

The Colorado Thyroid Disease Prevalence Study

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Context: The prevalence of abnormal thyroid function in the United States and the significance of thyroid dysfunction remain controversial. Systemic effects of abnormal thyroid function have not been fully delineated, particularly in cases of mild thyroid failure. Also, the relationship between traditional hypothyroid symptoms and biochemical thyroid function is unclear.

Objective: To determine the prevalence of abnormal thyroid function and the relationship between (1) abnormal thyroid function and lipid levels and (2) abnormal thyroid function and symptoms using modern and sensitive thyroid tests.

Design: Cross-sectional study.

Participants: Participants in a statewide health fair in Colorado, 1995 (N = 25 862).

Main Outcome Measures: Serum thyrotropin (thyroid-stimulating hormone [TSH]) and total thyroxine (T₄) concentrations, serum lipid levels, and responses to a hypothyroid symptoms questionnaire.

Results: The prevalence of elevated TSH levels (normal range, 0.3-5.1 mIU/L) in this population was 9.5%,

and the prevalence of decreased TSH levels was 2.2%. Forty percent of patients taking thyroid medications had abnormal TSH levels. Lipid levels increased in a graded fashion as thyroid function declined. Also, the mean total cholesterol and low-density lipoprotein cholesterol levels of subjects with TSH values between 5.1 and 10 mIU/L were significantly greater than the corresponding mean lipid levels in euthyroid subjects. Symptoms were reported more often in hypothyroid vs euthyroid individuals, but individual symptom sensitivities were low.

Conclusions: The prevalence of abnormal biochemical thyroid function reported here is substantial and confirms previous reports in smaller populations. Among patients taking thyroid medication, only 60% were within the normal range of TSH. Modest elevations of TSH corresponded to changes in lipid levels that may affect cardiovascular health. Individual symptoms were not very sensitive, but patients who report multiple thyroid symptoms warrant serum thyroid testing. These results confirm that thyroid dysfunction is common, may often go undetected, and may be associated with adverse health outcomes that can be avoided by serum TSH measurement.

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THE PREVALENCE of abnormal thyroid function continues to be debated. Numerous studies from various countries differ in their prevalence estimates for both hypothyroidism and hyperthyroidism. The difficulty with many of these studies lies in the variable definitions of disease states, the poorly defined and diverse populations studied, and the historically insensitive measures of thyroid function. In perhaps the best longitudinal study conducted to date, Tunbridge et al¹ found that 7.5% of women and 2.8% of men of all ages in Whickham, England, had serum thyrotropin (thyroid-stimulating hormone [TSH]) levels greater than 6 mIU/L. After reviewing 12 such studies across many different cultures, Vanderpump and Tunbridge² concluded that primary thyroid gland failure (TSH >6 mIU/L) occurs in 5% of multiple populations.

Several factors may affect prevalence. For example, virtually all studies report higher prevalence rates for hypothyroidism in women and with advancing age,²⁻⁷ with rates as high as 24% among women older than 60 years recruited from several senior citizens' centers and ambulatory clinics.⁴ Dietary iodine is another factor. The Framingham Study showed that 13.6% of US women older than 60 years had TSH levels greater than 5 mIU/L.⁵ In Italy, where dietary iodine is low, serum TSH levels greater than 5 mIU/L were found in only 1.5% of similarly aged women.⁸

Abnormal thyroid function has important public health consequences. Suppressed TSH levels have been associated with decreased bone density in some but not all studies^{9,10} and with an increased risk of atrial fibrillation¹¹ and premature atrial beats.¹² It has been known for decades that overt hypothyroidism contributes to

PATIENTS AND METHODS

STUDY POPULATION

The Colorado 9Health Fair is an annual statewide event that provides testing for such disorders as hypertension, colon cancer, glaucoma, and skin cancer, with optional blood analysis available at a nominal fee. Participants also complete a demographic survey at the time of their screening. In 1995, sensitive tests of thyroid function were added to the menu of blood analyses, and a questionnaire for hypothyroid symptoms was included with the survey. (The Thyroid Health Survey is available upon request from the authors.) Written informed consent was obtained from all participants.

THYROID HEALTH SURVEY

The Thyroid Health Survey was one page of the Colorado 9Health Fair questionnaire. Questions on personal history, family history, and demographic characteristics were included. There were also 14 questions on symptoms of hypothyroidism, which were chosen based on the results of a previous study.³⁴ In this study of traditional hypothyroid symptoms, symptom questions were asked in 2 ways: Was the symptom present at the time the questionnaire was completed ("current" symptom)? Was the symptom new from the previous year ("changed" symptom)? Three "current" and 11 "changed" symptoms became the Colorado 9Health Fair Thyroid Health Survey symptom questions.

