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Age-Specific Distribution of Serum Thyrotropin and Antithyroid Antibodies in the U.S. Population: Implications for the Prevalence of Subclinical Hypothyroidism

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Context: Measurements from all age groups defined the upper limit of the TSH reference range in National Health and Nutrition Examination Survey III. The TSH median, 97.5 centile and prevalence of subclinical hypothyroidism (SCH), normal serum T_4 and TSH greater than 4.5 mIU/liter, increased progressively with age. Age-adjusted reference ranges would include many people with TSH greater than 4.5 mIU/liter.

Objective: We determined whether increasing 50 and 97.5 centiles with age resulted from more patients with SCH in populations with normal TSH distribution or whether age-specific population shifts to higher serum TSH might account for these findings.

Design/Setting/Patients: We analyzed TSH, antithyroid antibodies, and TSH frequency distribution curves for specific age deciles in populations without thyroid disease, with or without antithyroid antibodies.

Results: Without thyroid disease, 10.6% of 20- to 29-yr-olds had TSH greater than 2.5 mIU/liter, increasing to 40% in the 80+ group, 14.5% of whom had TSH greater than 4.5 mIU/liter. When TSH was greater than 4.5 mIU/liter, the percentage with antibodies was 67.4% (age 40–49 yr) and progressively decreased to 40.5% in the 80+ group. TSH frequency distribution curves of the 80+ group with or without antibodies was displaced to higher TSH, including TSH at peak frequency. The 97.5 centiles for the 20–29 and 80+ groups were 3.56 and 7.49 mIU/liter, respectively. Seventy percent of older patients with TSH greater than 4.5 mIU/liter were within their age-specific reference range.

Conclusion: TSH distribution progressively shifts toward higher concentrations with age. The prevalence of SCH may be significantly overestimated unless an age-specific range for TSH is used. **(*J Clin Endocrinol Metab* 92: 4575–4582, 2007)**

MANY REPORTS SUGGEST an increasing incidence of hypothyroidism and antithyroid antibodies with aging (1–8). The largest study in a carefully characterized population was an analysis of the concentrations of serum T_4, TSH, and antithyroid antibodies in people participating in National Health and Nutrition Examination Survey (NHANES) III (Ref. 8 and http://www.cdc.gov/nchs/data/nhanes/nhanes3/cdrom/nchs/manuals/labman.pdf). In that study, the designation of 4.5 mIU/liter as the 97.5 centile used data from all age groups. Most older patients found to have raised concentrations of serum TSH have a minimal increase above the upper limit of the reference range, greater than 4.5 mIU/liter and less than 10 mIU/liter (7–11), and the prevalence of serum TSH greater than 4.5 mIU/liter increased with age. In a population without reported or known thyroid disease or antithyroid antibodies, not taking thyroid medication, and with no other risk factors for thyroid dysfunction (reference population), the serum TSH was greater than 4.5 mIU/liter in approximately 6% of the 70- to 79-yr-old group and 10% of patients 80 yr of age or older. Moreover, the median and 97.5 centile also increased progressively with age (8).

We considered the possibility that an age-related shift in distribution of TSH to higher values might raise the 97.5 centile for older individuals, which would then encompass many values currently considered above the current reference limit, greater than 4.5 mIU/liter. An increase in median and 97.5 centile for TSH in any age group could result from greater skew toward higher TSH concentrations because of a higher prevalence of thyroid disease or from a shift in the entire TSH distribution curve toward higher values, including the TSH concentration at peak frequency, which would imply a higher reference range. A combination of these explanations is also possible.

In this investigation, we tested the hypothesis that the reference range for serum TSH is set at higher TSH concentrations in elderly people than younger individuals. We examined the age-specific distribution of serum TSH and antithyroid antibodies and prepared and analyzed the frequency distribution curves for serum TSH within specific age groups in both NHANES III (NH-III) (1988–1994) and NHANES 1999–2002 (NH-99_02).

Subjects and Methods

The NHANES studies are designed to give national normative estimates of the health and nutritional status of the U.S. civilian, noninstitutionalized population. The two surveys examined in this study were NH-III and NH-99_02, using a stratified, multistage probability design.

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Abbreviations: NHANES, National Health and Nutrition Examination Survey; NH-III, NHANES III, 1988–1994; NH-99_02, NHANES 1999–2002.

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Young children, older people, blacks, and Mexican Americans were oversampled to provide sufficient numbers for studies of these groups. This study focused on individuals aged 12 yr or older who did not report thyroid disease or goiter or taking thyroid-related medications; the NH-III disease-free population.

