

Subclinical hypothyroidism: a historical view and shifting prevalence

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SUMMARY

Background and Aims: Accurate diagnosis and treatment of subclinical hypothyroidism (SCH) is challenging in clinical practice because of differing upper limits of normal (ULN) for thyroid-stimulating hormone (TSH). This review summarises the various definitions of SCH and their impact on reported SCH prevalence. **Methodology:** Articles reporting the prevalence of SCH in relation to the ULN of TSH in human studies were identified through an English-language PubMed search for 'subclinical hypothyroidism,' 'prevalence,' and 'TSH' within the title and/or abstract. Relevant articles and related literature were selected for inclusion. **Results:** Estimates for the prevalence of SCH varied by sex, age, race/ethnicity, and geographic location (range, 0.4–16.9%). Higher rates of SCH were consistently reported in women (0.9–16.9%) and older individuals (2.7–16.9%). However, the ULN of TSH in those considered free of thyroid disease and not at risk increased progressively with age, suggesting that reports of SCH prevalence in elderly people may be overestimated. Multiple studies reported an increased risk of progression to overt hypothyroidism among individuals with elevated TSH and antithyroid antibodies. **Conclusions:** Given the variable definition of SCH based on an inconsistent ULN for TSH, it is currently difficult to ascertain the true prevalence of SCH and to correctly label and treat patients with SCH; use of age-adjusted definitions may be considered when assessing prevalence. A diagnosis of SCH does not necessarily merit treatment, especially if TSH elevations are transient (i.e. not persistent for > 3–6 months) and the patient lacks other risk factors for developing overt hypothyroidism.

Introduction

Subclinical hypothyroidism (SCH) is a commonly encountered laboratory finding in clinical practice, characterised by elevated levels of thyroid-stimulating hormone (TSH) in serum in the presence of normal serum levels of free thyroxine (FT4), as compared with population-based reference ranges for these values (1). In contrast, overt hypothyroidism is characterised by elevated TSH in combination with subnormal levels of FT4. Individuals classified as having SCH are usually asymptomatic, although signs and symptoms of hypothyroidism, such as dry skin, fatigue, cold sensitivity, constipation and muscle cramps, are sometimes present. SCH may or may not progress to overt hypothyroidism (1). In patients younger than 65 years, SCH has been reported to be associated with ischemic heart disease (2); in a broader population, SCH is associated with modest

Review criteria

Studies were identified through a PubMed search for 'subclinical hypothyroidism' (SCH), 'prevalence,' and 'TSH' (thyroid-stimulating hormone) within the title and/or abstract field. The results were limited to English-language studies in humans. Abstracts were reviewed, and studies reporting the prevalence of SCH in relation to the upper limit of normal for TSH were selected for inclusion, as well as additional relevant articles.

Message for the clinic

The true prevalence of SCH is currently difficult to precisely assess, as the current definition of SCH has not been consistently applied in previous studies and does not account for individual patient factors, including the age-adjusted upper limit of normal for TSH, positivity for thyroid antibodies, and racial and ethnic differences. A diagnosis of SCH does not necessarily mean that treatment is merited.

elevations in total serum cholesterol, low-density lipoprotein (LDL) cholesterol and triglycerides (3). SCH is highly prevalent in patients with chronic kidney disease (4).

Worldwide, overt hypothyroidism is most commonly caused by environmental iodine deficiency; however, in iodine-replete regions, chronic autoimmune thyroiditis is the most common cause of hypothyroidism (1). Autoimmune thyroiditis is characterised by elevated antithyroid antibodies, including antithyroglobulin antibodies (TgAbs) and antimicrosomal/antithyropoxidase antibodies (TPOAbs); Hashimoto's thyroiditis (the most common form of autoimmune thyroiditis) is further distinguished by the presence of goitre. Similar to overt hypothyroidism, the TSH elevations that can indicate SCH may be due to a variety of underlying causes (e.g. subacute thyroiditis or postpartum thyroiditis; Table 1), as comprehensively reviewed

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Table 1 Causes of thyroid-stimulating hormone elevations that may indicate subclinical hypothyroidism (adapted from Franklyn 2013) (5)

Causes related to thyroid disease and its treatment
Autoimmune thyroid disease (Hashimoto thyroiditis)
Previous radioiodine treatment for hyperthyroidism
Previous thyroid surgery
Antithyroid drugs
Previous hyperthyroidism because of Graves' disease
Postpartum, subacute and other types of thyroiditis
Thyroxine therapy – poor compliance or inadequate dose prescription
Other causes or associations
Radiotherapy to head or neck
Other autoimmune diseases (e.g. type 1 diabetes, rheumatoid arthritis, Addison disease, pernicious anaemia)
Down syndrome
Therapy with iodine-containing drugs (e.g. a miodarone)
Other causes for iodine excess (e.g. kelp ingestion, radiographic contrast agents)
Lithium therapy
'Nonthyroidal' illnesses – especially during the recovery phase

recently by Franklyn (5). SCH is most frequently caused by Hashimoto's thyroiditis and may persist even after the initiation of levothyroxine treatment as a result of inadequate dosages of thyroxine (6) or differences in the bioavailability of alternative thyroxine preparations (7). Alternatively, SCH may be observed in the aftermath of hyperthyroid treatment with ^{131}I (8) or by surgery (partial thyroidectomy), or as a result of the natural clinical course of Graves' disease (9).

