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Original Research

Thyroid volume—new reference values for defining thyroid enlargement

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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 3 independent cohorts (SHIP-START, SHIP-TREND, and KORA-F4) in Germany. SHIP-START-0, a population-based health survey, was carried out in Northern Germany, from 1997 to 2001. SHIP-TREND-0, a second independent sample of the same study region, was carried out between 2008 and 2012. KORA-F4, a population-based health survey, was conducted between 2006 and 2008 in Southern Germany.

Methods: A total of 11 549 individuals (51% women) were included in the data analysis. Eight thousand six-hundred and six 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: The overall reference value was 38.7 mL for men and 28.6 mL for women. According to the established cut-offs, 34% of the overall population would have had goitre compared with 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 the use of medical resources.

Keywords: thyroid enlargement, goitre, thyroid volume, reference values

Significance

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 has a thyroid volume above the upper limit and could potentially be labelled as 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 overdiagnosis 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

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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 3 standard deviations based on data from 6 studies from the Netherlands, Germany, Denmark, Sweden, and the United States.[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.[2,3,5,16] 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 by 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 by 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 3 German population-based studies.

Materials and methods

Study population

The present analyses are based on data from 2 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 6265 eligible individuals. In total, 4308 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 8016 eligible individuals. SHIP-TREND-0 was carried out between 2008 and 2012, with 4420 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 to 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 25-74 years. A total sample of 6640 individuals was drawn, of which 4261 individuals participated in the baseline study S4. Of those, 3080 also participated in the follow-up study (F4).[26] The study was performed according 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 Bavarian Medical Association (EC No. 06068).

The overall study population of all 3 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 ($n = 1721$), thyroid surgery ($n = 415$), radioiodine therapy ($n = 212$), intake of thyroid medication ($n = 1034$), thyroid-stimulating hormone (TSH) levels outside the study-specific reference range ($n = 1395$),[27-29] thyroid volume > 100 mL ($n = 18$), and pregnant women ($n = 31$) (overlaps exist). After the exclusion of these 2934 individuals, the thyroid-healthy reference population consisted of 8606 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 7 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 of feeling of obstruction in the throat, difficulty 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 the 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 afterward annually during the studies; analyses were performed according to Bland & Altman.[32] All measurements of the thyroid volume 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

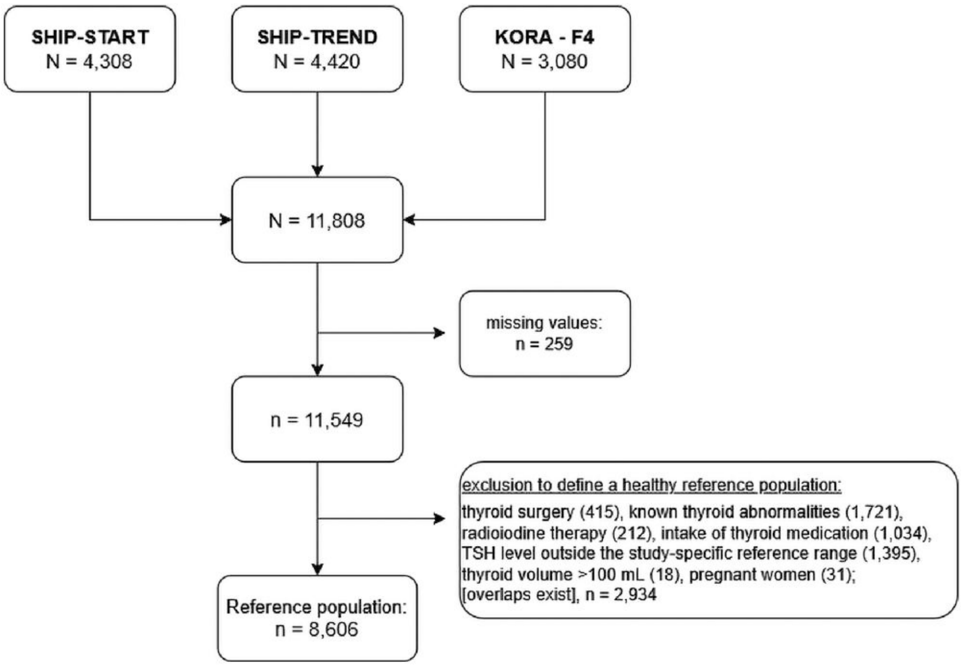

Figure 1. Flow chart of the study population.