SERUM ASSAYS

Subjects who opted for blood analysis were requested to fast for 12 hours prior to having their blood drawn. All serum assays were performed by a central laboratory (Quest Diagnostics Inc, Denver Co [formerly Corning Clinical Laboratories]). Serum TSH concentrations were measured by a third-generation immunochemiluminescent procedure having a functional detection limit of 0.01 mIU/L and a normal range of 0.3 to 5.1 mIU/L, inclusive.⁴³ Serum total thyroxine (T₄) concentrations were measured by enzyme immunoassay. Serum lipid levels were determined using the autoanalyzer method. Age- and sex-adjusted reference ranges were used to define the limits of normality for serum lipid levels. Thyroid status was defined as follows:

- Euthyroid (TSH level within the normal range, 0.3-5.1 mIU/L, inclusive)
- Hypothyroid (TSH level >5.1 mIU/L and T₄ level <57.9 nmol/L, [<4.5 $\mu\text{g/dL}$])
- Subclinical hypothyroid (TSH level >5.1 mIU/L and T₄ level ≥ 57.9 nmol/L [≥ 4.5 $\mu\text{g/dL}$])
- Hyperthyroid (TSH level ≤ 0.01 mIU/L)

- Subclinical hyperthyroid (TSH level, 0.01 to <0.3 mIU/L)

Because total (T₄) and not free (FT₄) thyroxine levels were used in this study, some total T₄ concentrations may have been slightly elevated because of increases in thyroid hormone binding proteins in patients who were receiving certain concomitant medications; for example, estrogens. We therefore categorized hyperthyroid states according to TSH levels alone, as above, assuming that virtually all hyperthyroid patients have undetectable serum TSH levels. Similarly, the population of patients with subclinical hypothyroidism may be overestimated because of concomitant estrogen administration.

DATA COLLECTION

Data were entered directly from the Colorado 9Health Fair Survey forms and verified using double entry. Laboratory results collected by the Colorado 9Health Fair were later linked to survey information by site and subject identification number. The Colorado Medical Society, Englewood, provided appropriate medical follow-up for participants with abnormal laboratory test results identified through the Colorado 9Health Fair.

DATA ANALYSIS

All data were analyzed using SAS statistical software package (SAS Institute, Cary, NC). Measures of significance between groups were calculated using the χ^2 test and analysis of variance (ANOVA). The Pearson correlation coefficient was calculated between the TSH level and the percentage of reported symptoms in order to relate symptoms to progressively worsening thyroid function. Logistic regression was used to determine which symptoms were independent predictors of a disease state, while controlling for other symptoms. Receiver operating characteristic (ROC) areas were calculated using the ROC Curve Analyzer, version 6 (R. Centor and J. Keightley, University of Alabama, Birmingham). The symptom index was calculated in the manner of Billewicz et al.³⁵ The Billewicz group assigned a weight to each sign and symptom of hypothyroidism. For each patient, the numerical weights of the patient's reported symptoms, present and absent, were summed to calculate the Billewicz score. These patient scores may discriminate between hypothyroid and euthyroid persons better than individual symptoms. In our study population, symptom weights were calculated using the overt hypothyroid group relative to a randomly chosen subset of the euthyroid group. This subgroup, of equal size to the hypothyroid group, was matched with the hypothyroid group for age, sex, and whether or not the individual was taking thyroid medication.

elevated serum cholesterol levels,¹³⁻²¹ and recent studies suggest this may also be true with subclinical hypothyroidism.²²⁻²⁶ However, the impact of various degrees of thyroid dysfunction remains unsettled, perhaps caused in part by differing laboratory definitions and small study populations.²⁷⁻³⁰

Identifying thyroid disease clinically can be challenging. Symptoms often develop so insidiously that they go unnoticed.³¹ When symptoms are reported, they are frequently confused with other health problems.³¹⁻³³ Cli-

nicians have tried to identify patients with a higher likelihood of hypothyroidism based on physical findings and symptoms and have suggested using symptoms to guide testing.³⁴⁻³⁹ Similar strategies may also apply to subclinical hypothyroidism and subclinical hyperthyroidism, since both have been associated with reversible clinical symptoms when assessed by controlled symptom questionnaires.⁴⁰⁻⁴²

In the present study, a large cohort provided a unique opportunity to conduct a cross-sectional study of abnor-

Table 1. Population Characteristics

Characteristic	% of Subjects	
	Study Population (N = 25 862)*	Colorado Population (N = 3 655 714)†
Age distribution, y‡		
18-24	1.3	10.2
25-34	6.2	18.6
35-44	16.7	17.2
45-54	23.4	10.2
55-64	24.3	7.6
65-74	20.0	5.9
>74	8.2	4.1
Age, y (median)	56.0	32.5
Sex	(n = 25 816)	
Female	55.8	50.5
Male	44.2	49.5
Education	(n = 23 228)	
≥12 y	94.5	84.4
≥16 y	37.6	27.0
Race	(n = 23 215)	
White	94.4	88.2
Nonwhite	5.6	11.8

*The study population shown is the evaluable population.
 †Colorado population data shown are from 1994 or the 1990 census.
 ‡1990 Colorado population data; 26.2% are younger than 18 years.

mal thyroid function. The principal inquiries were (1) the prevalence of abnormal thyroid function, (2) the relationship of abnormal thyroid function to abnormal serum lipid concentrations, and (3) the relationship between abnormal thyroid function and symptoms of hypothyroidism using modern and sensitive tests of thyroid function.

