THYROID
Volume 25, Number 6, 2015

DOI: 10.1089/thy.2014.0574

Thyrotropin Versus Age Relation as an Indicator of Historical Iodine Intake

Annenienke C. van de Ven,[1] Romana T. Netea-Maier,[1] Johannes W. Smit,[1] Ron Kusters,[2] Jos W.J. van der Stappen,[3] Claudia J. Pronk-Admiraal,[4] Madelon M. Buijs,[4] Christian H.H. Schoenmakers,[5] Stephan G.A. Koehorst,[6] Monique J.M. de Groot,[7] Fred C.G.J. Sweep,[8] Ad R.M.M. Hermus,[1] and Martin den Heijer[1,9]

Background: In populations with mild iodine deficiency, the serum level of thyrotropin (TSH) is negatively and the serum free thyroxine (FT_4) is positively associated with age. An ongoing decrease of TSH and increase of FT_4 can be found after iodine supplementation. The aim of this study was to investigate whether there are current differences in the relation between thyroid function and age in relation to differences in iodine intake in the past.
Methods: Eight medical laboratories in several regions of The Netherlands, which are all iodine sufficient at present but with a difference in iodine status in the past, provided the results of all TSH and FT_4 measurements performed from 2006 until 2011, resulting in 330,802 TSH and 103,940 FT_4 measurements.
Results: The negative association between TSH and age in the elderly is only present in areas with a historical iodine deficiency (regression coefficients [RC] −0.008, 95% confidence interval [CI] −0.009; −0.007). In the historically iodine-sufficient population, TSH shows no obvious increase or decrease with age. In both the historically iodine-sufficient and iodine-deficient populations, FT_4 levels were positively associated with age in the elderly (RC 0.009, 95% CI 0.008; 0.010 and RC 0.008, 95% CI 0.007; 0.010, respectively).
Conclusions: There are differences in relation between thyroid function and age between populations with differences in iodine intake in the past, despite an adequate iodine status at present. This raises the question whether the present but also historical iodine status of a population should be taken into account when establishing the reference limits of TSH and FT_4.

Iodine is an important component of thyroid hormones. Severe iodine deficiency can cause primary hypothyroidism and cretinism. In case of mild iodine deficiency, several autoregulatory mechanisms within the thyroid are triggered to prevent hypothyroidism (1). When these mechanisms fail, there is an increase of thyrotropin (TSH) secretion through hypothalamic/pituitary feedback in order to maintain euthyroidism. The compensatory mechanisms within the thyroid and the continuous TSH stimulation eventually may lead to growth and autonomous function of the thyroid gland and, especially when iodine is supplemented later, to hyperthyroidism.

Some large population-based studies, such as the NHANES III study, reported that the serum TSH level is positively associated with age in populations with adequate or high iodine intake (2–6). The fact that the elderly have on average higher TSH values in these iodine-sufficient populations is one of the reasons why it has been suggested to increase the upper reference limit of normal serum TSH in the elderly (7,8). However, other cross-sectional population studies have shown that in populations with mild or moderate iodine deficiency, the average serum level of TSH is negatively and that of free thyroxine (FT_4) positively associated with age, probably due to autonomous function of the thyroid gland (9–12). The

[1]Department of Medicine, Division of Endocrinology, [8]Department of Laboratory Medicine, Radboud University Medical Centre, Nijmegen, the Netherlands.
[2]Laboratory for Clinical Chemistry and Haematology, Jeroen Bosch Hospital, 's-Hertogenbosch, the Netherlands.
[3]Department of Laboratory Medicine, Canisius-Wilhelmina Ziekenhuis, Nijmegen, the Netherlands.
[4]Atal-Medial Diagnostic Centers, Hoofddorp, The Netherlands.
[5]Department of Laboratory Medicine, Elkerliek Hospital, Helmond, the Netherlands.
[6]Department of Laboratory Medicine, Slingeland Hospital, Doetinchem, the Netherlands.
[7]Department of Laboratory Medicine, Amphia Hospital, Breda, the Netherlands.
[9]Department of Internal Medicine, Section of Endocrinology, VU Medical Center, Amsterdam, the Netherlands.

suggestion of increasing the upper limit of the reference range of serum TSH in the elderly seems therefore not appropriate for these populations.