In the NH-III data set, 16,533 of this population had measurements for TSH, T_4, thyroid peroxidase antibodies, and thyroglobulin antibodies. When people were pregnant or taking estrogens, androgens, or lithium, with positive thyroid peroxidase or thyroglobulin antibodies or with laboratory evidence of overt hyper- or hypothyroidism were removed from the disease-free population, 13,344 individuals remained, representing a U.S. population of 152,047,466 Americans with no known thyroid disease or risk factors for thyroid dysfunction, the NH-III reference population.

In the NH-99_02 data set using a one third sample, 4392 individuals aged 12 yr old or older had TSH measured. Of these, 4213 did not report thyroid disease or taking medication, the 99_02 disease-free population. Thyroid antibody measurements are not available in the NH-99_02 data set. Details for NH-III on the serum analytic methods for TSH and thyroid antibodies have been previously reported (8). In NH-99_02, TSH was assayed by the Coulston Foundation (Alamogorda, NM) using microparticle enzyme immunoassay for the quantitative determination of TSH for samples collected in 2001. Samples from 2002 were analyzed by Collaborative Laboratory Services (Ottumwa, IA) using a chemiluminescent immunoassay (Access Immunoassay System; Beckman Instruments, Fullerton, CA). Analytic data from these two laboratories were evaluated by the Centers for Disease Control and Prevention and determined to be comparable (9).

We used SAS (version 9.1; SAS Institute Inc., Cary, NC) for data preparation and preliminary calculations. Wilcoxon scores (rank sums) and Kruskal-Wallis test were used to compare the nonparametric TSH distributions of the different age groups. Also, a *t* test was used to compare the logarithmic transformation of the TSH concentrations. Means, geometric means, medians, and percentiles were calculated using SUDAAN (version 9.0.1; RTI International, Research Triangle, NC) to accommodate the sampling methodology. The frequency distribution curves of TSH concentration were prepared using log-transformed values of TSH.

Results

We analyzed the age-specific distribution of serum TSH in the disease-free population (Table 1A). Serum TSH concentrations were arbitrarily categorized as less than 0.4, 0.4–2.49, 2.5–4.5, and greater than 4.5 mIU/liter; 86.7% of young people 20–29 yr of age had TSH concentrations in the category of 0.4–2.5 mIU/liter, 8.1% were in the 2.5–4.49 mIU/liter category, and 2.5% were greater than 4.5 mIU/liter. The TSH distribution among the age deciles progressively shifted toward higher TSH concentrations with aging. The percentage of measurements in the 0.4–2.5 mIU/liter category decreased progressively with age from 86.7% in young people to 57.3% of people 80 yr old and older; the percentage in the 2.5–4.5 mIU/liter range and the greater than 4.5 mIU/liter category progressively increased from 8.1 to 25.5% and 2.5 to 14.5%, respectively, with age. Thus, TSH is redistributed toward higher concentrations with aging in about 30% of the disease-free population.

We then determined the influence of antithyroid antibodies on these changes in age-specific distribution of TSH by removing 2157 people who had antithyroglobulin or antithyroid peroxidase antibodies from the disease-free population. This established a new population of 14,376 people, disease-free population without antithyroid antibodies (Table 1B). The progressive redistribution of TSH with age noted in the disease-free population (Table 1A) was also observed in the disease-free population without antithyroid antibodies (Table 1B). In addition, 88.8% of people 20–29 yr of age had TSH concentrations in the 0.4–2.49 mIU/liter category, and this percentage progressively decreased, particularly after 50 yr of age, to 61.5% in the 80 yr and older group. Similar to the disease-free population in concentration categories above 2.5 mIU/liter, the percentage of TSH measurements increased progressively with age from approximately 6.5 to 23.9% (2.5–4.5 mIU/liter) and 2.0% to 12.0% (>4.5 mIU/liter) in the 20- to 29-yr-old group and the 80-yr and older group, respectively. These findings in the disease-free population without antithyroid antibodies ap-

TABLE 1. TSH distribution among different age groups in disease-free U.S. population, NHANES III (1988–1994)[a]

