Age- and Gender-Specific TSH Reference Intervals in People With No Obvious Thyroid Disease in Tayside, Scotland: The Thyroid Epidemiology, Audit, and Research Study (TEARS)

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Objective: The aim of the study was to examine the association of tested TSH with age, gender, and diabetes in a large population-based cohort without evidence of thyroid disease.

Design: Record-linkage technology was used retrospectively to identify people without evidence of thyroid disease in the general population of Tayside, Scotland, from July 1, 2003, to December 31, 2009.

Cohort: All Tayside residents who had thyroid function tests performed were identified. Using a unique patient identifier, data linkage enabled a cohort without thyroid disease to be identified by excluding anyone with thyroid or antithyroid prescription, thyroid-related admission or surgery, treatment with radioactive iodine and/or positive thyroid antibodies. Cases below 18 years of age were also excluded.

Outcome Measures: We measured TSH distribution among different age groups and by gender.

Results: We identified the latest TSH measurements in 153 127 people from the reference population after applying the exclusion criteria. There was a significant increase in median TSH (1.58 mU/L at 31–40 y to 1.86 mU/L at >90 y; $P < .001$) and 97.5th centile TSH (3.98 to 5.94 mU/L, respectively) with increasing age. The 2.5th centile decreased with age (0.51 to 0.31 mU/L). Patients with diabetes had marginally higher TSH concentration (1.80 vs 1.70 mU/L; $P < .001$).

Conclusion: The use of these age-specific reference intervals for TSH, especially in those over 70 years old, would result in the reclassification of many TSH results from "abnormal" to "normal" (within the 95th centile reference interval) and avoid unnecessary treatment. **(*J Clin Endocrinol Metab* 98: 1147–1153, 2013)**

TSH is an important marker for the diagnosis of thyroid dysfunction. Recent studies have shown that the TSH distribution progressively shifts toward a higher concentration with age, and it is debatable whether this is due to a real change with age or an increasing proportion of unrecognized thyroid disease in the elderly (1–3). In 2002, Hollowell et al (1) investigated TSH distribution in a representative sample (n = 16 533) of the US population from the National Health and Nutrition Examination Survey III (NHANES III) and reported that TSH levels were greater in females and increased with age even in the reference population without thyroid antibodies. Surks and Hollowell (2) reported in 2007 that the increasing median and 97.5th centile for TSH that occur with aging represent

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Abbreviation: TPO, thyroid peroxidase.

changes in age-specific population distributions of TSH and are not due to an increase in the prevalence of hypothyroidism. Using the principles of NHANES analyses in 2009, Boucai and Surks (3) investigated TSH distribution and reference ranges in a clinically defined population free of thyroid disease attending hospital outpatient clinics in the United States. Based on these data, they recommended that age- and race-specific TSH distributions and reference limits should be employed in order to provide clinicians with appropriate limits for specific populations and guidance for further evaluation of thyroid dysfunction (4).

By contrast, the 1977 UK Whickham study comprising 2779 people reported no significant association between TSH and increasing age in men or in women with negative thyroid antibody tests (5), although this might be explained partly by the use of older, less precise TSH assays. However, a more recent study in Western Australia using 148 938 samples from patients without evidence of thyroid disease reported that although increasing age is associated with an increase in TSH levels, the use of age-specific reference intervals for TSH has only minor effects on the classification of thyroid status (6).

To address these uncertainties, we investigated the association between population-tested TSH and age and TSH and gender in a large population-based cohort without evidence of thyroid disease. Diabetes is more common in patients with thyroid disease (7). Therefore, we also investigated the distribution of TSH in diabetes patients.

Subjects and Methods

The study was carried out using databases stored at the Health Informatics Centre (HIC) of the University of Dundee. All the data sets are held by HIC under the Data Protection Act for the purposes of research and audit . Data are anonymized after linkage using Standard Operating Procedures (http://www.dundee.ac.uk/hic/work/sop/). Data linkage was carried out using the Community Health Index (CHI) number. All Tayside residents registered with a general practice in Scotland are assigned to a unique 10-digit health index, known as CHI number. CHI is used as a patient identifier that facilitates the linkage of all health care-related records.