Knudsen *et al.* (10) showed a different association between serum TSH level and age in two areas in Denmark with slightly different iodine status. In Aalborg, an area with moderate iodine insufficiency, there was a decline in serum TSH levels with age, whereas in Copenhagen, an area with only a very mild iodine insufficiency, this decline was not present. So, even within a relatively small geographic area, differences of iodine intake seem to influence the relation between thyroid function and age.

In the past, mild iodine deficiency was present in the eastern and southern part of The Netherlands (13–15). After the introduction of the water supply system (around 1900), the prevalence of goiter increased in the eastern and southern part of the country. The groundwater that was used for the water supply system contained less iodine than the previously used more superficial ground water and contained less iodine in the eastern and southern part of The Netherlands than in other parts of the country (15). Iodine supplementation was instituted as of 1935. Since then, several additional measures such as the compulsory use of iodized salt in bakeries, instituted in 1963, were implemented to achieve a daily intake of iodine within the optimal range as recommended by the World Health Organization (WHO) (16). Despite these efforts at increasing iodine intake, in 1981 the iodine status was still insufficient in the eastern part of The Netherlands and goiter was more prevalent in comparison to the western part of The Netherlands (15,17). Therefore, in 1982, the amount of iodized salt in bakeries was increased. Currently, the iodine status of The Netherlands is considered to be adequate, based on studies regarding iodine intake and urinary excretion in several regions in The Netherlands (18–24).

In subjects of the Nijmegen Biomedical Study (NBS), a large population-based survey in the eastern part of The Netherlands, serum TSH level is negatively associated with age and FT_4 level is positively associated with age (12). Despite the adequate iodine status of this population at this moment, a currently ongoing decrease of TSH levels and increase of FT_4 levels in subjects 50–72 years old was found in a longitudinal study (25). The decrease of TSH and increase of FT_4 with age in this population is probably caused by the mild iodine deficiency in the past. Iodine deficiency in the past may have led to autonomous thyroid function, which at present causes an ongoing increase of FT_4 levels and decrease of TSH levels over time.

These studies suggest therefore that both the current and the past iodine intake can influence the relation between thyroid function and age. Because iodine insufficiency in the past seems to cause an ongoing increase of FT_4 and decrease of TSH even after attaining an adequate iodine status, we hypothesized that there might also be differences in the relationship between thyroid function and age in populations that had a different iodine intake in the past. Therefore, the aim of this study was to investigate the relation between thyroid function and age in populations from several geographic regions in The Netherlands that are iodine sufficient at present but had a different iodine intake in the past.

Materials and Methods

To sample several regions with different iodine intake in the past we used routinely achieved TSH and FT_4 levels from laboratories that perform these measurements ordered by general practitioners for screening purposes. Because thyroid hormone assays are ordered with high frequency we hypothesized that the results are representative for the regional population. Eight large medical laboratories were invited to participate. The laboratories were chosen for their geographic localization in The Netherlands, namely either in the historically iodine deficient southern/eastern part of The Netherlands or in the historically iodine sufficient western part of The Netherlands (15). The participating laboratories were situated in the cities Nijmegen, 's-Hertogenbosch, Doetinchem, Helmond, Breda, Haarlem, Amsterdam, and Leiden. They each provided the results of all TSH and FT_4 measurements performed at the respective laboratories from 2006 until 2011 (the measurements from Leiden were performed in 2013 only, the measurements from Amsterdam were performed from 2006 until 2013). For each person in whom TSH or FT_4 level was measured, data on age and sex were provided. All measurements of TSH and FT_4 were performed on request of a general practitioner in outpatients. Serum TSH (third-generation assay) and FT_4 levels were measured by random access analyzers (electrochemiluminescence assay [ECLIA] Modular E170, Roche Diagnostics, Mannheim, Germany; luminescent enzyme immunoassay [LEIMA] Cobas 6000, Roche; ECLIA Dimension Vista, Siemens Healthare, Erlangen, Germany; LEIMA Immulite 2000, Siemens; chemiluminescence immunoassay [CLIA] Dxl 800, Beckman Coulter, Woerden, The Netherlands). Details of the participating laboratories and the laboratory methods are shown in Supplementary Table S1 (Supplementary Data are available online at www.liebertpub.com/thy).

