CLINICAL RESEARCH STUDY

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Does Subclinical Hypothyroidism Add Any Symptoms? Evidence from a Danish Population-Based Study

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ABSTRACT

BACKGROUND: Few studies have scrutinized the spectrum of symptoms in subclinical hypothyroidism.
METHODS: From 3 Danish Investigation on Iodine Intake and Thyroid Diseases (DanThyr) cross-sectional surveys performed in the period 1997 to 2005, a total of 8903 subjects participated in a comprehensive investigation including blood samples and questionnaires on previous diseases, smoking habits, alcohol intake, and education. From the 3 surveys we included patients with subclinical hypothyroidism (n = 376) and euthyroid controls (n = 7619). We explored to what extent patients with subclinical hypothyroidism reported 13 previously identified hypothyroidism-associated symptoms (tiredness, dry skin, mood lability, constipation, palpitations, restlessness, shortness of breath, wheezing, globus sensation, difficulty swallowing, hair loss, dizziness/vertigo, and anterior neck pain). In various uni- and multivariate regression models we searched for circumstances predicting why some patients have more complaints than others.
RESULTS: Subclinically hypothyroid patients did not report higher hypothyroidism score [(median, interquartile range), 2 (0-4) vs 2 (0-4), $P = .25$] compared with euthyroid controls. Within the group of subclinical hypothyroid patients, comorbidity had the highest impact on symptoms (tiredness, shortness of breath, wheezing; all $P < .001$); TSH level had no impact on symptom score; and younger age was accompanied by higher mental burden (tiredness, $P < .001$; mood lability, $P < .001$; restlessness, $P = .012$), whereas shortness of breath was associated with high body mass index ($P < .001$) and smoking ($P = .007$).
CONCLUSION: Patients with a thyroid function test suggesting subclinical hypothyroidism do not experience thyroid disease-related symptoms more often than euthyroid subjects. In subclinical hypothyroidism, clinicians should focus on concomitant diseases rather than expecting symptomatic relief following levothyroxine substitution.
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KEYWORDS: Case-control study; Hypothyroidism; Overt hypothyroidism; Population-based study; Subclinical hypothyroidism; Symptoms

SEE RELATED COMMENTARY, p.1061

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INTRODUCTION

Hypothyroidism is a very common disorder worldwide.[1] We have previously reported the lifetime risk for developing overt hypothyroidism in Denmark to be 3.5% in women and 1.0% in men.[2] However, the lifetime risk of developing subclinical thyroid dysfunction is even higher.[3,4]

A variety of symptoms and signs may be present in overt hypothyroidism.[5,6] According to guidelines on overt hypothyroidism,[7,8] symptom relief is one of the treatment goals. Several studies have quantified the spectrum of symptoms in overt hypothyroidism[9-13] and subclinical hypothyroidism.[14-16] However, no study has investigated in detail how the entire palette of symptoms is influenced by sex, age, thyroid autoantibodies, and comorbidity. The term "subclinical" was coined in the 1970s,[17] as patients with serum thyroid-stimulating hormone (TSH) above the upper reference limit, but with normal serum T4, did not exhibit the same burden of symptoms compared with overtly hypothyroid patients. Patients with subclinical hypothyroidism should be individually scrutinized to evaluate whether benefit from treatment may be expected.[18] However, as one of the treatment goals may be symptom relief, it is important to clarify to what extent subclinically hypothyroid patients differ from the euthyroid background population, and thus, to what extent they may expect symptom relief after treatment.

CLINICAL SIGNIFICANCE

- Subclinical hypothyroidism is very common.
- Subclinical hypothyroid patients do not present more symptoms than euthyroid controls.
- In subclinical hypothyroidism, comorbidity predicts numerous symptoms to be present.
- Subclinically hypothyroid symptomatic patients should be extensively investigated for underlying disorders giving rise to these symptoms.
- When treating subclinical hypothyroidism, even with high symptom burden, one should not expect large relief from substitution therapy.

We have previously investigated which symptoms are present in patients newly diagnosed with overt hypothyroidism.[11-13] We identified 13 symptoms most often presented in such patients. To explore the clinical presentation of subclinical hypothyroidism, we recruited from cross-sectional surveys, a large group of participants never treated for thyroid disease, and among those, identified patients with unknown subclinical hypothyroidism and subjects with normal thyroid function.

SUBJECTS AND METHODS

Prior to the initiation of the iodine fortification of salt in Denmark, we established the Danish Investigation on Iodine Intake and Thyroid Diseases (DanThyr).[19] Several DanThyr investigations have been performed, including 2 large cross-sectional studies (C1+C2), a smaller study (C3), and a continuously running register study identifying patients with new overt hypothyroidism. We recruited 8903 participants from the 3 cross-sectional studies (C1+C2+C3, Figure 1), and from the previously published Register Study,[2] 685 patients newly diagnosed with overt hypothyroidism.

Cross-Sectional Study, C1

In the period 1997-1998, women aged 18-22, 25-30, and 40-45 years, in combination with both women and men aged 60-65 years, were invited to participate.[20] Subjects were randomly drawn from the Civil Registration System[21] in which all subjects living in Denmark are registered. Citizens from a well-defined region within the capital Copenhagen (East Denmark, mild iodine deficiency) and from surrounding municipalities around Aalborg (West Denmark, moderate iodine deficiency) were invited. A total of 4649 volunteers participated in our study.

Cross-Sectional Study C2

In the period 2004-2005, a new cross-sectional study was performed identical to the C1 cross-sectional survey.[20] Women and men representing the same age spans as for C1 were investigated. In all, 3570 subjects participated in this study.

Cross-Sectional Study C3

In the period 1998-2001, we invited women and men specifically in the age groups not represented in C1+C2. In all, we investigated 684 subjects, most of them men, as C1+C2 included only men in the age group 60-65 years. This study has not been published.

Register Study

In the study period from March 1997 to December 2000, an open but well-defined population cohort comprising 538,734 citizens were under surveillance (2,027,208 person-years of observation). Patients with newly diagnosed overt hypothyroidism were registered (n = 685).[2] Most of those had autoimmune overt hypothyroidism (n = 578).[2,22] We have previously presented results on symptom presentation among 140 autoimmune overt hypothyroid patients.[23-25] For comparison, we used this well-defined and thoroughly described group of patients with overt hypothyroidism.

