Title: Symptoms in older adults with subclinical thyroid dysfunction: cross-sectional study in general practice

Short running title: Subclinical thyroid dysfunction and symptoms in older adults

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ABSTRACT

Background: Subclinical thyroid dysfunction, characterized by abnormal serum thyrotrophin (thyroid stimulating hormone [TSH]) concentrations with normal free thyroxine (FT4), is common in the elderly. Whether individuals with subclinical serum status experience an increased symptom profile remains unclear.

Aim: To compare the prevalence of those symptoms typically associated with overt thyroid dysfunction in older individuals with a subclinical and euthyroid serum profile.

Design and setting: Cross-sectional, nested within the Birmingham Elderly Thyroid Study (BETS), 19 general practices, UK.

Method: Community dwelling adults (aged ≥65 years), without overt thyroid dysfunction or associated treatment, self-reported presence or absence of 18 symptoms (whilst serum result naïve). Serum concentrations of TSH and FT4 were measured to establish thyroid status.

Results: 2870 individuals were screened, 2703 (94%) were categorized as euthyroid (normal), 29 (1%) subclinically hyperthyroid and 138 (5%); subclinically hypothyroid. Weight gain was reported by 54% (CI; 45.3-61.7%) and fast thinking by 31% (CI; 17.3-49.2) of individuals with subclinical hypo- and hyperthyroidism respectively. No significant differences in the prevalence of individual symptoms were observed between the euthyroid and subclinical hypothyroid groups nor in comparison with the subclinically hyperthyroid group. Multivariate logistic regression analysis failed to reveal an association between individual or multiple symptoms and subclinical status.

Conclusion: Findings suggest that subclinical thyroid dysfunction does not confer a symptom burden in older individuals and support adherence to guidelines in the non-treatment of subclinical thyroid dysfunction. GPs may use the findings to reassure older people presenting with symptoms that subclinical thyroid dysfunction is an unlikely explanation. The presence of persistently abnormal TSH concentrations may be linked to long-term risks of cardiovascular disease, especially Atrial Fibrillation, but whether this should prompt treatment and whether such treatment alters vascular outcomes is unknown.

How this fits in

Subclinical thyroid dysfunction is a biochemical diagnosis that is common in older age. Although older patients with this diagnosis may report symptoms like those found in overt thyroid dysfunction, it is unknown whether subclinical thyroid dysfunction itself is associated with symptom excess. This large population-based survey demonstrates that subclinical thyroid dysfunction in the older population does not confer additional symptom burden. Findings support current guidance for not treating subclinical thyroid dysfunction in older individuals and provide an evidence base for GPs to use in discussion with patients experiencing symptoms who have mildly abnormal thyroid function test results.

Introduction

Subclinical thyroid dysfunction is characterised by TSH concentrations outside the stated reference range accompanied by FT4 concentrations within the reference range. (1) Thyroid function tests are commonly requested for older adults in primary care either routinely or in response to presentation of symptoms and identify large numbers of individuals with subclinical thyroid dysfunction. (2-6)

We have previously demonstrated low levels of progression (<0.5%) of subclinical thyroid dysfunction to overt disease in older individuals over a period of up to 5 years, supporting guidelines that indicate treatment of subclinical dysfunction is not necessary to prevent progression.(7) However, a better understanding of whether subclinical thyroid dysfunction itself is associated with any symptom excess which may be amenable to intervention is still required to guide clinical management of this condition.

A previous community-based population study demonstrated symptoms to be poorly predictive of TSH, (8) although other research suggests a higher prevalence of symptoms in individuals with subclinical thyroid dysfunction. (9-11) These studies however have significant limitations in their application to primary care or community-based populations being derived from endocrine clinic populations. (9-11). Additionally, these data relate to middle aged populations (all studies have mean ages in the range 43-47 years), where the overlap of symptoms attributable to older age and thyroid dysfunction are likely to be less widespread and hence more discriminatory.

Therefore there continue to be calls for further research in subclinical thyroid dysfunction due to the poor understanding of how to best manage this condition. (12,13) This study aimed to build on previous work and definitively explore whether subclinical thyroid dysfunction in older adults confers additional symptom burden and also whether specific symptom clusters are associated with subclinical thyroid dysfunction rather than being typical of older age presentations. Such understanding may enable reductions in the cost of repeat testing in this patient group and also advise further trial outcomes.

