Thyroid Function and Prevalence of Anti-Thyroperoxidase Antibodies in a Population with Borderline Sufficient Iodine Intake: Influences of Age and Sex

Elizabeth H. Hoogendoorn,[1*] Ad R. Hermus,[1] Femmie de Vegt,[2] H. Alec Ross,[1,3]
Andre L.M. Verbeek,[2] Lambertus A.L.M. Kiemeney,[2] Dorine W. Swinkels,[4]
Fred C.G.J. Sweep,[3] and Martin den Heijer[1,2]

Background: We present a large European population-based study of thyroid function, performed in a population with longstanding borderline sufficient iodine intake.

Methods: The Nijmegen Biomedical Study is a population-based survey conducted in the eastern part of The Netherlands. Randomly selected inhabitants received a postal questionnaire on lifestyle and medical history, which was filled out by 9371 individuals (41.7%). We measured serum thyroid-stimulating hormone (TSH), free thyroxine (FT$_4$), and anti-thyroperoxidase antibodies (TPOAbs) in 6434 responders. A reference population of 5167 individuals was selected by excluding those at risk for thyroid disease.

Results: Overt thyrotoxicosis was found in 0.4% of the total population and subclinical thyrotoxicosis in 0.8%. Overt hypothyroidism was found in 0.4% and subclinical hypothyroidism in 4.0%. In individuals older than 60 years, mean FT$_4$ concentrations increased with age. Mean TSH decreased with age, from 1.46 mIU/L at 18–24 years to 1.07 mIU/L after 85 years. The mean TSH in the total population did not differ from the mean TSH in the reference population; the exclusion of those at risk for thyroid disease, however, lowered the upper limit of the TSH reference interval considerably. In the total population, 8.6% of males and 18.5% of females had positive TPOAbs. The presence of TPOAbs was associated with abnormally high and low TSH concentrations.

Conclusion: In inhabitants of the eastern part of The Netherlands, serum TSH gradually decreases with age, whereas after age 60, serum FT$_4$ increases, possibly because of the development of thyroid autonomy after longstanding borderline sufficient iodine intake.

© 2006 American Association for Clinical Chemistry

Thyroid dysfunction is common *(1–4)*. In the Third National Health and Nutrition Examination Survey (NHANES III),[5] a recent large population-wide survey in the United States, hypothyroidism was found in 4.6% (0.3% overt and 4.3% subclinical) and hyperthyroidism in 1.3% (0.5% overt and 0.7% subclinical) of the total population *(2)*. Interpretation of data on the prevalence of thyroid disease in a certain area must take into account the influence on these data of the iodine intake in that region. A high iodine intake is associated with lower prevalence of goiter and higher prevalence of hypothyroidism, whereas a low iodine intake is associated with a higher prevalence of hyperthyroidism *(5)*. Sex and age are also important, e.g., hypothyroidism is far more common among elderly women than among other groups, particularly in the presence of thyroid autoantibodies *(1–3, 6)*.

The NHANES III study found a median serum thyroid-stimulating hormone (TSH) concentration in the total population of 1.49 mIU/L with 2.5th and 97.5th percentiles of 0.33 and 5.8 mIU/L, respectively *(2)*. However, in

Departments of [1] Endocrinology, [2] Epidemiology and Biostatistics, [3] Chemical Endocrinology, and [4] Clinical Chemistry, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands.

*Address correspondence to this author at: 471, Department of Endocrinology, Radboud University Nijmegen Medical Centre, PO Box 9101, 6500 HB Nijmegen, The Netherlands. Fax 31-24-3618809; e-mail e.hoogendoorn@endo.umcn.nl.

[5] Nonstandard abbreviations: NHANES III, Third National Health and Nutrition Examination Survey; TSH, thyroid-stimulating hormone; FT$_4$, free thyroxine; TPOAb, anti-thyroperoxidase antibody; and CI, confidence interval.

a reference population (excluding those who self-reported thyroid disease or pregnancy, use of thyroid medication, estrogens, androgens, or lithium; those with detectable thyroid antibodies; and/or those with laboratory evidence of hyper- or hypothyroidism), the median serum TSH concentration was 1.39 mIU/L with 2.5th and 97.5th percentiles of 0.45 and 4.12 mIU/L, respectively. The difference in TSH values between these 2 populations, particularly the 97.5th percentiles, has initiated a discussion on whether the TSH reference interval should be based on the total population or on such a reference population *(7)*.

To date, there has not been a European population-based study of this size in which participants have had their serum TSH (using a third-generation assay), free thyroxine (FT_4), and anti-thyroperoxidase antibodies (TPOAbs) determined with a sensitive assay. We collected data on a large population from the city of Nijmegen, in the eastern part of The Netherlands close to the German border, where inhabitants have borderline sufficient iodine intake *(8, 9)*. We measured the prevalence of thyroid dysfunction and TPOAbs in inhabitants of Nijmegen and investigated whether thyroid function in this area is influenced by age, as was seen in other large studies *(1, 10)*, and whether the TSH reference interval, as in NHANES III, is influenced by age, sex, and the presence of TPOAbs.