Thyroid hormone levels are regulated as part of a negative feedback control loop within the hypothalamic-pituitary-thyroid axis (10). The hypothalamus secretes thyrotropin-releasing hormone (TRH), which stimulates the pituitary gland to release TSH. In response to TSH, the thyroid gland releases thyroxine, which is subsequently converted to its more bioactive form, triiodothyronine. In a healthy individual with an intact hypothalamic-pituitary-thyroid axis, these hormones are maintained in equilibrium (often referred to as the setpoint); even a small reduction in the levels of thyroxine leads to a disturbance of the homeostasis, causing a nonlinear increase in TSH and resulting in the development of hypothyroidism (11).

Reports on the prevalence of SCH in the general population have varied considerably (12). As SCH is defined using a cut-off value for the upper limit of normal (ULN) for the concentration of TSH, the choice of threshold value contributes to this variabil-

ity. In addition, testing considerations should take into account the reproducibility of the TSH elevation, which may be affected by factors including transient elevations in association with acute illness, iodine intake and by diurnal and seasonal fluctuations in TSH levels up to 50% of the mean (13–16). Over time, investigators have determined that what constitutes a 'normal' upper limit depends in part on characteristics of the study population, such as age, sex and race. Thus, as the ULN threshold for TSH has varied over time, the reported prevalence of SCH has also changed. The purpose of this review was to examine the shifting definition of SCH and the impact of variable definitions of the ULN of TSH on the prevalence of SCH reported in the literature. Furthermore, we will discuss how modifying definitions of SCH may affect the decision to label and treat patients with SCH.

Methods

PubMed was searched on December 10, 2013, with the following search string: ('subclinical hypothyroidism'[Title/Abstract]) AND prevalence[Title/Abstract] AND TSH[Title/Abstract]. The results were limited to English-language studies in humans, which yielded 197 articles. Abstracts were reviewed, and studies reporting the prevalence of SCH in relation to the ULN for TSH were selected for inclusion. Additional references were identified from the bibliographies of selected articles and subsequent publications identified by the authors. Supporting literature was included as necessary for context.

Historical prevalence of SCH

First-generation TSH radioimmunoassays were useful for the identification of hypothyroidism when TSH levels greater than controls (initially, > 10 mIU/l; later, > 5–7 mIU/l) were documented. Second- and third-generation TSH assays, which expanded the useful range of TSH detection down to 0.1 mIU/l and below, had little impact on the expected upper limit of 4–5 mIU/l, which was usually derived from convenience populations by assay manufacturers. Thus, while TSH assay performance has generally improved over time, it is unlikely that the clinical diagnosis of SCH was affected, as the sensitivity for mild elevations of TSH has remained about the same. Studies reporting the prevalence of SCH for approximately the past 35 years are presented in Table 2. In addition to the upper limit of the TSH concentration, other factors that may affect the prevalence of SCH include age (see below), geography, season and iodine content in the environment in which the study population is located (13). Estimates

Table 2 Reported prevalence of subclinical hypothyroidism (adapted from Wiersinga 1995) (12)

Year	Investigator	Country	Population	Age, years	TSH threshold, mIU/l	Prevalence, %	
						Women	Men
1977	Tunbridge et al. (19)	UK	General population	> 18	> 6.0	7.5	2.8
1979	Sawin et al. (18)	USA	Senior citizens	> 60	≥ 5.0 to < 10.0	16.9	8.2
					≥ 10.0	7.1*	2.7*
1981	Nyström et al. (29)	Sweden	General population	44–66	8.0–14.0	5.1	
1981	Riniker et al. (20)	Switzerland	General medical department	> 9	> 6.0	3.1 (men and women)	
1983	Falkenberg et al. (30)	Sweden	Rural community	> 60	> 7.0	0.9	
1985	Sawin et al. (27)	USA	Senior citizens	> 60	5.0–10.0	7.7 [†]	3.3 [†]
					> 10.0	5.9 [‡]	2.4 [‡]
1988	Brochmann et al. (31)	Norway	Rural community	> 70	4.6–6.0	3.5	2.4
					> 6.0	3.5	2.4
1990	Drinka et al. (32)	USA	Nursing home	> 60	> 4.5	14.6	9.7
1990	Bagchi et al. (33)	USA	Urban community	> 55	> 6.0	8.5	4.4
1991	Parle et al. (34)	UK	General practice	> 60	> 5.0	11.6	2.9
1993	Konno et al. (17)	Japan	Health examination	Mean = 46	> 5.0	2.1	0.4
1993	Geul et al. (35)	The Netherlands	Community	Mean = 55	> 4.2	4.0	
			Community (same cohort)	Mean = 65	> 4.2	7.3	
2000	Canaris et al. (21)	USA	General population (1995 data)	≥ 18	> 5.1	9.0 (men and women)	
2002	Hollowell et al. (23)	USA	Total population of NHANES III (1988–1994)	≥ 12	> 4.5	4.3 (men and women)	
2003	Völzke et al. (36)	Germany	General population [§]	20–79	> 3.0	0.5 (men and women)	
2006	Hoogendoorn et al. (37)	The Netherlands	General population**	≥ 18 46% ≥ 60	> 4.0	4.9	3.0
2011	Benseñor et al. (38)	Brazil	Low-income elderly population	≥ 65	> 5.0	6.7	6.1
2013	Asvold et al. (25)	Norway	General population (1995–1997)	≥ 20	> 4.5	3.0	2.1
			General population (2006–2008)	≥ 20	> 4.5	1.1	1.0

*45.5% of these men and women (10/22) had thyroxine levels below normal. [†]38.9% of these men and women (37/95) had thyroxine levels below normal. [‡]12.7% of these men and women (16/126) had thyroxine levels below normal. [§]Previously iodine-deficient region. **Borderline sufficient iodine intake region. NHANES, National Health and Nutrition Examination Survey; TSH, thyroid-stimulating hormone.

of the prevalence of SCH have ranged from 0.4% in Japanese men (17) to 16.9% in women older than 60 years in the United States (18).