The study was approved by the Tayside Research Ethics Committee, and permission for the case record validation audit was obtained from Tayside Caldicott Guardians.

Databases

Seven principal databases were used in this study. These databases cover primary, secondary, and private health care.

Tayside population demographic database

This served as a master index to provide information on gender, date of birth, date of death, and dates registered with general practitioner. It was used to define the study population from which cases were identified.

Biochemistry database

This contained all thyroid function tests during our study period: TSH, free and total T_4, and total T_3. Each entry comprised the patient's anonymized CHI, the test performed, date, and the results. In this study, the results of TSH concentration (milliunits per liter) were used. All biochemistry tests were carried out in a centralized laboratory for the region. Roche Modular E170 (Roche Diagnostics, Lewes, East Sussex, United Kingdom) was used to analyze TSH concentration in the blood samples. The record of diabetes was extracted from the Regional Diabetes DARTS Register (8) which had 96% sensitivity for diagnosing diabetes. Diagnoses of diabetes are based on the World Health Organization criteria.

Scottish morbidity record 1

This consisted of hospital admission data routinely validated and collated by the Information and Statistics Division of the National Health Service in Scotland. The International Classification of Diseases (ICD) 9th and 10th revision codes were used for diagnostic classification for all hospital inpatient episodes (9). The Office of Population, Censuses, and Surveys Classification of Surgical Operations and Procedures (OPCS) was used to classify operations, procedures, and interventions carried out on a patient during an episode of health care in the hospital.

Scottish morbidity record 2

This was generated for patients receiving care in the obstetrics specialties and contained information relating to pregnancy such as date of admission, date of delivery, number of births, and type of abortions.

Tayside prescription data

This dataset contained all prescriptions dispensed from all community pharmacies in Tayside. Each entry comprised the patient's anonymized CHI, prescription date, drug name, formulation, dosage, frequency, and duration.

Radioactive iodine database

This data set contains information on dose and date of administration for all patients who have received radioactive iodine treatment in Tayside, dating back to 1958.

Immunology database

This contained results of TSH receptor antibody and thyroid peroxidase (TPO) antibody measurement during the study period. Both of the assays are run on commercial ELISA kits. The anti-TSH receptor antibodies are measured on the RSR limited, ELISA RSR TRAb 3rd generation ELISA and the anti-TPO antibodies measured on the Orgentec, IgG anti-TPO ELISA run on a DS2 processor. Each entry in the database comprised the patient's anonymized CHI, test performed, date, and results.

TSH measurements

All thyroid function tests performed from July 1, 2003, to December 31, 2009, were identified. Subjects were excluded based on the criteria below in order to derive a reference cohort without thyroid disorders:

Table 1. TSH Distribution Among Different Age Groups

Age, y	Overall, n (%)	TSH Category, n (%)		
		Group 1	Group 2	Group 3
18–30	20740 (13.5)	233 (1.1)	19886 (95.9)	621 (3.0)
31–40	20201 (13.2)	229 (1.1)	19 482 (96.4)	490 (2.4)
41–50	26778 (17.5)	232 (0.9)	25 755 (96.2)	791 (3.0)
51–60	26126 (17.1)	318 (1.2)	24 813 (95.0)	995 (3.8)
61–70	23851 (15.6)	397 (1.7)	22 384 (93.8)	1 070 (4.5)
71–80	20934 (13.7)	506 (2.4)	19 146 (91.5)	1 282 (6.1)
81–90	12233 (8.0)	351 (2.9)	10 894 (89.1)	988 (8.1)
>90	2264 (1.5)	80 (3.5)	1952 (86.2)	232 (10.2)

Group 1, TSH < 0.4 mU/L; group 2, TSH = 0.4–4.0 mU/L; group 3, TSH > 4.0 mU/L.

1. Any subject younger than 18 yr old at baseline.
2. Any subject who had been taking T_4, carbimazole, propylthiouracil, amiodarone, or liothyronine at any time.
3. Any subject who had ever been treated with radioactive iodine.
4. Any subject who had ever tested positive for thyroid antibodies.
5. Any subject who had ever undergone thyroid surgery.
6. Any subject who had ever been diagnosed with thyroid cancer or pituitary disorder.