Age groups (yr)	Sample size	Weighted size	Percent	Percent of age group in category			
				<0.4[b]	0.4–2.49	2.5–4.5	>4.5
A. Disease-free antibodies not excluded							
Total	16,533	195,134,687	100.0	1.8[c]	79.6	13.2	5.3
12–19	2,431	28,343,575	14.5	1.7	83.9	11.7	2.7
20–29	3,186	38,867,518	19.9	2.7	86.7	8.1	2.5
30–39	2,981	41,200,742	21.1	2.3	83.7	10.5	3.5
40–49	2,290	31,340,589	16.1	1.3	78.8	13.9	6.0
50–59	1,554	20,256,289	10.4	1.0	75.8	16.7	6.6
60–69	1,834	17,752,880	9.1	1.3	71.7	19.3	7.7
70–79	1,333	12,181,727	6.2	1.1	62.6	21.2	15.1
80+	924	5,191,366	2.7	2.7	57.3	25.5	14.5
B. Disease-free antibodies negative							
Total	14,376	166,380,393	100.0	1.9[c]	83.8	11.4	3.0
12–19	2,276	26,085,179	15.7	1.6	85.4	10.6	2.4
20–29	2,919	35,092,588	21.1	2.7	88.8	6.5	2.0
30–39	2,637	35,502,869	21.3	2.5	86.2	9.5	1.8
40–49	1,982	26,163,529	15.7	1.1	85.1	11.5	2.4
50–59	1,292	16,554,734	10.0	0.9	81.2	14.8	3.1
60–69	1,518	14,044,873	8.4	1.6	77.5	17.3	3.5
70–79	1,052	9,187,839	5.5	1.0	69.7	19.3	9.9
80+	700	3,748,782	2.3	2.6	61.5	23.9	12.0

[a] Disease-free population are people who did not report having thyroid disease or taking thyroid medications.
[b] TSH concentration (milliinternational units per liter).
[c] Percent in category.

pear qualitatively and quantitatively similar to those of the disease-free population (Table 1A). Combined, they suggest that a shift of at least 28–30% of serum TSH measurements occurs from the 0.4–2.49 mIU/liter category toward higher concentrations with aging, irrespective of the presence or absence of antithyroid antibodies. These data do not allow estimation of change in serum TSH within the established TSH categories. Only a small fraction of the increase in TSH concentration (~4%) was seen when antibodies were present.

The distribution of antithyroid antibodies was examined among different age groups within the same categories of TSH concentrations (Table 2A). In people between 20 and 29 yr of age with antithyroid antibodies, 67.1% were in the 0.4–2.5 mIU/liter TSH category, and 22.8% were in the TSH categories of 2.5 mIU/liter or higher (Table 2A). With increasing age, antibody distribution shifted significantly toward higher TSH concentrations. In the 80-yr and older group, 46.3% of those with antibodies were seen in the 0.4–2.49 mIU/liter category and 50.7% were seen in TSH categories of 2.5 mIU/liter or higher.

The percentage of patients within each TSH concentration category who had antithyroid antibodies also changed significantly with aging (Table 2B). Of patients in the disease-free population with TSH in the 0.4–2.5 mIU/liter category, 7.5% of those 20–29 yr of age had antithyroid antibodies, and this increased 3-fold to 22.5% in the 80-yr and older group. In the TSH category, 2.5–4.5 mIU/liter, about 27.4% of the younger group had antithyroid antibodies, and this increased to 32.2% in the oldest age group. More complex changes occurred with aging in individuals with TSH greater than 4.5 mIU/liter. The prevalence of antithyroid antibodies increased from 30.8% in the 20- to 29-yr-old age group, reached high prevalence of 61.9–67.4% in groups between ages of 40 and 69 yr, but then decreased in the 70s and then down to 40.5% in the 80-yr and older group.

Several findings from this analysis and NH-III (8) raised the question whether a TSH concentration of 4.5 mIU/liter, the 97.5th centile, the currently used upper limit of the reference range, which is derived from a composite of all age groups in the population, is appropriate for elderly people: 1) a significant increase in prevalence of TSH greater than 4.5 mIU/liter occurs with aging in the reference population, which currently has no documented risk factors for thyroid disease; 2) up to 30% of the disease-free population has a shift in TSH concentration from the 0.4–2.49 mIU/liter category to higher TSH concentrations, a finding that is related to the presence of antithyroid antibodies in a very small fraction of cases; 3) 60% of the 80-yr and older group with TSH greater than 4.5 mIU/liter do not have antithyroid antibodies; and 4) increasing age is associated with a progressive increase in TSH concentration at the 50 and the 97.5 centiles (8).

To determine whether the TSH range shifted toward higher concentrations with aging, we analyzed the frequency distribution curves for TSH in selected deciles of age; in the young (20–29 yr old), middle (50–59 yr old), and oldest (80 yr and older) age groups. An increase in median TSH and 97.5 centile because of an increased prevalence of hypothyroidism with aging should result in a distribution curve with a lower peak frequency, which would occur at an unchanged TSH concentration and increased skew toward higher concentrations. Alternatively, a shift in the range for the older population implies a shift in the entire distribution curve, including the peak frequency, to higher TSH concentrations.