To ensure that we included only the treatment-naïve patients we applied the following strategy. We assumed that when the thyroid hormone levels of a patient without previously known thyroid disease are measured, it is probably because of symptoms such as fatigue or weight gain, etc. Most of the time, the general practitioner will also order other blood analyses in order to screen for common diseases in such symptomatic patients. Some of the participating laboratories offer a package of several blood analyses to general practitioners to screen for some common causes of fatigue in patients. These packages for example include glucose level, erythrocyte sedimentation rate, hemoglobin level, and TSH level. When such a package was available at a laboratory, only these TSH measurements were included. If such a package was not available, only TSH measurements were included if glucose and hemoglobin level were measured at the same time. In one laboratory (Helmond), glucose levels were not available, but hemoglobin levels were required for inclusion. We assumed that most patients using thyroid medication get their thyroid hormones level monitored periodically by measuring TSH and/or FT_4 levels only. Therefore, we excluded all subjects in whom only a serum TSH and/or a FT_4 level was measured.

Historical data of iodine status in the regions of the participating laboratories are shown in Table 1. In Haarlem, Leiden, and Amsterdam, three cities situated in the western part of The Netherlands, low goiter prevalence has been reported in the past (1951) whereas a high goiter prevalence has been reported in the cities in the eastern/southern part of The Netherlands (26). Iodine intake was higher in Leiden in the late 1970s in comparison to some cities (including Helmond

Table 1. Overview of Historical Data on Iodine Status of Participating Regions

	Geographic region in The Netherlands	*Historical data on iodine status*
Nijmegen	Eastern part	1951 goiter prevalence 40–60% (26) 1977 urinary iodine excretion 80 μg/d, goiter prevalence 47% (15) 2006 median urinary iodine concentration 130 μg/L (25)
's-Hertogenbosch	Southern part	1951 goiter prevalence 20–30% (26)
Helmond	Eastern–southern part	1951 goiter prevalence 40–60% (26) 1987 urinary iodine excretion ♀111-♂135 μg/d, goiter prevalence 31–39% (13)
Doetinchem	Eastern part	1951 goiter prevalence >60% 26 1977 urinary iodine excretion ♀69–♂118 μg/d, goiter prevalence 20–50% (15) 1987 urinary iodine excretion ♀122–♂157 μg/d, goiter prevalence 20–35% (13) 1995 median urinary iodine concentration 151–166 μg/L, goiter prevalence 0.8% (20) 2006 urinary iodine excretion 236 μg/d (24) 2010 urinary iodine excretion 165 μg/d (24)
Breda	Southern part	1951 goiter prevalence 40–60% (26)
Haarlem	Western part	1951 goiter prevalence 0–20% (26) 1995 median urinary iodine concentration 142–168 μg/L, goiter prevalence 2.6% (20)
Amsterdam	Western part	1951 goiter prevalence 20–30% (26) 1995 median urinary iodine concentration 142–168 μg/L, goiter prevalence 2.6% (20)
Leiden	Western part	1951 goiter prevalence 20–30% (26) 1977 urinary iodine excretion ♀123–♂126 μg/d, goiter prevalence 8–10% (15) 1987 urinary iodine excretion ♀114–♂153 μg/d, goiter prevalence 7–32% (13)

and Nijmegen) in the eastern/southern part of The Netherlands (15). In the early 1980s, iodine intake was still insufficient in women (in Doetinchem and Helmond but also in Leiden) (13). For the past 20 years, a sufficient iodine intake has been reported in all regions of The Netherlands (18–24).