In addition, for the main study, TSH measurements greater than 20 mU/L were excluded on the grounds of indicating a high likelihood of thyroid disorder. A substudy was performed including these TSH measurements. Finally, TSH measurements that were taken during pregnancy and while hospitalized were also excluded because TSH values are known to be affected during an episode of severe acute illness.

Statistical analysis

All statistical analyses were performed using SPSS version 18.0 (SPSS Inc, Chicago, Illinois). The TSH measurements were grouped by 10-year age band, with all those aged older than 90 years grouped into a single band. The means, medians, and percentiles were calculated for each age group and gender. Two-tailed Mann-Whitney test and Kruskal-Wallis test were used to compare the nonparametric TSH distributions in different subpopulations because these were not normally distributed.

The frequency distribution curves of TSH concentration were plotted using log-transformed values of TSH. Surks and Hollowell (2) reported that an increase in median TSH and 97.5th centile due to an increased prevalence of hypothyroidism with aging should result in a distribution curve with lower peak frequency, which would occur at an unchanged TSH concentration and increased skew toward higher concentration. However, if there is a shift in the range for the older population, it should result in the entire distribution curve, including the peak frequency, to higher TSH concentration (2).

Results

TSH distribution among different age groups

A total of 153127 TSH measurements were identified in the reference population between July 2003 and 2009 after applying the exclusion criteria, comprising 62368 (40.7%) males and 90759 (59.3%) females. TSH concentrations were categorized into three groups: less than 0.4 mU/L (group 1), 0.4–4.0 mU/L (group 2), and greater than 4.0 mU/L (group 3) (Table 1). The percentages of TSH measurements in groups 1 and 3 increased progressively with age. For example, in group 3, the percentage of measurements increased with age from 2.4% in the 31- to 40-year-old group to 10.2% in the >90-year-old group (Table 1). The percentage of TSH measurements in group 2 decreased progressively with age from 96.4% in the 31- to 40-year-old group to 86.2% in the >90-year-old group (Table 1). Overall, there was a significant increase in median TSH with increasing age ($P < .001$). The 2.5th centile of TSH decreased with age, and the 97.5th centile of TSH increased with age, especially above the age of 70 years (Table 2). When people with a TSH greater than 20 mU/L were included, the overall results were virtually identical (data not shown).

Influence of antithyroid antibody on TSH concentration

Of 153995 people (including those who had positive thyroid antibodies), 7471 (4.9%) had their thyroid antibodies checked. Of these, 868 (11.6%) were tested positive for TPO and/or TSH receptor antibody. Because a substantial number of people in the cohort did not have thyroid antibody checked, the influence of antithyroid antibodies on TSH concentration was determined.

Table 2. Median, 2.5th, and 97.5th Centiles of TSH Among Different Age Groups

Age, y	2.5th Centile	Median	97.5th Centile
18–30	0.52	1.67	4.15
31–40	0.51	1.58	3.98
41–50	0.54	1.65	4.15
51–60	0.51	1.72	4.36
61–70	0.48	1.77	4.59
71–80	0.40	1.82	4.96
81–90	0.36	1.81	5.49
>90	0.31	1.86	5.94

Table 3. Distribution of Antibodies Within Specific Age Groups by TSH Concentration

Antibodies	Age, y	Overall, n (%)	TSH Category, n (%)		
			Group 1	Group 2	Group 3
Positive	Total	443	19 (4.3)	308 (69.5)	116 (26.2)
	30–50	291 (65.7)	9 (3.1)	222 (76.3)	60 (20.6)
	>70	152 (34.3)	10 (6.6)	86 (56.6)	56 (36.8)
Negative	Total	3523	196 (5.6)	2768 (78.6)	559 (15.9)
	30–50	2087 (59.2)	57 (2.7)	1832 (87.8)	198 (9.5)
	>70	1436 (40.8)	139 (9.7)	936 (65.2)	361 (25.1)

Group 1, TSH < 0.4 mU/L; group 2, TSH = 0.4–4.0 mU/L; group 3, TSH > 4.0 mU/L.

