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Disorders of peroxisome biogenesis due to mutations in PEX1: phenotypes and PEX1 protein levels

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CLINICAL STUDY

A survey of iodine intake and thyroid volume in Dutch schoolchildren: reference values in an iodine-sufficient area and the effect of puberty

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Abstract

Background: Iodine deficiency and endemic goiter have been reported in the past in The Netherlands, especially in the southeast.

Objective: To evaluate iodine intake and thyroid size in Dutch schoolchildren, contrasting those living in a formerly iodine-deficient region in the east (Doetinchem) with those living in an iodine-sufficient region in the west (Amsterdam area).

Design: Cross-sectional survey of 937 Dutch schoolchildren aged 6–18 years, of whom 390 lived in the eastern and 547 in the western part of the country.

Methods: Thyroid size was assessed by inspection and palpation as well as by ultrasound. Iodine intake was evaluated by questionnaires on dietary habits and by measurement of urinary iodine concentration.

Results: Eastern and western regions were similar with respect to median urinary iodine concentration (15.7 and 15.3 µg/dl, NS, Mann-Whitney *U* test), goiter prevalence by inspection and palpation (0.8 and 2.6%, *P* = 0.08, chi-squared test), and thyroid volumes. The P97.5 values of thyroid volumes per age and body surface area group were all lower than the corresponding sex-specific normative WHO reference values.

Iodized salt was not used by 45.7% of households. Daily bread consumption was five slices by boys and four slices by girls. Weekly milk consumption was 3 liters by boys and 2 liters by girls. Seafish was consumed once monthly. From these figures we calculated a mean daily iodine intake of 171 µg in boys and 143 µg in girls, in good agreement with the measured median urinary concentration of 16.7 µg/dl in boys and 14.5 µg/dl in girls. The sex difference in iodine excretion is fully accounted for by an extra daily consumption of one slice of bread (20 µg I) and one-seventh of a liter of milk (8.3 µg I) by boys.

Thyroid volume increases with age, but a steep increase by 41% was observed in girls between 11 and 12 years, and by 55% in boys between 13 and 14 years, coinciding with peak height velocity. Girls have a larger thyroid volume at the ages of 12 and 13 years, but thyroid volume is larger in boys as of the age of 14 years.

Conclusions: (1) Iodine deficiency disorders no longer exist in The Netherlands. (2) Bread consumption remains the main source of dietary iodine in The Netherlands; the contribution of iodized table salt and seafish is limited. (3) The earlier onset of puberty in girls renders their thyroid volume larger than in boys at the age of 12–13 years, but boys have a larger thyroid volume as of the age of 14 years.

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Introduction

It is well known that iodine deficiency existed in The Netherlands in the past. Iodine-deficient regions were located in the eastern and southern parts of the country, whereas iodine supply was higher in the areas bordering the North Sea. Iodine supplements were instituted as of 1935. Goiter prophylaxis was

revised in 1982 (1). Iodized salt for household use was reintroduced with a content of 25 mg KI/kg ('Jozo' salt). The KI content of bread salt ('Jobrozo' salt, of which the use was compulsory for bakeries as of 1968) was increased to 60 mg/kg. It was calculated that these measures should guarantee an adequate daily iodine intake of 160–200 µg, within the optimal range of 150–300 µg as recommended by the WHO. These

calculations assumed a daily consumption of four slices of bread (containing $4 \times 20 \mu\text{g} = 80 \mu\text{g}$ iodine) and of 4 g table salt ($4 \times 25 \mu\text{g} = 100 \mu\text{g}$ iodine). In 1984, however, the Supreme Court of the Netherlands ruled that the bakeries could not be compelled to use iodized bread salt.

The effect of the 1982 and 1984 rulings was investigated in 1985 and 1986 in adolescents of the age of 12–18 years living in various regions (2). Goiter prevalence as estimated by inspection and palpation ranged from 19 to 39% in girls and from 4 to 31% in boys, the highest figures being observed in areas with endemic goiter in the past. The goiter prevalence was rather high in view of the normal or marginally low iodine intake, and it was postulated that other environmental goitrogens might be involved in the affected regions. The observed goiters were mostly small and not visible; the visible goiter rate was 2–6% in girls and 0–2% in boys.

