Thyroid volume – new reference values for defining thyroid enlargement

Individualised reference equations for the upper limit of thyroid volume

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Abstract

Objective

Upper reference values for thyroid volume are 25 ml for men and 18 ml for women. Thyroid volume alters with age, body weight, body height and iodine status, which is not considered in the current limits. The aim was to develop reference equations, considering age, body weight and height to calculate individual reference values for thyroid volume.

Design

This cross-sectional study, used data from three independent cohorts (SHIP-START, SHIP-TREND, KORA-F4) in Germany. SHIP-START-0, a population-based health survey carried out in Northern Germany, from 1997-2001. SHIP-TREND-0, a second independent sample of the same study region, carried out between 2008-2012. KORA F4, a population-based health survey, conducted between 2006-2008 in Southern Germany.

Methods

A total of 11,549 individuals (51% women) were included in data analysis. 8,606 individuals (45% women) were used as the thyroid-healthy reference population, when developing equations. Sex-stratified quantile regression models for the 95th percentile using age, body weight and height as explanatory variables, were performed.

Results

Overall reference value for men was 38.7 ml, for women 28.6 ml. According to the established cut-offs, 34% of the overall population would have had goitre compared to 7% when using our equations.

Conclusion

Upper reference values for thyroid volume are too low for an adult, previously iodine deficient population and do not consider age, body weight and height. Using individualised equations reduces the prevalence of thyroid enlargement substantially and can lead to a decrease in overdiagnoses and use of medical resources.

Significance Statement

The reference values for the upper limit of thyroid volume were established at the end of the last century not considering age, body weight and height. A large proportion of the German population have a thyroid volume above the upper limit and could potentially be labelled having goitre. Using our individualised reference equations based on gender, age, body weight and height reduces the goitre prevalence from 34% to 7% in Germany. We suggest the use of these individualised reference equations to reduce the number of patients potentially being labelled as having goitre. Thus, reducing over-diagnosis of goitre and the use of medical resources. Our equations can also be used in regions with similar iodine status like Germany.

Introduction

Goitre is defined as an enlargement of the thyroid volume. In the general population the worldwide prevalence is approximately 15% (1).Iodine deficiency is the major risk factor for an enlarged thyroid volume and, thus, there is a huge regional variation in the prevalence of goitre worldwide (1). Germany is a country of north-central Europe with a history of iodine deficiency resulting in a frequent diagnosis of goitre between 20 and 50%, depending on age, sex and geographical region (2–5).

In adults, goitre is usually defined by sex-specific reference limits for thyroid volume (>18 ml in women and > 25 ml in men), which were established by Gutekunst et al. in 1988 when ultrasound became available (6). Since then, those reference values have been used in clinical care and research (7–9). The reference values from Gutekunst et al. are the mean thyroid volume plus three standard deviations based on data from six studies from Netherlands, Germany, Denmark, Sweden and the USA (6, 10–15). No detailed information about the method used calculating the reference values was provided.

It is known that the thyroid volume and thus the prevalence of goitre changes with age, dependent on the iodine status of populations (2, 3, 16, 5). Also body weight and height are correlated with thyroid volume (17–21). While reference limits for thyroid volume are dependent on age and body surface area (BSA) (20), such factors were not taken into account from Gutekunst et al. when providing the previous reference values (6). In a recent study from China, age- and BSA-specific reference limits were established based on data from an iodine-replete region (22). The resulting reference limits are even lower than those provided from Gutekunst et al. and are not transferable to regions with a history of iodine deficiency. Due to previous iodine deficiency in Germany, a substantial proportion of subjects has a volume above the reference limit from Gutekunst et al. (4, 23). Independent of the iodine status of a region, low reference values are likely to lead to overdiagnosis of goitre and disease mongering.

Therefore, the aim of our study is to develop sex-specific equations to calculate individual reference values for thyroid volumes depending on age, body weight and height based on data from three German population-based studies.

Materials and methods

Study population

The present analyses are based on data from two cohorts of the Study of Health in Pomerania (SHIP-START-0 and SHIP-TREND-0) and the Cooperative Health Research in the Region of Augsburg (KORA-F4).

SHIP-START-0 was performed as a population-based cross-sectional survey carried out in Western Pomerania, Northern Germany, between 1997 and 2001. A sample of adults aged 20-79 years was drawn from population registries. The sample, excluding migrated or deceased persons, comprised 6,265 eligible individuals. In total, 4,308 individuals participated in the baseline survey. SHIP-TREND-0 is the baseline study of a second independent sample of the same study region, which was drawn from the registries in 2008, comprising 8,016 eligible individuals. SHIP-TREND-0 was carried out between 2008 – 2012, with 4,420 participating individuals (24). All participants gave written informed consent. The study was performed according to the principles of the Declaration of Helsinki and approved by the Ethics Committee of the University of Greifswald. More details about the Study of Health in Pomerania can be found elsewhere (25).

The KORA F4 study was carried out between 2006 and 2008. KORA-F4 is the first follow-up examination of the KORA S4 study (the baseline from 1999-2001), a population-based health survey conducted in the Region of Augsburg, Southern Germany. Participants were randomly selected from population registries of the study region including individuals with German nationality aged 25 to 74 years. A total sample of 6,640 individuals was drawn, of which 4,261 individuals participated at the baseline study S4. Of those, 3,080 also participated in the follow-up study (F4) (26). The study was performed to the principles of the Declaration of Helsinki, including written informed consent of all participants. The study was approved by the Ethics Committee of the of the Bavarian Medical Association (EC No. 06068).