Methods

Recruitment and participants

This cross-sectional survey was nested within a longitudinal study of thyroid function in an established cohort (the Birmingham Elderly Thyroid Study (BETS) cohort) of 5881 community dwelling individuals (aged ≥65 years at initial screen) from 19 practices representative of the UK. (3,7,14-15). GPs confirmed eligibility and suitability of follow-up for participants of the original BETS cohort as previously reported.(7) Individuals were excluded if they were no longer registered with the practice, were deceased, had a diagnosis of overt thyroid dysfunction, had received treatment for thyroid dysfunction or were judged to be inappropriate for contact (e.g. recently bereaved or terminally ill).

Eligible participants received a postal invitation letter, reply slip and free post envelope addressed to the research office. Patients interested in participating were sent a symptoms questionnaire with a request to complete it prior to attending the research clinic for venepuncture. At the clinic, consent was obtained and a blood sample for thyroid function testing acquired. Samples were collected in plastic vacuette 4ml serum separator clot activator tubes. Research clinics were conducted over a period of 19 months with symptom details being provided concurrent to individual patient appointments.

Evaluation of symptoms

Participants self-reported the presence or absence of 18 classic symptoms of overt hypo- and hyperthyroidism by questionnaire. The questionnaire was a supplemented version of the Colorado Hypothyroid Symptom survey, a validated questionnaire for assessment of symptoms of thyroid hormone deficiency. (16-17). The format of the original survey was preserved; however, six hyperthyroid symptoms identified from the literature were added. (18-19). The final questionnaire comprised: six hyperthyroid symptoms (weight loss, fast thinking, frequent palpitation, sensitivity to heat, tremor and excessive perspiration), nine hypothyroid symptoms (hoarse voice, deep tone of voice, dry skin, puffy eyes, muscle cramps, constipation, slow thinking, sensitivity to cold and weight gain) and three symptoms (poor memory, lethargy and weak muscles) which can be associated with both hyper- and hypothyroidism.

The questionnaire was piloted by 10 volunteers aged ≥65 years to assess user understanding and experience. Refinements were made based upon the feedback obtained.

Thyroid function testing

Thyroid function testing was performed by the Regional Endocrine Laboratory at the University Hospital Birmingham, National Health Service Foundation Trust (UHB). Serum TSH and FT4 concentrations were determined for all individuals. If a serum TSH concentration above or below the limits of the reference range was identified, serum free tri-iodothyronine (FT3) was also measured. Serum TSH, FT4, and FT3 concentrations were measured by electrochemiluminescent immunoassays using the Roche E170 (Roche Diagnostics, Burgess Hill, UK). The TSH assay was calibrated against the second international reference preparation 80/558. The associated inter-assay coefficient of variation for TSH was 1.5% (0.5-33.0 mIU/L), FT4 2.0-2.5% (9.0-66.0 pmol/L) and FT3 2.0-3.5% (4.0-21.0 pmol/L). The lower limit of reporting for the TSH assay was 0.02 mIU/L and the manufacturer's quoted mean functional sensitivity was 0.014 mIU/L. Algorithms relating to current local clinical practice and laboratory reference criteria were used to classify thyroid status (Table 1).

Table 1. Classification of thyroid status based upon TSH and FT4 concentration

Demographic and lifestyle data
Age and deprivation score were calculated from the participants' date of birth and postcode, respectively. The Index of multiple deprivation 2004 (IMD) was used as a proxy measure of socioeconomic status with higher IMD scores indicating greater deprivation. (20) Primary care medical records were reviewed to collect data on medical history and concomitant prescription medication pre-specified as likely to be associated with category of thyroid function, with reported symptoms or to interfere with tests of thyroid function. Participants self-reported smoking status.

Statistical analysis
T tests and chi squared tests were used to compare the participants with subclinical hypo- and hyperthyroidism with euthyroid participants with respect to patient characteristics (e.g demographics, medical history, concomitant disease and prescription medication). Univariate logistic regression techniques were used to establish unadjusted odds ratios representing the odds of subclinical hypo- or hyperthyroidism in subjects reporting presence of individual symptoms divided by the odds of subclinical hypo-or hyperthyroidism in subjects reporting absence of the symptom.