Participants and Methods

SAMPLE DESIGN

The Nijmegen Biomedical Study is a population-based survey conducted by the Department of Epidemiology and Biostatistics and the Department of Clinical Chemistry of the Radboud University Nijmegen Medical Centre. Approval to conduct the study was obtained from the Institutional Review Board. Nijmegen is a town in the eastern part of The Netherlands with 156 000 inhabitants, ~87% of Caucasian descent. Age- and sex-stratified randomly selected adult inhabitants of Nijmegen (n = 22 452) received an invitation to fill out a postal questionnaire on lifestyle and medical history. Three questions were used to collect data on thyroid disease and thyroid medication: Has thyroid disease ever been diagnosed in you by a doctor, and if yes, at what age? What kind of operations did you have? Which medication did you use for at least 6 months or are you currently using?

A total of 9371 (41.7%) recipients responded to the questionnaire, and 6455 (68.9%) of the responders each donated 8.5 mL of blood. Serum TSH, FT_4, and TPOAbs were measured in all of these samples. For 21 samples, the blood volume obtained was insufficient to determine TSH, FT_4, and/or TPOAbs. No physical examination was done. We analyzed results for 6434 participants, 46.3% male and 53.7% female. The highest number of participants was in the 60–69 years age group, and the lowest number in the 85 years and older group (see Table 1 in the Data Supplement that accompanies the online version of

this article at http://www.clinchem.org/content/vol52/issue1/). Almost all participants (96.0%) were of Caucasian descent. Of the total population (n = 6434), 5.3% (261 females and 79 males) reported thyroid disease (n = 328), and/or thyroid surgery (n = 41), and/or the use of thyroid medication [L-thyroxine (n = 102), thyrostatic drugs (n = 18), or both (n = 6)]. The remaining 6094 participants were defined as the disease-free population.

A reference population of 5167 participants (80.3% of the total population) was selected, excluding those who reported thyroid disease, and/or thyroid surgery, and/or thyroid medication use (n = 340); pregnant women (n = 24); those who did not report thyroid disease but who evinced overt thyrotoxicosis (n = 8) or overt hypothyroidism (n = 23); those on lithium (n = 23), amiodarone (n = 11), kelp (n = 3), oral glucocorticoids (n = 114), or dopamine agonists (n = 12); and those with positive TPOAbs with or without other exclusionary characteristics (n = 897).

LABORATORY METHODS

We measured serum TSH by an immunoluminometric assay on a random-access analyzer (Architect; Abbott Diagnostics Division). The between-run SD of a control sample with a very low TSH concentration (0.0348 mIU/L) was 0.0013 mIU/L. This value is assumed to be representative for lower concentrations as well. Thus, at a concentration of 0.007 mIU/L the between-assay CV will be ≤20%. This value of 0.007 mIU/L was considered as the functional detection limit. At higher concentrations, between-run CVs were as follows: 3.3% at 0.250 mIU/L; 3.6% at 1.72 mIU/L; and 3.0% at 9.86 mIU/L. The reference interval used in our laboratory is 0.4–4.0 mIU/L.

We measured serum FT_4 with a luminescence enzyme immunoassay on a random-access assay system (Vitros ECI; Ortho Clinical Diagnostics). This assay uses a labeled anti-T_4 antibody in a medium that is essentially free of other extraneous T_4-binding proteins. Serum samples may be diluted up to 8-fold without significant effects on measurement results. Between-run CVs were as follows: 3.8% at 10.1 pmol/L; 4.5% at 15.8 pmol/L; and 4.6% at 28.7 pmol/L. Our laboratory reference interval is 8.0–22.0 pmol/L.

TPOAbs were measured with a fluorescence immunoenzymometric assay for the quantitative measurement of the IgG class of anti-thyroperoxidase antibodies (Ax-SYM Anti-TPO; Abbott Diagnostics Division). The reference interval was defined as <12 kIU/L (data provided by manufacturer). The mean value for a negative control sample was 4.1 kIU/L (between-run CV of 13%); a positive control sample averaged 64.2 kIU/L (between-run CV, 7.3%). The functional detection limit was estimated in the same way as for TSH; the CV of 13% at 4.1 kIU/L implies a 20% CV at 2.6 kIU/L, assuming that the SD does not decrease further with concentration.

The precision data cited above all pertain to the period in which the assays for this study were performed *(10*

weeks). Blood was drawn September 2002 through December 2003, between 0800 in the morning and 2000 in the evening.

DATA ANALYSIS

Thyrotoxicosis was classified as overt if TSH was ≤ 0.1 mIU/L and FT_4 >22 pmol/L and as subclinical if TSH was ≤ 0.1 mIU/L and FT_4 ≤ 22 pmol/L. Hypothyroidism was classified as overt if TSH was >4.0 mIU/L and FT_4 <8.0 pmol/L and as subclinical if TSH was >4.0 mIU/L and FT_4 ≥ 8.0 pmol/L. A TSH concentration of 0.1–0.4 mIU/L was considered mildly suppressed. We analyzed all data with the SPSS 12.0 statistical software package (SPSS Inc.). For TSH, we calculated the means, SE, and SD from log-transformed values, and for FT_4 we used arithmetic means. To generate possible reference values for TSH, we calculated the 95% probability intervals with the mean (1.96) × SD from log-transformed values in 3 different populations (total, disease-free, and reference population, as defined above) (7). We considered the 95% probability interval of the reference population the reference interval for TSH values. To study the characteristics of persons with high or low TSH values and/or positive TPOAb values, we calculated prevalence and prevalence differences.

Results

PREVALENCE OF THYROID DYSFUNCTION

Thyroid disease, thyroid surgery, and/or thyroid medication use were reported by 261 females and 79 males, 5.3% of the total population. Of those on L-thyroxine (108 persons; 1.7%), 11.1% were classified having overt thyrotoxicosis and 9.3% as having subclinical thyrotoxicosis, 13.9% showed a mildly suppressed TSH, and 12.0% were classified as subclinical hypothyroid. Only 53.7% showed a TSH in the reference interval while on L-thyroxine.