RESULTS

POPULATION DEMOGRAPHICS

There were 33 661 subjects who presented to the 118 Colorado 9Health Fair screening sites. We excluded 6319 subjects for not returning the Thyroid Health Survey, non-evaluable responses, or inconsistent demographic data that made matching survey responses to laboratory data potentially inaccurate. Another 1480 subjects did not have blood drawn. Demographic data on the remaining 25 862 individuals, representing 111 testing sites, are shown in **Table 1**. When compared with the general population of Colorado, the study population was older and had more women, a greater proportion who were white, and more high school and college graduates. Similar population characteristics have been reported by other community health fairs.^{44,45}

THYROID FUNCTION TESTS

Based on the above definitions of thyroid status, an abnormal serum TSH concentration was found in 11.7% of subjects (**Table 2**). There were 2450 subjects (9.5%) with an elevated TSH concentration, most of whom were subclinically hypothyroid. Among those with an el-

Table 2. Prevalence of Thyroid Abnormalities

Thyroid Status*	No. of Subjects (%)
Total subjects	(N = 25 862)
Euthyroid	22 842 (88.3)
Hypothyroid	114 (0.4)
Subclinical hypothyroid	2336 (9.0)
Hyperthyroid	35 (0.1)
Subclinical hyperthyroid	535 (2.1)
Subjects taking thyroid medication	(n = 1525)
Euthyroid	916 (60.1)
Hypothyroid	11 (0.7)
Subclinical hypothyroid	269 (17.6)
Hyperthyroid	13 (0.9)
Subclinical hyperthyroid	316 (20.7)
Subjects not taking thyroid medication	(n = 24 337)
Euthyroid	21 926 (90.1)
Hypothyroid	103 (0.4)
Subclinical hypothyroid	2067 (8.5)
Hyperthyroid	22 (0.1)
Subclinical hyperthyroid	219 (0.9)

*See "Patients and Methods" section for definition of thyroid status.

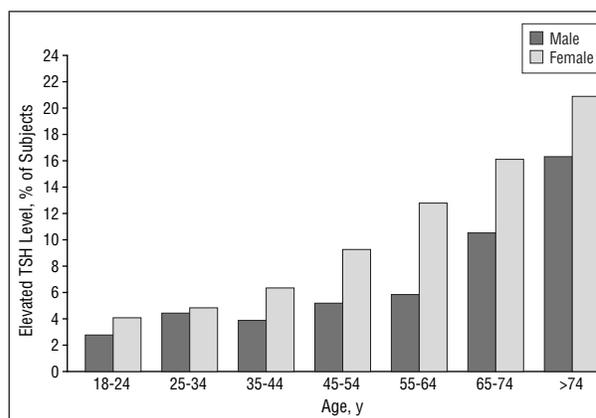


Figure 1. The percentage of subjects with an elevated thyrotropin (thyroid-stimulating hormone [TSH]) level by sex and decade of age. Percentages of hypothyroidism ranged from 4% to 21% in women and from 3% to 16% in men.

evated serum TSH concentration, 1799 subjects (74%) had a level between 5.1 and 10 mIU/L; 619 subjects (26%) had a value greater than 10 mIU/L. The distribution of subjects with an elevated TSH level is shown by age and sex in **Figure 1**. The percentage of subjects within each decade of age and with an elevated TSH concentration is shown, ranging from about 4% to 21% in women and from 3% to 16% in men. The percentage of subjects with an elevated TSH concentration was greater for women than men in each decade of age, reaching statistical significance for each decade after age 34 years ($P < .01$). There were 570 participants with a low TSH concentration (2.2%). The remaining 22 842 participants (88.3%) had normal serum TSH concentrations. Among patients not taking thyroid medication, 8.9% had increased TSH and 1.0% had low TSH concentrations. Thus, 9.9% of the population had a thyroid abnormality that had most likely gone unrecognized.

In the total study population, men were more often euthyroid than women ($P < .001$). Subclinical hypothy-

roidism and subclinical hyperthyroidism were both more common in women ($P < .001$). Interestingly, there was no statistically significant difference between women and men with regard to overt hypothyroidism, perhaps owing in part to the small number of overt hypothyroid individuals. Also, women who were taking estrogen preparations may have been misclassified into the subclinically hypothyroid group (from the overt hypothyroid group) because thyroid status was defined using T_4 rather than FT_4 levels.

Of the 25 862 participants, 1525 (5.9%) reported taking thyroid medication at the time of the survey. The medications reported may have been taken for thyroid hormone replacement or for suppression therapy. The proportion of individuals in each thyroid classification is shown in Table 2. Participants taking thyroid medication were significantly more likely to have an abnormal serum TSH level (39.9%) than those not taking thy-

roid medications (9.9%; $P < .001$). More than one fifth of the population taking thyroid medication was either hyperthyroid or subclinically hyperthyroid. Of the patients in the total population with a low serum TSH concentration ($n = 570$), 57.7% were taking thyroid medication, whereas only 11.4% of subjects with an elevated TSH concentration ($n = 2450$) were taking thyroid medication ($P < .001$).