Questionnaires

All participants answered questionnaires concerning previous diseases and information on several symptoms experienced during the last 12 months. In a recent study, we identified 13 hypothyroidism-associated symptoms, all meeting the criterion of a Bonferroni-statistically significant ($P < .0015$) higher symptom prevalence among

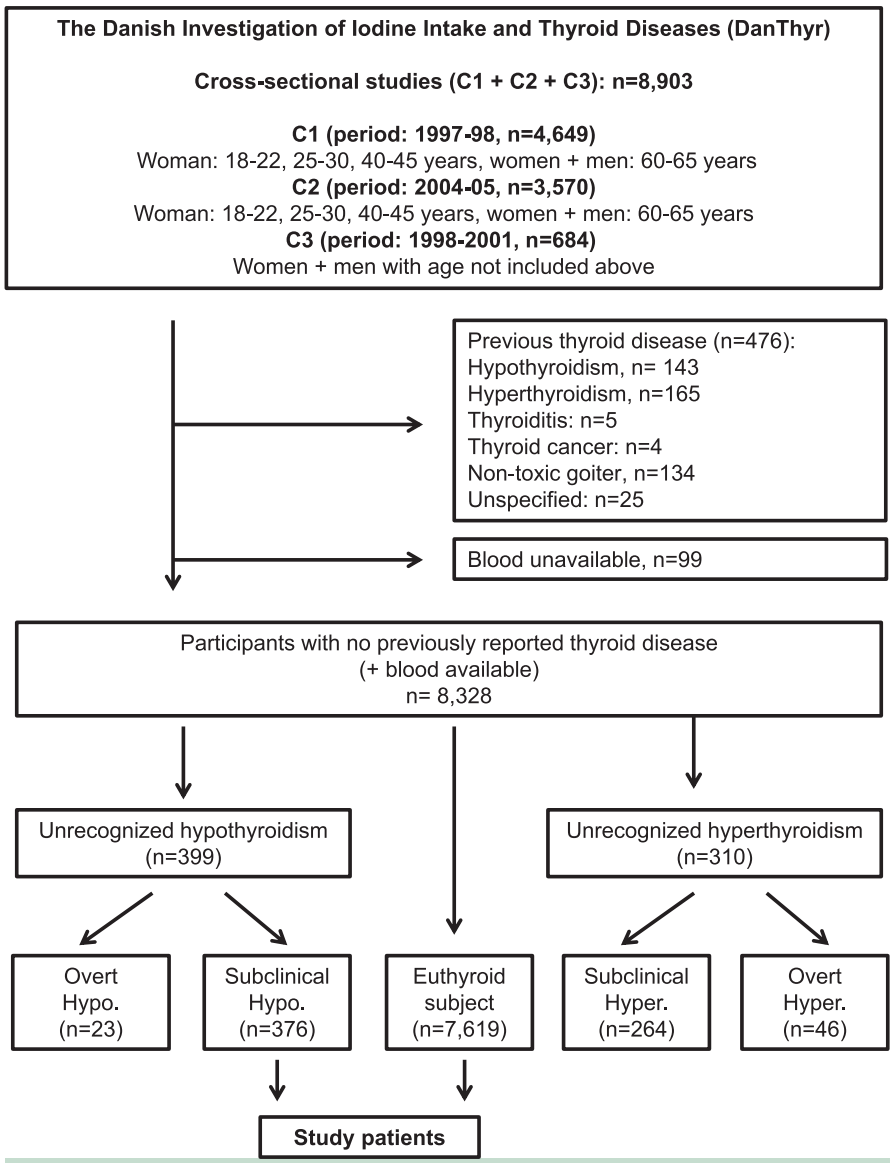

Figure 1 Flowchart depicting the selection of study subjects (subclinical hypothyroidism, n = 376; euthyroid controls, n = 7619) from 3 Danish cross-sectional surveys.

overtly hypothyroid cases compared with euthyroid controls.[11] The symptoms included mental symptoms (tiredness, dizziness, restlessness, and mood lability), neck-related symptoms (globulus, difficulty swallowing, and anterior neck pain), respiratory symptoms (wheezing and shortness of breath), cardiac complaint (palpitations), gastrointestinal discomfort (constipation), and dermatological changes (hair loss and dry/sensitive skin). Symptoms were combined into a "hypothyroidism compound score" defined as the number of hypothyroidism-associated symptoms (range: 0-13). The precise questions asked are listed in supplementary table 2

Subjects also provided information on educational level, smoking habits, alcohol consumption, and comorbidity (cardiovascular: history of acute myocardial infarction, angina pectoris, cardiac arrhythmia, hypertension, or cerebral stroke; noncardiovascular: previous epilepsy, diabetes mellitus, asthma, chronic obstructive pulmonary disease, or gastrointestinal ulcer).

Blood Samples

Of all participants, 8804 had blood drawn. C1+C3 participants had serum TSH, free T4, and free T3 concentrations analyzed by LUMItest (BRAHMS, Berlin, Germany), whereas C2 subjects had thyroid function test analyzed with Roche Modular E-system (Roche Diagnostics, Indianapolis, Ind) by electrochemical luminescence using Elecsys TSH, fT3, and fT4 agents. All assay specifications have been given previously, and doublet analysis (LUMItest vs ELECSYS) of 198 blood samples from the C1 survey showed no significant differences in TSH or fT4.[26] Reference ranges from the C1 survey was used, and based on the normal values (serum TSH, 0.4-3.6 mU/L; fT4, 9.8-20.4

pmol/L; fT3, 3.6-6.9 pmol/L[27]), we classified subjects into the following thyroid function status:

1) Overt hyperthyroidism: serum TSH <0.4 mU/L and fT3 >6.9 pmol/L or fT4 >20.4 pmol/L
2) Subclinical hyperthyroidism: serum TSH <0.4 mU/L and no overt hyperthyroidism
3) Euthyroidism: serum TSH 0.4-3.6 mU/L
4) Subclinical hypothyroidism: serum TSH >3.6 mU/L and no overt hypothyroidism
5) Overt hypothyroidism: serum TSH >3.6 mU/L and fT4 <9.8 pmol/L

Of the 8903 C1-C3 participants, 476 reported previous thyroid disease, 99 had no blood sample drawn and were subsequently excluded, leaving 8328 subjects for further analysis. A total of 7619 (91.5%) had normal thyroid function, and 376 (4.5%) had subclinical hypothyroidism.