Table 1. Characteristics of the study cohorts.

	SHIP-START-0	SHIP-TREND-0	KORA-F4	Total
N	4263 (36.9%)	4395 (38.1%)	2891 (25.0%)	11 549 (100.0%)
Age in years	51 (36; 64)	53 (40; 64)	56 (44; 67)	53 (40; 65)
Sex				
Females	2169 (50.9%)	2261 (51.4%)	1470 (50.8%)	5900 (51.1%)
Males	2094 (49.1%)	2134 (48.6%)	1421 (49.2%)	5649 (48.9%)
Body height (cm)	169 (162; 176)	170 (163; 177)	169 (162; 176)	169 (162; 176)
Body weight (kg)	77 (67; 88)	80 (69; 92)	78 (67; 88)	78 (68; 89)
Body mass index (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	1519 (35.8%)	1597 (36.5%)	1269 (43.9%)	4385 (38.1%)
Former	1437 (33.9%)	1603 (36.6%)	1096 (38.0%)	4136 (35.9%)
Current	1289 (30.4%)	1177 (26.9%)	523 (18.1%)	2989 (26.0%)
Years of education				
Less than 10 years	1690 (39.9%)	1024 (23.3%)	1463 (50.7%)	4177 (36.3%)
10 years	1848 (43.6%)	2256 (51.4%)	719 (24.9%)	4823 (41.9%)
More than 10 years	697 (16.5%)	1106 (25.2%)	704 (24.4%)	2507 (21.8%)
Self-reported thyroid disorder	271 (6.4%)	817 (18.6%)	633 (21.9%)	1721 (15.0%)
Thyroid medication intake	274 (6.4%)	452 (10.3%)	308 (10.7%)	1034 (9.0%)
Thyroid surgery	107 (2.5%)	181 (4.1%)	127 (4.4%)	415 (3.6%)
Radioiodine therapy	19 (0.4%)	128 (2.9%)	65 (2.2%)	212 (1.8%)
Thyroid volume (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	1605 (37.6%)	1390 (31.6%)	969 (33.5%)	3964 (34.3%)
Thyroid nodule	968 (22.8%)	1575 (35.8%)	1838 (63.6%)	4381 (38.0%)
Hypoechogenic thyroid pattern	315 (7.4%)	100 (2.3%)	368 (12.7%)	783 (6.8%)
TSH (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 (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 (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	3698 (87.4%)	3857 (88.1%)	2480 (87.9%)	10 035 (87.8%)
Low TSH	401 (9.5%)	362 (8.3%)	251 (8.9%)	1014 (8.9%)
High TSH	130 (3.1%)	161 (3.7%)	90 (3.2%)	381 (3.3%)
Positive anti-thyroid peroxidase (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).

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

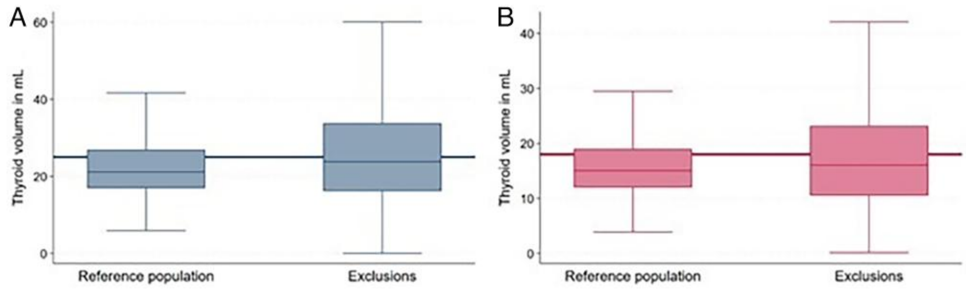

Figure 2. Box plots for included (healthy reference population) and excluded individuals; (A) men and (B) women; the solid lines represent the cut-offs proposed by Gutekunst et al. (25 mL in men and 18 mL in women).