The TSH frequency distribution curves for the selected age deciles, 20–29 yr, 50–59 yr, and 80 yr and older group in the disease-free population (Fig. 1A) and reference population (Fig. 1B) appear to show a progressive shift in the peak

TABLE 2. Disease-free population: distribution of antibodies within specific age groups by TSH concentration, NHANES III (1988–1994)[a]

Age (yr)	Sample	Total	Percent in category with positive antibodies			
			<0.4[b]	0.4–2.49	2.5–4.5	>4.5
A. Antibodies positive						
Total	2157[c]	100.0	1.6	55.6	23.9	19.0
12–19	155	7.9	2.4	66.1	25.0	6.6
20–29	267	13.1	2.0	67.1	22.8	8.1
30–39	344	19.8	1.2	68.2	16.4	14.2
40–49	308	18.0	2.3	47.3	25.9	24.5
50–59	262	12.9	1.3	51.4	25.0	22.3
60–69	316	12.9	0.2	49.4	26.9	23.6
70–79	281	10.4	1.4	40.6	27.1	30.9
80+	224	5.0	3.0	46.3	29.5	21.2
B. Antibodies not excluded						
Total	16533[d]	14.7	12.7[e]	10.3	26.6	52.6
12–19	2,431	8.0	11.5	6.3	17.0	19.1
20–29	3,186	9.7	7.3	7.5	27.4	30.8
30–39	2,981	13.8	6.9	11.3	21.7	56.3
40–49	2,290	16.5	29.5	9.9	30.9	67.4
50–59	1,554	18.3	24.0	12.4	27.4	61.9
60–69	1,834	20.9	2.6	14.4	29.1	63.8
70–79	1,333	24.6	31.4	15.9	31.4	50.4
80+	924	27.8	30.6	22.5	32.2	40.5

[a] Disease-free population are people who did not report having thyroid disease or taking thyroid medications.
[b] TSH concentration group (milliinternational units per liter).
[c] Number in population with antibodies. Percentages cited are the relative frequencies in the population represented by the sample.
[d] Number in total disease-free population. Percentages cited are the relative frequencies in the population represented by the sample.
[e] Percent positive in category.

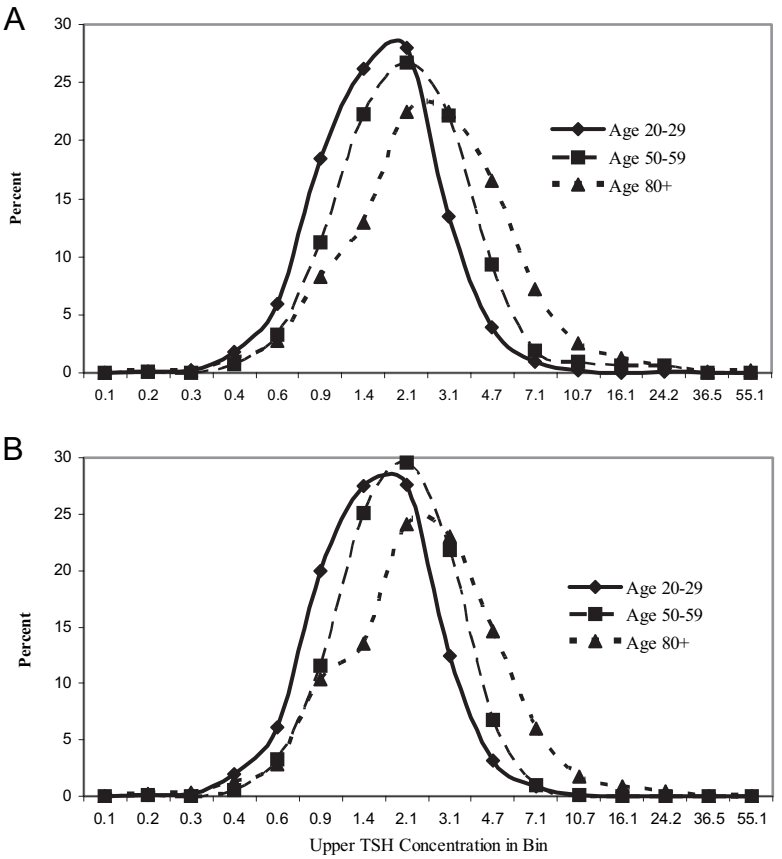

FIG. 1. TSH distribution by age groups in the United States. A, Disease-free population. B, Reference population, NHANES III (1988–1994).

relative frequencies toward higher TSH concentrations. The base of the curve for the 80-yr and older group appears to widen, and the peak relative frequency appears lower but occurs at a higher TSH concentration than in the younger age groups.