The clinical assessment of thyroid size has been shown to be imprecise for small goiters. Misclassification between thyroid size grade 0 and 1 can be as high as 40%, resulting in an incorrect prevalence rate (3). Therefore, the frequency distribution of thyroid volume measured by ultrasonography is highly recommended, especially in areas where the visible goiter rate is low (4). In view of these methodological remarks and the continuing concern about the adequacy of iodine intake in The Netherlands, we decided to investigate urinary iodine concentration and thyroid volume by ultrasonography in schoolchildren, in agreement with the recommendations of WHO, UNICEF and the International Council for the Control of Iodine Deficiency Disorders (3). In addition, we determined thyroid size by inspection and palpation and assessed iodine intake by questionnaires. Two study sites were selected in order to contrast a formerly iodine-deficient region with an iodine-sufficient region: one was the town of Doetinchem in the eastern part of the Netherlands (the same location as studied in 1985 and 1986) (2), the other was the Amsterdam area in the west close to the North Sea.

Subjects and methods

Subjects

The study was approved by the Committee on Medical Ethics of the Academic Medical Center in Amsterdam. After obtaining permission from the headmaster, schoolchildren aged 6–18 years were asked to participate. Some days before the actual investigation, the schoolchildren received written information on the project, a questionnaire on sex, age and dietary habits and an informed consent form. Consent had to be given by the parents for the children aged 6–13 years, and by the children themselves in the age group 14–18 years. Children were investigated class by class in the

'ThyroMobil', a specially equipped Mercedes van. This mobile unit contained a sonographic device, a computer for processing the thyroid measurements on the spot, and facilities for the collection and storage of urine samples. Height and weight were measured. Urine samples were collected just before or after thyroid echography. Assessment of thyroid size by inspection and palpation was done before ultrasonography. In case of abnormality in the clinical or echographic examination of the thyroid, the parents of the children received a written note directed to the family physician describing the abnormal results of the examination.

Schoolchildren of one elementary and one secondary school in Doetinchem composed the study population of the eastern region. In the western region the schoolchildren came from two elementary schools (in Velsbroek and Landsmeer) and two secondary schools (in Amsterdam and Haarlem), all within a distance of 15 km of each other. The study was performed in 1995 and 1996.

Methods

Assessment of thyroid size was done by one experienced investigator (JP). Thyroid volume was determined using real-time echography according to Brunn *et al.* (5) with a Siemens Sonoline SI-400, using a 7.5 MHz linear array transducer. Longitudinal and transverse scans were performed allowing the measurement of the depth (d), width (w) and length (l) of each lobe. The volume of the lobe was calculated by the formula: $V \text{ (ml)} = 0.479 \times d \times w \times l \text{ (cm)}$. The thyroid volume was the sum of the volumes of both lobes. The volume of the isthmus was not included. Thyroid volumes were analyzed according to sex, age and body surface area (BSA). BSA (in m^2) was calculated by using the formula: $\text{BSA} = W^{0.425} \times H^{0.725} \times 71.84 \times 10^{-4}$, where W is the weight in kg and H the height in cm.

Thyroid size determined by inspection and palpation was graded as follows: grade 0, no goiter, subdivided into grade 0^A (thyroid not palpable) and grade 0^B (thyroid palpable but lateral lobes smaller than the terminal phalanges of the thumbs of the examined person); grade I^A, goiter detectable only by palpation (lateral lobes greater than the terminal phalanges of the thumbs of the examined person) and not visible when the neck is fully extended; grade I^B, goiter palpable, and visible only when the neck is fully extended; grade II, goiter visible with the neck in normal position; grade III, very large goiter that can be recognized at a considerable distance (3, 6).