In the total population, the prevalence of overt thyrotoxicosis was 0.4% (20 females and 7 males; age range, 24–85 years; Table 1). The majority (19 of 27) of those with overt thyrotoxicosis reported thyroid disease, thyroid surgery, and/or use of thyroid medication: 44.4% used L-thyroxine and 7.4% thyrostatic drugs. Of the 21 persons with FT_4 >22 pmol/L and TSH >0.1 mIU/L, 5 were using L-thyroxine and 7 amiodarone. There were 52 persons (0.8% of the total population; 12 males and 40 females) with subclinical thyrotoxicosis. One woman was pregnant; she did not report thyroid disease. No persons with subclinical thyrotoxicosis reported use of TSH-influencing medications such as oral glucocorticoids or dopamine agonists. Several participants reported use of thyroid medication: 9 used L-thyroxine, 2 used thyrostatic drugs, and 1 used both. Another 202 individuals (3.1% of the total population) showed mildly suppressed TSH combined with FT_4 concentrations within the reference interval.

Overt hypothyroidism was found in 26 individuals (0.4% of the total population; 5 males and 21 females; age range, 32–80 years). Only 3 of 26 (11.5%) of those with hypothyroidism reported a history of thyroid disease. Of these individuals, none was using thyroid medications, and TPOAbs were detected in 88.5% (Table 1). Subclinical hypothyroidism was found in 4.0% of the total population, more frequently in females than males; of those with subclinical hypothyroidism, 13.5% reported thyroid disease, thyroid surgery, and/or use of thyroid medications (12 used L-thyroxine and 1 used thyrostatic drugs), and 61.4% were found to have positive TPOAbs.

FT_4

The mean FT_4 for all participants was 13.56 pmol/L [95% confidence interval (95% CI), 13.50–13.62 pmol/L]. There was no difference in mean FT_4 between the total, disease-free, and reference populations (see Fig. 1 in the online Data Supplement). In male and female participants older than 60 years, mean FT_4 increased with age (Fig. 1). The lowest mean FT_4 [13.0 pmol/L (95% CI, 12.8–13.2 pmol/L)] was found in participants 30–34 years of age. In participants older than 85 years, mean FT_4 was

Table 1. Prevalence and characteristics of thyroid abnormalities in the Nijmegen Biomedical Study.[a]

	No. (% of total)	Males, n (% of males)	Females, n (% of females)	Thyroid pathology,[b] n (% of group)	Positive TPOAbs, n (% of group)
Overt thyrotoxicosis	27 (0.4%)	7 (0.2%)	20 (0.6%)	19 (70.4%)	11 (40.7%)
Subclinical thyrotoxicosis	52 (0.8%)	12 (0.4%)	40 (1.2%)	22 (42.3%)	16 (30.8%)
Mildly suppressed TSH and normal FT_4	202 (3.1%)	85 (2.9%)	117 (3.4%)	28 (13.9%)	30 (14.9%)
Euthyroid	5838 (90.7%)	2762 (92.8%)	3076 (89.0%)	224 (3.8%)	654 (11.2%)
Subclinical hypothyroidism	259 (4.0%)	90 (3.0%)	169 (4.9%)	35 (13.5%)	159 (61.4%)
Overt hypothyroidism	26 (0.4%)	5 (0.2%)	21 (0.6%)	3 (11.5%)	23 (88.5%)

[a] Results of TSH, FT_4, and TPOAb measurements were available for 6434 individuals. Thyrotoxicosis was classified as overt if TSH was ≤ 0.1 mIU/L and FT_4 >22 pmol/L and as subclinical if TSH was ≤ 0.1 mIU/L and FT_4 ≤ 22 pmol/L. Hypothyroidism was classified as overt if TSH was >4.0 mIU/L and FT_4 <8.0 pmol/L and as subclinical if TSH was >4.0 mIU/L and FT_4 ≥ 8.0 pmol/L. A TSH concentration between 0.1 and 0.4 mIU/L was considered mildly suppressed. Not included in Table 2 are persons with a TSH concentration between 0.4 and 4.0 mIU/L and a FT_4 concentration <8 pmol/L (n = 9), and persons with a TSH between 0.1 and 10.0 mIU/L and FT_4 >22 pmol/L (n = 21).

[b] Thyroid pathology means reporting thyroid disease, thyroid surgery, and/or use of L-thyroxine and/or thyrostatic drugs. This group consisted of 340 individuals, of whom 9 are not included in the table because they belong to the group of 30 persons mentioned above who were not included in Table 2.
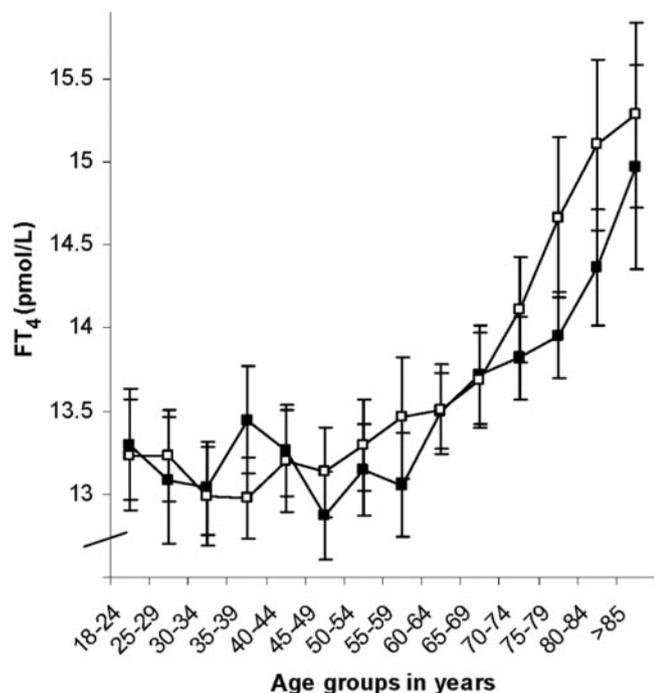
Fig. 1. Mean serum FT$_4$ in different age groups (by sex) in the total population.