Statistical analysis

We standardized the TSH and FT_4 values in order to show the results of different laboratories combined, using *z* scores (the number of standard deviations that a value differs from the mean). Because of a skewed distribution of TSH, TSH measurements were (natural) log transformed and we displayed geometric means of TSH with its 95% confidence intervals when presenting the results per laboratory separately (Supplementary Fig. S1). Linear regression analysis was used in order to describe the association between thyroid hormones (z scores, TSH after log transformation) and age. Because of a nonlinear relationship between thyroid hormones and age, as shown in Figure 1, the population was divided in different age categories (0–35; 35–60; 60 years or older) and linear regression analyses was performed per age category. In order to compare the regression coefficients (RC), we included an interaction term in the regression model.

Results

In total, 894,435 TSH measurements and 448,655 FT_4 measurements were obtained. A total of 330,802 TSH and 103,940 FT_4 measurements were performed in combination with (glucose and) hemoglobin measurements and these results were used for analyses. The numbers of included TSH and FT_4 measurements per laboratory are shown in Supplementary Table S1.

Figure 1 shows the standardized values of TSH and FT_4 for the eastern/southern part ('s-Hertogenbosch, Nijmegen, Doetinchem, Helmond, and Breda) and the western part of The Netherlands (Amsterdam, Leiden, and Haarlem). In both the eastern/southern part and the western part, average TSH levels are negatively associated with age during young adulthood. In the eastern/southern part, average TSH levels then increase gradually from approximately 35 years until the age of 60 years. In the elderly (60 years or older), average TSH levels decrease with age (RC −0.008, 95% CI −0.009; −0.007, this corresponds with a decrease of 0.7% of the average TSH level per year). In the western part, TSH shows no obvious increase or decrease with age in the population of approximately 35 years and older (age 60 years or older: RC −0.002, 95% CI −0.003; −0.001, this corresponds with a decrease of 0.1% of the average TSH level per year). The effect size is only very small and when considering Figure 1, we conclude that there is no obvious trend of decrease or increase of TSH in elderly in the western part. The difference in RC between the eastern/southern part and western part in the elderly is 0.006, 95% CI 0.004–0.007, $p < 0.001$.

The average FT_4 levels in the eastern/southern part show the opposite pattern of the TSH levels in this area: the FT_4