Multivariate logistic regression analysis was then undertaken to further examine the relationship between individual symptoms and thyroid function category and establish the likelihood of subclinical thyroid dysfunction after controlling for the effects of the covariates; age, gender, deprivation score, smoking status, concomitant disease and prescription medication. To enable further exploration of the relationship between category of thyroid function and presence of multiple symptoms, uni- and multivariate logistic regression was undertaken to establish the change in odds of a subclinical hypo- or hyperthyroid result as the total number of symptoms reported increased, with and without all other factors being equal.

Results

Four thousand four hundred and forty-seven individuals were invited to participate in the follow-up screening study (*Figure 1).* Participants were excluded from the original cohort (n=5881) if during the 5-year interval period they had died (n=501), deregistered from participating practice (n=453), or become unsuitable for contact, as judged by the responsible general practitioner (n=381). Individuals who had been diagnosed with or received treatment for thyroid dysfunction were also excluded (n=99). Overall, 66% (2936/4447) of those invited attended a research clinic and consented to participate. In total, 2870 (65%) were fully screened and included in the analysis. Reasons for exclusion from the analysis were missing TFT results or missing symptom data (n=13) and newly identified treatment for thyroid dysfunction (n=53).

Description of the subgroups

A total of 2703 participants (94%, n=2870) were classified as euthyroid, 138 (5%) as subclinically hypothyroid and 29 (1%) subclinically hyperthyroid. The euthyroid group were slightly younger than the subclinically hyperthyroid group (mean age 76.8 versus 79.1 years respectively, p=0.02) and the subclinically hypothyroid group (mean age 76.8 versus 77.7 years respectively, p=0.05). The three groups were similar with respect to gender and deprivation score. A significantly higher proportion of the euthyroid group compared with the subclinically hypothyroid group had a previous diagnosis of pulmonary disease (12.9% versus 3.6%, p=0.03) but there were no statistically significant differences between the euthyroid and subclinical groups with respect to any other concomitant disease or prescription medication. (data not shown).

Symptom expression and subclinical hypothyroidism

There were no significant differences between the euthyroid and subclinical hypothyroid groups with respect to presence of individual or multiple hypothyroid symptoms (*Table 2*). Unadjusted and adjusted odds ratios representing the odds of subclinically hypothyroid status in subjects reporting symptom presence divided by the odds of subclinical status in subjects reporting symptom absence are reported. Visual exploration of the distribution of total number of symptoms reported by the euthyroid and subclinical hypothyroid groups did not demonstrate a clear relationship between multiple symptoms and thyroid function category (*Figure 2*).

Symptom expression and subclinical hyperthyroidism

For completeness we report in Table 3 the prevalence of individual symptoms and total number of symptoms reported in the euthyroid and subclinical hyperthyroid groups, although acknowledge that a low number of identified subclinically hyperthyroid cases restricts interpretation. No significant differences between the groups were observed with respect to presence of any individual hyperthyroid symptom or total number of symptoms reported. Visual exploration of the distribution of total number of symptoms reported by the groups also failed to demonstrate a clear relationship between total number of symptoms reported and thyroid function category (*Figure 3*).

Discussion

Summary

This population survey suggests that symptoms commonly associated with overt thyroid dysfunction are relatively prevalent in older community dwelling individuals. This study did not however demonstrate a greater prevalence of any established symptoms in those with subclinical thyroid dysfunction compared to euthyroid controls. Furthermore, presence of multiple symptoms were not associated with subclinical thyroid dysfunction.

Strengths and limitation

The strengths of this study are the large number of unselected older individuals investigated and the simultaneous and detailed evaluation of thyroid function, self-reported symptoms, concomitant disease and prescription medication. Evidence based development of the symptoms questionnaire was employed to ensure that the most relevant and sensitive symptoms, reflecting a variety of metabolic processes and involving a range of organ systems, were selected and captured. Furthermore, all participants completed the questionnaire prior to thyroid function testing so that their responses were not influenced by knowledge of their thyroid status.