The overall study population of all three studies comprised 11,808 individuals, from which we excluded 259 individuals with missing data in thyroid volume, body height or body weight. To define a healthy reference population, we further excluded participants with self-reported thyroid disease (n= 1,721), thyroid surgery (n= 415), radioiodine therapy (n= 212), intake of thyroid medication (n= 1,034), TSH levels outside the study-specific reference range (n= 1,395) (27–29), thyroid volume > 100 ml (n= 18), and pregnant women (n= 31) (overlaps exist). After exclusion of these 2,934 individuals, the thyroid-healthy reference population consisted of 8,606 individuals (**Figure 1**).

Measurements

In all studies, trained and certified staff performed standardised personal interviews. The interviews included thyroid-related questions as well as a question on smoking status. All participants were asked to bring to the interview all medications taken in the seven days prior to the examination. In both KORA and SHIP, medication data were obtained online using the IDOM software (online drug database of medication assessment) (26). The medications were categorised according to the Anatomical Therapeutic Chemical (ATC) code. Thyroid medication intake was defined using the ATC code H03. The goitre-related symptoms feeling of obstruction in the throat, difficulties swallowing, and feeling of suffocation were assessed by questionnaire in the SHIP cohorts only.

Height and weight were measured and the BSA was calculated according to Dubois: BSA = 0.007184*Height^0.725 * Weight^0.425 (30).

Both SHIP and KORA performed a collaborative quality management for thyroid ultrasound. The KORA-F4 sonographers were trained and certified at the SHIP examination centre to warrant best possible comparability between the studies. Ultrasonography was performed with an ultrasound VST-Gateway with a 5 MHz linear array transducer (Diasonics, Santa Clara, CA, USA) in SHIP-START-0, with a portable device using a 13 MHz linear array transducer (Vivid-I, General Electrics, Frankfurt, Germany) in SHIP-TREND-0, and with an ACUSON X300 (Siemens Medical Solutions, Mountain View, CA, USA) or SONOLINE G50 (Siemens Medical Solutions), 5 MHz linear array transducer in KORA-F4. Thyroid volume was calculated as length*width*depth*0.479 (ml) for each lobe (31). Within and between both studies, the intra- and inter-observer as well as inter-device reliabilities were assessed before the start of each study and afterwards annually during the studies; analyses were performed according to Bland & Altman (32). All measurements of the thyroid volume for within and between study comparisons showed Spearman's correlation coefficients of >0.85 and mean differences (± 2*SD) of the mean bias <5% (<25%).

Statistical analysis

We present study characteristics by median, 25th and 75th percentile for continuous data and by absolute numbers and percentages for categorical data. The thyroid volume between included and excluded subjects was compared using box plots. We developed reference limits for thyroid volume using sex-stratified quantile regression models for the 95th percentile of the reference population using age, body height, and body weight as explanatory variables. Fractional polynomials were tested to account for non-linear relationships between the explanatory variables and the reference limits. We plotted the reference limits against age, body height and body weight. We compared the prevalence of the goitre-related symptoms *feeling of obstruction in the throat, difficulties swallowing, and feeling of suffocation* in individuals with goitre according to the limits proposed by Gutekunst et al. and our new reference limits. All analyses were conducted with Stata 18.0 (Stata Corporation, TX, USA).

Results

Participants of KORA-F4 were older than those of the two SHIP studies (**Table 1**). Individuals in SHIP-TREND-0 and KORA-F4 reported more frequently a thyroid disorder and more often the intake of thyroid medication compared to individuals in SHIP-START-0. Self-reports of thyroid surgery were twice as high in SHIP-TREND-0 and in KORA-F4 as in SHIP-START-0. The median thyroid volume was slightly higher in SHIP-START-0 compared to SHIP-TREND-0 and KORA-F4. The overall prevalence of goitre according to the limits of Gutekunst et al. was 34.3%. We found a higher percentage of thyroid nodules in SHIP-TREND-0 and KORA-F4 compared to SHIP-START-0, which can be explained by the higher solution of ultrasound devices used in the former studies. Median serum TSH levels were higher in SHIP-TREND-0 and KORA-F4 compared to SHIP-START-0. After application of the study-specific reference limits for TSH, the frequency of low and high TSH were comparable across the studies.

Men with self-reported thyroid disease, thyroid surgery, radioiodine therapy, intake of thyroid medication or TSH levels outside the study-specific reference range, had a 2.7 ml higher thyroid volume compared to individuals in the healthy reference population (23.8 ml vs. 21.1 ml) (**Figure 2**). In women this difference was 1.1 ml (16.1 ml vs. 15.0 ml). There were 7 men and 31 women who took thyroid medication without comprising any of the other exclusion criteria.

The thyroid-healthy reference population consisted of 4,710 men and 3,896 women aged 20 to 84 years (median age 50 years). The overall reference limits (95^{th} percentile) for thyroid volume were 38.7 ml (95% CI: 37.8 – 39.5 ml) in men and 28.6 ml (95% CI: 27.7 – 29.5 ml) in women. In men and women, the reference limits increased with age (**Figure 3**). In men, but not in women, individuals with a higher body height had a higher reference limit for thyroid volume (**Figure 4**). On the other hand, body weight was positively associated with the reference limit of thyroid volume in women but not in men (**Figure 5**).