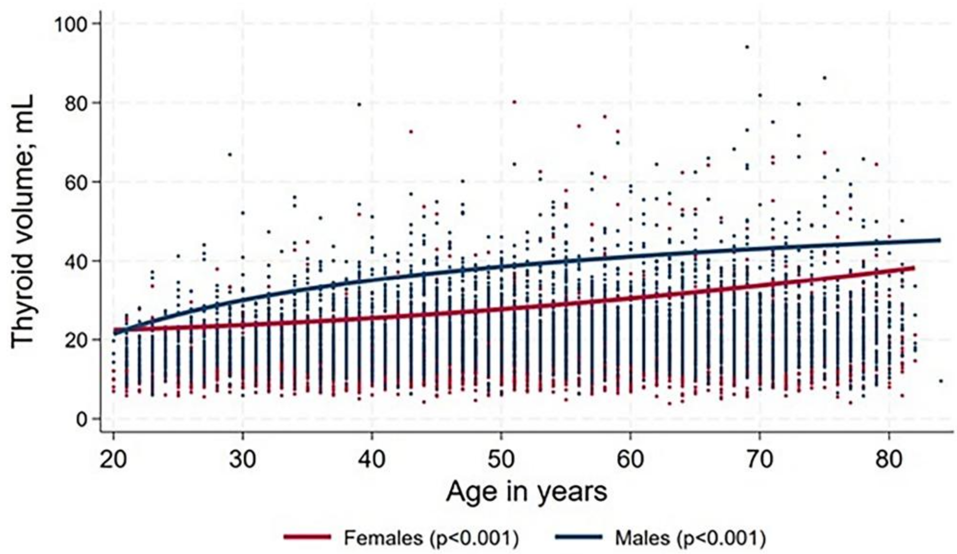

Figure 3. Age- and sex-specific reference limits for thyroid volume.

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 of *feeling of obstruction in the throat, difficulty 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 2 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 with 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 with 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 with 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 with SHIP-START-0. After the 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 with individuals in the healthy reference population (23.8 vs. 21.1 mL) (Figure 2). In women, this difference was 1.1 mL (16.1 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 4710 men and 3896 women aged 20-84 years (median age 50 years). The overall reference limits (95th 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:

$$9.066889 - 207.886 * (1/\sqrt{\text{age}}) + 0.31143 * \text{body height (cm)} + 0.0472153 * \text{body weight (kg)} \text{ in men and}$$

$$0.049582 + 0.0024958 * \text{age}^2 + 0.0486403 * \text{body height (cm)} + 0.1881983 * \text{body weight (kg)} \text{ in women}$$

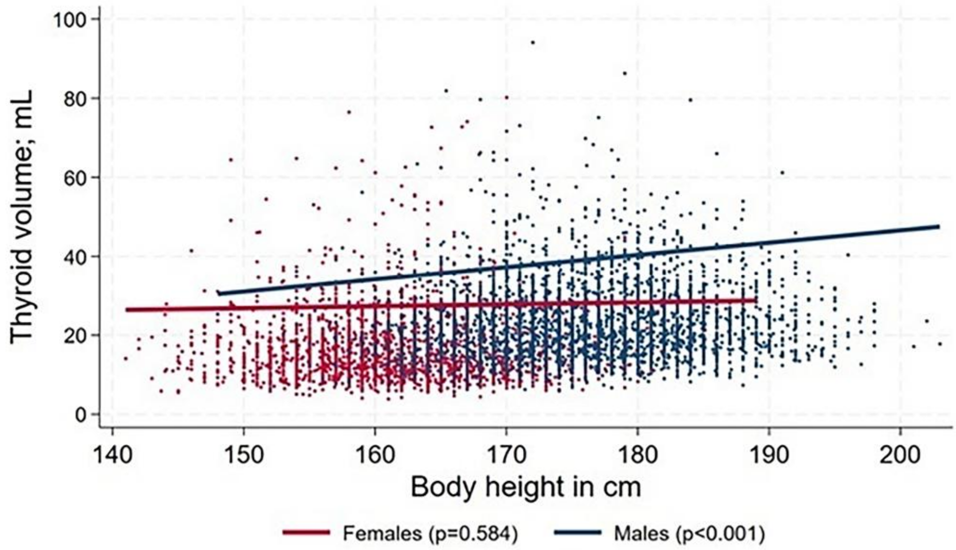

Figure 4. Body height- and sex-specific reference limits for thyroid volume.