This study did not evaluate other clinical effects, such as altered cardiac morphology, that may be attributed to subclinical thyroid dysfunction. Further evidence in such impacts is needed in relation to unselected populations to fully determine any consequence of living with marginally altered TSH or FT4.

Comparison with existing literature

This study failed to identify symptoms which alone or in combination are associated with subclinical thyroid dysfunction in older individuals. This contrasts with previous studies (9-11) which identified an increased symptom burden, but whose findings are likely to be influenced by the recruitment from a secondary care endocrine settings and smaller cohorts.

It is also noted that direct comparison with these studies is not supported by the much younger populations recruited, with this being the first significant screening study to explore symptom profiles in an older cohort, ie the general population who are most likely to receive thyroid function testing and be identified with sub-clinical thyroid states.

These findings support those of a smaller retrospective case-note study conducted in a primary care geriatric service which found no significant difference in the frequencies of any signs or symptoms associated with hypothyroidism between subclinical and euthyroid individuals. (21).

Implications for practice and research

Overall findings suggest that subclinical thyroid dysfunction does not confer a symptom burden in older community dwelling individuals. This lack of association further supports adherence to guidelines in the non-treatment of subclinical thyroid dysfunction and provides an evidence base for GPs to use in discussion of symptoms and associated likelihood of subclinical dysfunction explaining these in their older patients.

In older individuals the diagnosis of subclinical thyroid dysfunction should be based upon laboratory results indicating persistently (over a period of 3-6 months to effectively

exclude acute non-thyroidal and drug related causes) abnormal TSH levels alongside FT4 levels within reference range. (22)

In terms of management of subclinical thyroid dysfunction, the findings of a recent meta-analysis and systematic review incorporating data from 21 trials do not support the routine use of thyroid hormone therapy in adults with subclinical hypothyroidism. Results of this review consistently demonstrated no association of therapy with improved outcomes. (23)

The evidence to guide management of subclinical hyperthyroidism remains inconclusive with few interventional studies showing benefit in clinically important outcomes. Since epidemiological data demonstrate an increased rate of atrial fibrillation, heart failure and coronary heart disease with subclinical hyperthyroidism, current European Thyroid Association guidelines recommend that treatment of subclinical hyperthyroidism be considered in older patients with cardiovascular disease, diabetes and renal failure to avoid longer-term risks. (15,24,25) NICE guidelines on the assessment and management of thyroid disease are in development and are scheduled for publication November 2019. (26) Considering this evidence, in the presence of persistently low levels of TSH (especially levels <0.1mIU/) alongside pre-existing cardiovascular disease and increased cardiovascular risk factors, GPs may want to discuss with their patients the possible long-term risks of subclinical hyperthyroidism in order to determine whether to intervene or abstain from treatment. Such discussions will however be limited by uncertainty whether this association is clinically significant and the lack of any evidence on the effectiveness of treatment for reducing any risks associated with subclinical hyperthyroidism. Treatment of all grades of hyperthyroidism should most appropriately be instituted by endocrine specialists.(27)

Further large-scale, longitudinal research is required to establish the clinical significance of the etiolgy of subclinical hyperthyroidism and the impact of treatment on cardiovascular endpoints to guide management strategies.

Figure 1. Study flow diagram

Figure 2. Total number of hypothyroid symptoms reported by the euthyroid and subclinical hypothyroid groups

Table 2. Prevalence of hypothyroid symptoms and risk factors for subclinical hypothyroidism

Figure 3. Total number of hyperthyroid symptoms reported by the euthyroid and subclinical hyperthyroid groups

Table 3. Prevalence of hyperthyroid symptoms and risk factors for subclinical hyperthyroidism

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Conflicts of interest
None declared

Ethical approval
Ethical approval for the study was obtained from the North Staffordshire Local Research Ethics Committee; reference number: 07/H1204/136, approval date; 19/12/2007 prior to commencement of the research.

Contributions
The study was designed by LR, DM and SH and funding was secured by LR, JP and FDRH. DM undertook day-to-day management of the study and data collection. DM and LR were responsible for data management and quality assurance. SH provided senior quantitative methodological support for the design of the statistical analysis. DM undertook all analyses supported by SH. All authors contributed to data interpretation. DM wrote the first draft of this paper and all authors were responsible for subsequent critical revision of the manuscript.