To better evaluate the possible impact that estrogen may have had on the results, we looked at the information on estrogen supplementation that was available for the 1288 women who reported taking thyroid medication. Of the women taking thyroid medication, 506 (39%) reported also taking a form of estrogen. The proportion of women in each disease state (ie, overt hypothyroid or euthyroid) was not significantly different between women reporting supplemental estrogen and those not taking estrogen.

Table 3. Mean Lipid Levels by Disease State*

Disease State	Total	LDL	HDL	Triglycerides, ‡
	Cholesterol, †	Cholesterol, †	Cholesterol, †	
	mmol/L (mg/dL)	mmol/L (mg/dL)	mmol/L (mg/dL)	mmol/L (mg/dL)
Hypothyroid	6.5 (251)	4.4 (170)	1.4 (53)	2.0 (180)
Subclinical hypothyroid	5.8 (224)	3.8 (146)	1.4 (53)	1.8 (156)
Euthyroid	5.6 (216)	3.6 (140)	1.3 (51)	1.7 (147)
Subclinical hyperthyroid	5.4 (210)	3.4 (131)	1.5 (56)	1.6 (141)
Hyperthyroid	5.2 (202)	3.4 (130)	1.3 (50)	1.6 (140)

*LDL indicates low-density lipoprotein; HDL, high-density lipoprotein.

†Trend analysis, $P < .001$.

‡Trend analysis, $P = .02$.

SERUM LIPID CONCENTRATIONS

Mean serum lipid concentrations are presented according to disease state in **Table 3**. The trends across disease states for mean serum total cholesterol (TC), low-density lipoprotein (LDL) cholesterol, and triglyceride levels were statistically significant ($P < .001$ for TC and LDL cholesterol; $P = .02$ for triglycerides). The relative proportions of elevated, low, and normal serum lipid levels by disease state are shown in **Figure 2**. A higher proportion of hypothyroid subjects had elevated serum levels of TC ($P < .001$) and LDL cholesterol ($P < .001$) compared with the euthyroid group. A higher proportion of subclinically hypothyroid subjects had elevated TC levels compared with subjects with normal thyroid function ($P < .001$).