Iodine intake was assessed from questionnaires asking for the use of iodized salt and the consumption of bread, milk and seafood. Urinary iodine concentration was measured by the colorimetric ceric ion arsenious acid wet ash method based on the Sandell–

Table 1 Characteristics of the population of Dutch schoolchildren living in the eastern or the western part of the country (age and urinary iodine as median values).

| | Eastern region | | | Western region | | | All | | |
|-------|----------------|-------------|-------------------------------------|----------------|-------------|-------------------------------------|----------|-------------|-------------------------------------|
| | <i>n</i> | Age (years) | Urinary iodine ($\mu\text{g/dl}$) | <i>n</i> | Age (years) | Urinary iodine ($\mu\text{g/dl}$) | <i>n</i> | Age (years) | Urinary iodine ($\mu\text{g/dl}$) |
| Boys | 172 | 12 | 16.55 | 236 | 11† | 16.82 | 408 | 12 | 16.71 |
| Girls | 218 | 12 | 15.11 | 311 | 13 | 14.15‡ | 529 | 12 | 14.52§ |
| All | 390 | 12 | 15.73 | 547 | 12 | 15.26 | 937 | 12 | 15.44 |

† $P = 0.03$ vs Eastern boys; ‡ $P = 0.002$ vs Western boys; § $P = 0.004$ vs all boys.

Kolthoff reaction (7) using a Technicon auto-analyzer (8).

Statistical analysis

The frequency distributions of both thyroid volume and urinary iodine were mostly asymmetrical and skewed towards high values. A logarithmic transformation was used to normalize the distribution. The Kolmogorov–Smirnov test was applied to check normality of the transformed variable in each age group and BSA group, separately for boys and girls. Means and standard deviations of the logarithm of thyroid volume were used as parameters to fit a normal distribution to the data of each group. On the basis of these normal distribution, percentiles were computed from the standard normal distribution.

Differences between the eastern and the western regions were analyzed by the chi-square test, by the Mann–Whitney U test for urinary iodine concentrations, and by analysis of variance for thyroid volumes. In all analyses the level of significance was taken as $\alpha = 0.05$.

Results

The characteristics of the 937 investigated schoolchildren aged 6–18 years are listed in Table 1. Participation rate was 85–89% of schoolchildren from the elementary schools, but in the order of 60% for schoolchildren from the secondary schools. In the

oldest group of 18 years, 6 of the 25 boys and 5 of the 32 girls were 19 years old. Urine samples were collected in 816 children, 87% of the total study population.

Urinary iodine concentration

No differences were observed in urinary iodine concentrations between schoolchildren living in the eastern or the western part of the country. The urinary iodine concentration did not differ between the various age groups (data not shown), but was lower in girls than in boys (Table 1). The median value of urinary iodine concentrations of all investigated children was 15.44 $\mu\text{g/dl}$, clearly above the threshold level of 10 $\mu\text{g/dl}$ for iodine deficiency (3).

Thyroid size by inspection and palpation

The frequency distribution of thyroid grades 0 and I is given in Table 2. Thyroid grades II and higher were not observed. The proportion of thyroid grades was not different between the eastern and western regions. The prevalence of goiter (grade I) is 0.8% in the east and 2.6% in the west ($\chi^2 = 3.08$, $P = 0.08$). The figures are well below 5%; a prevalence $>5\%$ indicates endemic goiter (3).

Thyroid volume by ultrasound

Thyroid volumes increased with advancing age. Analysis of variance indicated no difference in thyroid volumes between the eastern and western regions, neither for the boys ($P = 0.60$, NS) nor for the girls ($P = 0.92$, NS). This was true for the whole age range as well as for the age group 6–14 years.

The data from the eastern and western regions were combined to construct reference values of thyroid volumes for Dutch boys and Dutch girls according to age and BSA (Fig. 1). The Kolmogorov–Smirnov tests were all non-significant, indicating a normal distribution after logarithmic transformation of the data. The computed P97.5 values of thyroid volumes per age and BSA group were all lower than the corresponding sex-specific P97 values derived from a reference population of 3265 schoolchildren aged 6–15 years living in

Table 2 Thyroid size determined by inspection and palpation in Dutch schoolchildren living in the eastern or western part of the country.