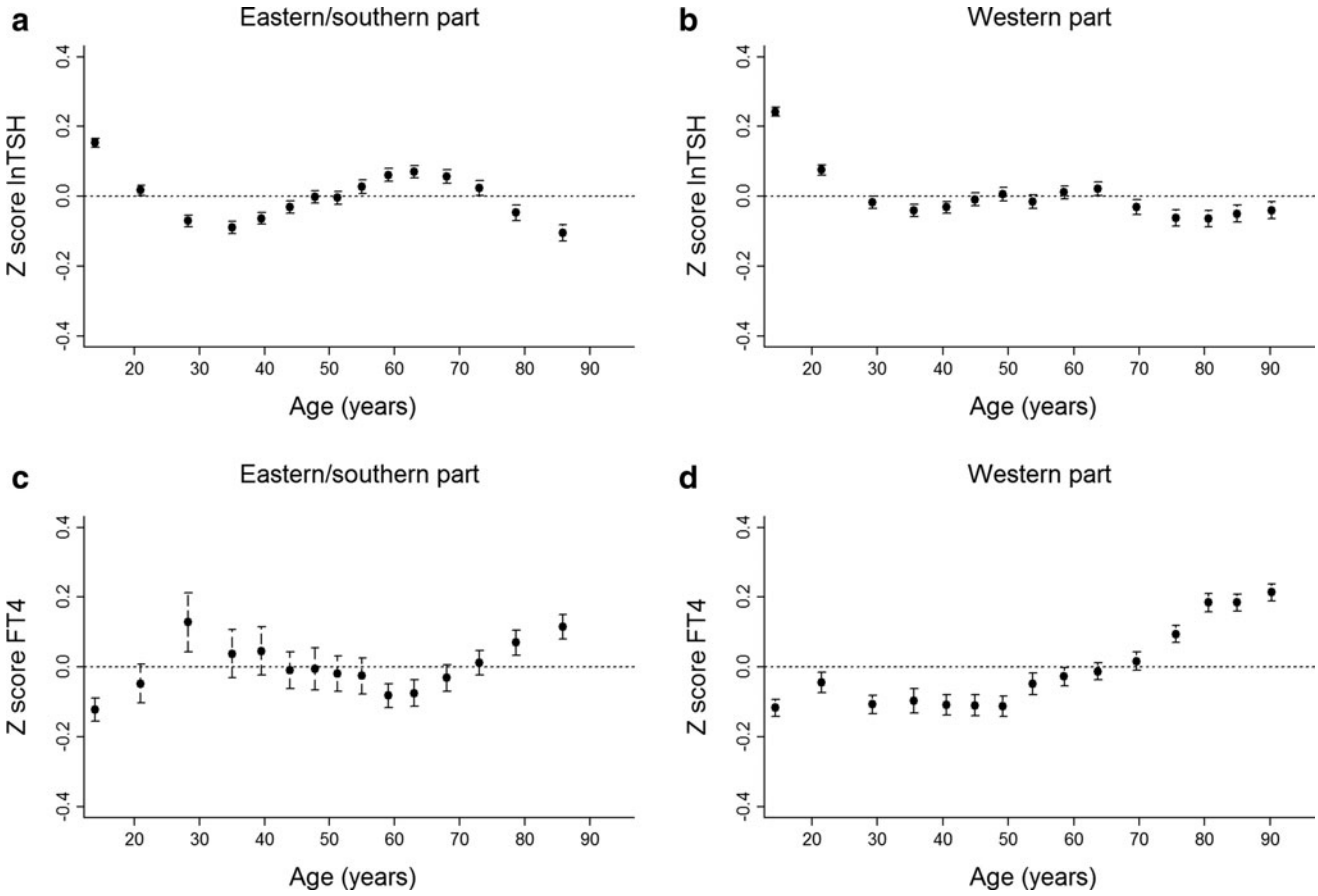

FIG. 1. Standardized values of serum TSH **(a)** and FT_4 **(c)** for the eastern/southern part (historical iodine deficient areas: 's-Hertogenbosch, Nijmegen, Doetinchem, Helmond, and Breda) and the western part of The Netherlands **(b** and **d)** (historical iodine sufficient areas: Amsterdam, Leiden, and Haarlem). Total number of measurements: serum TSH eastern/southern part, 178,074; western part, 152,728; serum FT_4 eastern/southern part, 26,297; western part, 77,643. TSH, thyrotropin; FT_4, free thyroxine.

levels are positively associated with age during young adulthood and then decrease until the age of 60 years. In subjects aged 60 years or older, FT_4 levels further increase with age (RC 0.008, 95% CI 0.007–0.010, this corresponds with an increase of 0.04 pmol/L of the average FT_4 level per year). In the western part, FT_4 levels show no obvious increase or decrease with age until the age of 60 years. In subjects, 60 years or older, FT_4 levels are positively associated with age (RC 0.009, 95% CI 0.008; 0.010, this corresponds with an increase of 0.04 pmol/L of the average FT_4 level per year).

Supplementary Figure S1 shows the geometric means of TSH levels by age per laboratory. Supplementary Figure S2 shows the means of FT_4 levels by age per laboratory.

Discussion

The aim of this study was to investigate whether there are differences in the relation between thyroid function and age between populations with differences in iodine intake in the past, despite an adequate iodine status at present, indicating that the TSH/FT_4 versus age relation could be used as an indicator of historical iodine status. Our results show that the negative association between TSH and age in the elderly (60 years or older) is only present in areas with a history of (mild) iodine deficiency. In the areas with historically more adequate iodine status, TSH levels were neither positively nor negatively associated with age. An explanation for these findings could be the fact that due to mild iodine deficiency in the past, several compensatory mechanisms within the thyroid and continuous TSH stimulation have led to growth and autonomous function of the thyroid. Thereafter when iodine intake is supplemented, a tendency to hyperthyroidism may develop. Another explanation could be that iodine deficiency has an epigenetic effect early in life, perhaps even prenatally, which is persistent despite of iodine repletion.