Of note, TSH cut-offs for defining SCH have also varied across studies. In the early Whickham study in the United Kingdom ($N = 2779$), 5.0% of individuals older than 18 years were classified as having SCH, defined as $TSH > 6$ mIU/l in the absence of symptoms of hypothyroidism (19). In 1981, Riniker et al. (20) reported a prevalence of SCH of 3.1% among 945 patients in a general medical department in Switzerland. In this study, SCH was defined for asymptomatic individuals as $TSH > 6$ mIU/l in combination with $FT4 > 51$ nmol/l (20). Among participants ≥ 18 years of age in a state-wide health fair in Colorado in 1995 ($N = 25,862$), the prevalence of SCH, defined as $TSH > 5.1$ mIU/l and thyroxine ≥ 57.9 nmol/l, was 9.0% (21). More recent

estimates have defined abnormal levels of TSH using lower cut-offs. In 2002, Demers and Spencer reported a TSH ULN of approximately 4.0–4.5 mIU/l; at that time, the authors noted that the ULN might be reduced to 2.5 mIU/l in the future because of the increased sensitivity of TSH immunometric assays and a reference range of 0.4–2.5 mIU/l that was observed in 95% of rigorously screened normal euthyroid volunteers (22). However, subsequent studies have not supported this suggestion, as they reported a higher ULN, as described below.

The National Health and Nutrition Examination Survey (NHANES III, 1988–1994) included measures of TSH, thyroxine, and TgAbs from a population of 17,353 individuals ≥ 12 years of age representative of the geographic and ethnic distribution in the United States (23). SCH was defined

according to the standard reference range (TSH > 4.5 mIU/l and thyroxine \geq 57.9 nmol/l) for the assay system that was used. Using this definition, the prevalence of SCH in the general population was 4.3%. A reference group ($N = 13,344$) was selected from this population; they were considered free from thyroid disease and other risk factors, including pregnancy, androgen or oestrogen use, biochemical hypothyroidism or hyperthyroidism, and the presence of thyroid antibodies. In the thyroid disease-free reference group, the 97.5th percentile for TSH concentration was 4.12 mIU/l; the authors therefore suggested that the ULN for TSH should be reduced from 4.5 to 4.12 mIU/l (23).

The Hanford Thyroid Disease study included 3440 individuals with a median age of 51 years (range, 45–57 years) from whom a subset of participants ($N = 766$; 480 men and 286 women) who had no current evidence or history of thyroid disease, were seronegative for thyroid autoantibodies, and had a normal thyroid ultrasound (24). In this population, it was estimated that 20% of participants had TSH levels > 2.5 mIU/l and 10.2% had TSH levels > 3.0 mIU/l. The best estimate of the 97.5th percentile was 4.1 mIU/l. The authors concluded that the ULN of the TSH reference range should be approximately 4.0 mIU/l, further supporting the results from NHANES III.

In a recent study, Asvold and colleagues reported that the prevalence of untreated SCH in Norway decreased over an 11-year period from 1995 to 1997 (HUNT 2 study) to 2006–2008 (HUNT 3 study) (25). In HUNT 2 and HUNT 3, SCH was defined as TSH > 4.5 mIU/l combined with normal levels of FT4. In women, the relative decrease in the prevalence of untreated SCH from HUNT 2 ($N = 23,274$; 3.0%) to HUNT 3 ($N = 26,822$; 1.1%) was 64%, with a concomitant relative increase (60%) in the prevalence of treated hypothyroidism. In men, the relative decrease in the prevalence of untreated SCH from HUNT 2 ($N = 10,643$; 2.1%) to HUNT 3 ($N = 22,358$; 1.0%) was 54%, with a 100% relative increase in the prevalence of treated hypothyroidism. The authors attributed the observed changes in the prevalence of treated and untreated hypothyroidism to increased screening of thyroid function and more liberal treatment of SCH.

