (1.4–2.6)	1.1 (0.7–1.5)	0.9 (0.5–1.4)

yr of age and in women younger than 70 yr of age. The positive association between TSH and systolic and diastolic blood pressure was present in former and current smokers as well as never-smokers and in overweight as well as normal weight people (Table 1).

In both sexes, the prevalence of hypertension increased with increasing TSH within the reference range, but the association was stronger in men than in women (Table 2). Comparing TSH of 3.0–3.5 mU/liter (upper part of the reference) with TSH of 0.50–0.99 mU/liter (lower part of the reference), the odds ratio for hypertension was 1.98 (95% CI 1.56–2.53) in men and 1.23 (95% CI 1.04–1.46) in women.

In a separate analysis, including the entire range of TSH, systolic and diastolic blood pressure and pulse pressure increased with increasing TSH in women, except for women whose TSH was lower than 0.10 mU/liter. In these women, both systolic pressure and pulse pressure were higher than for women with TSH within the reference range (Table 3). The prevalence of hypertension was higher in women with TSH lower than 0.10 mU/liter (odds ratio 1.70, 95% CI 1.09–2.66) or TSH 3.6–9.9 mU/liter (odds ratio 1.20, 95% CI 1.06–1.36), compared with women with TSH within the reference range. In men with TSH outside the reference range, mean systolic and diastolic blood pressure, pulse pressure, and the prevalence of hypertension, did not clearly differ from men with TSH within the reference range (Table 4).

TABLE 2. Odds ratio (OR) for hypertension (systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg or current or previous use of antihypertensive medication), by categories of TSH, in men and women

TSH (mU/liter)	No.	No. hypertension	OR[a]	95% CI	
Men					
0.50–0.90	1648	812	1.0 (Ref.)		
1.00–1.4	2863	1548	1.18	1.04	1.34
1.5–1.9	2481	1412	1.27	1.11	1.45
2.0–2.4	1391	830	1.39	1.19	1.62
2.5–2.9	740	490	1.68	1.39	2.04
3.0–3.5	442	317	1.98	1.56	2.53
P^b			<0.001		
Women					
0.50–0.99	3237	1490	1.0 (Ref.)		
1.00–1.4	5030	2388	1.02	0.92	1.13
1.5–1.9	4566	2410	1.15	1.03	1.27
2.0–2.4	2803	1652	1.38	1.22	1.55
2.5–2.9	1596	955	1.29	1.12	1.48
3.0–3.5	989	589	1.23	1.04	1.46
P^b			<0.001		

Ref., Reference group.
[a] Adjusted for age and smoking status.
[b] *P* value for linear trend across the categories of TSH.

Discussion

In this population study of more than 30,000 men and women, we found that both systolic and diastolic blood pressure increased linearly with increasing TSH within the reference range of 0.50–3.5 mU/liter. We also found that the prevalence of hypertension increased with increasing TSH

TABLE 3. Mean systolic (SBP) and diastolic (DBP) blood pressure and pulse pressure (PP) in mm Hg, by categories of TSH, in men and women

TSH (mU/liter)	No.	SBP[a]	P^b	DBP[a]	P^b	PP[a]	P^b
Men							
<0.10	10	132.9	0.12	76.3	0.14	56.6	0.35
0.10–0.49	137	140.4	0.42	79.6	0.06	60.8	0.64
0.50–3.5	8,014	141.6	Ref.	81.3	Ref.	60.3	Ref.
3.6–9.9	406	143.0	0.13	82.5	0.04	60.6	0.68
≥10.0	32	139.8	0.57	81.3	0.99	58.5	0.43
Women							
<0.10	88	144.6	0.01	80.6	0.20	64.0	0.01
0.10–0.49	322	138.3	0.31	77.9	0.07	60.4	0.96
0.50–3.5	14,721	139.4	Ref.	79.0	Ref.	60.4	Ref.
3.6–9.9	1,139	141.7	<0.001	80.3	<0.001	61.4	0.01
≥10.0	157	144.2	<0.01	81.1	0.02	63.1	0.01

Ref., Reference group.
[a] Adjusted for age and smoking status.
[b] *P* value for the difference from the reference group (TSH 0.50–3.5 mU/liter).