The total population consists of 6434 adults. The *error bars* represent 95% CIs of arithmetic means, calculated using the SE. ■, males; □, females.
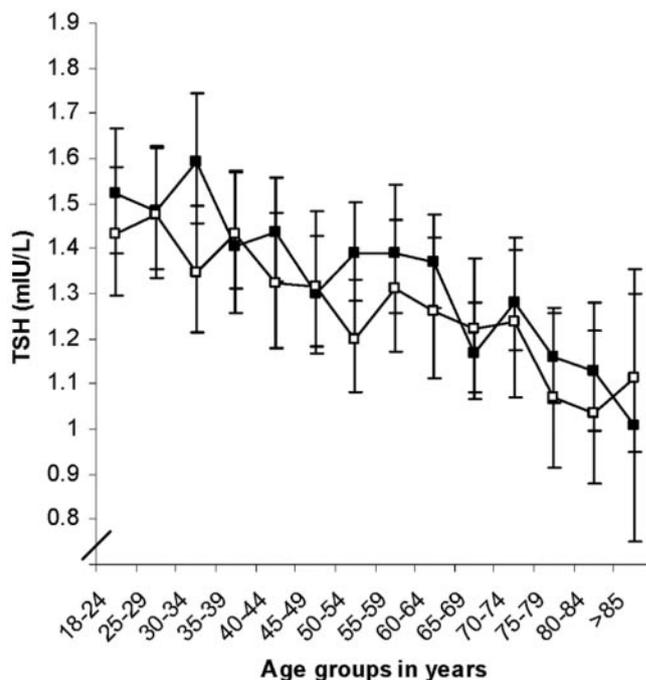

Fig. 2. Geometric mean serum TSH in different age groups (by sex) in the total population.

The total population consists of 6434 adults. The *error bars* represent 95% CIs of means, calculated using the SE calculated from log-transformed values. ■, males; □, females.

15.2 pmol/L (95% CI, 14.7–15.6). The increase in FT$_4$ with age was seen in the total, disease-free, and reference populations (Fig. 1 in the online Data Supplement). The highest FT$_4$ value (52.1 pmol/L) was found in a 55-year-old woman with fully suppressed TSH and the lowest (2.1 pmol/L) in a 38-year-old woman with a TSH of 94.42 mIU/L. Neither reported thyroid disease or use of thyroid medication.

The mean FT$_4$ concentration, after correction for age and sex, was 0.50 pmol/L (95% CI, 0.32–0.68 pmol/L) and was lower in those with positive TPOAbs than in those with negative TPOAbs.

TSH

TSH decreased gradually with age in both males and females (Fig. 2). The (geometric) mean TSH was 1.46 mIU/L (95% CI, 1.36–1.57 mIU/L) in those 18–24 years of age and 1.07 mIU/L (95% CI, 0.92–1.24 mIU/L) in those over 85 years of age. The mean TSH in the total population did not differ from the mean TSH in the reference population: 1.29 (95% CI, 1.26–1.32) mIU/L vs 1.26 (1.24–1.29) mIU/L. In the overall, the disease-free, and the reference populations, the mean TSH concentrations were lower in the older age group (Table 2).

We used the log-transformed values of TSH to calculate the 95% probability intervals for the different populations to obtain possible reference values *(7)* (Table 2). The lower limits of the 95% probability intervals of the 3 populations were only marginally different; however, the upper limit of the total population was considerably higher than the upper limit of the reference population. The largest difference was seen in the 55–59 years age group, in which the reference population had an upper limit of 3.82 mIU/L, whereas the total population had an upper limit of 8.17 mIU/L.

TPOAbs

TPOAbs were found more frequently in females than in males (Table 3). Women 75–79 years of age had the highest percentage, 25.5%, compared with 8.5% in women 18–24 years of age. Among men, the highest percentage was seen men 70–74 years of age (14.3%), whereas no TPOAbs were found in men 18–24 years of age.

In the group that reported thyroid disease, thyroid surgery, and/or use of thyroid medications, 31.6% of males and 42.9% of females had TPOAbs. In the total population, these proportions were 8.6% for males and 18.5% for females. TSH values outside the reference interval were associated with a higher prevalence of positive TPOAbs (Fig. 3). Among all participants with a TSH concentration between 0.4 and 4.0 mIU/L, 11.0% had positive TPOAb results, and among all participants with a TSH concentration ≤0.1 mIU/L, 35.1% had positive TPOAb results. The highest positive TPOAb rate (81.3%) was found among individuals with a TSH >10 mIU/L.