Our results agree with those of Knudsen *et al.* (10), which showed a different association between TSH and age in two areas in Denmark with slightly different iodine status at present. In our study, in the previously iodine-deficient area, we could detect the negative association between TSH and age in the elderly (60 years or older) only. By contrast, in younger subjects (aged 35–60 years old), TSH was positively associated with age, causing a remarkable curve in the TSH–age relation figure. The reason for this might be the fact that the younger subjects are not exposed to iodine deficiency in the past, due to the mandatory use of iodized salt in bakeries in the Netherlands since 1963 and the successive efforts of the Dutch government to achieve an adequate iodine status since then. Therefore, the younger subjects are less likely to

have developed growth and autonomous function of the thyroid. We hypothesize that if one would examine the relationship between TSH and age in several decades in this area, one might find a positive association between TSH and age in all age groups 35 years or older. Probably the results would then be more in line with the results of the NHANES III study, a large population study in an iodine sufficient area, which reported a positive association between TSH and age in all age groups (2).

In the historically iodine-deficient area, FT_4 levels are negatively associated with age in subjects aged 35–60 years and positively associated with age in the young subjects aged 35 years or younger and in the elderly, aged 60 years or older (i.e., the exact opposite of the associations between TSH levels and age in this area) as one would expect. However, despite the lack of a positive or negative association between TSH levels and age in the historical iodine sufficient area, FT_4 levels were positively associated with age in the elderly in this population. It has been previously hypothesized that there is a change of the pituitary TSH set point in the elderly and higher FT_4 levels do not cause the same TSH suppression as in younger individuals (4,5). Possible mechanisms for this are an altered pituitary sensitivity for thyroid hormones, a decrease in TSH bioactivity and/or a decreased responsiveness of the thyroid gland to TSH in the elderly. The studies of Bremner *et al.* (4) and Waring *et al.* (5) showed in iodine-sufficient populations an increase of TSH with age without decrease or even a small increase of FT_4 levels with age in elderly.

The fact that elderly have on average higher TSH values in these two study populations and in several other iodine-sufficient populations is one of the reasons why it has been suggested to increase the upper reference limit of TSH level in the elderly (4–8). However, the present study and other studies reporting a lower average TSH in the elderly in current or historical iodine-insufficient populations raise the question whether, besides age and race/ethnicity, the present and historical iodine status of a population should be taken into account when establishing the reference limits of TSH and FT_4 (9–12). Guan *et al.* (27) compared three areas with different levels of iodine intake and showed that the average TSH level and the 2.5th and 97.5th percentiles were lowest in the iodine-deficient area and highest in the population with iodine excess, even in a rigorously selected reference population after exclusion of subjects with thyroid disease, thyroid antibodies, thyroid nodules/goiter, or a family history of thyroid disease.

In our study, there was a striking negative association between TSH and age and the concordant positive association between FT_4 and age in the young subjects (aged 35 years and younger). In particular the negative association between TSH and age was a consistent finding in all the laboratories. Most population-based studies include adults only, so little is known about the relationship between thyroid function and age in children and teenagers. The population study of Guan *et al.* (27) shows similar results: the mean TSH level in the youngest age group (14–19 years old) was approximately 20–30% higher than those in other age groups, even after exclusion of subjects with thyroid disease, thyroid antibodies, thyroid nodules/goiter, or a family history of thyroid disease. Further studies, preferably performed in an iodine-sufficient population and after exclusion of subjects with thyroid disease and risk factors for thyroid disease, are needed to confirm these interesting findings.