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Table 1. Classification of thyroid status based upon TSH and FT4 concentration

Thyroid status	Serum thyrotrophin (TSH) mIU/L	Serum thyroxine (FT4) pmol/L
Overt hyperthyroidism	<0.30	>10
Subclinical hyperthyroidism	< 0.30	10-22
Euthyroid	0.3 – 4.5	10-22
Subclinical hypothyroidism	>4.50	10-22
Overt hypothyroidism	>4.50	<22

Table 2. Prevalence of hypothyroid symptoms and risk factors for subclinical hypothyroidism

Symptoms	Euthyroid n=2703 % (95% CI)	Subclinical hypothyroidism n=138 % (95% CI)	Unadjusted OR (95% CI) p value	Adjusted OR[a] (95% CI) p value
9 symptoms typically associated with overt hypothyroidism				
Hoarse voice	6.0 (5.2-7.0)	8.0 (4.5-13.8)	1.3 (0.7-2.6) 0.35	1.4 (0.7-2.8) 0.24
Deep voice	6.4 (5.5-7.4)	9.5 (5.6-15.6)	1.5 (0.9-2.8) 0.15	1.5 (0.8-2.7) 0.23
Dry skin	32.2 (30.4-34.0)	33.3 (26.0-41.6)	1.1 (0.7-1.5) 0.78	1.0 (0.7-1.5) 0.87
Puffy eyes	13.3 (12.1-14.7)	15.9 (10.8-23.0)	1.2 (0.8-2.0) 0.38	1.2 (0.7-1.9) 0.48
Muscle cramps	15.1 (13.8-16.5)	15.2 (10.2-22.1)	1.0 (0.6-1.6) 0.97	0.9 (0.6-1.5) 0.80
Constipation	13.2 (11.9-14.5)	14.5 (9.6 -21.3)	1.1 (0.7-1.8) 0.65	1.0 (0.6-1.7) 0.99
Sensitivity to cold	34.8 (33.0-36.7)	37.2 (29.6-45.6)	1.1 (0.8-1.6) 0.56	1.1 (0.8-1.6) 0.64
Slow thinking	7.9 (6.9-8.9)	11.6 (7.3-18.9)	1.5 (0.9-2.6) 0.12	1.5 (0.9-2.7) 0.13
Weight gain	48.5 (46.7-50.4)	53.6 (45.3-61.7)	1.2 (0.9-1.7) 0.24	1.2 (0.9-1.8) 0.25
3 symptoms which can be associated with overt hyper or hypothyroidism				
Poor memory	9.7 (8.6-10.9)	8.0 (4.5-13.7)	0.8 (0.4-1.5) 0.50	0.8 (0.4-1.6) 0.56
Weak muscles	14.3 (13.0-15.7)	14.5 (9.6-21.3)	1.0 (0.6-1.7) 0.95	01.0 (0.6-1.7) 0.90
Lethargy	16.4 (15.0-17.8)	10.9 (6.7-17.3)	0.6 (0.4-1.1) 0.10	0.6 (0.4-1.1) 0.12
Multiple symptoms				
Total number of symptoms reported	Median (IQR) 2.0 (2.0)	Median (IQR) 2.0 (2.0)	1.0 (0.95-1.1) 0.33	1.0 (0.9-1.1) 0.44

[a] adjusted odds of subclinical hypothyroidism after controlling for sociodemographic factors (age, gender, deprivation score, smoking status) and concomitant disease and prescription medication.
Bonferroni adjusted alpha value to control for type 1 error resulting from multiple comparisons = 0.004

Table 3. Prevalence of hyperthyroid symptoms and risk factors for subclinical hyperthyroidism