All participants from the 3 cross-sectional studies had thyroid autoantibodies (thyroid-peroxidase autoantibody [TPOAb] and thyroglobulin autoantibody [TgAb]) measured. Assay characteristics including cut-off levels (TPOAb+: >30 kU/L, TgAb+: 20 kU/L) has been extensively described in previous studies.[28,29]

For patients diagnosed with overt hypothyroidism in the Register Study, we used the TSH and T4 values from the clinical laboratories at the day of diagnosis. The precise algorithm for diagnosing overt hypothyroidism and the use of assays has been described previously.[2,30]

Other Investigations

Thyroid volume was calculated according to the 3-axis method using ultrasound.[31,32] All participants had their height and weight measured, and body mass index (BMI) was calculated.

Statistical Analysis

IBM Statistical Package for Social Sciences version 26.0 (SPSS, Inc, Chicago, Ill) was used for calculations. Comparison analyses were performed by Pearson's χ^2-test, Fisher's exact test, Mann-Whitney U test, or Kruskal-Wallis test. All tests were corrected by Bonferroni's formula ($P < 1 - \sqrt[x]{0.95}$) to avoid a type I error due to multi-comparison.

We have previously evaluated the symptom presentation in a group of overt hypothyroid patients. Now, we investigate the complaints in a group of subclinical hypothyroid patients assumed to have lesser symptom burden. We explored the presence of each of 13 hypothyroidism-associated symptoms, and in accordance with common practice[10,16,33,34] we calculated a 'hypothyroidism compound score' by adding up the total number of symptoms reported (range: 0 to 13).[11] Sensitivity analyses were performed to reveal any biases and to assess the magnitude of any association in relevant subgroups. We illustrated the symptom presence in various subgroups by a nautilus diagram.[13]

In patients with subclinical hypothyroidism, we used multivariate linear and logistic regression models to evaluate which patients bear the heaviest symptom burden. As dependent factors we used the hypothyroidism compound score, freedom from symptoms (yes/no), and the presence (yes/no) of each of the 13 specific symptoms in subjects with subclinical hypothyroidism in several models. In each model, as explanatory variables we used sex, age, region of inhabitancy, level of thyroid insufficiency (serum TSH), thyroid autoantibody level (TPOAb or TgAb), BMI, educational level (basic school and up to 2 years vocational training vs more), smoking (current vs no smoking), alcohol intake (units per week), and all-cause comorbidity (yes/no). We used the backward regression approach to search for significant variables associated with the dependent outcome variables.

In the regression models we checked that all required assumptions were met (normally distributed residuals, no heteroscedasticity present, independent observations, little or no multicollinearity, and extreme outliers). In linear regression with hypothyroidism compound score as a dependent variable, the data were logarithmized to obtain normal distribution of the data.

Ethical Approval

The study was approved by Regional Ethics Committees in North Jutland and Copenhagen (VN97/208mch). Registry permission was obtained from the Danish Data Protection Agency. All participants gave their written informed consent. We report no conflicts of interest.

RESULTS

Participant Characteristics

The participant characteristics of the 376 subclinical hypothyroid cases and the 7619 euthyroid controls with no previous thyroid disease are given in Table 1. The patients with subclinical hypothyroidism had a median age of 43.9 years, had a median serum TSH of 4.57 mU/L, and harbored thyroid autoantibodies in every second case (TPOAb: 53.6%, TgAb: 44.8%).

Expression of Symptoms to Guide the Clinician

Patients with subclinical hypothyroidism had the same spectrum of symptoms compared with the euthyroid controls both in terms of the hypothyroidism compound score [median (interquartile range): 2 (0-4) vs 2 (0-4), $P = .79$] and presence of no symptoms (26.7 vs 27.8%, $P = .66$). The distribution of the 13 hypothyroidism-associated symptoms is depicted in Figure 2. In subclinical hypothyroidism, tiredness is the dominating symptom, affecting half of the patients, but not different from the euthyroid group. No difference was observed in presence of any of the symptoms when comparing subclinical hypothyroid patients with euthyroid controls. For comparison, we also included previously presented data on the higher prevalence of all symptoms in overt hypothyroidism.[9-11]

Interaction between age and symptom presentation in overt hypothyroidism has previously been published.[11] Sensitivity analyses were thus performed at various age

Table 1 Baseline Characteristics of Participants

	Subclinical Hypothyroidism n = 376	Matched Euthyroid Control Subjects n = 7619	*P* Value
Age in years, median (IQR)	43.9 (27.5-62.3)	42.8 (26.9-62.4)	.33
Women	329 (87.5)	1.600 (78.8)	< .001
Inhabitancy			
Aalborg (moderate ID)	177 (47.1)	3.822 (50.2)	.25
Copenhagen (mild ID)	199 (52.9)	3.797 (49.8)	
Weight (kg), median (IQR)	71.7 (62.4-81.6)	68.5 (60.7-78.9)	< .001
Height, m	167 (163-173)	168 (164-173)	.091
BMI, kg/m^2	25.1 (22.2-29.5)	24.2(21.8-27.3)	< .001
Serum TSH (mU/L), median (IQR)	4.57 (3.91-5.89)	1.37 (0.97-1.91)	< .001
Serum free T4 (nmol/L), median (IQR)	14.2 (12.9-15.8)	15.4 (13.7-17.0)	< .001
TPOAb, kU/L	39,1 (<30-1.246)	<30	< .001
TPOAb+, >30 kU/L	53,6	15.5	< .001
TgAb, kU/L	<20 (<20-71.9)	<20 (<20-<20)	< .001
TgAb+, > 20 kU/L	44.8	14.0	< .001
Thyroid volume by ultrasonography, mL	9.3 (7.3-12.2)	12.1 (9.3-16.2)	< .001
Education			
Basic school and up to 2 years vocational training	52.0	55.4	
More	48.0	44.6	.20
Smoking history			
Never smoker	49.7	42.6	
Previous smoker	29.0	21.6	
Current smoker	21.3	35.8	< .001
Alcohol intake			
Units/week (median, IQR)	4 (2-8)	4 (2-9)	
0 = abstainer	13.6	13.5	
≥1 units per week	86.4	86.5	.14
Comorbidity			
All causes*,†	39.5	38.1	.59
Cardiovascular*	22.9	21.8	.67
Noncardiovascular†	23.7	23.9	.85

BMI = body mass index; IQR = interquartile range; TgAb = thyroglobulin antibody; TPOAb = thyroid-peroxidase auto-antibody; TSH = thyroid-stimulating hormone.