A limitation of our study is the fact that we had no data on medical history of thyroid disease or thyroid autoimmunity of the participating subjects. In order to address this problem, we included only the subjects in whom a screening package of several laboratory measurements was performed and assumed that these subjects were less likely to have a known thyroid disease. Subjects taking thyroid medication more likely would have their thyroid hormones level monitored periodically by measuring TSH (and/or FT_4) levels only. The results of the laboratory of Nijmegen, that offered a standard package, including a glucose level, erythrocyte sedimentation rate, hemoglobin level and TSH, to general practitioners to screen for some common causes of fatigue in patients, were similar to the results of the other laboratories in the historical iodine deficient area. Moreover, they were also similar to the results of these laboratories when subjects in whom only TSH and/or FT_4 levels were measured were not excluded (data not shown). Because of the large number of measurements, the effect of the few subjects with thyroid disease who might have been undesirably included despite our selection of combined measurements of glucose, hemoglobin, and TSH is probably negligible.

In conclusion, this study shows that there are differences in the relation between thyroid function and age between populations with differences in iodine intake in the past, despite an adequate iodine status at present. The negative association between TSH and age in the elderly is only present in areas with a history of (mild) iodine deficiency. This raises the question whether, in addition to age and race/ethnicity, the present but also historical iodine status of a population should be taken into account when establishing the reference limits of TSH and FT_4.

Author Disclosure Statement

No competing financial interests exist.

References

1. Obregon MJ, Escobar del RF, Morreale de EG 2005 The effects of iodine deficiency on thyroid hormone deiodination. Thyroid **15:**917–929.
2. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE 2002 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 **87:**489–499.
3. Boucai L, Surks MI 2009 Reference limits of serum TSH and free T4 are significantly influenced by race and age in an urban outpatient medical practice. Clin Endocrinol **70:** 788–793.
4. Bremner AP, Feddema P, Leedman PJ, Brown SJ, Beilby JP, Lim EM, Wilson SG, O'Leary PC, Walsh JP 2012 Age-related changes in thyroid function: a longitudinal study of a community-based cohort. J Clin Endocrinol Metab **97:**1554–1562.
5. Waring AC, Arnold AM, Newman AB, Buzkova P, Hirsch C, Cappola AR 2012 Longitudinal changes in thyroid function in the oldest old and survival: the cardiovascular health study all-stars study. J Clin Endocrinol Metab **97:**3944–3950.