The equations for the reference limits were:

9.066889 - 207.886*(1/√age) + 0.31143*body height [cm] + 0.0472153*body weight [kg] in men and 0.049582 + 0.0024958*age^2 + 0.0486403*body height [cm] + 0.1881983*body weight [kg] in women.

Applying these reference limits to our total study population of 11,549 individuals, 854 individuals were classified as having goitre (7.4 %). While 850 individuals are classified as having goitre with both our and the Gutekunst reference limits, 3,114 (27 %) individuals are classified as having goitre with the Gutekunst definition only, and four individuals are classified as having goitre with our new reference limits only (Table 2).

We also calculated cut-offs across age groups for women and men. In the age group 20-29 the cut-off for women was 22.6 ml and for men 27.2 ml. The cut-off increased with each age group and arrived at 35.7 ml for women and 43.8 ml for men in the age group 70-81 years. The cut-offs for each age group are displayed in figure 6 and 7. However, using the equations the reference limits are more precise and individual, because they consider the specific age, instead of age groups and also consider body weight and height.

Within the two SHIP studies we compared moderate to severe goitre symptoms in individuals with goitre according to our and the Gutekunst limits. This revealed only small differences between the two goitre definitions (feeling of obstruction in the throat: 10.0 % with our definition vs. 9.9 % with the Gutekunst definition; difficulties swallowing: 2.8 % vs. 3.5 %; dyspnea: 5.6 % vs. 5.7 %; feeling of suffocation: 1.1 % vs. 1.4 %).

In addition, we calculated reference limits for thyroid volume using BSA instead of body height and weight as explanatory variable. This revealed the following equations:

$37.64908 - 181.379*(1/\sqrt{age}) + 13.07982*BSA\ [m^2]$ in men and

$-6.882714 + 0.0025558*age^2 + 15.88545*BSA\ [m^2]$ in women.

Applying these reference limits to our total study population of 11,549 individuals, the number of individuals classified as having goitre was 857 (7.4%) and, thus, similar to our formulas including height and weight instead of BSA.

Discussion

Summary of the main results

According to Gutekunst et al. from 1988, thyroid enlargement was defined by a thyroid volume above 18 ml for women and above 25 ml for men (6). Those limits result in a prevalence of 34% of goitre in our study population. The overall reference limits for thyroid volume according to our calculation, were 38.7 ml for men and 28.6 ml for women. Considering the increase of thyroid volume with increasing age, higher body height in men and higher body weight in women, the prevalence of goitre according to our equations was

7%. There was no relevant difference in frequencies of moderate to severe goitre symptoms when comparing our individualised reference values with the Gutekunst reference values.

Clinical meaning of the results and comparison with literature

A previously published article critically reviewed the reference values for thyroid volume and came to the conclusion that the reference limits of 18 ml for women and 25 ml for men, are inappropriate due to the evidence that more factors than only sex, influence the thyroid volume (7). Studies show that thyroid volume physiologically increases with age, body surface, weight and height (20, 33–35). Since the reference values from Gutekunst et al. do not consider those factors, they are more likely to lead to overdiagnosis and disease mongering. The use of our equations reduces the prevalence of goitre substantially, from 34% to 7%. Thus, applying our reference values will reduce overdiagnoses and the use of limited medical resources.

The mean thyroid volume in populations is dependent on iodine intake (36, 37). The average thyroid volume in different countries range considerably, between 5.8 and 17.5 ml for women and between 6.7 and 19.6 ml for men (7). A large proportion of our study population have a thyroid volume above the highest mean volume in other countries. This is a consequence of previously long-term iodine deficiency in Germany (38). Thus, our reference intervals can also be applied to populations with similar iodine status. Using the established reference values from Gutekunst et al., this large proportion could be labelled as having goitre and be subject to surveillance and medical treatment. However, in the absence of clinical symptoms, nodules or functional alterations, a thyroid volume above the reference value has no clinical relevance (39). Also, our data showed nearly no difference in moderate to severe goitre symptoms comparing the Gutekunst limits with our reference limits.

Strengths and limitations

This is the first study including data of 8,606 individuals from the age of 20 years, to develop a sex-specified equation, taking age, body weight and height into account, to calculate individual reference values for goitre. While another recently published study focussed on new thyroid volume reference values for 6 to 17 year old children and young adolescents (40), our study focused on adults up to an age of 84 years. Moreover, there is an increase in thyroid volume during pregnancy (35). We excluded pregnant women when calculating the equations because there were only 31 pregnant women in our study population. Studies showed a lower mean volume in other countries, certainly mainly due to difference in iodine intake. Therefore, our equations should be only used in regions with similar iodine status like Germany and need to be evaluated in other countries. We excluded individuals with clinically relevant thyroid disease to define a healthy reference population Therefore, the equations may also be applicable to regions with a different iodine status, but further studies from other regions with different history of iodine supply are needed. Of note, the reference values from Gutekunst et al, which were frequently used over the last 35 years, were based on not further characterized populations from Sweden, Netherlands, Denmark, USA and Germany.

Conclusion

The currently used reference values for thyroid volume from Gutekunst et al. are too low and do not consider age, body weight and height. Using our individualised reference equations would reduce the prevalence of goitre substantially. Overdiagnoses and, thus, the use of limited medical resources and low value care could be reduced using our equations as individualised reference values. Reference values for upper thyroid volumes should be reassessed and calibrated in population with different iodine status.

Conflict of Interest

HV received speaker honorarium and a travel grant from Sanofi-Aventis. All other authors have no conflicts of interest.

