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Thyroid volume in Swedish school children; a national, stratified, population-based survey.

Running title: Thyroid volumes in Swedish children

Helena Filipsson Nyström MD, PhD¹, Maria Andersson Msc², Gertrud Berg MD, PhD³, Robert Eggertsen MD, PhD⁴, Elisabeth Gramatkowski Msc⁵, Marie Hansson Bsc, PhD⁶, Lena Hulthén Msc PhD⁵, Mille Milakovic MD, PhD⁴, Ernst Nyström MD, PhD¹

Departments of ¹Endocrinology and ³Oncology Institute of Clinical Sciences, Sahlgrenska University Hospital, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden ²Laboratory for Human Nutrition, Institute of Food, Nutrition and Health, Swiss Federal Institute of Technology Zürich, Zürich, Switzerland ⁴Department of Primary Health Care, Mölnlycke Primary Health Care and Research Centre, Mölnlycke, Sweden ⁵Department of Clinical Nutrition, Sahlgrenska Academy at University of Gothenburg, Gothenburg, Sweden ⁶Department of Radiation Physics, University of Gothenburg, Gothenburg, Sweden

Corresponding author and reprint request: Helena Filipsson, Department of Endocrinology, Gröna Stråket 8, Sahlgrenska University Hospital, S-41345 Göteborg, Sweden Email: helena.filipsson@telia.com Fax: +4631821524 Telephone: +46705833398

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Abstract

Background/ Objectives:

Sweden has had a salt iodination program since 1936. This first national surveillance study on iodine nutrition infers an adequate level of urinary iodine concentration (UIC 125 ug/L) and the aim is now to evaluate thyroid volume (Tvol) in the same national sample.

Subjects/ Methods:

A stratified probability proportionate to size cluster sampling was used to obtain a representative national sample of Swedish children aged 6-12 years. Median Tvol obtained ultrasonographically and the prevalence of enlarged thyroid glands were compared with an international reference standard. Regional differences were evaluated through comparisons of Tvol between coastal and inland areas, urban and rural regions, and former goitre and non-goitre regions.

Results:

Tvol correlated to age, body surface area (BSA), weight, height, and BMI for both sexes, ($p < 0.0001$) but not to UIC. The most important predictors for Tvol were age (girls: $p < 0.0001$, boys: $p = 0.001$) and BSA (girls: $p < 0.0001$, boys $p < 0.01$). Median Tvol was higher in Sweden than in the reference study ($p < 0.0001$). The prevalence of goitre was higher in Sweden (age 22.3%, BSA 15.7%, weight 17.6%, height 12.9%) than in the international reference (age 2.5%, BSA 2.5%, weight 2.5%, height 2.5%) ($p < 0.0001$). Thyroids were larger in boys from urban and former non-goitre areas.

Conclusion:

Tvols were higher in Swedish school children than in the international reference study although iodine intake is considered optimal in Sweden. These findings underline the importance of regular monitoring of iodine intake, especially concerning the decreased intake of table salt that is likely to follow health campaigns.

Key words: thyroid volume, iodine, goitre, national, Sweden, children

Introduction

In Sweden, goitre was first described by Carl von Linné in 1747, and in the beginning of the 20th century, goitre was detected in 60% of cases in certain areas (Sjoberg and Sundlof 1971) and in 18% of the total population (Greenwald 1960) . A national survey conducted in 1929 confirmed endemic goitre regions located in the inner or eastern part of the country (Figure 1) (Höjer 1931): these iodine deficient areas were known as the “goitre-belt”.

These observations contributed to initiation of the Swedish national iodine fortification program for salt in 1936. Initially, 10 mg of potassium iodide (KI) was added to every kilogram salt. In 1966, this was increased to the current level of 50 mg/kg salt (Sjoberg 1978), as goitre was still prevalent in some regions of the country (Johnsson 1965, Sjoberg and Sundlof 1971).

The first national evaluation of iodine status in Sweden was performed according to the recommendations of the World Health Organization (WHO) (World Health Organization 2007, Zimmermann 2009) and the results have been presented (Andersson et al 2009). Urinary iodine concentration (UIC) was measured in a representative national sample of children aged 6-12 years: the national median UIC is 125 µg/L, indicating optimal iodine nutrition. Although, median UIC measures the current iodine intake in the population, thyroid volumes (Tvol) reflect thyroid function, resulting from long-term iodine exposure (Zimmermann et al 2008). The iodization program in Sweden has been fixed since 1966 and long-standing iodine sufficiency in the population is assumed.