Table 2. Serum TSH (geometric mean and upper and lower limits of 95% probability interval) in the different age groups for the total, the disease-free, and the reference populations.[a]

				TSH, mIU/L					
	Total population			**Disease-free population**			**Reference population**		
		95% probability interval[b]			**95% probability interval[b]**			**95% probability interval[b]**	
Age, years	**Mean**	**Lower limit**	**Upper limit**	**Mean**	**Lower limit**	**Upper limit**	**Mean**	**Lower limit**	**Upper limit**
18–24	1.46	0.40	5.39	1.49	0.53	4.23	1.47	0.54	4.03
25–29	1.48	0.42	5.15	1.50	0.50	4.49	1.42	0.56	3.60
30–34	1.44	0.35	5.83	1.46	0.39	5.50	1.44	0.55	3.78
35–39	1.42	0.34	5.89	1.43	0.37	5.58	1.35	0.50	3.61
40–44	1.37	0.29	6.48	1.40	0.35	5.63	1.35	0.47	3.82
45–49	1.31	0.21	8.06	1.38	0.39	4.80	1.31	0.46	3.70
50–54	1.28	0.26	6.30	1.31	0.32	5.38	1.26	0.36	4.45
55–59	1.35	0.22	8.17	1.39	0.29	6.62	1.34	0.47	3.82
60–64	1.31	0.21	8.31	1.37	0.29	6.50	1.28	0.37	4.47
65–69	1.20	0.17	8.32	1.23	0.21	7.11	1.16	0.25	5.53
70–74	1.26	0.18	8.64	1.27	0.21	7.86	1.14	0.22	5.82
75–79	1.12	0.16	7.68	1.16	0.21	6.34	1.10	0.24	4.97
80–84	1.09	0.16	7.62	1.15	0.22	6.09	1.07	0.22	5.26
>85	1.07	0.13	8.99	1.08	0.14	8.33	1.07	0.13	8.66
All	1.29	0.22	7.43	1.33	0.29	6.15	1.26	0.34	4.66

[a] The total population consisted of 6434 adults. The disease-free population consisted of 6094 adults: the total population minus those self-reporting thyroid disease, thyroid surgery, and/or taking thyroid medication (n = 340). The reference population consisted of 5156 adults, the disease-free population minus the following: pregnant women; those with overt thyrotoxicosis or overt hypothyroidism; those using lithium, amiodarone, kelp, oral glucocorticoids, and/or dopamine agonists; and/or those with positive TPOAbs.

[b] The 95% probability intervals for TSH were calculated using the mean ± 1.96(SD) from log-transformed values.

Discussion

In a large population inhabiting an area with borderline sufficient iodine intake, thyrotoxicosis was found in 1.2% (overt in 0.4%, subclinical in 0.8%) and hypothyroidism in 4.4% (overt in 0.4%, subclinical in 4.0%) of adults. TPOAb results were positive in 8.6% of males and in 18.5% of females, and the presence of TPOAbs was associated with abnormal thyroid function. In participants older than 60 years, mean FT_4 concentrations in-

Table 3. Percentage of persons with positive TPOAbs in the total and the disease-free populations in different age groups (by sex).[a]

	Positive TPOAbs, %			
	Total population		**Disease-free population**	
Age, years	**Males**	**Females**	**Males**	**Females**
18–24	0.0	8.5	0	8.6
25–29	5.2	14.5	5.2	14.7
30–34	4.4	15.4	4.4	14.0
35–39	7.2	16.0	7.2	14.6
40–44	7.1	17.5	6.1	15.9
45–49	6.5	19.2	6.2	16.2
50–54	7.9	18.1	7.5	16.5
55–59	8.2	20.0	7.3	18.8
60–64	9.4	22.3	9.2	18.9
65–69	10.4	22.0	9.3	18.9
70–74	14.3	21.0	13.9	17.3
75–79	9.8	25.5	9.4	24.6
80–84	8.7	17.5	6.5	17.5
>85	10.0	16.1	9.2	12.0
Overall	8.6	18.5	8.0	16.5

[a] The total population consisted of 6434 adults. The disease-free population consisted of 6094 adults: the total population minus those self-reporting thyroid disease, thyroid surgery, and/or taking thyroid medication (n = 340).
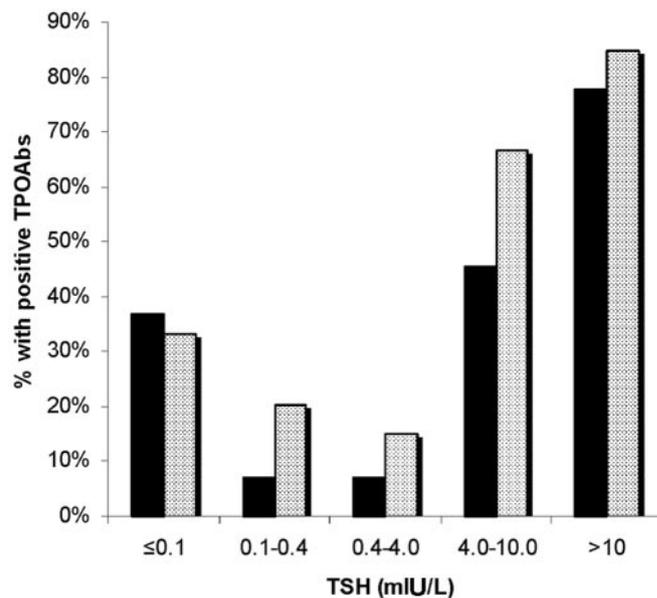

Fig. 3. Percentages of males (■) and females (▨) in the total population with positive TPOAbs for different serum TSH ranges.

creased with age, whereas in all participants, TSH concentrations decreased gradually with age throughout life. The lower limits of the 95% probability intervals of the TSH concentrations of the total and the reference populations were only marginally different, but the upper limit of the 95% probability interval of the TSH concentrations in the total population was considerably higher than the upper limit in the reference population.