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Data Availability Statement

SHIP data are available on reasonable request according the bylaws of the Community Medicine Research Network of the University Medicine Greifswald.
https://www.fvcm.med.uni-greifswald.de/dd_service/data_use_ intro.php.

KORA data are available on reasonable request according to the terms and conditions of Helmholtz Munich (https://helmholtz-muenchen.managed-otrs.com/external) and subject to the approval by the KORA board.

Author Contribution

TI and SK had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. TI, AA, JFC, HV, SK interpreted the data. All authors made substantial contributions to the concept of the work, finalized, provided critical review and approved the final manuscript.

Literature Cited

1. Benoist B de. Iodine status worldwide: WHO global database on iodine deficiency. Geneva: Dept. of Nutrition for Health and Development, World Health Organization; 2004.

2. Völzke H, Thamm M. Epidemiologie von Schilddrüsenerkrankungen in Deutschland. Präv Gesundheitsf 2007; 2(3):149–52.

3. Meisinger C, Ittermann T, Wallaschofski H, Heier M, Below H, Kramer A et al. Geographic variations in the frequency of thyroid disorders and thyroid peroxidase antibodies in persons without former thyroid disease within Germany. Eur J Endocrinol 2012; 167(3):363–71.

4. Kiel S, Ittermann T, Steinbach J, Völzke H, Chenot J-F, Angelow A. The course of thyroid nodules and thyroid volume over a time period of up to 10 years: a longitudinal analysis of a population-based cohort. Eur J Endocrinol 2021; 185(3):431–9.

5. Reiners C, Wegscheider K, Schicha H, Theissen P, Vaupel R, Wrbitzky R et al. Prevalence of thyroid disorders in the working population of Germany: ultrasonography screening in 96,278 unselected employees. Thyroid 2004; 14(11):926–32.

6. Gutekunst R, Becker W, Hehrmann R, Olbricht T, Pfannenstiel P. Ultraschalldiagnostik der Schilddrüse. Dtsch Med Wochenschr 1988; 113(27):1109–12.

7. Seifert P, Gühne F, Drescher R, Freesmeyer M. Sonographische Normwerte für das Schilddrüsenvolumen Erwachsener – woher kommen sie und wie sind sie zu bewerten? Laryngorhinootologie 2024; 103(1):35–9.

8. Knudsen N, Perrild H, Christiansen E, Rasmussen S, Dige-Petersen H, Jørgensen T. Thyroid structure and size and two-year follow-up of solitary cold thyroid nodules in an unselected population with borderline iodine deficiency. Eur J Endocrinol 2000; 142(3):224–30.

9. Carlé A, Krejbjerg A, Laurberg P. Epidemiology of nodular goitre. Influence of iodine intake. Best Pract Res Clin Endocrinol Metab 2014; 28(4):465–79.

10. Gutekunst R, Smolarek H, Wächter W, Scriba PC. Strumaepidemiologie. IV. Schilddrüsenvolumina bei deutschen und schwedischen Schulkindern. Dtsch Med Wochenschr 1985; 110(2):50–4.

11. Hegedüs L, Perrild H, Poulsen LR, Andersen JR, Holm B, Schnohr P et al. The determination of thyroid volume by ultrasound and its relationship to body weight, age, and sex in normal subjects. J Clin Endocrinol Metab 1983; 56(2):260–3.

12. Klima G, Lind P, Költringer P, Eber O. Sonographisch ermittelte Schilddrüsenvolumina bei 7- bis 11jährigen Kindern. Acta Med Austriaca 1986; 13(1):1–4.

13. Olbricht T, Schmitka T, Mellinghoff U, Benker G, Reinwein D. Sonographische Bestimmung von Schilddrüsenvolumina bei Schilddrüsengesunden. Dtsch Med Wochenschr 1983; 108(36):1355–8.

14. Pankow BG, Michalak J, McGee MK. Adult human thyroid weight. Health Phys 1985; 49(6):1097–103.

15. Berghout A, Wiersinga WM, Smits NJ, Touber JL. Determinants of thyroid volume as measured by ultrasonography in healthy adults in a non-iodine deficient area. Clin Endocrinol (Oxf) 1987; 26(3):273–80.

16. Guo W, Tan L, Dong S, Jin Y, Zhu M, Wei H et al. New Reference Values for Thyroid Volume and a Comprehensive Assessment for Influencing Factors in Chinese Adults with Iodine Sufficiency. Eur Thyroid J 2021; 10(6):447–54.

17. Xiao Y, Mao J, Mao X, Wang Q, Li X, Chen G et al. Metabolic syndrome and its components are associated with thyroid volume in adolescents. BMC Endocr Disord 2021; 21(1):176.

18. Adibi A, Haghighi M, Hosseini SR, Hashemipour M, Amini M, Hovsepian S. Thyroid abnormalities among first-degree relatives of children with congenital hypothyroidism: an ultrasound survey. Horm Res 2008; 70(2):100–4.

19. Wesche MF, Wiersinga WM. Relation between lean body mass and thyroid volume in competition rowers before and during intensive physical training. Horm Metab Res 2001; 33(7):423–7.

20. Zimmermann MB, Hess SY, Molinari L, Benoist B de, Delange F, Braverman LE et al. New reference values for thyroid volume by ultrasound in iodine-sufficient schoolchildren: a World Health Organization/Nutrition for Health and Development Iodine Deficiency Study Group Report. Am J Clin Nutr 2004; 79(2):231–7.