| | | <i>n</i> | Thyroid size | | | |
|----------------|-------|----------|----------------------|----------------------|----------------------|----------------------|
| | | | Grade 0 ^A | Grade 0 ^B | Grade 1 ^A | Grade 1 ^B |
| Eastern region | Boys | 172 | 88.0% | 12.0% | 0% | 0% |
| | Girls | 218 | 86.5% | 12.0% | 0.5% | 1.0% |
| | All | 390 | 87.2% | 12.0% | 0.3% | 0.5% |
| Western region | Boys | 236 | 84.5% | 12.7% | 2.4% | 0.4% |
| | Girls | 311 | 83.9% | 13.8% | 2.0% | 0.3% |
| | All | 547 | 84.1% | 13.3% | 2.2% | 0.4% |

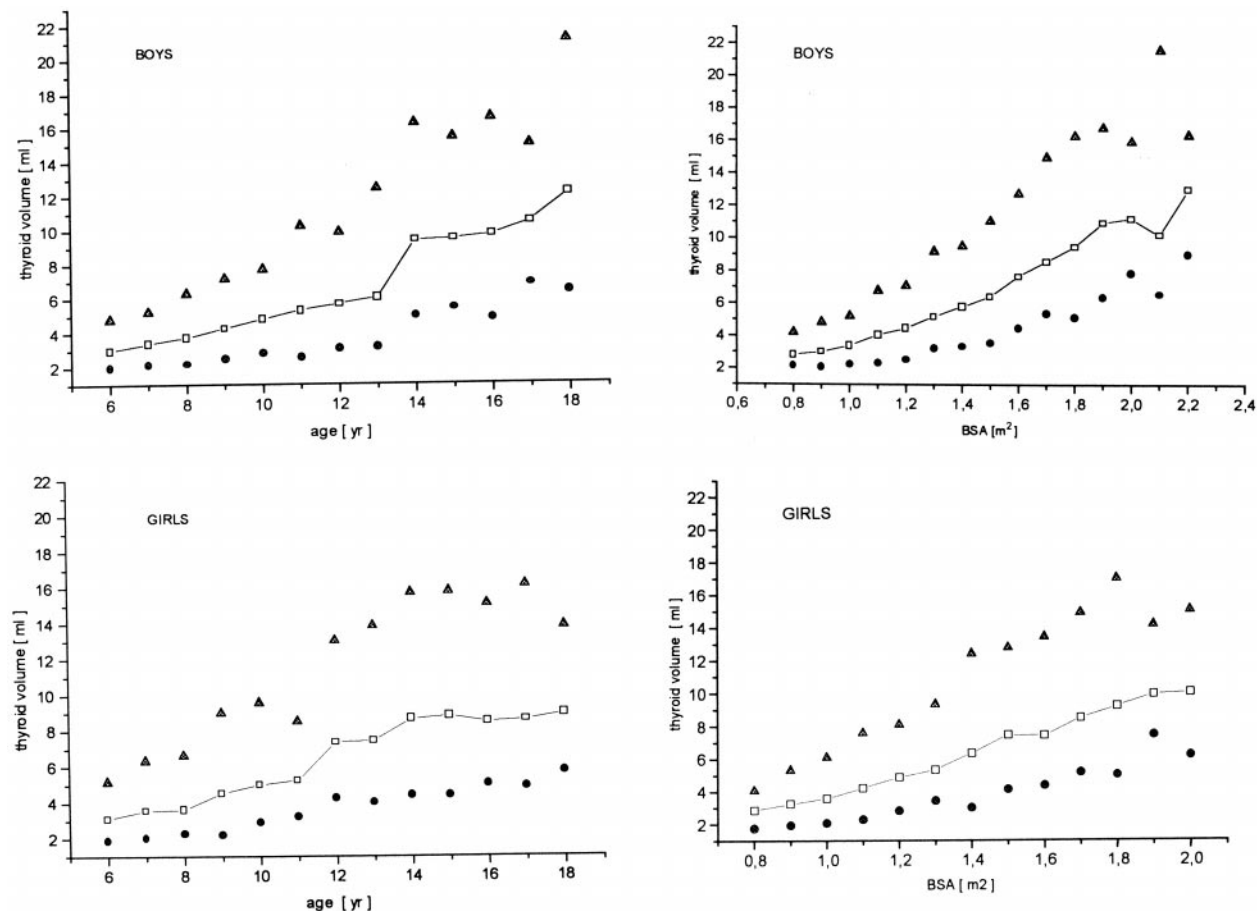


Figure 1 Thyroid size determined by ultrasound in Dutch schoolchildren (408 boys and 529 girls) according to age (left panels) and to BSA (right panels). Median values and the percentiles P2.5 and P97.5 are depicted of thyroid volumes after logarithmic transformation to obtain a normal distribution.

iodine-sufficient areas of four European countries, published in 1997 (9).