Our study can be compared with several other population-based studies. The Whickham survey, performed in the northeastern part of England at a time when no sensitive TSH assays were available, found thyrotoxicosis in 1.6%, overt hypothyroidism in 1.1%, and a TSH concentration >6 mIU/L in 5.0% of participants *(3)*. The prevalence of overt hypothyroidism in our study is lower than that in the Whickham survey but in line with the findings of NHANES III *(2)*. We found the same prevalence of subclinical hypothyroidism as in Whickham, an iodine-replete area. A large study performed in Colorado with a TSH cutoff concentration of 5.1 mIU/L found twice as much subclinical hypothyroidism (9.0%) *(1)*. A Danish survey in an area with borderline iodine deficiency found thyrotoxicosis in 2.0% and hypothyroidism in 1.4% of the participants, with subclinical hypothyroidism in only 0.6% of participants *(11)*. German researchers recently concluded that reference intervals of thyroid function tests in a formerly iodine-deficient region are distinct from the reference intervals that were established in areas with iodine sufficiency *(12)*.

Thyroid abnormalities in populations with low iodine intake and in those with high iodine intake develop in opposite directions: more goiter and thyroid hyperfunction are seen when iodine intake is relatively low, whereas more hypothyroidism is seen when iodine intake is relatively high. This trend was demonstrated very elegantly in a study by Laurberg et al. *(5)*, which compared elderly persons in Iceland (an area with a high iodine intake) with elderly persons in Jutland (an area with a low iodine intake). In Iceland, hypothyroidism was common, and none of the participants had a TSH concentration <0.4 mIU/L, whereas in Jutland, hyperthyroidism was common and hypothyroidism rare. The pattern of thyroid dysfunction seen in our study is compatible with a (marginally) sufficient iodine intake in our area.

The principal difference in results between our study and the NHANES III survey is the decrease of TSH with age in our study, whereas in NHANES III an increase in TSH with age was reported. A possible explanation for this discrepancy is the difference in iodine intake. In the United States, iodine intake has been relatively high in the past, as demonstrated by the NHANES I survey in the early 1970s, which found urine iodine concentrations >500 μg/L in 27.8% of the population *(10)*. According to the International Council for the Control of Iodine Deficiency Disorders (ICCIDD), The Netherlands currently is an iodine-sufficient area. Indeed, a study in 2001 found that goiter was rare among Dutch schoolchildren *(13)*.

However, in the past goiter was prevalent in The Netherlands, and for that reason iodization of bread salt was made mandatory in 1968. Nevertheless, in 1985/1986, the prevalence of goiter was 38%–45% among girls and 20%–31% among boys in the eastern parts of The Netherlands *(14)*. Moreover, several studies conducted in 1981–1993 showed that urinary iodine excretion was <100 μg/24 h in 13%–50% of individuals in The Netherlands *(8, 9)*.

It is well known that in patients with a goiter attributable to long-standing iodine deficiency, autonomously functioning thyroid tissue, characterized by the ability to function without TSH stimulation, can develop within the goiter and lead to subclinical and, later, overt thyrotoxicosis *(15)*. Iodine deficiency induces thyroid hyperplasia in children and nodular transformation and ultimately autonomous function of the thyroid later in life *(16)*, as illustrated by a population-based study in a previously iodine-deficient area of Germany. This study found that the prevalence of thyroid nodules increased with every decade of life and that persons with nodules had a lower median TSH concentration *(17)*. The lower TSH concentrations and higher FT_4 concentrations among the elderly in our study suggest more autonomous thyroid function in this group, possibly caused by the relatively low iodine intake in the past *(18)*. Apparently, the iodine intake in Nijmegen has not been so insufficient as to lead to rates of hyperthyroidism as high as those in truly iodine-insufficient areas such as Jutland. Neither has the iodine intake in the United States been high enough to increase the rates of hypothyroidism to those of areas of clear iodine excess, such as Iceland *(5)*.

TPOAbs are considered to be a sensitive marker for autoimmune thyroid disease *(19)*. In NHANES III, positive TPOAbs were detected in 8.7% of males and 17.0% of females. In our survey, we found TPOAbs in 8.6% of males and 18.5% of females in the total population. A small difference between NHANES III and our survey is that NHANES III found a progressive increase with age in the percentage of people with positive TPOAb results, whereas we observed a maximum value in the 70–79 years age group. A possible explanation for the slightly lower percentage of positive TPOAbs found among those older than 80 years compared with those in their 70s is the selection of healthy seniors in our survey *(20)*. Participants were not institutionalized and had to be able to fill out an extensive questionnaire. In this way, we may have excluded individuals at higher risk for thyroid autoimmunity. As expected, TPOAbs were found more often in the group that reported thyroid disease, thyroid surgery, and/or use of thyroid medication. As in a study performed in Norway, TPOAbs were associated with abnormally low and high TSH concentrations *(21)*.