Patient-specific characteristics affecting the estimated prevalence of SCH

Age

Although the prevalence of SCH seemingly increases with age (Table 3), there is a strong evidence that the ULN for TSH also increases with age, potentially

leading to overestimates of the prevalence of SCH in elderly people (26). In the Framingham study, the effect of age was greater in men than in women. TSH was mildly elevated (i.e. 5–10 mIU/l) in 2.5% of men 60–69 years of age compared with 7.9% of men 80–89 years of age; TSH was mildly elevated in 7.7% of women 60–69 years of age compared with 8.1% of women 80–89 years of age (27). Data from the reference population included in NHANES III demonstrated that 9.7% of patients \geq 80 years of age had TSH levels > 4.5 mIU/l (23,26). The TSH median and 97.5th percentile increased progressively with age. In the thyroid disease-free reference population, the 97.5th percentile for TSH concentration among individuals 20–29 years of age was 3.6 mIU/l, compared with 4.0 mIU/l for patients aged 50–59 years, 4.3 mIU/l for those aged 60–69 years, 5.9 mIU/l for patients 70–79 years, and 7.5 mIU/l for those 80 years or older (26). In fact, 70% of patients 80 years or older with TSH levels > 4.5 mIU/l were within the 97.5th percentile for their age-specific range. Further analysis revealed that the 97.5th percentile for TSH concentration increased by 0.031 mIU/l for every 1-year increase in age (28). Thus, the age of the individual has an impact on the TSH threshold that should be used to establish a diagnosis of SCH, which in turn impacts the reported prevalence of SCH. Especially among elderly people, using a single ULN for all age groups may lead to misclassifying individuals with a diagnosis of SCH and may result in overestimates for the prevalence of SCH. Furthermore, the ULN as defined for entry into a clinical trial will likely impact the results of the trial. A lower TSH threshold will result in more euthyroid individuals being labelled with SCH. This will bias the results of studies seeking to identify morbidities and potential improvement of morbidities with the introduction of hypothyroid therapy. TSH measurements from different age groups can be used to adjust the ULN based on 97.5th percentiles, as described by Boucai et al., who also included additional terms for sex and race (28).

Sex

Across studies, the prevalence of SCH (like overt hypothyroidism) is consistently higher in women than in men (Table 2) (17–21,23,25,27,29–38). In the Whickham study, the prevalence of SCH in women was 7.5%, nearly three times the prevalence in men (2.8%) (19). In the total population included in NHANES III, the percentage of patients with TSH > 4.5 mIU/l was significantly higher in females than males (5.8% vs. 3.4%) (23). Further analysis of the NHANES data revealed that sex was an independent predictor of median TSH levels and reference limits

Table 3 Reported thyroid-stimulating hormone reference ranges by age in reference populations free of thyroid disease and risk factors for thyroid disease

Age range, years	TSH Concentration, mIU/l										
	Surks and Hollowell, 2007* (26)					Bremner et al., 2012 (67)			Waring et al., 2012† (68)		
	Median	97.5th percentile	2.5th percentile	Median	97.5th percentile	Lower limit‡	Mean	Upper limit‡	2.5th percentile	Median	97.5th percentile
12–19§¶	1.35	4.07	0.41	1.30	3.78	0.51	1.34	3.54			
20–29	1.26	3.56	0.40	1.30	3.60						
30–39**	1.29	3.69	0.38	1.25	3.60	0.48	1.25	3.21			
40–49††	1.40	3.82	0.44	1.40	3.90	0.44	1.32	3.92			
50–59‡‡	1.50	4.03	0.49	1.50	4.20	0.42	1.31	4.09			
60–69§§	1.67	4.33	0.46	1.66	4.70	0.38	1.34	4.70			
70–79¶¶	1.76	5.90	0.47	1.74	5.60	0.52	1.66	5.28	0.71	1.56	2.67
80–84***	1.90	7.49	0.44	1.90	6.30				0.60	2.20	6.16
85–89									0.51	2.59	6.41
≥ 90									0.20	2.53	7.96

*2.5th percentile not reported. †Study included only an elderly population. ‡Mean \pm 2 SD of log-transformed serum TSH concentrations. §13–19 for Boucai et al. ¶< 30 for Bremner et al. **30–40 for Bremner et al. ††40–50 for Bremner et al. ‡‡50–60 for Bremner et al. §§60–70 for Bremner et al. ¶¶> 70 for Bremner et al.; 75–79 for Waring et al. *** \geq 80 for Surks and Hollowell and Boucai et al. TSH, thyroid-stimulating hormone.

(28). Men had significantly higher 2.5th and 50th percentiles for TSH concentrations than women, although 97.5th percentiles were not significantly different.

Pregnancy

During pregnancy, the hypothalamic-pituitary-thyroid axis adapts to meet the increased metabolic needs associated with gestation (39); thus, TSH and thyroxine levels differ in healthy pregnant women compared with healthy non-pregnant women (40). During the first trimester, there is a transient reduction in TSH levels and TSH reference ranges, which slowly increase over the second and third trimesters, although the reference interval remains reduced compared with healthy non-pregnant women (41–43). Measures of TSH in healthy pregnant women suggest that the ULN is approximately 2.5–3.0 mIU/l (40). Pregnancy-specific reference ranges for TSH concentration are as follows: first trimester, 0.1–2.5 mIU/l; second trimester, 0.2–3.0 mIU/l; and third trimester, 0.3–3.0 or 3.5 mIU/l (1,40). If TSH is elevated, serum FT4 should be estimated, with mindfulness of the limitations of common clinical FT4 assays in this setting, to distinguish between SCH and overt hypothyroidism (40). During pregnancy, SCH is defined as a normal FT4 level and a serum TSH < 10 mIU/l, with the following upper limits for TSH concentration: > 2.5 mIU/l in the

first trimester, > 3.0 mIU/l in the second trimester, and > 3.0 or 3.5 mIU/l in the third trimester (1,40). It should be noted that the recommended upper limits for TSH levels during the second and third trimester of pregnancy are similar to the 97.5th percentile of TSH found for individuals aged 20–39 years in a reference cohort free of thyroid disease and not at risk in NHANES III (26).