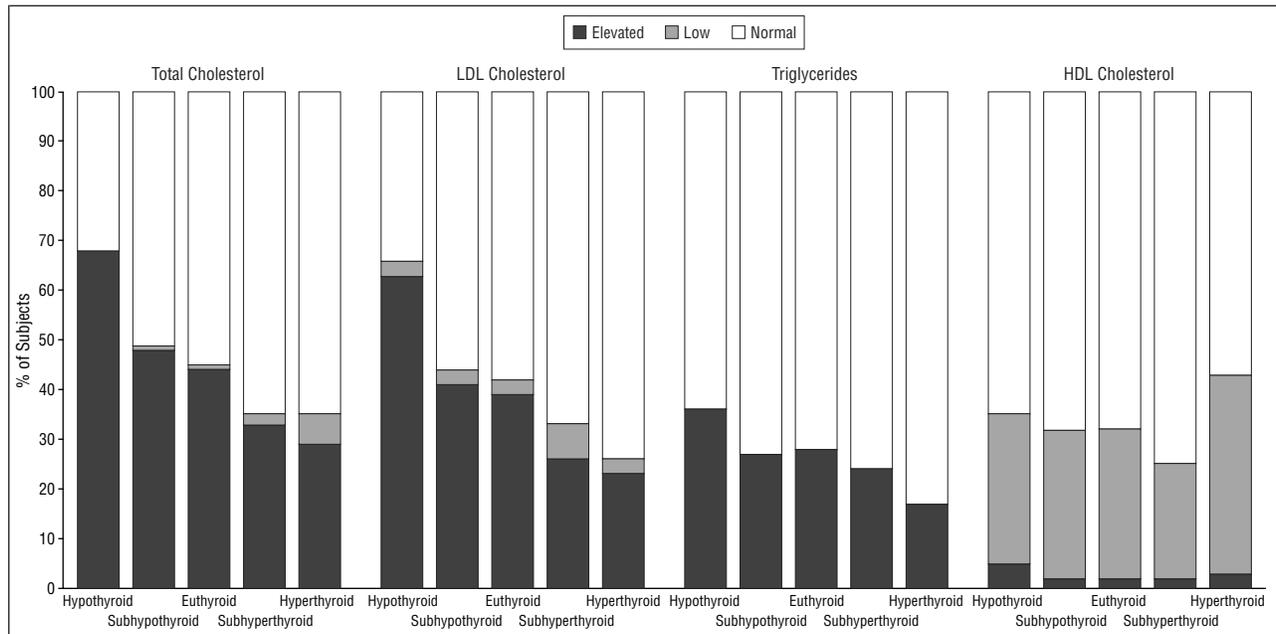


Figure 2. The proportions of elevated, normal, or low lipid levels in 25 862 subjects according to thyroid function status. Thyroid function was defined by serum thyrotropin (thyroid-stimulating hormone [TSH]) and thyroxine (T_4) concentrations as follows: euthyroid (TSH level within the normal range, 0.3-5.1 mIU/L), hypothyroid (TSH level > 5.1 mIU/L and T_4 level < 57.9 nmol/L [< 4.5 μ g/dL]), subclinical hypothyroid (TSH level > 5.1 mIU/L and T_4 level ≥ 57.9 nmol/L [≥ 4.5 μ g/dL]), hyperthyroid (TSH level ≤ 0.01 mIU/L), or subclinical hyperthyroid (TSH level, 0.01 to < 0.3 mIU/L). LDL indicates low-density lipoprotein; HDL, high-density lipoprotein.

To further investigate the relationship between declining thyroid function and serum lipid concentrations, the total study population was divided into incremental TSH levels. Mean serum TC (**Figure 3**) and LDL cholesterol concentrations progressively increased with increasing serum TSH levels ($P < .001$). Serum triglyceride and high-density lipoprotein (HDL) cholesterol levels did not change significantly. The percentage of patients with elevated serum TC and LDL cholesterol levels also rose progressively with incremental increases in TSH levels ($P < .001$).

The mean serum TC level among patients with serum TSH levels between 5.1 and 10 mIU/L was significantly higher than the mean TC level in euthyroid subjects (5.8 mmol/L [223 mg/dL] vs 5.6 mmol/L [216 mg/dL]; $P < .003$). The mean LDL cholesterol level among those with serum TSH concentrations between 5.1 and 10 mIU/L was also significantly greater than that of the euthyroid group (3.7 mmol/L [144 mg/dL] vs 3.6 mmol/L [140 mg/dL]; $P < .003$). Other serum lipid levels were not significantly different.

Women had higher serum HDL cholesterol levels across all disease states than men, contributing to their slightly higher TC levels (**Table 4**). The difference in TC levels cannot be attributed to age, since there was no

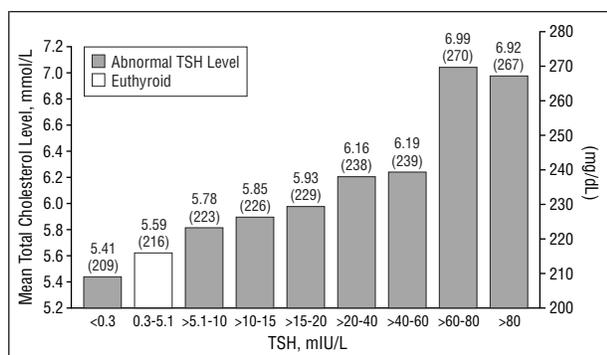


Figure 3. Mean total cholesterol levels for categories of increasing serum thyrotropin (thyroid-stimulating hormone [TSH]) levels in 25 862 subjects. All mean cholesterol levels are significantly different from the mean cholesterol level of the euthyroid participants (TSH level, 0.3-5.1 mIU/L; $P < .003$).

difference in age between men and women. Lipid levels also differed between women who reported taking supplemental estrogen and women who did not. For the women who reported taking thyroid medication, those who were also taking estrogen had higher total cholesterol levels than women not taking estrogen (5.9 mmol/L [227.1 mg/dL] vs 5.7 mmol/L [220.5 mg/dL]). The women taking supplemental estrogen also had higher HDL cholesterol levels (1.6 mmol/L [63.3 mg/dL] vs 1.4 mmol/L [54.5 mg/dL]) but lower LDL cholesterol levels (3.5 mmol/L [135.5 mg/dL] vs 3.7 mmol/L [141.8 mg/dL]). The mean age of these 2 groups did not differ ($P = .04$, $\alpha = .02$).

SYMPTOMS

Overt hypothyroid subjects reported a greater percentage of symptoms than did the subclinically hypothyroid group (**Table 5**). Overt and subclinically hypothyroid subjects all reported significantly more total symptoms than euthyroid individuals ($P < .001$). The association between disease state and the percentage of reported symptoms was statistically significant ($P < .001$), but weak (ANOVA, $r^2 = 0.003$; Pearson correlation coefficient, $r = 0.03$). Each symptom except one (deep voice) was reported more frequently by hypothyroid than euthyroid subjects. Only the symptoms of hoarser voice and deeper voice did not differ significantly between those with elevated vs normal TSH levels (**Figure 4**).