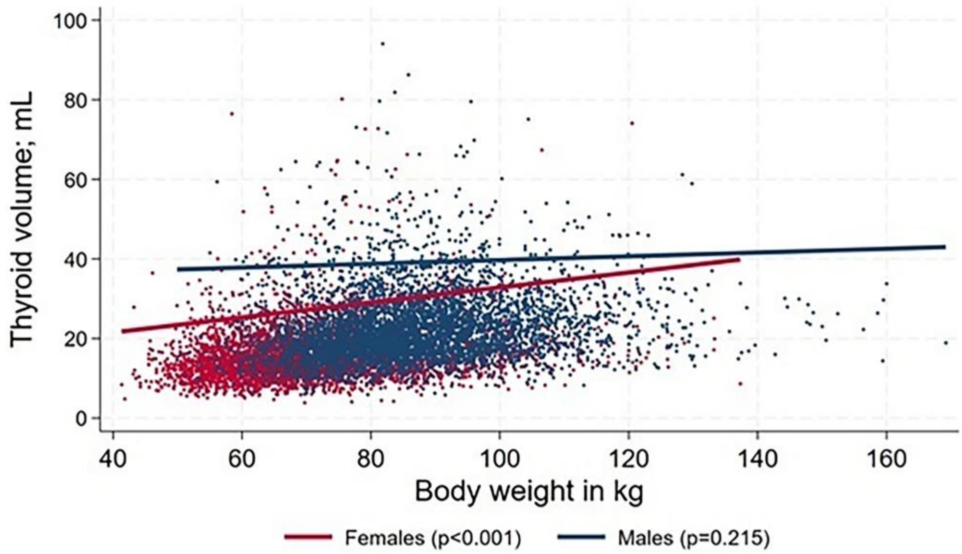

Figure 5. Body weight- and sex-specific reference limits for thyroid volume.

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, 3114 (27%) individuals are classified as having goitre with the Gutekunst definition only, and 4 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 was 22.6 mL for women and 27.2 mL for men. 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 Figures 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.

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		Total
	No	Yes	
No	7581 (65.6%)	4 (0.03%)	7585 (65.7%)
Yes	3114 (27%)	850 (7.4%)	3964 (34.3%)
Total	10 695 (92.6%)	854 (7.4%)	11 549 (100%)

Within the 2 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 2 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.

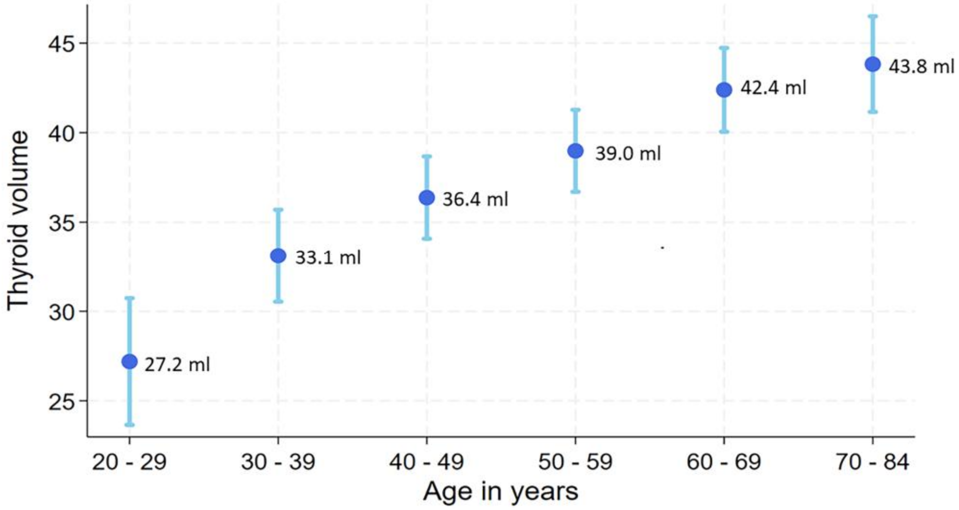

Figure 6. Reference values across age groups for men.