Depicted are number of participants (percentage) or medians (interquartile range, 25%-75% range). Some data were missing for weight (n = 2 + 19), height (n = 2 + 23), BMI (n = 2 + 26), serum fT4 (n = 22 + 577), TPOAb (n = 1 + 29), TgAb (n = 1 + 28), thyroid volume by US (n = 2 + 12), education (n = 5 + 74), smoking (n = 10 + 112), alcohol (n = 1 + 23), comorbidity (n = 1 + 5).

*Questionnaire obtained information on myocardial infarction, angina pectoris, cardiac arrhythmia, hypertension, or cerebral stroke.

†Questionnaire obtained information on epilepsy, diabetes mellitus, asthma, chronic obstructive pulmonary disease, or gastrointestinal ulcers.

*P < .05, **P < .01, ***P < .001 for sex difference (asterisks are depicted in female column if statistically different from men).

intervals (<30 vs 30-59 vs >60 years) (Figure 3). Patients with subclinical hypothyroidism had the same symptom presentation as euthyroid controls irrespective of age. Interestingly, in subclinical hypothyroidism, young age (<30 years) was associated with higher prevalence of mental complaints (tiredness, P < .001; mood lability, P < .001; restlessness, P = .012). Among the euthyroid subjects, all symptoms under investigation were reported more often by the young (P < .001 for all symptoms except wheezing [P = .038] and vertigo [P = 0.015]).

Sensitivity analyses were also performed for different sex and inhabitancy (data not shown). However, in both sexes, no differences in frequency of symptoms was observed between patients with subclinical hypothyroidism and euthyroid controls. In addition, no difference in symptom burden was reported by patients from the 2 study regions representing various levels of iodine insufficiency.

Predictors for Symptom Presence in Subclinical Hypothyroidism

The group of subclinical hypothyroid patients was studied further. In a sensitivity analysis, we compared 3 degrees of subclinical hypothyroidism (TSH: 3.6-4.99 vs 5-6.29 vs ≥6.3 mU/L). No association was found between any symptom and serum TSH level (Figure 4). Neither did we find differences in the compound hypothyroidism score (data not shown, P = .29) or in the presence of no symptoms (25.2 vs 25.4 vs 34.7%, P = .30).

Wheezing was associated with low levels of TPOAb and TgAb (both, P = .001; data not shown). Otherwise, thyroid autoantibodies did not associate with any symptom.

When split by comorbidity (Figure 5), patients with subclinical hypothyroidism had no higher symptom burden

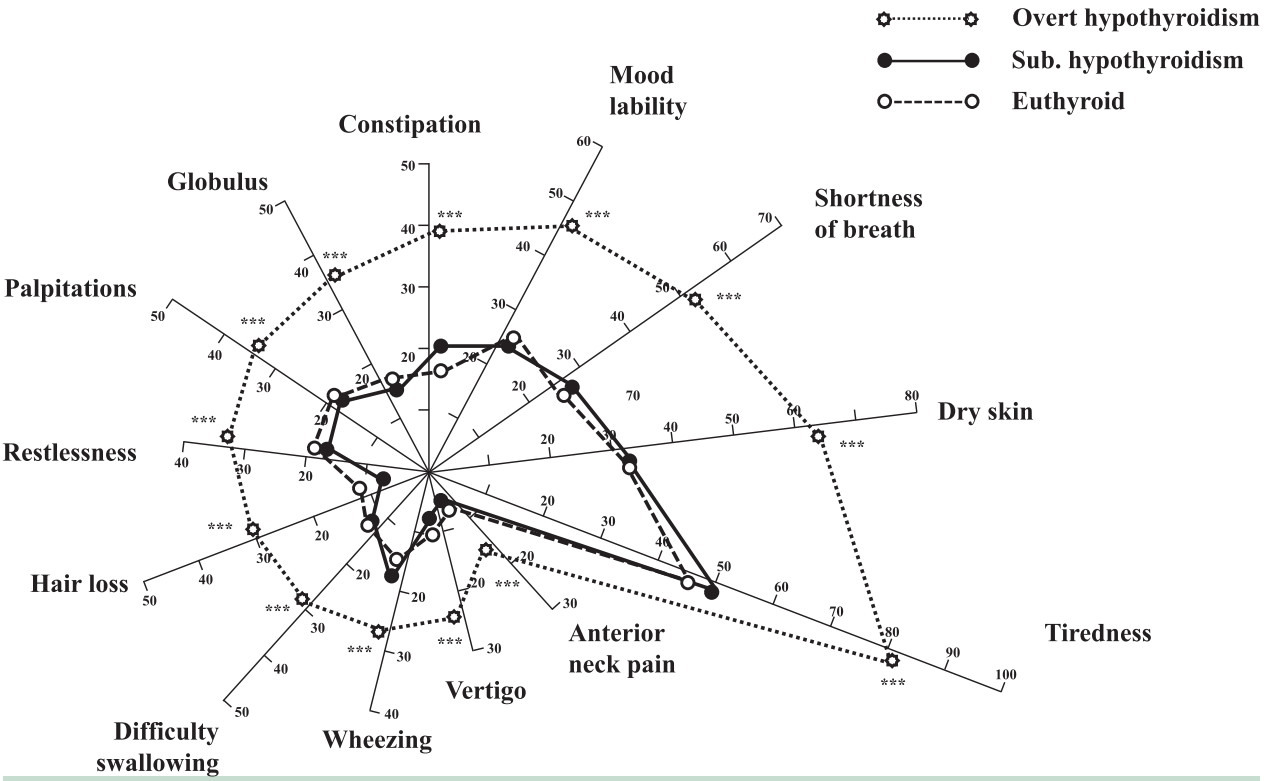

Figure 2 Nautilus diagram depicting the prevalence of 13 symptoms in euthyroid subjects (n = 1476), patients with subclinical hypothyroidism (n = 376), and patients newly diagnosed with overt autoimmune hypothyroidism (n = 140). Symptoms in all figures are ordered anti-clockwise according to prevalence in overt hypothyroidism (first tiredness being the most prevalent symptom). ***$P < .001$.

than euthyroid controls. However, in subclinical hypothyroidism, concomitant diseases were significantly associated with tiredness, shortness of breath, wheezing, and vertigo, while only borderline associated with palpitations and restlessness. In euthyroid controls, all symptoms explored associated significantly with comorbidity ($P < .001$ except for hair loss, $P = .010$).