Although some symptoms attained high specificity, sensitivities were generally low (2.9%-28.3%) for individual symptoms reported by subjects with elevated TSH levels (**Table 6**). Thus, the absence of a symptom would not rule out thyroid disease. Positive predictive values were also low (8%-12%), representing the proportion of all subjects reporting the symptom who also had disease. Likelihood ratios (LRs) were calculated to express the odds that a symptom would be reported by someone with hypothyroidism as opposed to someone who is euthyroid. The LRs for individual symptoms were modest (< 2.0). However, when calculated for the overt hypothyroid group, LRs exceeded 2.0 for current constipation and the changed symptom, feeling colder. Multiple logistic regression analysis with

Table 4. Mean Lipid Levels by Sex*

Lipid Level	Disease State				
	Hypothyroid	Subclinical Hypothyroid	Euthyroid	Subclinical Hyperthyroid	Hyperthyroid
Total cholesterol					
Women	6.9 (267)	5.9 (229)	5.7 (218)	5.4 (210)	5.4 (207)
Men	6.1 (233)	5.5 (214)	5.5 (213)	5.4 (208)	4.8 (187)
LDL cholesterol					
Women	4.6 (179)	3.8 (146)	3.6 (138)	3.3 (129)	3.4 (130)
Men	4.1 (160)	3.8 (146)	3.7 (143)	3.7 (141)	3.3 (127)
HDL cholesterol					
Women	1.6 (60)	1.5 (58)	1.5 (58)	1.5 (58)	1.4 (52)
Men	1.2 (45)	1.1 (43)	1.1 (44)	1.1 (44)	1.1 (41)
Triglycerides					
Women	1.9 (169)	1.8 (155)	1.6 (139)	1.6 (140)	1.7 (148)
Men	2.2 (192)	1.8 (158)	1.8 (156)	1.6 (145)	1.3 (113)

*Values are in millimoles per liter (milligrams per deciliter). LDL indicates low-density lipoprotein; HDL, high-density lipoprotein.

Table 5. Reported Symptoms by Disease State

Disease State	Current Symptoms, Mean % (Range)	Changed Symptoms, Mean % (Range)	Total Symptoms, Mean % (Range)
Hypothyroid (n = 114)	12.0 (0-3)	17.9 (0-8)	16.6 (0-8)*
Subclinical hypothyroid (n = 2336)	7.4 (0-3)	15.4 (0-11)*	13.7 (0-13)*
Euthyroid (n = 22 842)	7.7 (0-3)	13.4 (0-11)	12.1 (0-14)

*Significant difference from euthyroid group ($P < .05$).

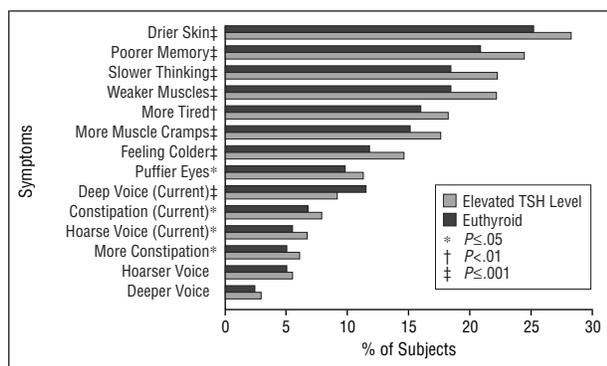


Figure 4. The percentage of euthyroid subjects compared with those with an elevated thyrotropin (thyroid-stimulating hormone [TSH]) level who reported each symptom.

disease state (overt hypothyroid or euthyroid) as the dependent variable and the 14 symptoms (age and sex as independent variables) identified 2 significant symptoms ($P < .05$). These were current constipation and feeling colder than the previous year.

The proportion of overt hypothyroid subjects reporting a certain number of symptoms rose as the number of symptoms increased (**Figure 5**). That is, as more symptoms were reported, the subject was more likely to be overtly hypothyroid. Subclinically hypothyroid individuals were intermediate between overt hypothyroid and euthyroid subjects.

Symptom scores were generated in the manner of Billewicz et al³⁵ (see “Data Analysis” section) because weighted scores using multiple symptoms may discriminate between hypothyroid and euthyroid persons better than individual symptoms. The calculated weights are listed in **Table 7**. The symptoms with the greatest discriminating ability were used to calculate the final cumulative score for each study subject. These 8 symptoms included the current symptoms of constipation, hoarse voice, and deep voice, and the changed symptoms of more constipation, hoarser voice, feeling colder, having puffier eyes, and having weaker muscles. The final cumulative scores for study subjects ranged from 25 to 250. Scores were divided into quintiles to show the percentage of overt hypothyroid and euthyroid subjects within each range of symptom scores. The proportion of hypothyroid individuals increased with increasing symptom score (**Figure 6**), as it did with the raw symptoms.

The test characteristics for different cutoffs of symptom scores are shown in **Table 8**. The LRs (reflecting

Table 6. Individual Symptoms*

Symptom	Sensitivity, %	Specificity, %
Current symptoms		
Hoarse voice	6.7	94.5
Deep voice	9.2	88.5
Constipation	7.9	93.1
Changed symptoms		
Hoarser voice	5.5	95.0
Deeper voice	2.9	97.6
Drier skin	28.3	74.7
Feeling colder	14.6	88.2
More tired	18.3	84.0
Puffier eyes	11.3	90.2
More muscle cramps	17.6	84.9
Weaker muscles	22.2	81.5
More constipation	6.1	95.0
Slower thinking	22.3	81.5
Poorer memory	24.5	79.1

*Total population, elevated thyrotropin level vs euthyroid.