With spot collection of UIC, the median UIC is calculated to estimate the iodine status of a population, but does not allow any conclusions of the iodine levels of a single individual: very large number of participants would be needed to allow comparisons

between groups/regions. In contrast, Tvol is an indicator of individual iodine status and can be used for comparisons between individuals and between groups. In this paper, Tvol of the Swedish UIC study population relating the results to age and body surface area (BSA) are reported. The Tvol were compared between different geographical areas, rural/urban regions and regions within the previous goitre belt and with the international standard reference population (Zimmermann et al 2004) to evaluate whether goitre still is present in Sweden and if the Swedish Tvol is comparable to international standards.

Subjects and Methods

Subjects

A stratified probability proportionate to size cluster sampling was used to obtain a representative national sample of Swedish children aged 6-12 years. The selection of study subjects has previously been described (Andersson et al 2009). Of the 1199 children selected, 889 (74%) participated in the UIC study and 796 (66%) in the Tvol study. Tvol were measured between January 25 and May 29, 2007, and only in subjects who had given a UIC sample. Of the 889 subjects providing a urine sample, 93 (10%) were not examined because of illness (n=49), vacancy (n=16), UIC results not available (n=14), refusal to participate (n=8), and because the child had moved to another school (n=6). Furthermore, in the final analyses, the results of nine individuals were excluded as they had reached 12 years of age when the volume determinations were made. In the study invitation, the parents were informed that if thyroid abnormalities were discovered, they would be notified and further investigations of the thyroid would take place within the regular health care system.

Ethics

Parents were informed in writing about the study and had the possibility to contact the study group. The children were included after written informed consent from the parents. The study protocol was approved by the Regional Ethical Review Board in Gothenburg, Sweden, and the study was performed in accordance with the Declaration of Helsinki.

Methods

Teams consisting of an investigator (MM, HF, or MH) and an assistant (GB, RE, EG, or EN) visited the selected schools. Standing height and weight were measured (WHO 1995) in conjunction with an ultrasound examination. The children wore indoor clothing with no shoes and empty pockets. Height was measured with a precision of 0.5 cm and weight to the nearest 0.5 kilogram. BSA (m²) was calculated using the formula: $\text{weight (kg)}^{0.425} \times \text{height (cm)}^{0.725} \times 71.84 \times 10^{-4}$ (Dubois and Dubois 1916).

The thyroid gland volume was measured with a portable ultrasound machine (SSD-900, Aloka, Tokyo, Japan). During the ultrasound examinations, the children were in supine position, with a pillow under the shoulders to extend the neck. Ultrasound examinations were performed by MM in 45.5% of cases, HF in 32.4% of cases and by MH in 22.1% of cases. For each thyroid lobe, the maximum width (W), length (L) and thickness (T) (the anteroposterior diameter of the lobe at a right angle to the mediolateral diameter) were measured (in cm) with an electronic calliper on the inner edge of the capsule. The volume of each lobe (in ml) was calculated according to Brunn *et al* (Brunn et al 1981) with the formula $W \times L \times T \times 0.479$. The total volume was calculated as the sum of the volumes of the two lobes not including the isthmus.

The investigators' technique was validated in another 30 children with the examiners blinded to previous measurement results. The observer inter-individual variations were 16.5% between MM and HF and 15.9% between MM and MH. The intra-individual variation was 13.5% for MM, 16.6% for HF, and 12.7%, for MH. This was not explained by a larger variation in any measure diameter.