21. Viduetsky A, Herrejon CL. Sonographic Evaluation of Thyroid Size: A Review of Important Measurement Parameters. Journal of Diagnostic Medical Sonography 2019; 35(3):206–10.

22. Lin Z, Lu C, Di Teng, Sun Y, Liu T, Li Y et al. Influencing Factors and New Reference Intervals of Adult Thyroid Volume in Iodine-Sufficient Areas of China. Biol Trace Elem Res 2023; 201(12):5652–61.

23. Remer T, Hua Y, Esche J, Thamm M. The DONALD study as a longitudinal sensor of nutritional developments: iodine and salt intake over more than 30 years in German children. Eur J Nutr 2022; 61(4):2143–51.

24. Völzke H, Alte D, Schmidt CO, Radke D, Lorbeer R, Friedrich N et al. Cohort profile: the study of health in Pomerania. Int J Epidemiol 2011; 40(2):294–307.

25. Völzke H, Schössow J, Schmidt CO, Jürgens C, Richter A, Werner A et al. Cohort Profile Update: The Study of Health in Pomerania (SHIP). Int J Epidemiol 2022; 51(6):e372-e383.

26. Holle R, Happich M, Löwel H, Wichmann HE. KORA--a research platform for population based health research. Gesundheitswesen 2005; 67 Suppl 1:S19-25.

27. Burkhardt K, Ittermann T, Heier M, Kirchberger I, Völzke H, Wallaschofski H et al. TSH-Referenzbereich bei süddeutschen Erwachsenen: Ergebnisse aus der bevölkerungsbasierten KORA F4-Studie. Dtsch Med Wochenschr 2014; 139(7):317–22.

28. Völzke H, Alte D, Kohlmann T, Lüdemann J, Nauck M, John U et al. Reference intervals of serum thyroid function tests in a previously iodine-deficient area. Thyroid 2005; 15(3):279–85.

29. Ittermann T, Khattak RM, Nauck M, Cordova CMM, Völzke H. Shift of the TSH reference range with improved iodine supply in Northeast Germany. Eur J Endocrinol 2015; 172(3):261–7.

30. Du Bois D, Du Bois EF. A formula to estimate the approximate surface area if height and weight be known. 1916. Nutrition 1989; 5(5):303-11; discussion 312-3.

31. Brunn J, Block U, Ruf G, Bos I, Kunze WP, Scriba PC. Volumetrie der Schilddrüsenlappen mittels Real-time-Sonographie. Dtsch Med Wochenschr 1981; 106(41):1338–40.

32. Bland JM, Altman DG. Statistical methods for assessing agreement between two methods of clinical measurement. Lancet 1986; 1(8476):307–10.

33. Semiz S, Senol U, Bircan, Gümüşlü S, Bilmen S, Bircan I. Correlation between age, body size and thyroid volume in an endemic area. J Endocrinol Invest 2001; 24(8):559–63.

34. Lass N, Barth A, Reinehr T. Thyroid Volume and Thyroid Function Parameters Are Independently Associated with Weight Status in Overweight Children. Horm Res Paediatr 2020; 93(5):279–86.

35. Vannucchi G, Covelli D, Vigo B, Perrino M, Mondina L, Fugazzola L. Thyroid volume and serum calcitonin changes during pregnancy. J Endocrinol Invest 2017; 40(7):727–32.

36. Kotwal A, Priya R, Qadeer I. Goiter and other iodine deficiency disorders: A systematic review of epidemiological studies to deconstruct the complex web. Arch Med Res 2007; 38(1):1–14.

37. Vanderpump MPJ. The epidemiology of thyroid disease. Br Med Bull 2011; 99:39–51.

38. Khattak RM, Ittermann T, Nauck M, Below H, Völzke H. Monitoring the prevalence of thyroid disorders in the adult population of Northeast Germany. Popul Health Metr 2016; 14:39.

39. NICE - National Institute for Health and Care Excellent. Thyroid disease: assessment and management; 2023 [cited 2024 Jun 13]. Available from: URL: https://www.nice.org.uk/guidance/ng145/chapter/recommendations#diagnosing-managing-and-monitoring-thyroid-enlargement-with-normal-thyroid-function.

40. Hirtz R, Thamm R, Kuhnert R, Liesenkötter K-P, Thamm M, Grasemann C. New Reference Values for Thyroid Volume by Ultrasound in German Children and Adolescents from a Population-Based Study. J Clin Endocrinol Metab 2024.

Figure legend

Figure 1 Flow chart of the study population

Figure 2 Box plots for included (healthy reference population) and excluded individuals; a) men (left side); b) women (right side); the solid lines represent the cut-offs proposed by Gutekunst et al. (25 ml in men and 18 ml in women)