TABLE 4. Odds ratio (OR) for hypertension (systolic blood pressure > 140 mm Hg and/or diastolic blood pressure > 90 mm Hg or current or previous use of antihypertensive medication), by categories of TSH, in men and women

TSH (mU/liter)	No.	No. hypertension	OR[a]	95% CI	
Men					
<0.10	13	6	0.40	0.13	1.23
0.10–0.49	162	81	0.79	0.57	1.10
0.50–3.5	9,565	5,409	1.0 (Ref.)		
3.6–9.9	541	359	1.11	0.91	1.35
≥10.0	40	22	0.82	0.42	1.60
Women					
<0.10	114	74	1.70	1.09	2.66
0.10–0.49	410	219	0.94	0.75	1.18
0.50–3.5	18,221	9,484	1.0 (Ref.)		
3.6–9.9	1,475	938	1.20	1.06	1.36
≥10.0	187	114	1.11	0.79	1.56

Ref., Reference group.
[a] Adjusted for age and smoking status.

within the reference range, although more consistently in men than in women.

Underlying mechanisms that may explain these findings are not fully understood, but increased systemic vascular resistance (1, 7) and arterial stiffness (7, 10, 19, 20) may accompany low thyroid function. A study of people with apparently normal thyroid function showed that relatively low thyroid function was associated with increased renal vascular resistance and increased blood pressure (14). In another study, TSH in the upper part of the reference range was associated with arterial stiffness (19). In studies of people with overt or subclinical hypothyroidism, it has been shown that vascular resistance (7, 11) and arterial stiffness (7, 10, 20) may be reduced after T_4 treatment. It has also been shown that thyroid hormones may have direct vasodilatory effects on vascular muscle cells (21) and that endothelial dysfunction may be more prevalent in hypothyroid patients (22, 23) and individuals with TSH in the upper part of the reference range (22).

In a study of families with high prevalence of hypertension, concentrations of TSH tended to be in the upper part of the reference range, suggesting that certain genetic variants may both affect blood pressure regulation and serum TSH concentration (24). Our data, however, show a remarkably linear association with blood pressure across the reference range of TSH. Therefore, our results may not support the hypothesis that a positive association between TSH within the reference range and blood pressure could be due to a genetic variant that specifically affects people with TSH in the upper part of the reference range nor that it could be due to the minimal thyroid dysfunction that is likely to be more prevalent among people with TSH in the upper part of the reference range (25).

Outside the reference range of TSH, our findings among women tend to support previous reports of increased blood pressure both associated with hypo- and hyperthyroidism (3–5). It should be acknowledged that the number of participants with clearly pathological TSH was small, especially in men, leading to imprecise estimates for these groups.

Pulse pressure may be a useful marker for central artery stiffness in older people and has been used to assess cardiovascular risk (26). Within the reference range of TSH, the positive association between TSH and pulse pressure was less pronounced and less consistent than the associations with systolic and diastolic blood pressure. The higher pulse pressure that we found among women with TSH of 10.0 mU/liter or higher is at variance with the suggestion that hypothyroidism is associated with a narrowed pulse pressure (1).

The association between TSH within the reference range and blood pressure was modest but displayed consistent and statistically significant patterns. The clinical significance of our findings is uncertain, but inaccuracies in blood pressure measurements indicate that the association between TSH and blood pressure is conservatively estimated. In the same population, we previously found linear associations between TSH within the reference range and serum lipids, in which relatively high TSH was associated with less favorable lipid concentrations (27).

In conclusion, we found a positive and linear association between TSH within the reference range and systolic and diastolic blood pressure. We also found increasing prevalence of hypertension with increasing TSH. Whether these associations are sufficiently strong to influence future risk of cardiovascular disease should be tested in prospective population-based studies.

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