Multivariate regression was used to identify which characteristics best predicted which subclinically hypothyroid patients had the highest symptom burden. Table 2 depicts the statistically significant associations between various predictors (at the top) and symptom measures (on the left). Clearly, comorbidity was the most important factor predicting which patients had the highest symptom burden. Again, low age (≤60 years) was a predictor for mental complaints (tiredness, mood lability, and restlessness). High BMI was associated with shortness of breath. Finally, absence of TPOAb or TgAb was associated with wheezing ($P < .001$), partly due to the fact that smokers had lower presence of thyroid autoantibodies.

Finally, Table 3 depicts the statistically significant associations between each concomitant disease (at the top) and various symptom measures (at the left). Cardiac arrhythmia and asthma (both: $P < .001$) were associated with the hypothyroidism compound score. For the 13 individual symptoms, cardiac arrhythmia was associated with palpitations ($P < .001$) and vertigo ($P < .001$), whereas asthma was associated with tiredness ($P = .002$), restlessness ($P < .001$), shortness of breath ($P < .001$), wheezing ($P < .001$), and vertigo ($P < .001$). Patients diagnosed with angina also reported anterior neck pain (borderline significant after Bonferroni correction, $P = .003$).

DISCUSSION

We previously identified 13 symptoms to be more frequent among patients with overt hypothyroidism at disease onset. We now report that patients with subclinical hypothyroidism did not report any of these symptoms more often than thyroid-healthy controls. Furthermore, we have shown that in subclinical hypothyroidism, comorbidity may explain why some patients are disabled by a large number of symptoms.

Comparison with Euthyroid Subjects

The dissimilar disease presentation between overt hypothyroidism vs subclinical hypothyroidism vs normal thyroid function is in accordance with results reported by Zulewski et al.[34] They also calculated a simple compound score based on presence of 14 symptoms and signs, and reported a score of 6.1 ± 3.0 (overt hypothyroidism, n = 50) vs 3.4 ± 2.0 (subclinical hypothyroidism, n = 93) vs 1.6 ± 1.5 (euthyroid thyroid-disease free controls, n = 189). The Colorado study also compared the group of subclinically hypothyroid

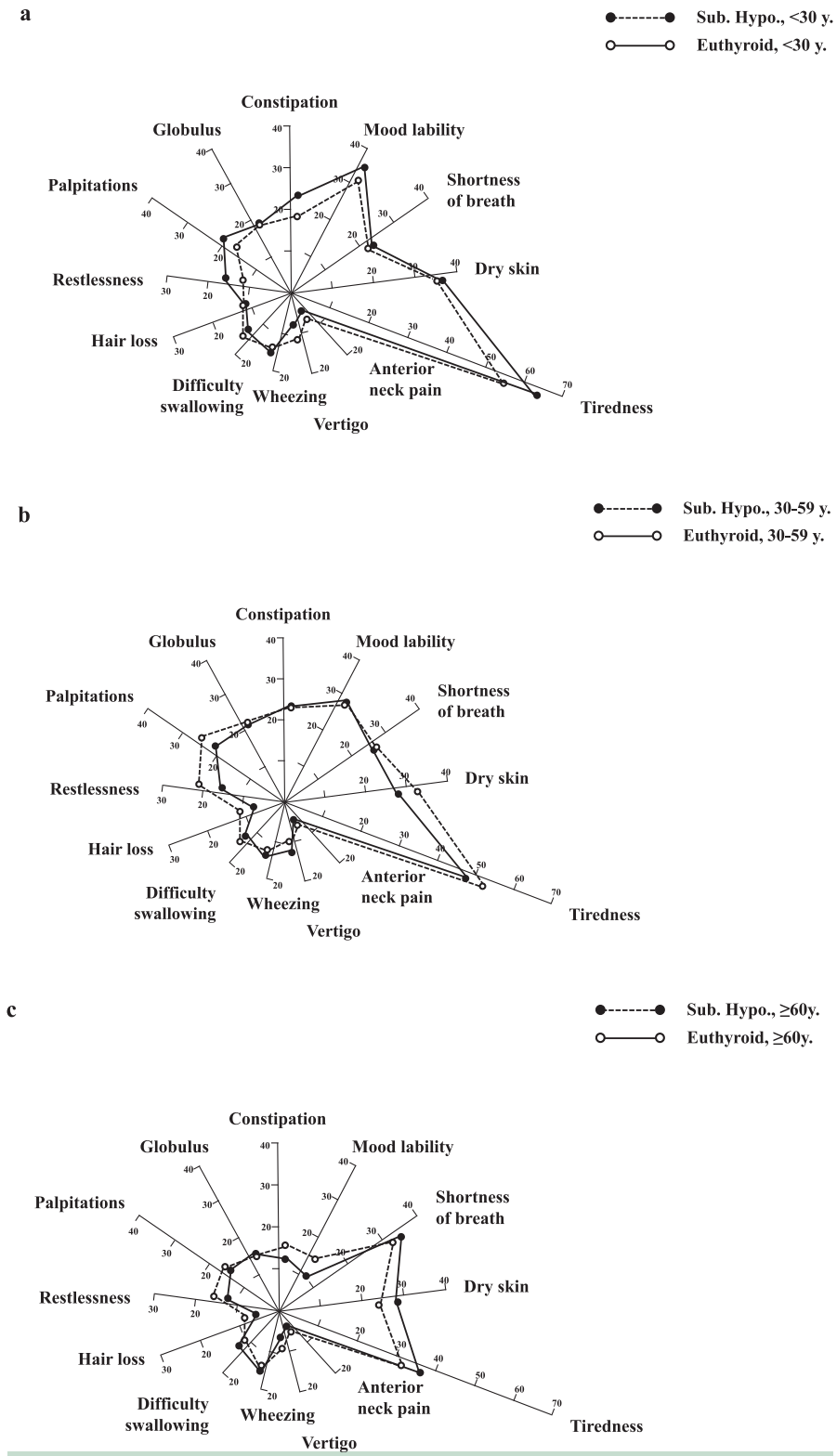

Figure 3 Nautilus diagram depicting the prevalence of 13 symptoms at various age intervals (<30 vs 30-59 vs ≥60 years) in subclinical hypothyroidism and in subjects with normal thyroid function.