Data Analyses

1. Tvols were correlated to age, BSA, weight, BMI and length for both boys and girls.
2. Tvols in Sweden were compared to an international reference standard (Zimmermann et al 2004) of the mean Tvol by ultrasound in 3529 6-12 year-old-children living in areas of long-term iodine sufficiency in North and South America, Central Europe, the Eastern Mediterranean, Africa, and the Western Pacific. The proportion of goitre, defined as thyroids with a volume >97.5 percentile of the WHO study (Zimmermann et al 2004), was evaluated.
3. National Tvols were compared with a local Tvol report of 561 children and adolescents from the Malmö region in Sweden (Svensson et al 2004).
4. The regions specified to evaluate possible regional differences in Tvol were:

a) Regions close to salt sea and regions in the rest of the country (Figure 1):

Regions adjacent to the North Sea (salt water), i.e. the western and southern parts of Sweden consisting of the counties of Västra Götaland, Halland, Skåne and Blekinge and regions adjacent to the Baltic Sea (fresh water) and inland regions.

b) Urban and rural regions:

Based on the regional population size, geographical areas in Sweden were classified as H1 (highest density of population) through H6 (lowest density) (Statistics Sweden 2003). Urban areas were defined as regions H1+H2 and rural areas as H5+H6.

c) Previous goitre regions and non-goitre regions (Figure 1):

Following the results of the goitre investigation in Sweden 1928-9 (Höjer 1931), which was carried out before the iodization program, previous endemic goitre regions were defined as having a prevalence of goitre >15%, while non-goitre regions were defined as a prevalence of 0-4%. Seven areas of the earlier goitre regions, with one participating school located in each region, were identified (Ankarsrum, Stigtomta, Kumla, Gävle, Gnarp, Stugun, and Föllinge). Fifteen earlier non-goitre regions were identified (Nynäshamn, Mölnlycke, Hjärup, Staffanstorps, Skepplanda, Bohus, Norrtälje, Luleå, Uppsala, Skara, Trångsund, Upplands-Väsby, Bålsta, Eskilstuna, Johanneshov) and one participating school was located in each of these regions.

Statistical analyses

Continuous variables were described with mean and range or mean, SD, median, and range. As Tvol was not normally distributed, all analyses were on log-transformed data. The boys and girls were analysed separately. Reference curves for Tvol as a function of age, BSA, weight and length were separately constructed through regression analysis, and presented as median, 2.5th and 97.5th percentiles. For comparison between Sweden and the International Reference study (Zimmermann et al 2004), the differences between observed Tvol and the calculated reference values from the international reference were analysed by Student's one sample t-test. For comparison of Tvol between different geographical areas, two sample t-tests were used. Adjusted analyses for geographical differences of Tvol were by covariance analyses with age and BSA as covariates. All significance tests were two-tailed and the significance level was set at 0.05. All statistical calculations used SAS 9 software.

Results

Thyroid volumes

Tvols correlated positively to age, BSA, weight, BMI, and length for both sexes, ($p < 0.0001$ for all) (Figures 2-3). The most important predictors of Tvol in boys were: age ($R^2 = 0.439$, $p = 0.0010$), BSA ($R^2 = 0.453$, $p < 0.01$), and length ($R^2 = 0.424$, $p < 0.0001$), and for girls: age ($R^2 = 0.596$, $p < 0.0001$) and BSA ($R^2 = 0.574$, $p < 0.0001$). Combining any two variables increased R^2 (boys 0.418-0.452, girls 0.549-0.596). The best R^2 was achieved between age and BSA. Tvol intervals, BSA and BMI for age groups are presented in Table 1. No pathology in the thyroid glands was detected by ultrasound and there was no association between Tvols and UIC (data not shown).

Comparison with international reference

Tvols from boys and girls were compared with international WHO reference data (Zimmermann et al 2004) (Figures 2-3). Tvols recorded in Sweden were significantly larger ($p < 0.0001$) in both sexes than in the international reference study, irrespective of whether volumes were expressed as a function of age, BSA, weight, or length. A comparison of this data with the results of a former study in the southern part of Sweden (Svensson et al 2004) indicated children in this study had larger thyroids (data not shown).

Prevalence of goitre

The prevalence of goitre related to age was higher (22.3 (95% confidence interval (CI) 19.4-25.4%) in Swedish children than in the reference population (2.5%, "by definition"), and also for goitre related to BSA (Swedish children: 15.7% (95% CI 13.2-18.5%); reference population 2.5%). The difference was significant for boys and girls in both comparisons ($p < 0.0001$).