6. Vadiveloo T, Donnan PT, Murphy MJ, Leese GP 2013 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). J Clin Endocrinol Metab **98:**1147–1153.
7. Surks MI, Hollowell JG 2007 Age-specific distribution of serum thyrotropin and antithyroid antibodies in the US population: implications for the prevalence of subclinical hypothyroidism. J Clin Endocrinol Metab **92:**4575–4582.
8. Surks MI, Boucai L 2010 Age- and race-based serum thyrotropin reference limits. J Clin Endocrinol Metab **95:** 496–502.
9. Laurberg P, Cerqueira C, Ovesen L, Rasmussen LB, Perrild H, Andersen S, Pedersen IB, Carle A 2010 Iodine intake as a determinant of thyroid disorders in populations. Best Pract Res Clin Endocrinol Metab **24:**13–27.
10. Knudsen N, Bulow I, Jorgensen T, Laurberg P, Ovesen L, Perrild H 2000 Comparative study of thyroid function and types of thyroid dysfunction in two areas in Denmark with slightly different iodine status. Eur J Endocrinol **143:**485–491.
11. Aghini-Lombardi F, Antonangeli L, Martino E, Vitti P, Maccherini D, Leoli F, Rago T, Grasso L, Valeriano R, Balestrieri A, Pinchera A 1999 The spectrum of thyroid disorders in an iodine-deficient community: the Pescopagano survey. J Clin Endocrinol Metab **84:**561–566.
12. Hoogendoorn EH, Hermus AR, de Vegt F, Ross HA, Verbeek AL, Kiemeney LA, Swinkels DW, Sweep FC, den Heijer M 2006 Thyroid function and prevalence of antithyroperoxidase antibodies in a population with borderline sufficient iodine intake: influences of age and sex. Clin Chem **52:**104–111.
13. van Rees-Wortelboer MM, Schroder-van der Elst JP, Lycklama A, van der Heide D 1987 [Iodine and goiter in The Netherlands]. Ned Tijdschr Geneeskd **131:**1821–1824.
14. Brug J, Lowik MR, Wedel M, Odink J 1992 Iodide excretion before and after revision of goiter prophylaxis (Dutch Nutrition Surveillance System). Eur J Clin Nutr **46:**671–678.
15. Netherlands Health Council 1981 Adviezen inzake jodiumvoorzieningen. Verslagen, adviezen, rapporten no. 78. Staatsuitgeverij, The Hague, The Netherlands.
16. World Health Organization, United Nations Children's Fund & International Council for Control of Iodine Deficiency Disorders 2001 Assessment of iodine deficiency disorders and monitoring their elimination. WHO/NHD/01.1.
17. Querido A, Tan WD 1981 Relating goiter incidence to urinary iodine excretion. Ann Endocrinol-Paris **42:**A39–A39.
18. Brussaard JH, Brants HA, Hulshof KF, Kistemaker C, Lowik MR 1997 Iodine intake and urinary excretion among adults in the Netherlands. Eur J Clin Nutr **51(Suppl 3):** S59–S62.
19. Brussaard JH, Hulshof KF, Kistemaker C, Lowik MR 1997 Adequacy of the iodine supply in The Netherlands. Eur J Clin Nutr **51(Suppl 4):**S11–S15.
20. Wiersinga WM, Podoba J, Srbecky M, van Vessem M, van Beeren HC, Platvoet-Ter Schiphorst MC 2001 A survey of iodine intake and thyroid volume in Dutch schoolchildren: reference values in an iodine-sufficient area and the effect of puberty. Eur J Endocrinol **144:**595–603.
21. Delange F, Benker G, Caron P, Eber O, Ott W, Peter F, Podoba J, Simescu M, Szybinsky Z, Vertongen F, Vitti P, Wiersinga W, Zamrazil V 1997 Thyroid volume and urinary iodine in European schoolchildren: standardization of values for assessment of iodine deficiency. Eur J Endocrinol **136:**180–187.
22. Netherlands Health Council 2011 Towards maintaining an optimal iodine intake. Publication no. 2008/14 Staatsuitgeverij, The Hague, The Netherlands.
23. de Benoist B, McLean E, Andersson M, Rogers L 2008 Iodine deficiency in 2007: global progress since 2003. Food Nutr Bull **29:**195–202.
24. Hendriksen MA, van Raaij JM, Geleijnse JM, Wilson-van den Hooven C, Ocke MC, van der A DL 2013 Monitoring salt and iodine intakes in Dutch adults between 2006 and 2010 using 24 h urinary sodium and iodine excretions. Public Health Nutr **17:**1431–1438.
25. van de Ven AC, Netea-Maier RT, Ross HA, van Herwaarden TA, Holewijn S, de Graaf J, Kiemeney BL, van Tienoven D, Wetzels JF, Smit JW, Sweep FC, Hermus AR, den Heijer M 2014 Longitudinal trends in thyroid function in relation to iodine intake: ongoing changes of thyroid function despite adequate current iodine status. Eur J Endocrinol **170:**49–54.
26. Health Organization TNO 1959 De endemische krop in Nederland. Van Gorcum, Assen, The Netherlands.
27. Guan H, Shan Z, Teng X, Li Y, Teng D, Jin Y, Yu X, Fan C, Chong W, Yang F, Dai H, Yu Y, Li J, Chen Y, Zhao D, Shi X, Hu F, Mao J, Gu X, Yang R, Chen W, Tong Y, Wang W, Gao T, Li C, Teng W 2008 Influence of iodine on the reference interval of TSH and the optimal interval of TSH: results of a follow-up study in areas with different iodine intakes. Clin Endocrinol **69:**136–141.

Address correspondence to:
Annenienke van de Ven, MD
Department of Medicine, Division of Endocrinology (471)
Radboud University Medical Centre
PO Box 9101
6500 HB Nijmegen
The Netherlands

E-mail: Annenienke.vandeVen@radboudumc.nl