Overall, median TSH was 2.78 mU/L in people who were tested positive for thyroid antibody; 2.5th and 97.5th centiles were 0.20 and 8.68 mU/L, respectively. For people with negative thyroid antibodies, median TSH was 2.00 mU/L, and 2.5th and 97.5th centiles were 0.21 and 6.14, respectively. Therefore, those who had positive thyroid antibodies had a 39% increase in TSH concentration. Of 153 127 people, thyroid antibody measurements were not available in 145 656 people (95.1%). Therefore, based on the percentage of people who had positive antibody (11.6%), we estimated that 16 896 people who did not have thyroid antibodies checked might have positive thyroid antibodies.

The distribution of thyroid antibodies was examined among 2 age groups (30- to 50-year-old and above 70 years old) (Table 3). In people between 30 and 50 years of age with positive thyroid antibodies, 76.3% were in group 2 (0.4–4.0 mU/L) and 20.6% were in group 3 (>4.0 mU/L). In the above 70 years of age group, 56.6% of those with antibodies were seen in group 2 and 36.8% were seen in group 3. Of patients who did not have thyroid antibodies in the age group between 30 and 50 years old, 87.8% were in group 2 and 9.5% were in group 3. In people above 70 years of age, 65.2% were in group 2 (0.4–4.0 mU/L) and 25.1% were in group 3 (>4.0 mU/L). TSH distribution shifted toward higher concentration with increasing age, regardless of the presence or absence of thyroid antibodies.

The shift in TSH range

The frequency distribution curves for TSH in 2 age groups (30–50 and above 70 y old) were analyzed. Figure 1 illustrates the TSH distribution curves for the 2 age groups (30–50 and above 70 y old) in the cohort. In the older population, the peak relative frequency was lower but occurred at a higher TSH concentration compared to the younger population.

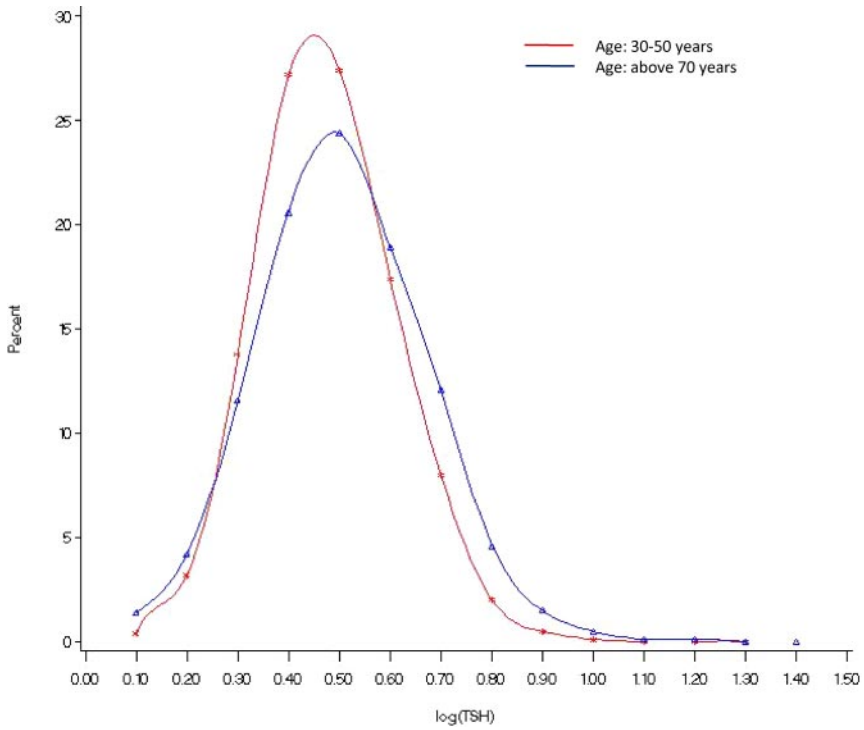

Figure 1. TSH distribution by age groups.

TSH distribution in males and females

We investigated the association between gender and TSH concentration. There was a significant difference in median TSH between males and females (median = 1.72 vs 1.70 mU/L; $P < .001$). The TSH distribution among different age groups in males and females is shown in Table 4. The percentages of TSH measurement in groups 1 and 3 increased progressively with age in both males and females. The percentage of TSH measurements in group 2 decreased with age in both males and females.