Figure 3 Age- and sex specific reference limits for thyroid volume

Figure 4 Body height- and sex specific reference limits for thyroid volume

Figure 5 Body weight- and sex specific reference limits for thyroid volume

Figure 6 Reference values across age groups for men

Figure 7 Reference values across age groups for women

Table 1: Characteristics of the study cohorts

	SHIP-START-0	SHIP-TREND-0	KORA-F4	Total
N	4,263 (36.9%)	4,395 (38.1%)	2,891 (25.0%)	11,549 (100.0%)
Age in years	51 (36; 64)	53 (40; 64)	56 (44; 67)	53 (40; 65)
Sex				
Females	2,169 (50.9%)	2,261 (51.4%)	1,470 (50.8%)	5,900 (51.1%)
Males	2,094 (49.1%)	2,134 (48.6%)	1,421 (49.2%)	5,649 (48.9%)
Body height in cm	169 (162; 176)	170 (163; 177)	169 (162; 176)	169 (162; 176)
Body weight in kg	77 (67; 88)	80 (69; 92)	78 (67; 88)	78 (68; 89)
Body mass index in kg/m^2	26.9 (23.8; 30.1)	27.5 (24.5; 31.0)	26.9 (24.3; 30.2)	27.1 (24.2; 30.5)
Smoking status				
never	1,519 (35.8%)	1,597 (36.5%)	1,269 (43.9%)	4,385 (38.1%)
former	1,437 (33.9%)	1,603 (36.6%)	1,096 (38.0%)	4,136 (35.9%)
current	1,289 (30.4%)	1,177 (26.9%)	523 (18.1%)	2,989 (26.0%)
Years of education				
less than 10 years	1,690 (39.9%)	1,024 (23.3%)	1,463 (50.7%)	4,177 (36.3%)
10 years	1,848 (43.6%)	2,256 (51.4%)	719 (24.9%)	4,823 (41.9%)
more than 10 years	697 (16.5%)	1,106 (25.2%)	704 (24.4%)	2,507 (21.8%)
Self-reported thyroid disorder	271 (6.4%)	817 (18.6%)	633 (21.9%)	1,721 (15.0%)
Thyroid medication intake	274 (6.4%)	452 (10.3%)	308 (10.7%)	1,034 (9.0%)
Thyroid surgery	107 (2.5%)	181 (4.1%)	127 (4.4%)	415 (3.6%)
Radio-iodine therapy	19 (0.4%)	128 (2.9%)	65 (2.2%)	212 (1.8%)
Thyroid volume in ml	18.8 (14.0; 25.6)	18.1 (13.9; 23.3)	17.7 (12.9; 24.6)	18.3 (13.7; 24.4)

Goitre according to Gutekunst	1,605 (37.6%)	1,390 (31.6%)	969 (33.5%)	3,964 (34.3%)
Thyroid nodule	968 (22.8%)	1,575 (35.8%)	1,838 (63.6%)	4,381 (38.0%)
Hypoechogenic thyroid pattern	315 (7.4%)	100 (2.3%)	368 (12.7%)	783 (6.8%)
TSH in mIU/L	0.66 (0.43; 0.97)	1.17 (0.79; 1.67)	1.27 (0.85; 1.85)	0.98 (0.61; 1.49)
fT3 in pmol/L	4.76 (4.38; 5.18)	4.65 (4.26; 5.05)	4.78 (4.39; 5.16)	4.73 (4.34; 5.12)
fT4 in pmol/L	14.2 (13.0; 15.50)	13.2 (12.2; 14.5)	13.7 (12.6; 15.1)	13.7 (12.6; 15.0)
Thyroid function status				
TSH in reference range	3,698 (87.4%)	3,857 (88.1%)	2,480 (87.9%)	10,035 (87.8%)
Low TSH	401 (9.5%)	362 (8.3%)	251 (8.9%)	1,014 (8.9%)
High TSH	130 (3.1%)	161 (3.7%)	90 (3.2%)	381 (3.3%)
Positive anti-TPO antibodies	195 (4.6%)	195 (4.4%)	101 (3.6%)	491 (4.3%)

Data are expressed as median, 25th and 75th percentile (continuous data) or as absolute number and percentages (categorical data)

Table 2: Number of individuals classified as having goitre according to Gutekunst et al. and according to our equations

Goitre according to Gutekunst et al.	**Goitre according to our equations**		
	No	**Yes**	**Total**
No	7,581 (65.6%)	4 (0.03%)	7,585 (65.7%)
Yes	3,114 (27%)	850 (7.4%)	3,964 (34.3%)
Total	10,695 (92.6%)	854 (7.4%)	11,549 (100%)

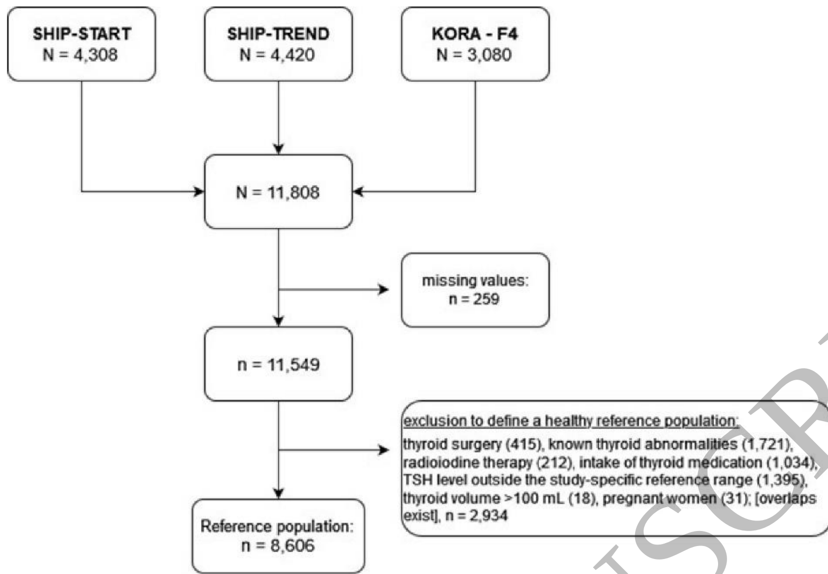

Figure 1: Flow chart of the study population

Figure 1
34x38 mm (DPI)