Inspection of the curves of median thyroid volume as a function of age (Fig. 1, left panels) shows a sudden increase of thyroid volume between the age of 13 and 14 in boys by 55%, and between the age of 11 and 12 in girls by 41%. This phenomenon is most likely linked to the earlier onset of puberty in girls as compared with boys. As evident from Fig. 2, thyroid volume of both sexes is almost similar up to the age of 11 or a BSA of 1.3 m^2 . At the ages of 12 and 13, girls have a larger thyroid volume than boys, associated with an increase of BSA in the girls from a median value of 1.29 at the age of 11 to 1.48 at the age of 12 and 1.54 at the age of 13. As of the age of 14 years, however, the thyroid volume of boys is larger than of girls, associated with an increase of BSA in the boys from a median value of 1.45 at the age of 13 to 1.68 at the age of 14 and 1.78 at the age of 15. The sex difference in thyroid volume is less marked if expressed by BSA than by age, but both indicate a larger thyroid gland in males than in females as of 14 years.

Other echographic findings

Additional findings on thyroid ultrasound are listed in Table 3. Diffuse hypoechogenicity of the thyroid tissue was found in four boys and five girls below the age of 13 years, and in seven girls of 13 years and older. Hypoechogenicity clearly suggestive of autoimmune thyroiditis occurred in 4 of the 14 subjects with a goiter (grade IA or IB); two were boys of 10 and 12 years, two were girls of 15 and 16 years, all had a thyroid volume greater than the age- and sex-specific P97.5 value. Anechogenic areas suggestive of small pseudocysts were found in the age groups of 12 years and older; the diameter ranged from 3 to 9 mm. The nodules occurred in an 8-year-old girl (size $7 \times 4 \times 8 \text{ mm}$) and in a 17-year-old girl (size $14 \times 10 \times 10 \text{ mm}$).

Dietary habits

Dietary habits as assessed from the questionnaires are presented in Table 4 and Fig. 3. About 55% of the households used iodized table salt. Bread consumption

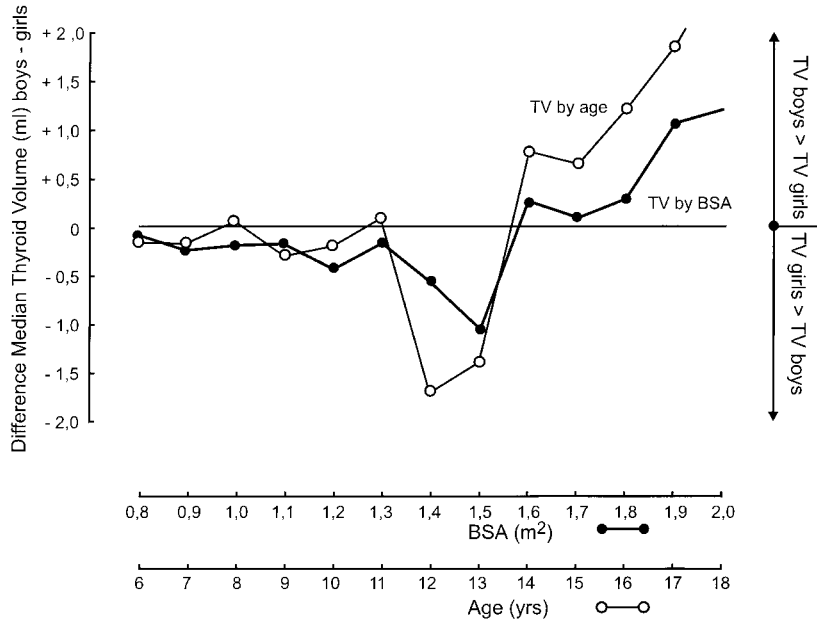


Figure 2 Sex differences in median thyroid volumes (TVs) according to age and BSA.