Regional comparisons

No regional differences of Tvols were observed between areas adjacent to salt sea and brackish water sea (data not shown). Neither were any regional differences observed for girls from rural, compared to urban areas (data not shown). However, significantly smaller thyroid glands were detected in boys from rural areas, compared to urban (rural (median-range) 3.28 (1.56-9.19) ml; urban 3.70 (1.56-10.42) ml, $p=0.009$), and from previous goitre areas, compared to non-goitre areas (previous goitre areas 3.54 (1.56-7.47) ml; non-goitre areas 3.88 (1.41-10.42) ml, $p=0.007$).

Discussion

This study was an extension of the first national study of iodine nutrition in Sweden undertaken in 2007 and recently reported in EJCN (Andersson et al 2009). The median UIC in school-aged children was 125 ug/L, with a low proportion of children with UIC <50 ug/L (5.5%) and >300 ug/l (3.0%), indicating optimal iodine intake. The present study indicates significantly larger Tvol for both boys and girls in Sweden than in the International Reference study of Zimmermann *et al* (Zimmermann et al 2004), irrespective of whether they were expressed as a function of age, BSA, weight, or length.

The larger Tvol were probably not explained by a lower median UIC than recorded in the international reference population (median UIC: 203 ug/L) (Zimmermann et al 2004), as Tvols and UIC do not correlate during circumstances of iodine sufficiency (Zimmermann et al 2004), although minor changes in iodine level in a population can affect Tvol (Knudsen et al 2000). In addition, as UIC levels in Sweden are lower than required during pregnancy and lactation (WHO 2005), the newborn may have an insufficient iodine supply, which may negatively influence Tvols (Zimmermann 2007).

The Swedish salt iodization program has been active for over 70 years; thus, a major part of the population has spent its entire life consuming iodine-fortified salt, as is the case with most children in the study population. In the Zimmermann study (Zimmermann et al 2004), performed to be normative for ultrasound estimates of Tvol in children from long-standing iodine sufficiency areas, there are significant differences in Tvol between children from different countries. Therefore, a higher estimate of Tvol could not be referred to previous iodine deficiency, which sustained slightly larger thyroids in the population, as is discussed concerning the earlier reference study from 1997 in Europe (WHO 1997). Additionally, the ultrasound measurements of the reference study were performed with children in the sitting position (Zimmermann et al 2004), whereas, in the present study, the children were in the supine position. However, this was considered to have a negligible effect on the measurements.

Three earlier studies report Tvol in Swedish school children (Gutekunst et al 1986, Milakovic et al 2004, Svensson et al 2004). The data from the study by Gutekunst *et al* (1986) included data from Germany that was used as reference for Tvol in iodine sufficiency and served as the first international standard for comparing Tvol between countries. However, the reference is criticized as being too low (Delange et al 1997). The local reports from Milakovic *et al* and Svensson *et al* imply normal Tvol.

In the comparison of Tvol in different regions, inhabitants from the western and southern part of Sweden were investigated to determine if they had smaller thyroid glands than the rest of Sweden. These regions are sometimes exposed to storms carrying salt containing iodine from the North Sea (Sjöberg 1972) and the coastal areas close to the North Sea are recorded as having a higher intake of salt water fish

in the early part of the 20th century than inland areas (Höjer 1931). There was no evidence of these regional differences occurring today.

No difference in Tvol was found between urban and rural areas, with the exception of larger thyroid glands in boys in urban areas. Nor was any difference between former goitre and non-goitre areas observed, with the exception of boys in the former non-goitre areas also having larger thyroid glands. This finding, that boys in urban areas and former non-goitre areas had larger glands, was unexpected and might be explained by significance of multiple comparisons; however, other explanations need to be considered. A systematic error or seasonal variation (Hegedus et al 1987) was unlikely, as the ultrasound measurements in these areas were not performed by a single individual and all children were investigated during a period of four months. In Sweden, the food consumption pattern does not differ and dairy food is not produced in the same dairy within these areas. Furthermore, any effect of thiocyanates from smoking (Erdogan 2003, Hansen et al 2004) is unlikely to affect such a young population. However, Tvol is determined by genetic factors (Hansen et al 2004) that may influence the results. Iodine deficiency with goitre was previously a severe problem in Sweden, as illustrated by the large national survey in 1929 (Höjer 1931) where 29 000 individuals from a population of 6.1 million (Statistics 1969) were affected: goitre was detected by palpation in more than 15% of the children (Höjer 1931) in some areas. In the present study, seven of the 30 schools participating were located within the previous "goitre belt". The comparison between these schools and the 15 schools within the non-goitre areas reflected that the previous goitre areas no longer were seen.