To determine whether the shift of the frequency distribution curve to higher TSH concentrations with age was unique to NH-III, we compared curves from NH-III to comparable TSH distribution curves for the disease-free population in NH-99_02 (Fig. 2). The shift in the distribution curves and peak frequency toward higher TSH concentrations in the 70- to 89-yr-old group in comparison with the 20- to 39-yr-old groups is apparent and almost identical in both NHANES surveys. We could not do a comparable analysis for the reference population because antithyroid antibodies were not determined in NH-99_02.

A progressive increase in mean, median, and 97.5 centile for TSH concentration occurred with age in the disease-free (Table 3A) and reference populations (Table 3B). These parameters were increased in those with antithyroid antibodies in comparison with those who did not have antithyroid antibodies. This analysis suggests that the 97.5 centile is about 3.6 mIU/liter in people who are 20–39 yr of age and 5.9 and 7.5 mIU/liter in those who are 70–79 and 80 yr old and older, respectively.

We analyzed the NH-III database further to determine the percentage of individuals who were considered to have raised TSH, based on using the 4.5 mIU/liter upper limit, who might be within the 97.5 centile when an age-specific upper limit is used. Figure 3 illustrates the TSH distribution in small increments of TSH for those individuals in the disease-free (antibodies not excluded) (Fig. 3A) and reference (Fig. 3B) populations whose TSH was greater than 4.5 mIU/liter. As previously reported for the 80-yr-old and older group in the disease-free and reference populations, 12.9 and 9.7% had TSH greater than 4.5 mIU/liter (8). Using the 80+ age group as an example, Fig. 3, A and B, suggest that 67 and 74%, respectively, of those with the TSH values that were

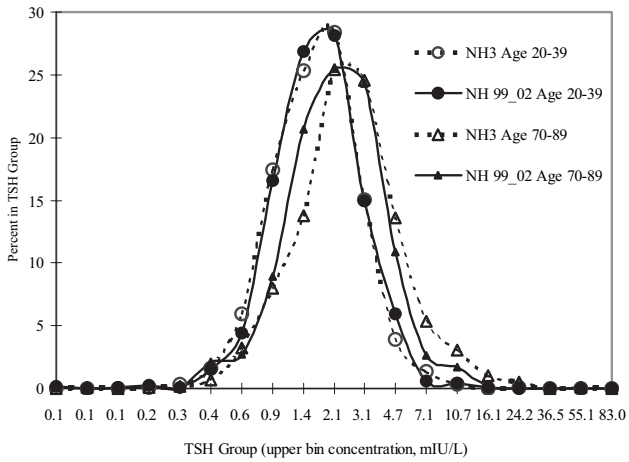

FIG. 2. TSH distribution: comparison of U.S. disease-free populations, NHANES III (1988–1994) and NHANES 1999–2002, by age groups.

TABLE 3. Mean and median TSH concentration with 97.5 centile (milliinternational units per liter) by age group in disease-free and reference populations, NHANES III (1988–1994)

Age groups (yr)	Sample size	Mean	SE mean	Geometric mean	SE geometric mean	Median	95% confidence limits	97.5 centile	95% confidence limits
A. Disease-free population[a]									
Total	16,533	1.97[b]	0.05	1.50	0.02	1.49	1.46–1.50	5.52	5.24–32.93
12–19	2,431	1.71	0.08	1.39	0.03	1.37	1.31–1.51	4.20	3.82–6.51
20–29	3,186	1.54	0.04	1.27	0.02	1.28	1.25–1.36	4.02	3.76–6.77
30–39	2,981	1.75	0.11	1.36	0.03	1.35	1.31–1.44	4.57	4.04–9.62
40–49	2,290	2.09	0.12	1.60	0.04	1.50	1.46–1.57	5.75	4.99–21.14
50–59	1,554	2.21	0.13	1.67	0.03	1.60	1.57–1.70	5.73	5.28–19.62
60–69	1,834	2.34	0.08	1.83	0.04	1.79	1.71–1.95	7.48	6.21–11.89
70–79	1,333	3.10	0.24	2.03	0.05	1.98	1.87–2.09	9.80	8.58–25.93
80+	924	2.85	0.14	2.02	0.09	2.08	1.92–2.28	9.36	7.71–19.75
B. Reference population[c]									
Total	13,344	1.64[b]	0.02	1.40	0.02	1.39	1.39–1.47	4.12	3.96–6.23
12–19	2,172	1.59	0.04	1.36	0.03	1.35	1.28–1.49	4.07	3.69–4.80
20–29	2,564	1.43	0.03	1.24	0.02	1.26	1.19–1.29	3.56	3.26–4.71
30–39	2,482	1.50	0.04	1.30	0.03	1.29	1.29–1.41	3.69	3.40–4.33
40–49	1,882	1.64	0.04	1.44	0.03	1.40	1.35–1.52	3.82	3.49–4.83
50–59	1,145	1.74	0.03	1.52	0.03	1.50	1.46–1.63	4.03	3.68–4.94
60–69	1,430	1.91	0.05	1.65	0.04	1.67	1.60–1.79	4.33	4.02–5.45
70–79	1,001	2.16	0.06	1.75	0.04	1.76	1.68–1.85	5.90	5.24–8.60
80+	668	2.44	0.12	1.86	0.08	1.90	1.74–2.13	7.49	6.17–10.85