patients (n = 2336) with patients with overt hypothyroidism (n = 114) and with euthyroid subjects (n = 22,842).[10] In terms of current symptoms, subclinically hypothyroid patients were more comparable with euthyroid subjects (7.4% vs 7.7%, NS) than with overt subclinical hypothyroid patients (12.0%). They also reported on "changed symptoms", that is, complaints emerged within the last year, and here subclinically hypothyroid patients had

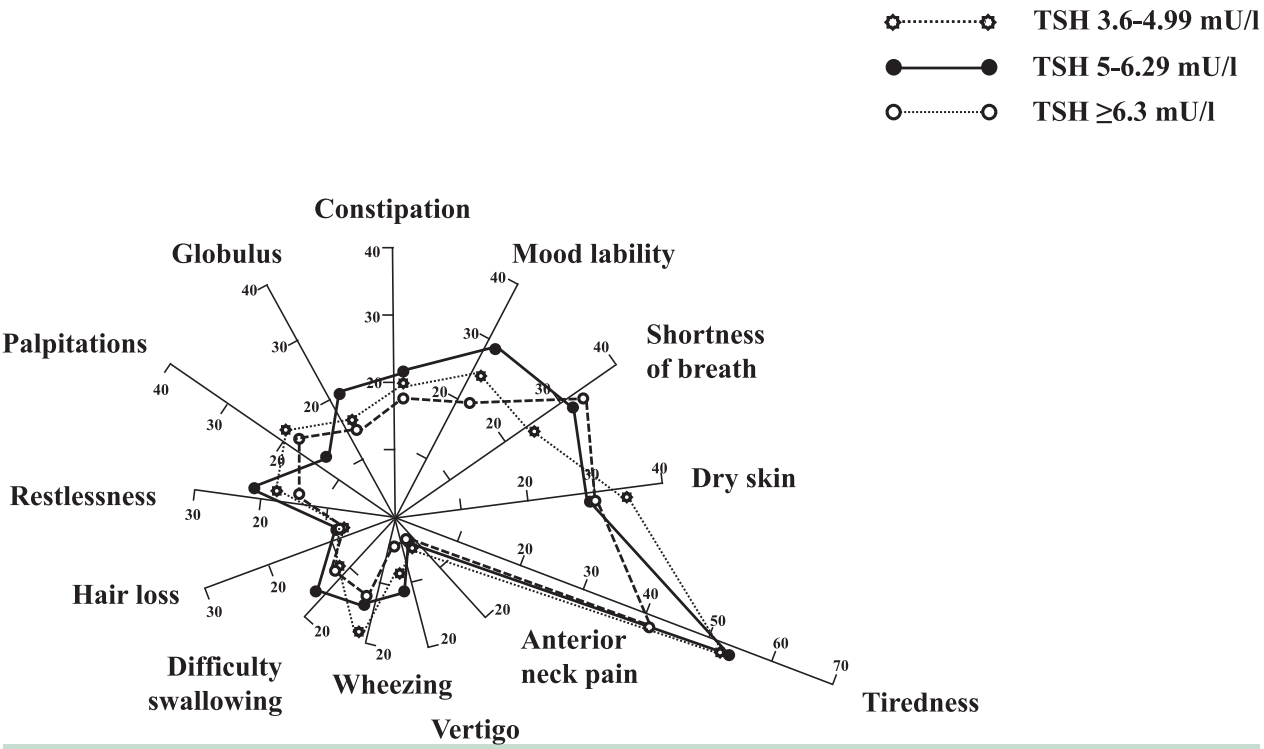

Figure 4 Nautilus diagram depicting the prevalences of 13 symptoms in subclinical hypothyroidism split by serum thyroid-stimulating hormone (TSH) levels.

borderline more symptoms compared with euthyroid controls (15.4% vs 13.4%, $P < .05$). Recently, The Thyroid Study of Age in Germany (TSAGE) reported lower quality of life (QoL; SF-36 and ThyPRO) in subclinical hypothyroidism.[35] However, most other studies did not report higher symptom prevalence in subclinical hypothyroidism vs normal thyroid function.[14-16,36,37] Interestingly, Samuels et al[38] experimentally induced subclinical hypothyroidism in patients optimally treated for thyroid failure. LT-4 doses were lowered, with a subsequent TSH increase from 2.2 to 17.4 mU/L, but with only modest symptom exacerbations in just 2 of 17 outcome measures (Billewicz score; $P = .08$; General Health as part of SF-36; $P = .08$).

Predictors of Thyroid-Associated Symptoms

The previously published finding of more symptoms in young overt hypothyroid patients[13] was now confirmed in subclinical hypothyroidism in the same DanThyr setting. Age was a predictor for mental complaints among the young patients with subclinical hypothyroidism. However, this was not different from the young population free from thyroid dysfunction.

We found no indication that high serum TSH in subclinical hypothyroidism influenced the reported symptoms. This is also in accordance with several other studies,[16,36,37,39,40] even in sustained subclinical hypothyroidism.[41] However, Zulewski et al[34] reported a correlation between their compound score and both TSH and fT4 in subclinical hypothyroidism ($P < .001$ in both). However, patients had higher TSH levels (mean: 13.7 ± 10.6) than patients in the present study (median, interquartile range: 4.58, 3.93-5.88 mU/L).

Watt et al[42] studied autoimmune hypothyroid patients and found a positive association between TPOAb levels and various symptoms. Patients were recruited from an endocrinological outpatient clinic, thus comprising referred patients with both overt and subclinical hypothyroidism, and most patients were included after commencing levothyroxine (L-T4) treatment. Ott et al[43] reported more symptoms in euthyroid TPOAb-positive women planning to undergo thyroid surgery. Baric et al[44] studied the presence of 16 symptoms/signs in 290 untreated Hashimoto patients, and found only borderline association between TgAb and 4 of these symptoms (P values between .0043 and .030).