The reliability of Tvol determination by ultrasound is limited. The major drawback is operator dependency and low reproducibility, resulting in high intra- and inter-

individual variability (Andermann et al 2007). Even for a single observer with one set of images, the selection of the correct diameter is arbitrary: in this study, the intra- and inter-individual variability was approximately 15%, which was in accordance with the results of Andermann *et al* (Andermann et al 2007).

The limitations of this national iodine nutrition study in Sweden are discussed in detail elsewhere (Andersson et al 2009). One limitation of the present study, relative to the UIC study, is that it was performed during the latter half of the period when UIC data were collected. The participation rate was only 66%, which is considered satisfactory due to the practical difficulties with in this type of study.

Tvol in Swedish children is slightly larger than in the WHO reference population for children (Zimmermann et al 2004), probably reflecting environmental or genetic factors, as UIC level in Sweden proposes iodine sufficiency. This study infers that the previous goitre areas no longer differ from previous non-goitre areas and confirms local reports that goitre is no longer a problem in Sweden (Milakovic et al 2001, Milakovic et al 2004, Sjoberg and Sundlof 1971). However, iodine deficiency may appear in subgroups, such as pregnant women, vegans, and certain ethnical groups. These results underline the importance of future frequent monitoring of iodine intake in Sweden, not least considering the new national recommendations for decreasing the salt intake from about 12 g/day to 5 g/day during the next few years. In the present situation, pregnant and lactating women may be at risk of low iodine intake, despite the fortification program.

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Conflict of interest

The authors have nothing to disclose.

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Table 1

Thyroid volumes (mean and range), body mass index (BMI), and body surface area (BSA) in a representative population sample of Swedish children aged 6-12 years in 2007.

Age (yrs)	Sex	BMI (kg/m ²)	BSA (m ²)	Length (cm)	Thyroid volume (ml)	Weight (kg)
6 (n=47)	Girls	16.1 (13.0-22.1)	0.9 (0.7-1.2)	122.3 (105.0-136.5)	2.6 (1.0-4.1)	24.3 (17.0-41.2)
6 (n=48)	Boys	16.7 (13.2-22.6)	0.9 (0.8-1.3)	124.7 (115.0-143.5)	2.6 (1.6-4.7)	26.0 (20.1-46.6)
7 (n=69)	Girls	16.8 (14.2-22.8)	1.0 (0.8-1.2)	128.3 (112.0-140.0)	3.0 (1.7-6.6)	27.8 (19.9-41.0)
7 (n=70)	Boys	16.6 (13.5-22.3)	1.0 (0.8-1.2)	128.5 (118.0-140.0)	3.0 (1.4-6.7)	27.5 (20.9-40.1)
8 (n=39)	Girls	17.5 (13.4-21.2)	1.1 (0.9-1.3)	132.6 (125.0-143.0)	3.2 (1.6-5.7)	30.8 (21.0-43.3)
8 (n=66)	Boys	17.5 (13.5-27.0)	1.1 (0.9-1.3)	133.4 (120.0-146.0)	3.5 (1.8-6.5)	31.3 (22.1-48.6)
9 (n=48)	Girls	16.8 (13.4-24.4)	1.1 (0.9-1.5)	139.3 (129.0-155.5)	3.6 (2.0-6.9)	32.8 (22.3-56.3)
9 (n=52)	Boys	18.5 (14.4-25.9)	1.2 (1.0-1.5)	140.9 (129.5-152.0)	3.8 (2.4-8.3)	37.0 (25.8-55.1)
10 (n=53)	Girls	18.6 (11.2-29.2)	1.3 (0.9-1.7)	146.4 (114.3-167.0)	4.7 (2.4-8.6)	40.2 (22.0-63.0)
10 (n=65)	Boys	17.9 (5.6-23.6)	1.3 (0.8-1.7)	147.6 (131.0-169.0)	4.4 (1.7-7.7)	39.4 (28.8-61.2)
11 (n=59)	Girls	19.6 (13.4-29.7)	1.4 (1.0-1.8)	151.5 (132.0-166.0)	5.2 (2.2-16.9)	45.4 (25.9-76.0)
11 (n=64)	Boys	19.6 (14.9-27.3)	1.4 (1.1-1.7)	151.3 (136.0-168.0)	4.8 (2.5-10.4)	45.1 (31.0-69.3)
12 (n=40)	Girls	19.7 (15.0-30.8)	1.5 (1.2-1.9)	156.9 (143.5-172.5)	5.9 (3.7-10.6)	48.7 (35.4-80.9)
12 (n=57)	Boys	20.3 (16.0-28.8)	1.5 (1.2-2.0)	160.8 (142.0-178.0)	5.7 (2.5-9.7)	52.9 (33.0-82.2)