[a] Disease-free population are people who did not report having thyroid disease or taking thyroid medications.
[b] TSH concentration (milliinternational units per liter).
[c] In the reference population, we excluded those who were pregnant; those reporting thyroid disease; those taking estrogens, androgens, lithium, or thyroid medications; and those with antibodies or laboratory evidence of overt hypo- or hyperthyroidism.

greater than 4.5 mIU/liter in the disease-free (antibodies not excluded) and reference populations were less than 7.5 mIU/liter, within their respective age-specific 97.5 centiles. Thus, the reported increased frequency of raised TSH values with aging becomes much less apparent when age-specific 97.5 centiles are used.

An additional analysis (data not shown) indicated that changes in ethnic distribution within specific age deciles did not account for these findings. Moreover, the findings were unchanged when males and females were analyzed separately.

Discussion

Although many issues surrounding subclinical hypothyroidism are controversial (10–12), all would agree that the diagnosis depends on a raised serum TSH. Thus, definition of the upper limit of the reference range is critical. The distribution of serum TSH is nonparametric and the reference range is usually calculated from logarithmic transformed values. In NH-III, the median was determined, and the 2.5 and 97.5 centiles were used as reference limits for the U.S. population (8). For the reference population, geometric mean TSH was 1.40 (SE 0.02) mIU/liter, the median was 1.39 mIU/liter, and the 2.5 and 97.5 centiles were 0.45 and 4.12 mIU/liter. Recently a discussion has begun concerning lowering the upper limit of the TSH reference range to 2.5 mIU/liter (13–15). We subdivided the reference range to 0.4–2.49 and 2.5–4.49 mIU/liter to provide data that might be helpful for that discussion. Our main focus, however, was determination of the upper limit of the TSH reference range.

Our analysis of NH-III appears to show age-specific increases in the TSH reference range that may be clinically relevant. Our data show that the TSH frequency distribution curves for populations of three selected age groups, although not superimposable, seem relatively close in shape and that their peak frequencies are shifted toward higher TSH concentrations with age. Thus, in a population of old people without apparent risk factors for thyroid disease, serum TSH appears distributed at higher concentrations than in young people and suggests that the increasing median and 97.5 centile for TSH that occur with aging, as reported in NH-III (8), represent, at least in part, changes in age-specific population distributions of TSH. If the increasing median and 97.5 centile noted with aging resulted simply from an increase in prevalence of hypothyroidism, the population TSH frequency distribution curve would not be shifted to higher TSH concentrations. The peak frequency would occur at the same TSH concentration as young individuals and a larger skew toward higher values would be noted. Our findings therefore suggest that increasing 97.5 centiles that occur with age are, at least to some extent, representative of the upper limits of the reference range for those age groups.