Race and ethnicity

Mean TSH levels measured in the total NHANES III population were higher in white subjects (1.53 mIU/l) and Mexican Americans (1.43 mIU/l) than in black subjects (1.17 mIU/l) (23). Similarly, the prevalence of SCH reported in the total population in NHANES III, where SCH was defined as TSH > 4.5 mIU/l, was higher in white subjects (4.8%) and Mexican Americans (3.9%) than in black subjects (1.6%). The effect of race and ethnicity on TSH levels was further analysed in the reference population ($N = 13,344$) of subjects that were considered free from thyroid disease, were without antithyroid antibodies, and who fell within the TSH range of 0.1–10 mIU/l (28). Black subjects had lower 2.5th, 50th and 97.5th percentiles for TSH concentrations (0.36, 1.25 and 3.70 mIU/l) than Mexican Americans (0.46, 1.40 and 4.37 mIU/l) or white subjects (0.049, 1.50 and 4.60 mIU/l). From these data, along with data on age and sex, the group developed a method to

predict TSH reference limits for specific subpopulations, thus enabling clinicians to classify patients within TSH reference ranges specific for their demographic characteristics.

Iatrogenic factors

Iatrogenic factors that may lead to hypothyroidism are often readily ascertained from the patient history. These include radioiodine or surgical treatment for hyperthyroidism (e.g. subtotal thyroidectomy), partial thyroidectomy for benign nodular thyroid disease, and total thyroidectomy for the treatment of thyroid cancer (1,5). Hypothyroidism may also result from incidental thyroid exposure to external beam radiation for head and neck malignancies not related to the thyroid, and from pharmacologic treatment with amiodarone or lithium, immunologics like interferon and interleukins, and tyrosine kinase inhibitors, which can induce thyroiditis. These factors will certainly increase the risk of SCH in individual patients and thus the prevalence of SCH in the general population.

Obesity

Multiple studies have reported the positive correlation between increased TSH level and body mass index (BMI) (44–46). In data from euthyroid subjects participating in NHANES 2007–2008 ($n = 3114$), a 3.8–4.0% increase in TSH was observed for each quartile increase in BMI for men and women, respectively (47). It has also been shown that weight loss (by either gastric bypass surgery or caloric restriction) is accompanied by a significant reduction in TSH values and resolution of SCH in many obese patients (48–50). It has been suggested that leptin produced by adipose tissue may play a crucial role in thyroid hormone regulation by stimulating the synthesis of TRH, ultimately resulting in the increased level of TSH (51). However, Rotondi reported on a study of 28 morbidly obese patients with SCH (BMI ≥ 40 kg/m²) and found that this group had significantly lower rates of elevated anti-thyroid antibodies when compared with 56 normal-weight patients with SCH (32.1% vs. 66.1%, respectively; $p < 0.005$), which suggests that the increased TSH levels associated with morbid obesity may not indicate true thyroid dysfunction (52). More recently, the same researchers provided further evidence that the TSH elevations associated with obesity are not diagnostic of hypothyroidism, emphasising the need for a multifaceted approach to diagnosis, when they found lower lipid levels in morbidly obese vs. non-obese individuals with similar TSH elevations (53). A review of this topic noted that the moderate TSH elevations observed with obesity is generally

associated with triiodothyronine levels higher than expected, resulting in an increase in resting energy expenditure consistent with an adaptive process (53,54).

The value of TSH in predicting progression to overt hypothyroidism

Close follow-up of individuals with TSH values within the normal range has demonstrated that the TSH level is a predictor of future overt hypothyroidism (Table 4). In fact, one of the first studies to report progression rates to overt hypothyroidism concerned a 20-year follow-up on the comprehensive survey of thyroid health in Wickham, England (55). In this landmark study, TSH values > 2.0 mIU/l were associated with an increased risk of developing subsequent overt hypothyroidism. Huber et al. reported a 3.3% annual incidence of progression to overt hypothyroidism among women with confirmed SCH (identified by 2 elevated TSH levels 1 month apart) diagnosed with TSH values > 6 – 12 mIU/l and an 11.4% annual incidence of progression among women with TSH values > 12 mIU/l (56).

More recently, Asvold et al. studied 15,106 men and women without previous thyroid disease and a median age of 51 years; among women, those with a baseline TSH between 0.5 and 1.4 mIU/l had the lowest rate (1.1%) of hypothyroidism when reassessed after 11 years of follow-up (57). Among women with TSH levels of 2.5–2.9 mIU/l, 8.2% progressed to hypothyroidism, and those with TSH values in the upper normal range of 4.0–4.5 mIU/l had the highest frequency (31.5%) of hypothyroidism at the time of reassessment. As TSH values increased through the normal range, women were significantly more likely to have developed overt hypothyroidism at follow-up. Men displayed a similar pattern but generally lower frequencies of hypothyroidism at follow-up. A baseline TSH concentration of 0.5–1.4 mIU/l predicted only a 0.8% frequency of later hypothyroidism, while the upper normal range of 4.0–4.5 mIU/l predicted hypothyroidism in 14.7% of men after 11 years of observation (57). This association appeared to be independent of age, smoking or body mass index at baseline.