Earlier studies found that the prevalence of undiagnosed thyroid disorders is high *(1, 2, 11, 21)*. There is an ongoing debate as to whether screening for thyroid dysfunction is useful in the general population *(22–24)*. In

6434 individuals over 18 years of age, we found 31 persons (0.5%) with unknown overt thyroid hyper- or hypofunction. Of the 27 individuals found to have hyperthyroidism, 8 were unaware of their thyroid disease. Hypothyroidism seemed to remain unnoticed more often: 23 of the 26 individuals with overt hypothyroidism did not report thyroid disease.

An even more controversial issue is whether screening for subclinical thyroid dysfunction is indicated (22, 25, 26). Surks et al. (25) concluded recently that there is insufficient evidence to support population-based screening for this condition because there are no convincing data from controlled trials that early treatment reduces morbidity in patients detected by screening. We found 259 individuals with subclinical hypothyroidism, of whom only 35 (13.5%) reported thyroid disease. TPOAbs were found in 61.4% of those 259 individuals, an important finding because the presence of TPOAbs in subclinical hypothyroidism is known to be associated with a higher risk of developing overt hypothyroidism later in life (27). Subclinical thyrotoxicosis is associated with an increased risk of atrial fibrillation (28) and osteoporosis (29, 30). We found 52 persons with subclinical thyrotoxicosis, of whom 22 (42.3%) were known to have thyroid disease and 10 (19.2%) reported L-thyroxine use. Our data show that more attention should be given to proper dosing in L-thyroxine therapy because 46.3% of those on L-thyroxine in our study had a serum TSH concentration outside the reference interval. NHANES III found that only 67% of those with thyroid disease had thyroid function tests in the euthyroid range (2).

It has been proposed that reference intervals for thyroid function tests should be based on the 95% probability intervals obtained in a well-selected group of healthy people (7). NHANES III, a survey designed to give national normative estimates of the health and nutritional status of the US population (17 353 participants older than 12 years), found in the total population a median serum TSH of 1.49 mIU/L with 2.5th and 97.5th percentiles of 0.33 and 5.8 mIU/L, respectively (2). However, in a reference population (excluding individuals with self-reported thyroid disease, goiter, taking thyroid medication, pregnancy, estrogen or androgen use, lithium, detectable thyroglobulin autoantibodies, TPOAbs, or laboratory evidence of hyper- or hypothyroidism), median TSH was 1.39 mIU/L with 2.5th and 97.5th percentiles of 0.45 and 4.12 mIU/L. In our survey, the geometric mean TSH in the total population was 1.29 mIU/L, with the upper and lower limits of the 95% probability interval being 0.22 and 7.43 mIU/L, respectively. In selecting a reference population, we used criteria comparable to those used in NHANES III and found that the geometric mean TSH in the reference population was 1.26 mIU/L with the upper and lower limits of the 95% probability interval being 0.34 and 4.66 mIU/L, respectively. In our study, therefore, as in NHANES III, the lower limit in the 2 populations was about the same, but the upper limit was considerably lower in the reference population than in the total population.

It is interesting to note that the skewed distribution of TSH values persisted after exclusion of those individuals with positive TPOAbs. The use of TPOAb screening, however, does not lead to the detection of all individuals with mild thyroid failure attributable to autoimmunity, as can be concluded from the substantial percentage of those with hypothyroidism who had negative TPOAbs in our study. Mild thyroid failure attributable to autoimmunity could well contribute to this skewed distribution. It is also important to acknowledge that population-based reference intervals have limitations when used for the interpretation of results of individual TSH values, because changes in an individual may remain undetected because of the high degree of intraindividual variance for TSH (31, 32).

In conclusion, our survey is the largest European population-based study to date to provide extensive data on serum FT_4, TSH (using a third-generation assay), and TPOAbs (using a sensitive assay). We found that serum TSH decreases gradually with age, whereas serum FT_4 increases with age in individuals older than 60 years, possibly because of development of thyroid autonomy after longstanding borderline sufficient iodine intake in the eastern part of The Netherlands. Excluding those at risk for thyroid disease lowers the upper limit of the TSH reference interval considerably.

References

1. Canaris GJ, Manowitz NR, Mayor G, Ridgway EC. The Colorado thyroid disease prevalence study. Arch Intern Med 2000;160: 526–34.

2. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, et al Serum TSH, T_4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab 2002;87:489–99.

3. Tunbridge WM, Evered DC, Hall R, Appleton D, Brewis M, Clark F, et al. The spectrum of thyroid disease in a community: the Whickham Survey. Clin Endocrinol (Oxf) 1977;7:481–93.

4. Sawin CT, Castelli WP, Hershman JM, McNamara P, Bacharach P. The aging thyroid. Thyroid deficiency in the Framingham Study. Arch Intern Med 1985;145:1386–8.

5. Laurberg P, Pedersen KM, Hreidarsson A, Sigfusson N, Iversen E, Knudsen PR. Iodine intake and the pattern of thyroid disorders: a comparative epidemiological study of thyroid abnormalities in the

elderly in Iceland and in Jutland, Denmark. J Clin Endocrinol Metab 1998;83:765–9.

6. Bagchi N, Brown TR, Parish RF. Thyroid dysfunction in adults over age 55 years. A study in an urban US community. Arch Intern Med 1990;150:785–7.

7. Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, et al. Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. Thyroid 2003;13:3–126.

8. Brussaard JH, Brants HA, Hulshof KF, Kistemaker C, Lowik MR. Iodine intake and urinary excretion among adults in the Netherlands. Eur J Clin Nutr 1997;51(Suppl 3):S59–62.