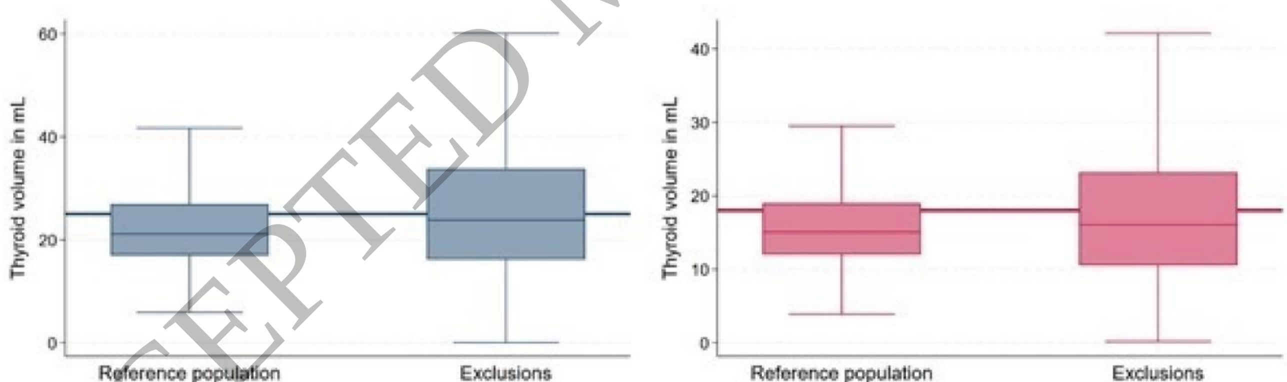

Figure 2-Box plots for included (healthy reference population) and excluded individuals; a) men (left side); b) women (right side); the solid lines represent the cut-offs proposed by Gutekunst et al. (25 ml in men and 18 ml in women)

Figure 2
34x38 mm (DPI)

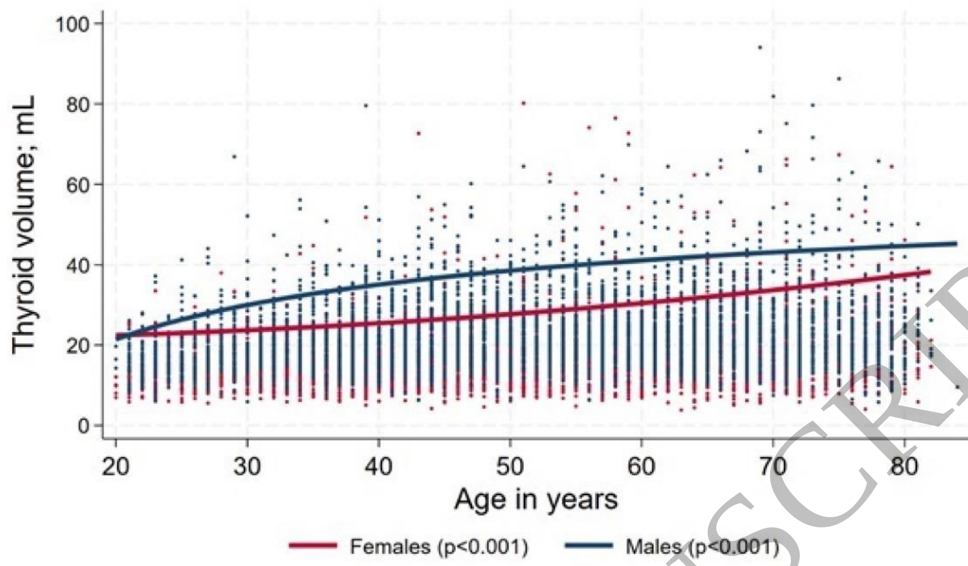

Figure 3. Age- and sex specific reference limits for thyroid volume

Figure 3
34x38 mm (DPI)

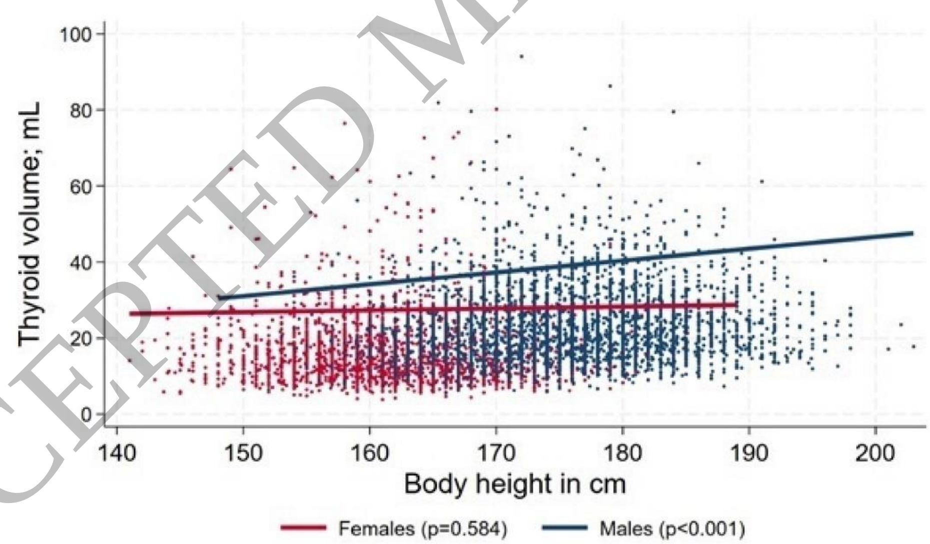

Figure 4. Body height- and sex specific reference limits for thyroid volume

Figure 4
34x38 mm (DPI)