The corollary to these findings is that the currently accepted high prevalence of subclinical hypothyroidism in older people, based on the current upper limit of the reference range, 4.5 mIU/liter, may be an overestimate. Our data suggest that the upper limit for TSH that was used in NH-III, greater than 4.5 mIU/liter, may not be applicable for older people (8). If an age-specific 97.5 centile is used instead of the fixed 4.5 mIU/liter, as suggested by the present analysis, the prevalence of raised TSH concentrations would be less in older people and greater in younger age groups than previously reported. Our analysis of the distribution of raised TSH, greater than 4.5 mIU/liter, in older individuals indicates that about 70% of the raised values for the 80-yr and older group fall within the 97.5 centile of their age-specific range. This observation com-

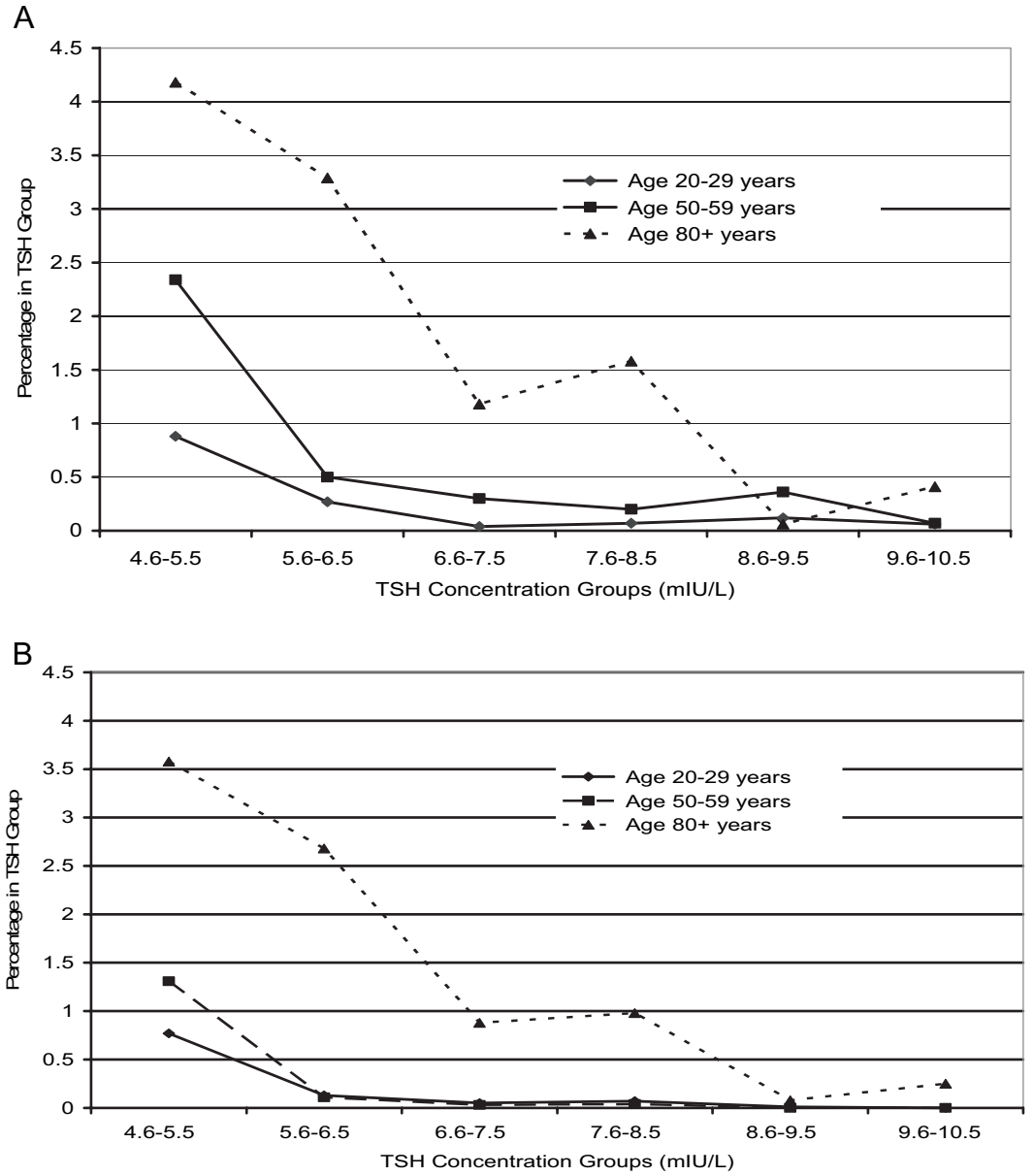

FIG. 3. Percent TSH concentration greater than 4.5 mIU/liter in the U.S. population by age and concentration groups. A, Disease-free population, antibodies not excluded. B, Reference population, NHANES III (1988–1994).

plements the finding that only 40% of that group with TSH greater than 4.5 mIU/liter have antithyroid antibodies. Moreover, considering the fact that a reference range implies that 2.5% of normal people may be above the 97.5 centile, it is possible that additional individuals identified to have subclinical hypothyroidism, even using an age-specific reference range may not have thyroid disease.