TSH distribution in people with diabetes

This study also showed that there is a significant difference in median TSH between patients with diabetes and those without diabetes (me-

Table 4. TSH Distribution Among Different Age Groups in Males and Females

Age, y	n (%)	TSH Category, n (%)		
		Group 1	Group 2	Group 3
Males				
18–30	6097 (9.8)	65 (1.1)	5803 (95.2)	229 (3.8)
31–40	6807 (10.9)	78 (1.1)	6551 (96.2)	178 (2.6)
41–50	10288 (16.5)	80 (.8)	9893 (96.2)	315 (3.1)
51–60	12252 (19.6)	114 (.9)	11699 (95.5)	439 (3.6)
61–70	11720 (18.8)	172 (1.5)	11073 (94.5)	475 (4.1)
71–80	9842 (15.8)	159 (1.6)	9104 (92.5)	579 (5.9)
81–90	4741 (7.6)	86 (1.8)	4267 (90.0)	388 (8.2)
>90	621 (1.0)	13 (2.1)	538 (86.6)	70 (11.3)
Females				
18–30	14643 (16.1)	168 (1.1)	14083 (96.2)	392 (2.7)
31–40	13394 (14.8)	151 (1.1)	12931 (96.5)	312 (2.3)
41–50	16490 (18.2)	152 (.9)	15862 (96.2)	476 (2.9)
51–60	13874 (15.3)	204 (1.5)	13114 (94.5)	556 (4.0)
61–70	12131 (13.4)	225 (1.9)	11311 (93.2)	595 (4.9)
71–80	11092 (12.2)	347 (3.1)	10042 (90.5)	703 (6.3)
81–90	7492 (8.3)	265 (3.5)	6627 (88.5)	600 (8.0)
>90	1643 (1.8)	67 (4.1)	1414 (86.1)	162 (9.9)

Group 1, TSH < 0.4 mU/L; group 2, TSH = 0.4–4.0 mU/L; group 3, TSH > 4.0 mU/L.

dian = 1.80 vs 1.70 mU/L; $P < .001$), after adjusting for age and gender (Table 5).

Discussion

This study was carried out in a population-based cohort without obvious evidence of thyroid disease and, with 153127 people, is the largest assessment of TSH concentration in the general population that we are aware of. Our analysis shows that the median and range of TSH increases with age. The 2.5th centile of TSH decreased with age and the 97.5th centile increased with age, and this was particularly notable above the age of 70 years. The 97.5th centile increased by 1.96 mU/L across the age range. The analysis on TSH distribution curves for populations of 2 selected age groups showed that their peak frequencies were shifted toward higher TSH concentration with age. Therefore, our findings suggest that the increased median TSH and the upper limit of the reference range with age, at least to some extent, represent the change in age-specific distribution of TSH, as found in previous studies (2). Our findings demonstrated that males and patients with diabetes had higher TSH concentration, but these are unlikely to be clinically relevant.

The findings on the association between age and TSH in this study are consistent with previous studies (1–4, 6, 10). In the NHANES study with 16533 people, the median TSH increased from 1.28 mU/L in the 20- to 29-year age group to 1.99 mU/L in the 80-year and above age group. The study also reported that the lower limit of TSH decreased with age, and the upper limit increased with age (1). A more recent study by Kahapola-Arachchige et al (6) reported that although the median TSH increased with increasing age, the use of age-specific reference ranges for TSH has only minor effects on thyroid status, except in those who are more than 85 years old. Surks and Hollowell (2) also reported that TSH distribution progressively shifts toward higher concentration with age, and the prevalence of subclinical hypothyroidism may be significantly overestimated unless an age-specific range for TSH is used. Another study in Australia comprising participants in the 1981 and 1994 Busselton Health Surveys reported that the largest increase in TSH was in people with the lowest TSH at baseline, suggesting that the TSH increase might be due to age-related alteration in the TSH set point or reduced TSH bioactivity, rather than occult thyroid disease (10).