In a report by Diez and Iglesias (58), patients ≥ 55 years of age were followed up for 6–72 months (mean follow-up, 31.7 months) after initial diagnosis and confirmation of SCH by duplicate TSH measurements. Overall, 26.2% of patients presenting with SCH eventually developed overt hypothyroidism and were treated with levothyroxine (58). The initial TSH concentration (> 5.0 mIU/l) at presentation had a significant impact on the progression to an indication for thyroid hormone replacement. Among

Table 4 Rate of progression from subclinical to overt hypothyroidism

Study	<i>n</i>	Age, mean, years	TSH threshold for SCH at baseline, mIU/l	TSH at baseline, mean, mIU/l	TPOAb+, %	SCH at baseline	Progression	Reversion
Huber et al. 2002 (56)	82	50.7 (SE, 1.4)	> 4.0–20 with normal FT4, TT4, and TT3 levels; 2 measurements 1 month apart	12.0 (SE, 1.1)	58.2	82 (100%)	23 of 82 (28%) after mean of 9.2 years	3 of 82 (4%) after mean of 9.2 years
Diez et al. 2004 (58)	107	62.2 (SD, 7.6; range, 55–83)	> 5.0–20 with FT4 of 0.75–2.0 ng/dl; 2 measurements 1–3 months apart	Women: 8.40 (IQR, 6.69–12.53) Men: 8.15 (IQR, 6.55–11.36)	75.7	107 (100%)	28 of 107 (26.2%) after mean of 2.6 years	40 of 107 (37.4%) after mean of 2.6 years
Gussekloo et al. 2004 (59)	558	85 (exact age, per study design)	> 4.8 with FT4 of 1.01–1.79 ng/dl; single measurements	NR	NR	30 (5%)	2 of 30 (6.6%) at age 88 years	11 of 30 (36.7%) at age 88 years
Somwaru et al. 2012 (60)	3996 (3594 analysed)	75.6 (SD, 5.7)*	4.5–19.9 with FT4 of 0.7–1.7 ng/dl; single measurements	6.7 (SD, 2.6)*	35*	459 (12.8%)	8 (2%) of 369 at year 2	128 (35%) of 369 at year 2

*In patients diagnosed with SCH at baseline. FT4, free thyroxine; IQR, interquartile range; NR, not reported; SCH, subclinical hypothyroidism; TT3, total triiodothyronine; TT4, total thyroxine; TPOAb, antimicrosomal/antithyropoxidase antibody; TSH, thyroid-stimulating hormone.

patients with TSH values of 5.0–9.9 mIU/l, 5.6% progressed to overt hypothyroidism, while a much higher percentage of patients (85.7%) with TSH values of 15.0–19.9 mIU/l progressed. When progression was measured in patient-years, only 1.76 cases progressed to overt hypothyroidism per 100 patient-years of follow-up for patients with initial TSH values of 5.0–9.9 mIU/l, whereas 19.67 and 73.47 cases per 100 patient-years progressed in those with baseline TSH values of 10.0–14.9 mIU/l and 15.0–19.9 mIU/l, respectively. These rates of progression may be higher than those in studies requiring only a single TSH measurement for inclusion.

Several studies have investigated the progression of SCH to overt hypothyroidism in elderly patients. Gussekloo observed no progression among elderly patients classified with SCH on the basis of a single TSH measurement > 4.8 mIU/l at 85 years of age among the 21 patients available for reassessment at 88 years of age (59). More recently, an investigation of SCH (TSH values between 4.5 mIU/l and 19.9 mIU/l at a single time point) among elderly people (≥ 65 years of age at enrolment; mean age at baseline, 75.6 years) noted progression to overt hypothyroidism or the initiation of levothyroxine after 2 years in 5.1% of patients with baseline TSH values ranging from 4.5 to 6.9 mIU/l and in 31.7% of patients with baseline TSH ≥ 10 mIU/l (60).

The impact of thyroid antibodies on progression to overt hypothyroidism

Thyroid antibodies

Hypothyroidism is clearly associated with antithyroid antibodies. In the British Whickham study, mean TSH levels in serum were significantly higher in individuals with microsomal thyroid antibodies (19). Microsomal thyroid antibodies were detected in 60% of patients with serum TSH > 6 mIU/l and in 80% of patients with serum TSH > 10 mIU/l. In the total population included in NHANES III, a TSH level > 4.5 mIU/l was associated with positive test results for TPOAb and TgAb, and the presence of TPOAb was strongly associated with clinical hypothyroidism (23). Among patients classified with SCH in the Nijmegen study in The Netherlands, 61.4% tested positive for TPOAbs (37).

Additional factors influence the degree, persistence, and progression of thyroid failure in patients diagnosed with SCH. More than 20 years ago, the presence of antithyroid antibodies, particularly TPOAb, was demonstrated to enhance the likelihood of progression to overt hypothyroidism, and thus, enhance the likelihood of hypothyroid morbidity. In a study of 1210 patients ≥ 60 years of age, 46% of those with TSH values > 5–10 mIU/l were positive

for antithyroid antibodies (either TgAb or TPOAb) and 81% of those with TSH > 10 mIU/l tested positive for antithyroid antibodies (34). The authors speculated that elevations of TSH were due to underlying autoimmune thyroid disease in the majority of patients thought to have SCH. In this study, 17.8% of patients progressed to overt hypothyroidism after 1 year of follow-up; the highest incidence of progression (35.7%) was among a subgroup of patients with TSH > 10 mIU/l in combination with a positive test for antithyroid antibodies (34).