Our findings that suggest a TSH range in elderly people that is higher than younger people do not agree with some published reports, as extensively reviewed (1). Serum TSH was in the normal range in the elderly after excluding patients with raised values and, when selected for the absence of nonthyroidal disease, serum TSH may be decreased (16). Also, a decrease in median TSH has been reported in healthy centenarians, a population that may not be representative of the vast majority of elderly people (17). However, most reports on this issue used relatively small numbers of highly selected patients. The NH-III data that we analyzed are unique for their very large numbers of individuals who were characterized with regard to risk factors for thyroid disease, which enabled the age-specific analysis we carried out. A limitation of our study is that all patients were from the United States, and the findings may not be applicable to other populations. For example, a markedly lower median and range for TSH has been reported for all age groups in a previously iodine-deficient area in Germany (18). That study excluded individuals with any anatomic abnormalities of the thyroid determined by thyroid ultrasonography. Another study with a similarly defined reference group showed no difference in

median TSH (19). However, too few patients older than 59 yr of age were studied to comment on effects of age.

Some people in all age groups have raised serum TSH, even when using an age-specific 97.5 centile, but do not have antithyroid antibodies. It is likely that some have thyroid disease because a raised serum TSH alone is associated with a small but significant increase in rate of progression to overt hypothyroidism, 2.5% per year (20). It is possible that more sensitive methods for antithyroid antibody determination than used in NH-III might have identified more patients with autoimmune thyroid disease in this population. Also, the use of thyroid ultrasound, which would be impractical for population studies, might have shown a decrease in thyroid echogenicity, a finding that is associated with autoimmune thyroid disease (21). However, the presence of hypoechogenicity, whereas possibly providing evidence of autoimmune thyroid disease, does not in itself indicate hypothyroidism. Most patients with autoimmune thyroid disease, young or old, have normal serum TSH between 0.4 and 2.5 mIU/liter.

Our findings also provide additional perspective on the controversial suggestion to decrease the upper limit of the TSH reference range to concentrations as low as 2.5 mIU/liter. Arguments for and against that suggestion have been published (14, 15). The data that entered into the suggestion to lower the upper limit were based on a TSH frequency distribution analysis that was a composite of all age groups. The population shift toward higher TSH concentrations with aging reported here suggests that even more older people would be mislabeled as having raised TSH should the upper limit of the TSH reference range be decreased. For the reference and disease-free populations in NH-III, 34 and 39%, respectively, of patients older than 70 yr of age have TSH greater than 2.5 mIU/liter and would be considered abnormal. This unlikely consequence of aging should give pause to this recommendation until other corroborating evidence is provided for the consequences of hypothyroidism as so defined.

An explanation for a shift in reference range to higher TSH concentrations in elderly people is not immediately apparent. The shift could either facilitate or be a consequence of healthy aging or may represent subtle thyroid deficiency that could be either beneficial or deleterious. One possibility is that ingestion of medications commonly prescribed for older individuals may limit the efficiency of the interaction between TSH with its receptor and/or subsequent generation of cAMP, thus requiring a slightly higher TSH concentration to regulate thyroid function normally. A similar effect possibly caused by medications or from age alone may influence the sensitivity of the hypothalamic-pituitary feedback system. Finally, there may be medication-induced or age-related changes in the post-translational processing of TSH within the thyrotroph, resulting in secretion of TSH molecules with somewhat decreased biologic activity (22). Some of these possibilities may be amenable to study.

Our studies relate to reference ranges for TSH and, possibly, may not reflect a putative range for truly normal individuals, as suggested by some, TSH less than 2.5 mIU/liter (14). A group of normals might be established starting from the reference population of NH-III and excluding people with nonthyroidal illness and those who ingest medications or have any abnormality in thyroid ultrasound and no antithyroid antibodies using sensitive methods. Whether sufficient numbers of older people for statistical analysis could be found that satisfy these criteria is uncertain. Also, such an effort to define a normal range in addition to a reference range for TSH may not serve well either patients or the public's thyroid health. The reference range or normal range should have clinical utility, defining those who do not have hypothyroidism and those who have it or may be at significant risk for hypothyroidism. Two ranges would likely result in confusion for most doctors caring for patients (23). This would principally affect older people because the prevalence of TSH greater than 2.5 mIU/liter progressively increases with age. Decreasing the upper limit to 2.5 mIU/liter, as proposed (14), could incorrectly designate as many as 35% of older people as hypothyroid. Unnecessary treatment with levothyroxine might not provide benefit and could adversely affect their health.

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