This study also reported that males had significantly higher median TSH compared to females. The magnitude

Table 5. TSH Distribution Among Patients With Diabetes

Diabetes Status	n (%)	TSH Category, n (%)		
		Group 1	Group 2	Group 3
No	138990 (90.8)	2079 (1.5)	131276 (94.4)	5635 (4.1)
Yes	14137 (9.2)	267 (1.9)	13036 (92.2)	834 (5.9)

Group 1, TSH < 0.4 mU/L; group 2, TSH = 0.4–4.0 mU/L; group 3, TSH > 4.0 mU/L.

of the difference was small and varied with age, suggesting that the clinical implication of this observation is not important. Our finding is similar to the recent study in Australia that reported that although in some age bands there were significant differences in median TSH between genders, the magnitude of the difference was small (6). In contrast, the NHANES study reported that TSH concentration was greater in females compared to males. The mean TSH concentration and the percentage of people with TSH greater than 4.5 mU/L were significantly higher in females than males in the total population and the disease-free population (1).

The strengths of our current study are that the data are from a very large and representative population of people, and as such, the findings will have a high validity. A robust exclusion criterion was applied to the cohort to ensure that those who were selected did not have thyroid disease on clinical grounds. In addition to age and gender, we also investigated the association between TSH concentration and diabetes, which has not been previously reported. However, we did not have sufficient data to examine the association between TSH concentration and race or ethnicity. We also did not have any data on the use of metformin, which may have an effect on TSH concentration. However, if there is an effect of metformin on lowering TSH concentrations, the difference between diabetic and nondiabetic patients would be greater. The sample is not truly randomized but included any patient who had a TSH measurement performed. Also, we may have included patients who might have positive thyroid antibody but had not had this checked. This may have biased the results because older people are more likely to have positive thyroid antibody (1).

Because we did not have thyroid antibody checked in most of the study population, we did an additional analysis comparing those patients with positive thyroid antibodies and those with negative thyroid antibodies. Our findings showed that the antibody distribution shifted toward higher concentration with increasing age, irrespective of the presence or absence of thyroid antibodies. We also reported that those who had positive thyroid antibodies had a 39% increase in TSH concentration. Therefore, the median TSH and 97.5th centile might have been overestimated, especially in the older people who are more likely to have positive thyroid antibody.

The 95th centile range is broader for all age groups than the current reference range, but this is particularly notable for those over 70 years old. These findings could have a significant clinical impact. Although every patient should be assessed according to their own clinical scenario, it would be anticipated that fewer people over the age of 70 years may be started on T_4 if the treatment threshold were increased. Interestingly, in one meta-analysis of 15 studies looking at subclinical hypothyroidism (11), patients under the age of 65 years had an increased risk of ischemic heart disease, whereas in those over 65 years of age there was no increased risk. In an observational study, the same group has shown that treatment with T_4 for subclinical hypothyroidism in those with a TSH greater than 5 mU/L was beneficial in younger, but not older patients (12). Taken together, these results suggest that for people over 65 years old a slightly elevated TSH concentration is not associated with ischemic heart disease and may be "normal," a finding that would be consistent with our current study. In another Canadian study of patients over 70 years old, patients treated with even modest doses of T_4 (44–93 μg/d) had an increased risk of fracture compared to those with lower doses (less than 44 μg/d) (13). This could reflect overtreatment in this age group, possibly as a result of T_4 doses being titrated up as a result of a possibly excessively low serum TSH target range. Furthermore, a recent longitudinal study has identified that TSH increased with age during a 13-year follow-up, but that increased TSH was not associated with mortality, although free T_4 concentrations were (14, 15). All these studies are consistent with the concept that higher TSH concentrations in the elderly could be tolerated without intervention.

Studies that have demonstrated an association between subclinical hypothyroidism and poor outcome have usually excluded people with a serum TSH of $<$5–7 mU/L (16–18), which reassuringly would not include the patients we have identified. Also, people over 65 years old with a TSH between 4.5 and 6.9 mU/L were shown to have a 46% chance of the TSH spontaneously reducing within 2 years (19).

Findings from current studies indicate that existing TSH reference intervals do not always reflect the distribution of TSH in different age groups. Therefore, new findings from at least 3 large cohorts in the United States, the United Kingdom, and Australia strongly indicate that the use of an age-specific reference range for TSH, especially in those over 70 years old, would avoid people with a serum TSH concentration between the 2.5th and 97.5th centiles being misclassified as "abnormal."

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