No previous study has scrutinized the role of several characteristics predicting the symptom spectrum. We found that higher comorbidity was highly correlated to the symptom presence both in terms of the overall complaints (hypothyroidism compound score) and several specific symptoms (tiredness, shortness of breath, and wheezing). This has 2 implications. Firstly, it should be expected that patients with known comorbidity, especially in terms of pulmonary disease, may present with more symptoms when diagnosed with subclinical hypothyroidism. Thus, it may be speculated that patients with pre-existing pulmonary disease may not expect large symptom relief after L-T4 substitutions therapy, as euthyroid subjects with the same degree of comorbidity express the same complaints. Secondly, when diagnosing patients with tiredness, shortness of breath, or

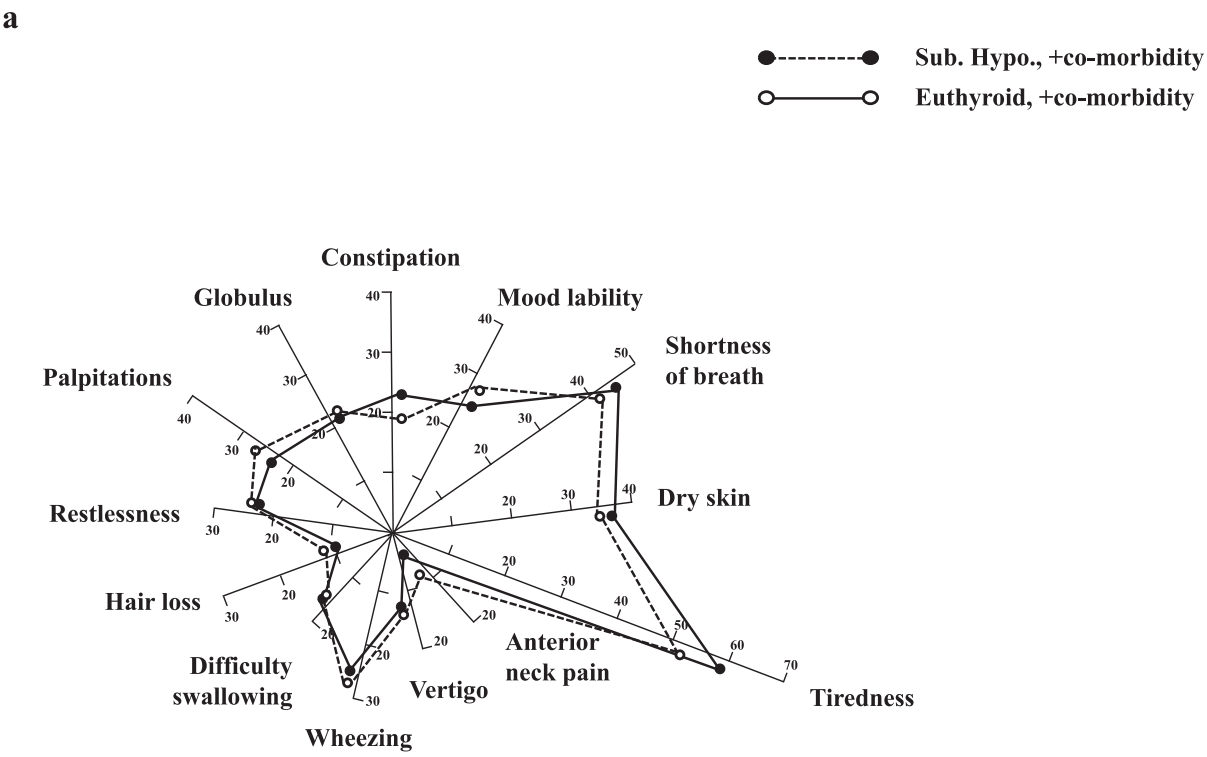

Figure 5 Nautilus diagram illustrating the prevalences of 13 symptoms in subjects with and without concomitant disease. Patients with both subclinical hypothyroidism and normal thyroid function are depicted.

wheezing, a broad case-finding strategy should be performed to exclude whether diseases other than thyroid condition could be responsible for the symptoms presented. Concomitant diseases may also partly be the reason why some hypothyroid patients still have complaints despite, from a biochemical point of view, being optimally treated.

Clinical Implication

It may be speculated, judging by the missing gap of symptoms between subclinical hypothyroid patients and subjects with normal thyroid function, that perhaps only little improvement from L-T4 substitution could be expected

Table 2 Backward Linear Logistic Regression with Outcome Characteristics (Left in Column) and Predicting Variables (on Top)

Multivariate Regression

	Sex	Age	TAb[1]	BMI	Smoking	Comorbidity
Test	Women	≤60 y	Ab+	>30 25-30	Present	Yes
Reference	Men	>60 y	Ab−	<25	No	No
Model 1						
Compound score		< .001				< .001
Model 2						
No symptoms, OR (95% CI)		2.39 (1.41-4.05)				2.70 (1.59-4.59)
P values		.001				< .001
Model 3						
Tiredness	2.64 (1.27-5.51)	2.26 (1.41-3.62)				2.37 (1.50-3.75)
P value	.0095	< .001				< .001
Mood lability		2.58 (1.58-4.22)				
P value		< .001				
Restlessness		2.09 (1.20-3.64)				
P value		.009				
Shortness of breath				4.62 (2.48-8.60) 1.77 (0.95-3.33)	2.30 (1.26-4.20)	4.06 (2.42-6.81)
P value				< .001	.007	< .001
Wheezing			0.35 (0.20-0.63)		2.75 (1.46-5.17)	2.68 (1.50-4.80)
P value			< .001		.002	< .001

Only variables involved in significant associations meeting criterion of $P < .01$ are shown. Significance after Bonferroni correction: $P < .0039$.
*Status on thyroid autoantibody (TAb) ie, positive (Ab+) for either TPOAb or thyroglobulin antibody (TgAb) vs negative (Ab−) for both.

from treatment. This is in accordance with a meta-analysis from 2009 by Villar et al[45] based on 7 randomized controlled trial studies showing no effect on symptoms, neuropsychological testing, or QoL following L-T4 treatment. In a later study by Razvi et al,[46] 100 subclinically hypothyroid patients were randomized to L-T4 vs placebo, and only improvement in tiredness among several outcome measures was reported. Most recently, Stott et al[47] failed to prove any beneficial effect treating subclinically hypothyroid patients above 65 years of age. Feller et al[48] performed a meta-analysis of 21 studies totaling 2192 adults that did not find any beneficial effect of L-T4 treatment on QoL or symptoms in patients with subclinical hypothyroidism.