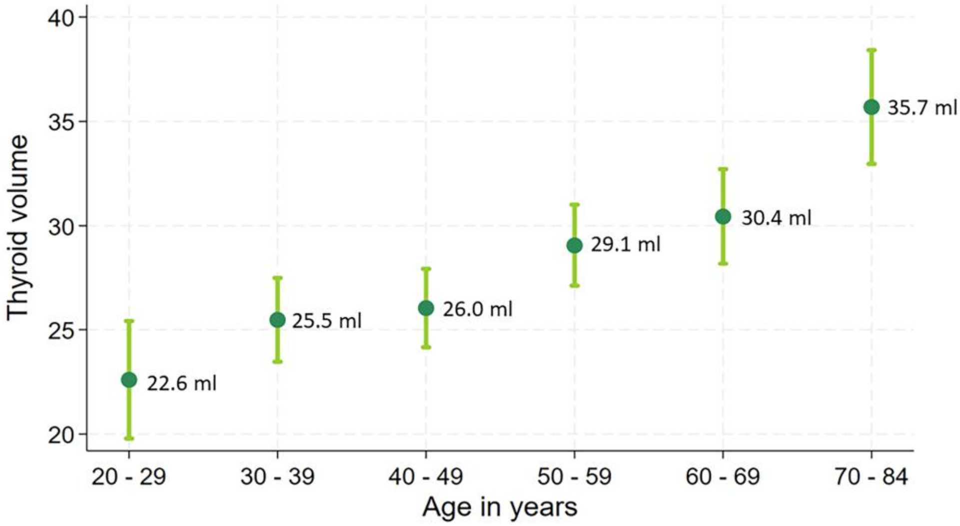

Figure 7. Reference values across age groups for women.

3.5%; dyspnoea: 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 variables. This revealed the following equations:

$$37.64908–181.379*(1/\sqrt{age}) + 13.07982*BSA\,(m^2)\text{ in men and } - 6.882714 + 0.0025558*age^2 + 15.88545*BSA\,(m^2)\text{ in women}$$

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 thyroid volume.[7] Studies show that the 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 ranges 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 has 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 8606 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 the 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 differences 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 characterised populations from Sweden, the Netherlands, Denmark, the United States, 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 populations with different iodine status.

Acknowledgments

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Authors' contributions

Till Ittermann (Formal analysis [equal], Investigation [equal], Methodology [lead], Project administration [lead], Resources [lead], Software [lead], Writing—original draft [lead]), Aniela Angelow (Conceptualization [equal], Validation [equal], Writing—review & editing [equal]), Jean-François Chenot (Methodology [equal], Resources [equal], Validation [equal], Writing—review & editing [equal]), Henry Völzke (Conceptualization [equal], Investigation [equal], Validation [equal], Writing—original draft [equal], Writing—review & editing [equal]), Margit Heier (Methodology [equal], Validation [equal], Writing—original draft [equal]), Birgit Linkohr (Methodology [equal], Validation [equal], Visualization [equal], Writing—original draft [equal]), Annette Peters (Investigation [equal], Methodology [equal], Validation [equal], Visualization [equal]), Christine Meisinger (Investigation [equal], Methodology [equal], Validation [equal], Visualization [equal], Writing—original draft [equal]), and Simone Kiel (Conceptualization [lead], Formal analysis [equal], Methodology [lead], Project administration [equal], Supervision [lead], Writing—original draft [lead])

T.I. and S.K. had full access to all the data in the study and took responsibility for the integrity of the data and the accuracy of the data analysis. T.I., A.A., J.-F.C., H.V., and S.K. interpreted the data. All authors made substantial contributions to the concept of the work, finalised, provided critical review, and approved the final manuscript.

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

Data availability

SHIP data are available on reasonable request according to 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 approval by the KORA board.

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