9. Brussaard JH, Hulshof KF, Kistemaker C, Lowik MR. Adequacy of the iodine supply in The Netherlands. Eur J Clin Nutr 1997; 51(Suppl 4):S11–5.

10. Hollowell JG, Staehling NW, Hannon WH, Flanders DW, Gunter EW, Maberly GF, et al. Iodine nutrition in the United States. Trends and public health implications: iodine excretion data from National Health and Nutrition Examination Surveys I and III (1971–1974 and 1988–1994). J Clin Endocrinol Metab 1998;83:3401–8.

11. Knudsen N, Jorgensen T, Rasmussen S, Christiansen E, Perrild H. The prevalence of thyroid dysfunction in a population with borderline iodine deficiency. Clin Endocrinol (Oxf) 1999;51:361–7.

12. Volzke H, Alte D, Kohlmann T, Ludemann J, Nauck M, John U, et al. Reference intervals of serum thyroid function tests in a previously iodine-deficient area. Thyroid 2005;15:279–85.

13. Wiersinga WM, Podoba J, Srbecky M, van Vessem M, van Beeren HC, Platvoet-Ter Schiphorst MC. A survey of iodine intake and thyroid volume in Dutch schoolchildren: reference values in an iodine-sufficient area an. Eur J Endocrinol 2001;144:595–603.

14. Rees-Wortelboer MM, Schroder-van der Elst JP, Lycklama A, van der Heide D. [Iodine and goiter in The Netherlands]. Ned Tijdschr Geneeskd 1987;131:1821–4.

15. Dremier S, Coppee F, Delange F, Vassart G, Dumont JE, van Sande J. Clinical review 84: Thyroid autonomy: mechanism and clinical effects. J Clin Endocrinol Metab 1996;81:4187–93.

16. Krohn K, Paschke R. Clinical review 133: Progress in understanding the etiology of thyroid autonomy. J Clin Endocrinol Metab 2001;86:3336–45.

17. Volzke H, Ludemann J, Robinson DM, Spieker KW, Schwahn C, Kramer A, et al. The prevalence of undiagnosed thyroid disorders in a previously iodine-deficient area. Thyroid 2003;13:803–10.

18. Studer H, Derwahl M. Mechanisms of nonneoplastic endocrine hyperplasia—a changing concept: a review focused on the thyroid gland. Endocr Rev 1995;16:411–26.

19. Demers LM, Spencer CA. Laboratory medicine practice guidelines: laboratory support for the diagnosis and monitoring of thyroid disease. Clin Endocrinol (Oxf) 2003;58:138–40.

20. Mariotti S, Chiovato L, Franceschi C, Pinchera A. Thyroid autoimmunity and aging. Exp Gerontol 1998;33:535–41.

21. Bjoro T, Holmen J, Kruger O, Midthjell K, Hunstad K, Schreiner T, et al. Prevalence of thyroid disease, thyroid dysfunction and thyroid peroxidase antibodies in a large, unselected population. The Health Study of Nord-Trondelag (HUNT). Eur J Endocrinol 2000;143:639–47.

22. Helfand M. Screening for subclinical thyroid dysfunction in non-pregnant adults: a summary of the evidence for the U.S. Preventive Services Task Force. Ann Intern Med 2004;140:128–41.

23. Gharib H, Tuttle RM, Baskin HJ, Fish LH, Singer PA, McDermott MT. Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. J Clin Endocrinol Metab 2005;90:581–5.

24. Ringel MD, Mazzaferri EL. Subclinical thyroid dysfunction—can there be a consensus about the consensus? J Clin Endocrinol Metab 2005;90:588–90.

25. Surks MI, Ortiz E, Daniels GH, Sawin CT, Col NF, Cobin RH, et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. JAMA 2004;291:228–38.

26. Surks MI. Subclinical thyroid dysfunction: a joint statement on management from the American Association of Clinical Endocrinologists, the American Thyroid Association, and the Endocrine Society. J Clin Endocrinol Metab 2005;90:586–7.

27. Vanderpump MP, Tunbridge WM, French JM, Appleton D, Bates D, Clark F, et al. The incidence of thyroid disorders in the community: a twenty-year follow-up of the Whickham Survey. Clin Endocrinol (Oxf) 1995;43:55–68.

28. Sawin CT, Geller A, Wolf PA, Belanger AJ, Baker E, Bacharach P, et al. Low serum thyrotropin concentrations as a risk factor for atrial fibrillation in older persons. N Engl J Med 1994;331:1249–52.

29. Faber J, Galloe AM. Changes in bone mass during prolonged subclinical hyperthyroidism due to L-thyroxine treatment: a meta-analysis. Eur J Endocrinol 1994;130:350–6.

30. Uzzan B, Campos J, Cucherat M, Nony P, Boissel JP, Perret GY. Effects on bone mass of long term treatment with thyroid hormones: a meta-analysis. J Clin Endocrinol Metab 1996;81:4278–89.

31. Andersen S, Pedersen KM, Bruun NH, Laurberg P. Narrow individual variations in serum T(4) and T(3) in normal subjects: a clue to the understanding of subclinical thyroid disease. J Clin Endocrinol Metab 2002;87:1068–72.

32. Browning MC, Ford RP, Callaghan SJ, Fraser CG. Intra- and interindividual biological variation of five analytes used in assessing thyroid function: implications for necessary standards of performance and the interpretation of results. Clin Chem 1986; 32:962–6.