The 20-year follow-up of the Whickham survey demonstrated that the risk of developing overt hypothyroidism in women was approximately 2.6% per year when an elevated TSH (TSH > 6 mIU/l) was present (55). Furthermore, the odds ratio [OR; 95% confidence interval (CI)] of developing overt hypothyroidism was 8 (3–20) when considering TSH > 6 mIU/l alone and 8 (5–15) when considering a positive test for antithyroid antibodies alone. When elevations in TSH and antithyroid antibodies were both present, the OR (95% CI) of developing overt hypothyroidism was 38 (22–65) during the 20-year follow-up interval. The results of this follow-up study allowed the authors to estimate that the 20-year risk of developing overt hypothyroidism for a 50-year-old woman with a TSH concentration of 6.0 mIU/l and a positive antithyroid antibody test was 57%.

Results from additional studies have supported the role of antithyroid antibodies in the progression to overt hypothyroidism. Huber et al. documented that development of overt hypothyroidism during an average 9.2-year observation period was more than doubled when antithyroid antibodies were present (58.5%) compared with not present (23.2%) (56). Likewise, Diez and Iglesias noted that the presence of TPOAb was associated with progression to overt hypothyroidism in a univariate analysis including 107 patients; however, this relationship was not observed in a multivariate analysis (58). More recently, Asvold et al. reported that among participants ($N = 211$) with baseline TSH levels ranging from 4.0 to 4.5 mIU/l, the risk of developing overt hypothyroidism after 11 years was substantially higher among individuals who tested positive for TPOAbs compared with those who had a negative test result for TPOAbs (women, 43.3% vs. 20.3%; men, 21.5% vs. 12.9%) (57).

Persistence and reversion of SCH

As would be expected, the observation of an elevated TSH level triggers concern for thyroid dysfunction, since even mild elevations of TSH may signal a risk for progression to overt disease (Table 4). However, repeat TSH testing does not always confirm a persis-

tent elevation of TSH; instead, normalisation of thyroid function (i.e. 'reversion') may be noted. After 1 year of follow-up, persistent SCH was noted in 76.7% of patients ≥ 60 years of age [the majority (64.9%) between 60 and 69 years old] who were originally included based on a single TSH level > 5.0 mIU/l; 60% of the patients had antithyroid antibodies (34). At least two studies have taken an approach to include a confirmatory TSH evaluation at baseline, thus avoiding misdiagnosis because of laboratory error or transitory changes in TSH often attributed to non-thyroidal illness. Among women with a thusly confirmed SCH at baseline, persistent SCH was observed in 68% of patients ($N = 82$; mean age at entry, 50.7 years) over 9.2 years of follow-up (56). Among patients ≥ 55 years of age with confirmed TSH levels > 5.0 mIU/l, 36.4% demonstrated persistent SCH over a mean follow-up of 31.7 months (58). In a population of much older patients (85 years of age at study entry), Gussekloo observed that SCH diagnosed as a result of a single elevated TSH (> 4.8 mIU/l) was persistent in only 8 of 21 patients (38.1%) whose thyroid function was reassessed 3 years later (59).

Of concern when assessing a patient for SCH is the frequency with which a mild, transient abnormality in TSH represents a disturbance of the pituitary-thyroid axis that may not be of sufficient duration to warrant concern for subsequent morbidities. Parle et al. followed 73 patients ≥ 60 years of age who had been classified with SCH (single TSH value > 5.0 mIU/l with normal thyroxine) in a single family practice (34). After 1 year of observation, TSH levels returned to normal in only 5.5% of these individuals; 76.7% of the patients had persistent SCH and 17.8% progressed to overt hypothyroidism. Among patients ≥ 55 years of age diagnosed with SCH based on 2 determinations of TSH, only 37.4% of the population was noted to be euthyroid at follow-up (mean observation period, 31.7 months) (58). Over a 9.2-year observation period, Huber et al. reported that TSH levels normalised in 4% of women (mean age, 50.7 years) with single baseline TSH values confirmed as 4.0–6.0 mIU/l (56). A review of TSH levels in a large primary care database revealed that 3.0% of 422,242 patients had elevated TSH levels (> 5.5 to ≤ 10 mIU/l) and 0.7% had highly elevated TSH (> 10 mIU/l) (61). Among 346,549 patients who were not treated with thyroid-specific medications, 62.1% and 27.7% of patients with elevated and highly elevated baseline TSH levels, respectively, reverted to euthyroidism after 5 years (61).

In a frequently quoted landmark study, Gussekloo observed normalisation of TSH (between 0.3 and 4.8 mIU/l) values among elderly patients with SCH

(85 years of age at study entry) after 3 years (59). When re-evaluated at age 88, 11 of the 21 remaining patients (53.4%) were considered euthyroid based on normalisation of TSH levels (59). The natural course of SCH (TSH 4.5–19.9 mIU/l with normal thyroxine) was evaluated in another study enrolling elderly patients 65 years and older (60). Of the 369 patients with available data after 2 years, 35% reverted to euthyroidism. The frequency of normalisation was associated with the degree of baseline TSH level elevations, as reversion to a euthyroid state was more common among patients with a baseline TSH 4.5–6.9 mIU/l (46%) compared with those with a baseline TSH \geq 7 mIU/l (8.8%). Patients that tested negative for TPOAbs were also significantly more likely to revert to euthyroidism compared with those that tested positive for TPOAbs (48% vs. 15%). Kim et al. (13) confirmed and expanded upon the observations of Konno et al. (17) on the impact of seasonal changes on TSH level and demonstrated that there was a direct influence upon the frequency of SCH diagnosis and reversion. During a median of 29 months of follow-up, 57.9% of those who had been designated as having SCH were reclassified as euthyroid. A smaller proportion (4.3%) of those initially categorised as euthyroid were later diagnosed with SCH during a median of 36 months of follow-up. Individuals originally thought to have SCH were 40% more likely to appear to be euthyroid when reassessed in the summer or fall compared with individuals reassessed in the winter or spring.