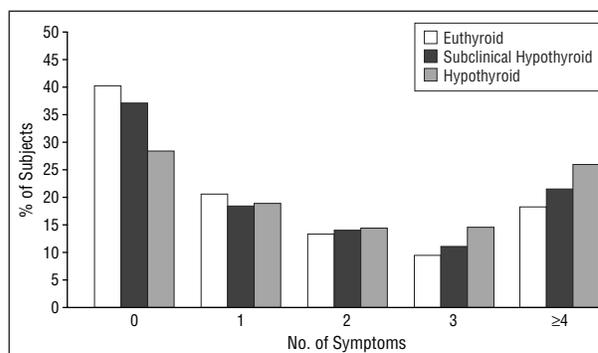


Figure 5. The percentage of euthyroid, subclinical hypothyroid, and hypothyroid subjects who reported no, 1, 2, 3, or 4 or more symptoms. Euthyroid subjects were more likely to have no symptoms, whereas hypothyroid subjects were more likely to have 3 or more symptoms.

the likelihood of overt hypothyroidism) increased with increasing symptom score. The positive predictive values also increased with increasing thresholds of symptom scores, so that 80% of all subjects with a symptom score greater than 200 were hypothyroid (**Table 8**). As may be expected, sensitivity declined with increasing thresholds of symptom scores. An ROC curve was constructed to evaluate symptoms as a test for hypothyroidism. The greater the area under the ROC curve, the better the test, with an equivocal test having an area of 0.50. The ROC analysis found the area under the curve for the symptom score cutoffs of **Table 8** to be 0.64. Thus, our symptom scores did not discriminate as well as those reported by Billewicz et al³⁵ or Seshadri et al.³⁶ This may be expected when applying the Billewicz et al scoring method to an unselected population. The populations previously studied by the Billewicz group and the Seshadri group were enrolled specifically because of suspected hypothyroidism. When inclusion criteria similar to those used by Seshadri et al were applied to our population, the discriminating value of hypothyroid symptoms rose considerably.

Table 7. Symptom Weights

Symptom	Weight	
	Presence	Absence
Current symptoms		
Constipation*	27	2
Hoarse voice*	30	1
Deep voice*	16	2
Changed symptoms		
More constipation*	43	3
Hoarse voice*	11	2
Deeper voice	0	4
Drier skin	4	5
Feeling colder*	35	-4
More tired	4	4
Puffier eyes*	35	-2
More muscle cramps	5	4
Weaker muscles*	-2	12
Slower thinking	-5	9
Poorer memory	1	7

*Symptom applied to index score.

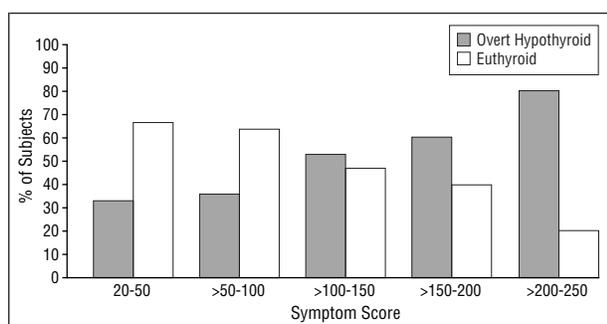


Figure 6. The percentage of overt hypothyroid and euthyroid subjects within the defined ranges of subject symptom scores. Subject symptom scores were calculated by the method used by Billewicz et al³⁵ and represent the sum of individual numerically weighted symptoms as reported by each patient. Higher scores reflect greater symptomatology. The percentage of overt hypothyroid subjects within each symptom score range increased with increasing symptom score.

COMMENT

Abnormal thyroid function has multiple implications for public health. However, the magnitude of the problem is not entirely known, nor are the exact relationships to other health problems well delineated.

The prevalence of an elevated serum TSH level in this population of 9.5% is within the range seen in the literature, and it is consistent with findings in an iodine-replete population.^{1,4,5,46,47} The proportion of subjects with an elevated TSH level was greater among women than men and increased with advancing age (Figure 1), both of which are supported in the literature.²⁻⁷ However, the prevalence of overt hypothyroidism was lower than some previous estimates.² Diverse study populations and various definitions of overt disease in other studies may account for this. In our study, concomitant estrogen use could have raised serum T₄ concentrations, reducing the number of overtly hypothyroid women while increasing the number who were classified as subclinically hypothyroid. However, since the proportion of women in

Table 8. Symptom Score Thresholds

Symptom Score	Sensitivity, %	Specificity, %	Positive Predictive Value, %	Likelihood Ratio (95% Confidence Interval)
>50	95.1	10.8	54.2	1.07 (0.97-1.19)
>100	79.3	41.9	60.2	1.36 (1.10-1.73)
>150	51.2	68.9	64.6	1.65 (1.12-2.48)
>200	14.6	95.9	80.0	3.61 (1.15-11.62)

each disease category was not significantly different between women reporting supplemental estrogen usage and those not taking estrogen, this may not be a significant factor. The low prevalence of overt disease may also be a phenomenon of the health fair itself. Nearly three quarters of those attending the Colorado 9Health Fair had participated in a previous fair, and the majority (62.5%) had seen a health care provider in the past year. This would suggest that prior testing may have detected overt hypothyroidism before the Colorado 9Health Fair, thus lowering the observed disease rate.