Symptoms	Euthyroid n= 2703 % (95% CI)	Subclinical hyperthyroidism n=29 % (95% CI)	Unadjusted OR (95% CI) p value	Adjusted OR[a] (95% CI) p value
6 symptoms typically associated with hyperthyroidism				
Heavy perspiration	3.1 (2.5-3.8)	3.4 (0.6-17.2)	1.1 (0.2-8.3) 0.92	1.4 (0.2-10.9) 0.73
Trembling hands	4.3 (3.6-5.1)	3.4 (0.6-17.2)	0.8 (0.1-6.0) 0.83	0.6 (0.8-5.0) 0.66
Frequent palpitation	6.0 (5.2-7.0)	6.9 (1.9-22.0)	1.2 (0.3-4.9) 0.85	1.3 (0.3-5.9) 0.72
Sensitivity to heat	10.7 (9.6-11.9)	13.8 (5.5-30.4)	1.3 (0.5-3.9) 0.59	1.6 (0.5-4.7) 0.42
Fast thinking	22.7 (21.1-24.3)	31.0 (17.3-49.2)	1.5 (0.7-3.4) 0.29	1.4 (0.6-3.2) 0.42
Weight loss	7.4 (7.0-9.1)	3.4 (0.6-17.2)	0.4 (0.1-3.3) 0.43	0.4 (0.05-2.8) 0.33
3 symptoms which can be associated with overt hyper or hypothyroidism				
Poor memory	9.7 (8.6-10.9)	0	0 1.0	0 0.99
Weak muscles	14.3 (13.0-15.7)	6.9 (1.9-22.0)	0.4 (0.1-1.9) 0.27	0.4 (0.1-1.9) 0.27
Lethargy	16.4 (15.0-17.8)	10.3 (3.6-26.4)	0.6 (0.2-2.0) 0.39	0.6 (0.2-2.0) 0.41
Multiple symptoms				
Total number of symptoms reported	Median (IQR) 1.0 (1.0)	Median (IQR) 1.0 (1.0)	0.9 (0.6-1.3) 0.44	0.8 (0.6-1.3) 0.41

[a] adjusted odds of subclinical hyperthyroidism after controlling for sociodemographic factors (age, gender, deprivation score, smoking status) and concomitant disease and prescription medication.
Bonferroni adjusted alpha value to control for type 1 error resulting from multiple comparisons = 0.005