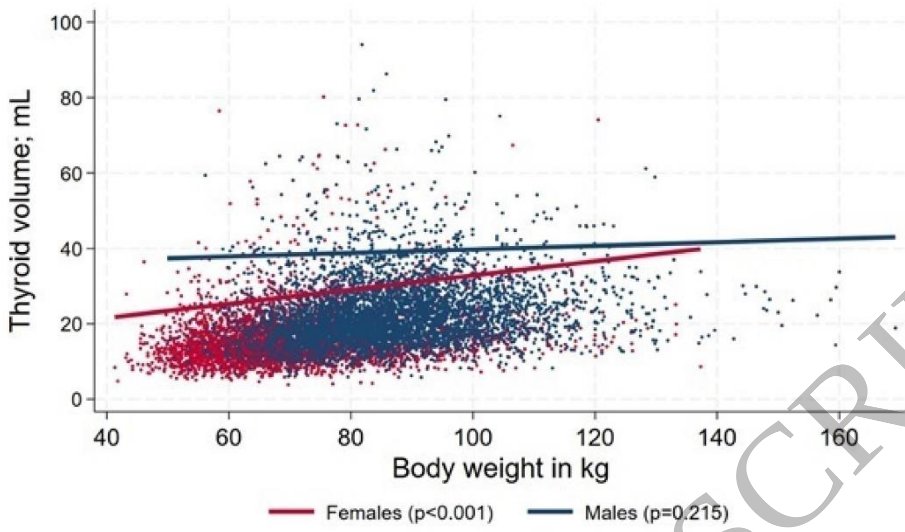

Figure 5. Body weight- and sex specific reference limits for thyroid volume

Figure 5
34x38 mm (DPI)

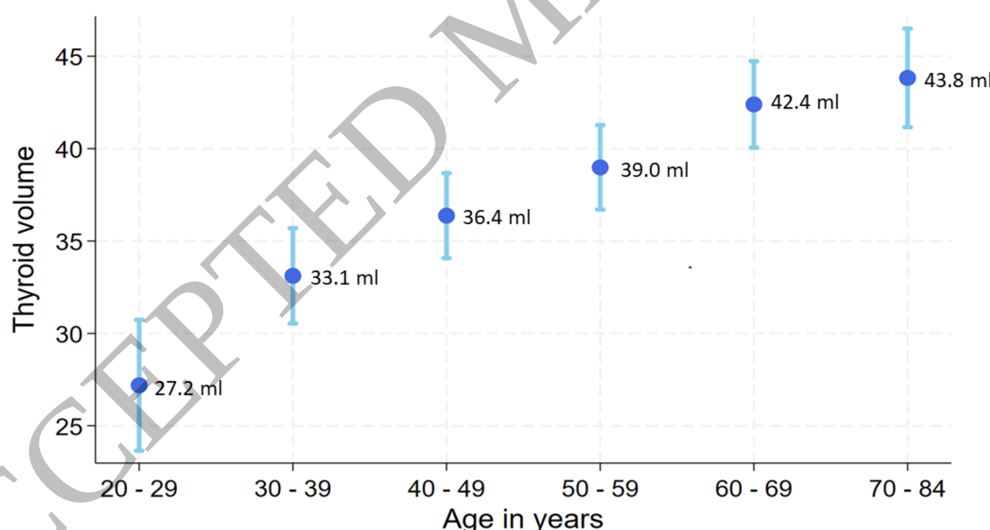

Figure 6: Reference values for thyroid enlargement across age groups for men

Figure 6
160x90 mm (DPI)

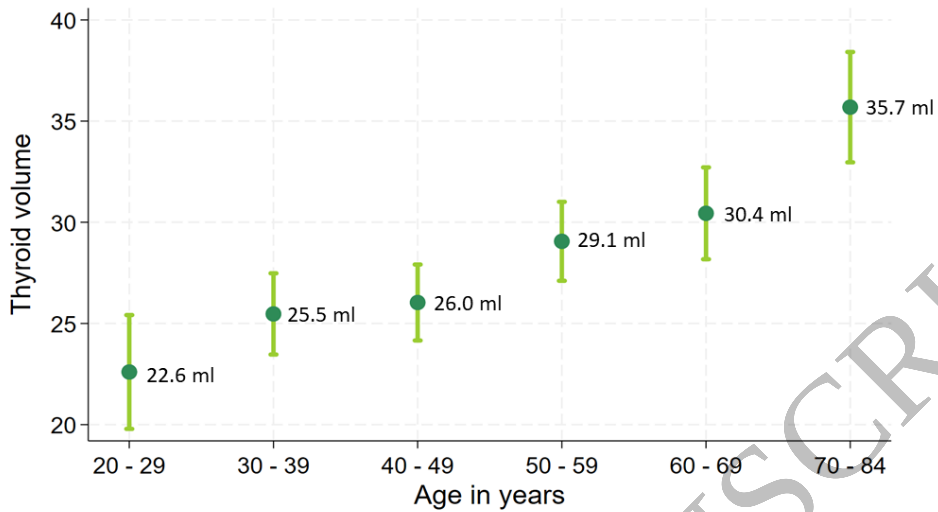

Figure 7: Reference values for thyroid enlargement across age groups for women

Figure 7
160x90 mm (DPI)