Of the 24 337 subjects who did not report taking thyroid medication, 9.9% had a functional abnormality of the thyroid gland that was apparently unknown. Most of these individuals (90%) had thyroid gland failure with an elevated serum TSH level. By extrapolation, there may be more than 165 000 adult cases of undetected thyroid gland failure in Colorado. If the Colorado experience can be generalized, there may be in excess of 13 million cases of undetected thyroid gland failure nationwide.

Of the group who reported taking thyroid medication, nearly 40% had an abnormal serum TSH level (Table 2). More than one fifth had a TSH level that was suppressed below normal. These observations are consistent with those of Ross et al,⁴⁸ who reported in a retrospective study that 32% of patients receiving levothyroxine replacement had abnormal TSH concentrations. Interestingly, 92% of the people taking thyroid medications had seen a health care provider in the previous year. These data show that there is an excess of patients who are not in the normal range of thyroid function. Such patients may be at risk for organic consequences of overtreatment or undertreatment or (in the case of those with suppressed TSH levels) may be taking thyroid hormones for reasons other than replacement.

One consequence of declining thyroid function is rising serum lipid levels, as observed in this study. Most hypothyroid individuals had an elevated lipid level. Mean TC, LDL cholesterol, and triglyceride levels rose with a significant trend across grades of thyroid function (Table 3). Not all investigators have found that triglyceride levels increase with increasing TSH levels.^{14,17,22} The difference may be explained by the markedly larger population in this study.

It was notable in this study that the mean TC level of subjects with modest elevations of serum TSH (ie, between 5.1 and 10 mIU/L) was higher than that of the euthyroid group (5.8 mmol/L [223 mg/dL] vs 5.6 mmol/L [216 mg/dL]). While several studies have linked hyperlipidemia with cardiovascular morbidity,⁴⁹⁻⁵¹ it is argu-

able whether this reflects a clinically significant difference. Normalizing subclinical hypothyroidism may have a role in the treatment of hyperlipidemia and perhaps the prevention of associated cardiovascular morbidity, but to what degree is unclear.

Lipid levels varied by sex. Women taking estrogen supplementation had higher serum HDL cholesterol levels than women not reporting supplemental estrogen usage, who in turn had higher HDL cholesterol levels than did men. The higher TC levels seen in women may be explained in part by the difference in HDL cholesterol levels. It is unlikely that age affected lipid levels, but thyroid status may be another factor, since there were more women than men with elevated TSH levels.

More symptoms were reported by hypothyroid than euthyroid subjects in this study. Reporting more symptoms, particularly symptoms that had changed in the previous year, increased the likelihood of disease. Furthermore, there was a positive association between the proportion of symptoms reported and progressive thyroid failure, although the relationship was weak. Sensitivities were low, so that not reporting a specific symptom did not rule out disease, and poor positive predictive values suggested a high number of false-positive individual symptoms. Several investigators support the use of multiple symptoms as a diagnostic tool.^{23,34-39} Seshadri et al³⁶ recognized the usefulness of a symptom score, but this group concluded that cutoff points must be individualized to the population under study. The lower, more sensitive symptom score thresholds of our study (Table 8) may be useful to identify who would be appropriate for subsequent TSH testing.

These results may be confounded by variables that cannot be controlled in the population studied. Health fair participants are a self-selected population. The demographic characteristics of this group may not be completely generalizable, but they may be more representative than many selected study populations in the literature.

Despite these constraints, the large study population provided enlightening information. The magnitude of thyroid dysfunction was confirmed. Nearly 10% of subjects not taking thyroid medications had a thyroid abnormality, which was probably unknown to them, and the abnormality was detected because of testing. Results from this study also highlighted the large number of patients taking thyroid hormones who were not in the therapeutic range. Clinicians may therefore consider monitoring patients on thyroid replacement more frequently. Regarding lipids, even modest elevations of TSH levels were shown to correspond to changes in cholesterol levels, perhaps affecting cardiovascular outcomes. The clinical scoring system of Billewicz et al, when applied to this population, identified persons more likely to be hypothyroid. Although the efficacy of this instrument was much less than that of serum TSH measurement, symptom scores may prove a useful adjunct in the diagnosis of hypothyroidism. Symptom scores may enhance the cost-effectiveness of thyroid testing, which compares favorably with other generally accepted practices in the analysis by Danese et al.³² The potential benefit of testing for abnormal thyroid function needs to be readdressed, and health care providers may have a higher index of suspi-

cion for those not yet diagnosed when traditional symptoms are reported.

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