Table 2

Comparison of thyroid volumes in children in regions with different in distances to the (salt) sea, density of population (H) and history of goitre prior to iodization.

Mean and Median divided by sex in comparison with geographical areas, population size (H-regions) and previous goitre areas					Adjusted for age and BSA	
Sex	Variable	Grouping	Mean (SD) Median (Min-Max) (ml)	p-value	Median (ml)	p-value
Girls	Areas close to salt water vs Rest of Sweden	South and western parts of Sweden	3.75 (1.44) 3.53 (1.05-8.64)	0.034	3.69	0.36
		Baltic coast + Inland	4.17 (1.80) 3.70 (1.61-16.88)		3.79	
	Urban vs Rural	H1+H2 (see text) H5+H6	3.64 (1.67) 3.18 (1.65-16.88) 5.36 (1.86) 5.12 (2.08-10.61)	<0.0001	3.79 3.89	0.60
	Previous goitre areas vs Non-goitre areas	> 15% goitre (see text) 0-4% goitre	4.57 (1.62) 4.47 (1.61-9.07) 3.87 (1.48) 3.56 (1.65-9.50)	0.0004	3.84 3.82	0.82
Boys	Areas close to salt water vs rest of Sweden	South and Western parts of Sweden	3.99 (1.705) 3.62 (1.41-9.74)	0.71	3.68	0.77
		Baltic coast + inland	3.88 (1.47) 3.66 (1.56-10.42)		3.64	
	Urban vs Rural	H1+H2 (see text) H5+H6	3.84 (1.42) 3.70 (1.41-10.42) 3.85 (1.57) 3.71 (1.56-9.19)	0.82	3.70 3.28	0.009
	Previous goitre areas vs Non-goitre areas	> 15% goitre (see text) 0-4% goitre	3.77 (1.21) 3.69 (1.56-7.47) 4.16 (1.716) 3.89 (1.41-10.42)	0.10	3.54 3.88	0.007