Together, these findings indicate that greater elevations of TSH may predict persistent SCH and, thus, progression of thyroid failure. The presence of anti-thyroid antibodies also significantly increases the likelihood of persistent SCH and may predict progression to thyroid failure. On the other hand, results in individuals without these additional features, especially elderly people, should be considered with caution when mild elevations of TSH are observed, as these findings frequently do not represent clinically significant disease that requires intervention.

Clinical impact: identifying people with SCH

The American Thyroid Association and the American Association of Clinical Endocrinologists (ATA/AACE) guidelines recommend using a TSH concentration of 4.12 mIU/l or the age-adjusted definition of SCH to identify which individuals should be classified with SCH (1). Although in many cases a single TSH cut-off value is still used when diagnosing SCH, an expert panel selected by the ATA/AACE and the Endocrine Society advised re-evaluation of thyroid function within 2 weeks to

3 months if the TSH level is high but FT4 has not been measured; the panel also recommended repeat testing every 6–12 months to monitor patients with an initial TSH level between 4.5 and 10 mIU/l before making a decision to initiate treatment (62). Adoption of confirmatory testing may aid in properly identifying those patients with persistent SCH and who might be more likely to benefit from treatment. The evidence for the use of ultrasonography of the thyroid to identify and predict the progression of SCH remains mixed. Although some studies have suggested that diffuse heterogeneous echogenicity findings by ultrasound consistent with the presence of Hashimoto's thyroiditis may be predictive of the progression of SCH and the eventual need for levothyroxine therapy (63,64), other research indicated that ultrasound findings did not predict persistence of SCH as opposed to a spontaneous return to the euthyroid state (65). In accordance with the ATA/AACE guideline recommendations, patients with a confirmed TSH cut-off level of $>$ 10 mIU/l should be considered for treatment with levothyroxine, as these patients have an increased risk of heart failure and cardiovascular mortality. However, some patients with lower TSH levels may also be considered suitable for levothyroxine therapy. For example, patients with a TSH level between the age-adjusted ULN and 10 mIU/l may also be considered for treatment based on individual factors, particularly testing positive for thyroid antibodies, having signs of atherosclerotic cardiovascular disease or heart failure, or having risk factors associated with cardiovascular disease (1).

Few studies have investigated outcomes specifically for younger patients receiving levothyroxine for the treatment of SCH. Among younger patients with SCH ($N = 3093$; 40–70 years of age) followed up for a median of 7.6 years in one study, those treated with levothyroxine experienced fewer ischemic heart disease events (68/1634; 4.2%) compared with untreated patients (97/1459; 6.6%) (66). The hazard ratio (HR) remained significant after multivariate adjustment (HR, 0.61; 95% CI, 0.39–0.95). In patients older than 70 years, the incidence of ischemic heart disease events was similar, after multivariate adjustment, in those who did or did not receive levothyroxine treatment for SCH (HR, 0.99; 95% CI, 0.59–1.33). Thus, the beneficial effect of levothyroxine treatment in younger patients with SCH has the potential to be masked by the inclusion of elderly patients labelled as having SCH, who may actually be euthyroid or who may have comorbidities that could be exacerbated by levothyroxine therapy. The adjusted definition of SCH can

be used to identify those people who should not be treated, as the risks associated with treatment outweigh any potential benefits. For example, a patient older than 85 years with a TSH level of 6 mIU/l, who is negative for thyroid antibodies, demonstrates good function, and is without dyslipidemia or a history of cardiovascular disease, may not represent a true state of hypothyroidism and may not benefit from treatment with levothyroxine. The patient's TSH level should likely be retested within 6 months, and then monitored at least annually, or more frequently if TSH levels increase but remain below 10 mIU/l. Conversely, a 40-year-old patient with the same TSH level of 6 mIU/l may have clinically significant SCH and may benefit from levothyroxine treatment as suggested by the results reported by Razvi et al. (66).

Conclusions

Given the variable definition of SCH based on inconsistent TSH ranges, it is currently difficult to ascertain the true prevalence of SCH; however, age-adjusted definitions should be used when assessing prevalence, as growing evidence suggests that individuals in some age groups may benefit from treatment. Regardless of results in the larger population, management of SCH in the individual patient depends on clinical judgment. Additional factors that may impact the decision to treat specific individuals include the absence or presence of antithyroid antibodies, cardiovascular risk factors, and other co-morbidities. A mildly elevated TSH level does not necessarily merit treatment, especially if the patient lacks other risk factors for developing overt hypothyroidism; a strategy of active surveillance may be advisable for these individuals.

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Author contributions

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