Figure 1 Study flow diagram

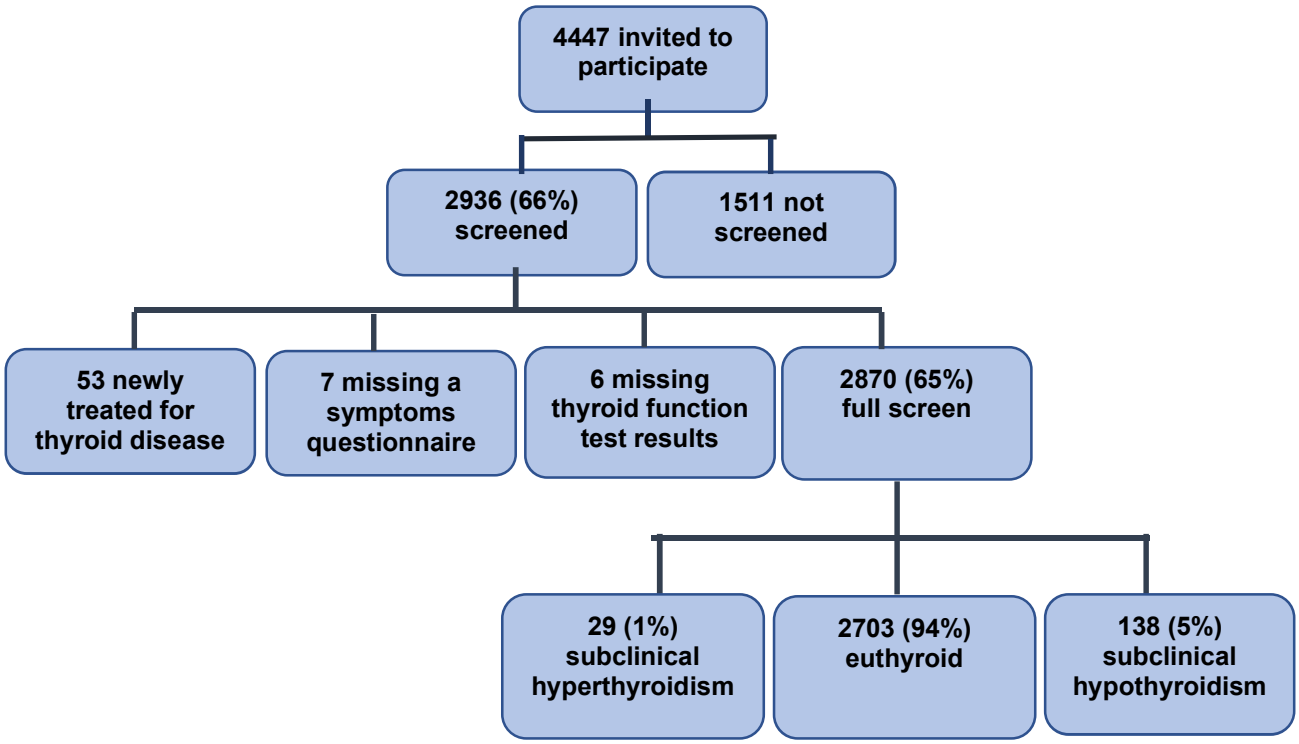

Figure 2 showing the total number of hypothyroid symptoms reported by the euthyroid and subclinical hypothyroid groups

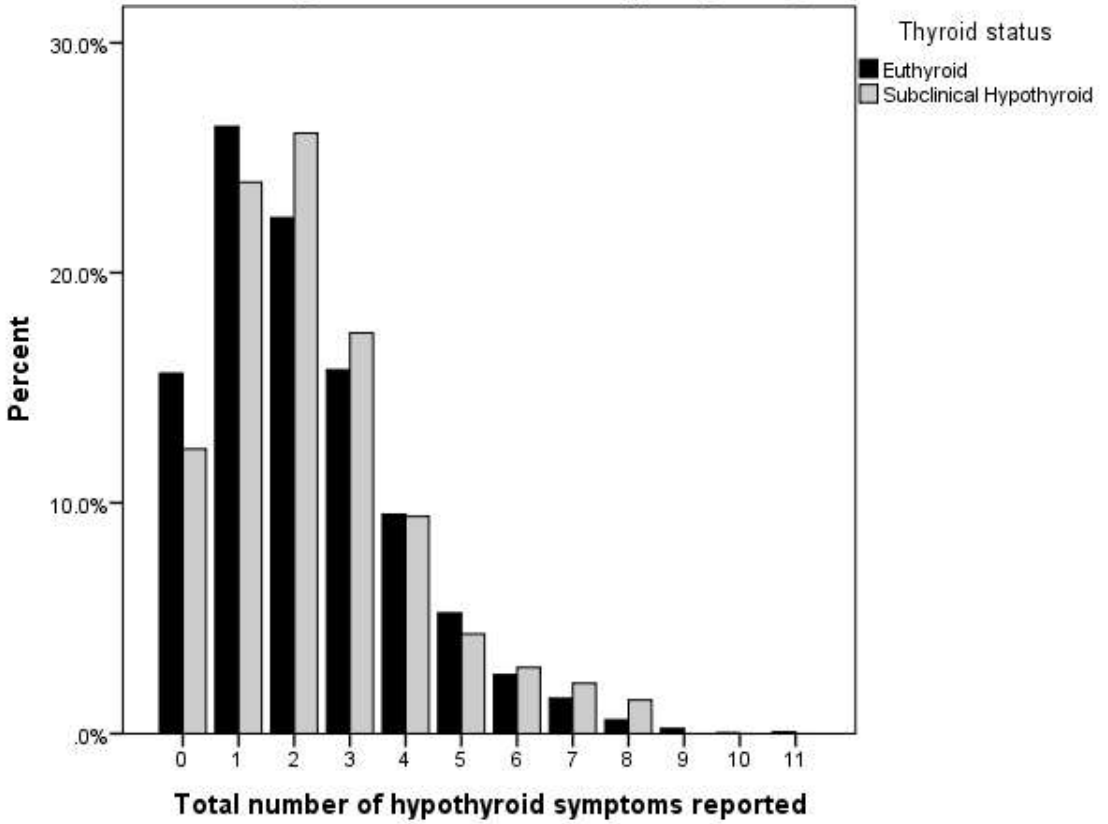

Figure 3 showing the total number of hyperthyroid symptoms reported by the euthyroid and subclinical hyperthyroid groups