Strengths and Limitations

The main strength of the study is the inclusion of a large number of subjects unaware of their present thyroid function status, allowing us to present data on both overt and subclinical hypothyroidism, as well as thyroid-healthy controls. Several studies have studied symptoms on the 2 disease entities merged, which hampered the generalizability.

This is, to our knowledge, the first study aiming to identify patient characteristics associated with higher symptom burden. Patients comprised a homogeneous group of patients with no prior thyroid disease, in contrast to many other studies[34,49] recruiting also patients with iatrogenic subclinical hypothyroidism.

We had serum TSH on all patients, but free thyroxine only from those recruited from C1+C2 (94% of the patients). However, sensitivity analysis excluding the small size of patients allocated from the C3 survey did not change the results. The magnitude of this potential information bias is limited, as 93.9% of patients from C1+C2 with elevated serum TSH had normal T4 levels.

All blood samples were taken when participants visited our center between 8 AM and 2 PM, with no demand on fasting state. This may, to some degree, have influenced the precise TSH level and thus, also the prevalence of subclinical hypothyroidism.[50] However, modest TSH differences were not associated with altered symptom presentation in the present study.

Some symptoms were not investigated in the present study. We did not ask about cold insensitivity, paresthesia, or cognitive deficits. Thus, we restricted comparative literature to papers concerning the same type of patient complaints as those scrutinized in the present study. In addition, we had no follow-up on historical data on body weight, which may have had a large impact on patients' QoL.

Another limitation of all studies mentioned in this paper, including our own, is lack of follow-up on thyroid status. It is known that many abnormal TSH values will normalize spontaneously within time. Perhaps results would have been different if only patients with consistently elevated serum TSH values were included.

CONCLUSION

Patients consulting their general practitioner may present a variety of symptoms. The present study indicates that no symptom could, with confidence, be attributed to the

Table 3 Backward Linear Logistic Regression with Outcome Characteristics (Left in Column) and Predicting Variables (on Top)

Multivariate Regression

	Angina Pectoris	Cardiac Arrhythmia	Bronchitis	Asthma
Compound score (0-13)				
P value	—	< .001	—	< .001
Symptoms (yes vs score = 0)				
OR	—	—	—	8.10 (1.92-34.2)
P value				.004
Tiredness				
OR	—	—	—	3.17 (1.54-6.51)
P value				.002
Mood lability				
OR	—	—	—	2.47 (1.26-4.83)
P value				.009
Palpitations				
OR	—	6.49 (2.67-15.8)	—	—
P value		< .001		
Restlessness				
OR	—	—	—	3.72 (1.85-7.48)
P value				< .001
Shortness of breath				
OR	—	—	2.73 (1.36-5.48)	4.61 (2.26-9.43)
P value			.005	< .001
Wheezing				
OR	—	—	—	5.70 (2.85-11.4)
P value				< .001
Difficulty swallowing				
OR	—	—	3.31 (1.55-7.03)	—
P value			.002	
Vertigo				
OR	—	6.05 (2.08-17.6)	—	4.80 (1.96-11.8)
P value		< .001		< .001
Anterior neck pain				
OR	14.0 (2.43-81.3)	—	—	—
P value	.003			

Only significant associations meeting criterion of $P<0.01$ are shown. Significance after Bonferroni correction: $P < 0.0039$.

presence of unknown subclinical hypothyroidism. Thus, in case of complaints such as tiredness, shortness of breath, or wheezing, other diseases should be screened for.

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SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.amjmed.2021.03.009.

Supplementary Table 1 Baseline Characteristics of Participants

	C1 Survey n = 4649	C2 Survey n = 3570	C3 Survey n = 684
Women	3712	2862	530
18-22 y	933	667	5
23-24 y	25*	33*	9
25-30 y	934	713	40
31-39 y	9*	13*	83
40-45 y	914	714	54
46-59 y	7*	14*	198
60-65 y	885	694	54
66+ y	5*	13*	87
Men	937	708	154
18-22 y	0	0	0
23-24 y	0	0	4
25-30 y	0	0	6
31-39 y	0	0	14
40-45 y	0	0	54
46-59 y	0	0	122
60-65 y	932	698	69
66+ y	5*	10*	317
Aalborg (moderate ID)	2222	1785	477
Copenhagen (mild ID)	2427	1785	207
Overt hypothyroidism	19	4	0
Subclinical hypothyroidism	169	185	22
Euthyroid	3957	3085	577
Subclinical hyperthyroidism	179	62	23
Overt hyperthyroidism	35	11	0

Depicted are number of participants or medians (interquartile range, 25%-75% range).

*Some patients fell outside the age intervals 18-22, 25-30, 40-45, 60-65 years as date on participation (not date on invitation) are registered.

Supplementary Table 2 Information on Symptom Expression was Obtained from the "Formal Questionnaire" and the "Mental Vulnerability Questionnaire" as Previously Reported[11]

1. DIFFICULTY SWALLOWING: Have you experienced swallowing problems within last twelve months?
2. SHORTNESS OF BREATH: Have you had shortness of breath if hurrying or climbing the stairway in slow speed within the last twelve months?
3. PALPITATIONS: Have you had sensation of palpitations within the last twelve months?
4. CONSTIPATION: Have you felt constipated within the last twelve months?
5. TIREDNESS: Have you suffered from tiredness within the last twelve months?
6. HAIR LOSS: Have you had hair loss within the last twelve months?
7. DRY SKIN: Have you had dry or sensitive skin within last twelve months?
8. MOOD LABILITY: Have you had very unstable mood within the last twelve months?
9. RESTLESSNESS: Have you suffered from restlessness within the last twelve months?
10. GLOBULUS: Have you had a sensation of a lump in the throat within the last twelve months?
11. ANTERIOR NECK PAIN: Have you had pain in the front region of the neck within the last twelve months?
12. WHEEZING: Have you experienced wheezing within the last twelve months?
13. DIZZINESS/VERTIGO: Do you often suffer from fits of dizziness?

Here we list the symptoms used for evaluating patients with subclinical hypothyroidism.