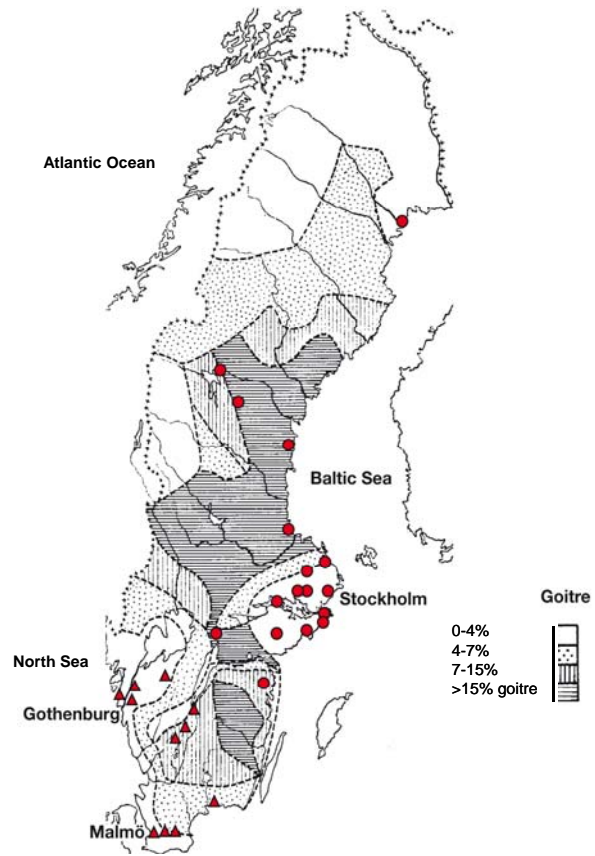


Figure 1

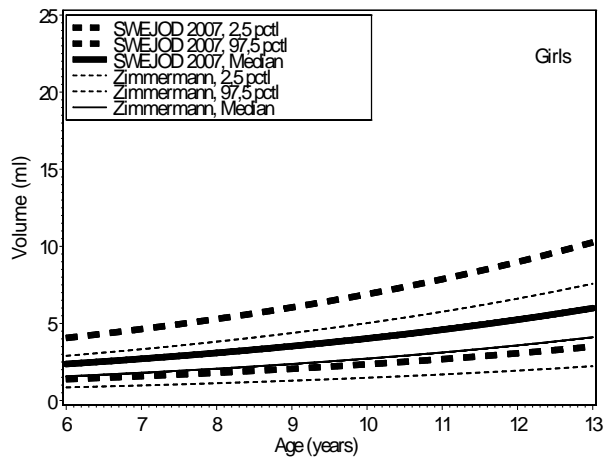
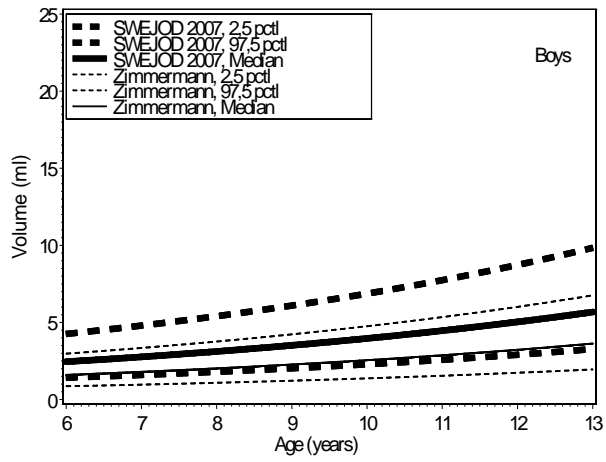


Figure 2

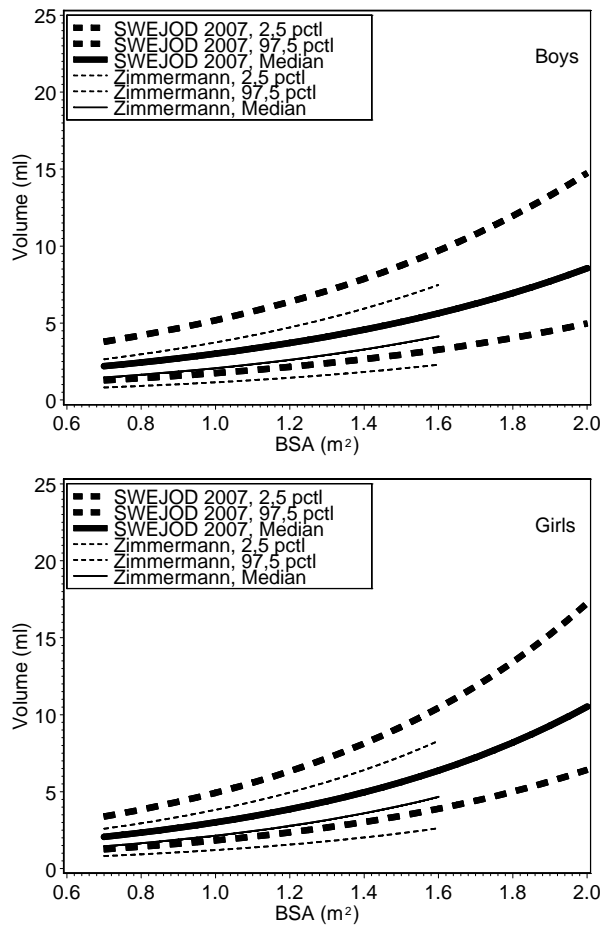


Figure 3