Table 3 Findings on thyroid echography in Dutch schoolchildren living in the eastern or the western part of the country.

| | Eastern region | | Western region | | All | |
|----------------------|----------------|-------|----------------|-------|------|-------|
| | Boys | Girls | Boys | Girls | Boys | Girls |
| Hypoechogenicity | 0 | 6* | 4 | 6 | 4 | 12 |
| Pseudocyst | 2 | 5 | 1 | 2 | 3 | 7 |
| Nodule | 0 | 1 | 0 | 1 | 0 | 2 |
| Hypoplasia left lobe | 2 | 0 | 0 | 1 | 2 | 1 |
| Total | 4 | 12 | 5 | 10 | 9 | 22 |

* One girl used thyroxine because of hypothyroidism.

was similar in both regions; boys ate daily five slices and girls four slices of bread (median values). Milk drinkers were more frequent in the east than in the west. Among milk drinkers, boys drank 3 liters weekly

both in the east and the west, and girls 2.5 liters in the east and 2 liters in the west (median values). Seafish was consumed more often by boys than by girls, and more frequently in the west than in the east. Among those eating seafish, the number of seafish meals per month was two for boys and girls in the west, and one for boys and girls in the east (median values).

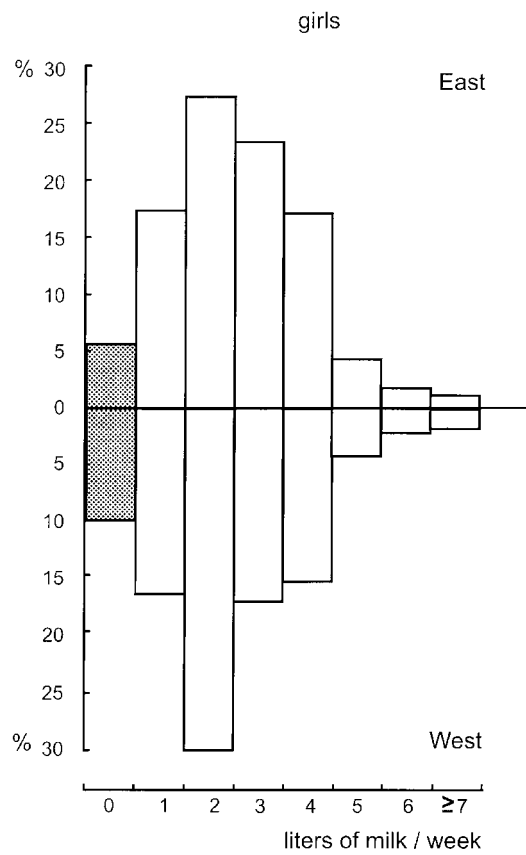
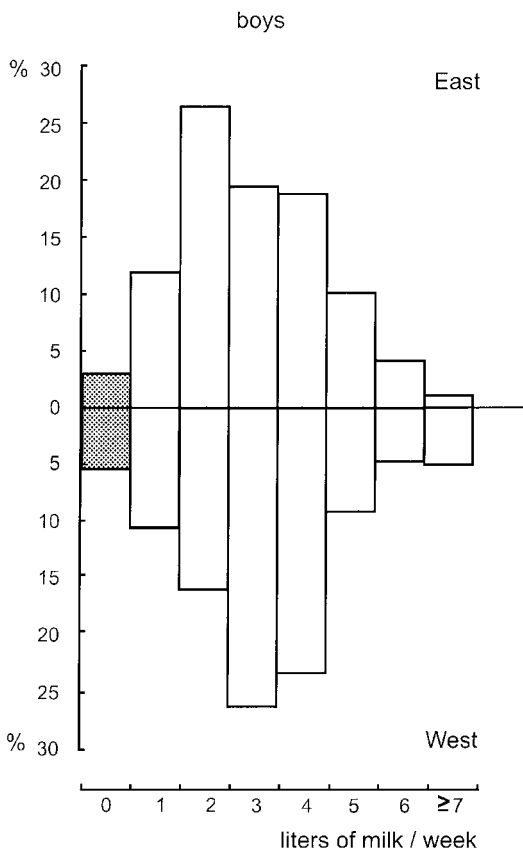
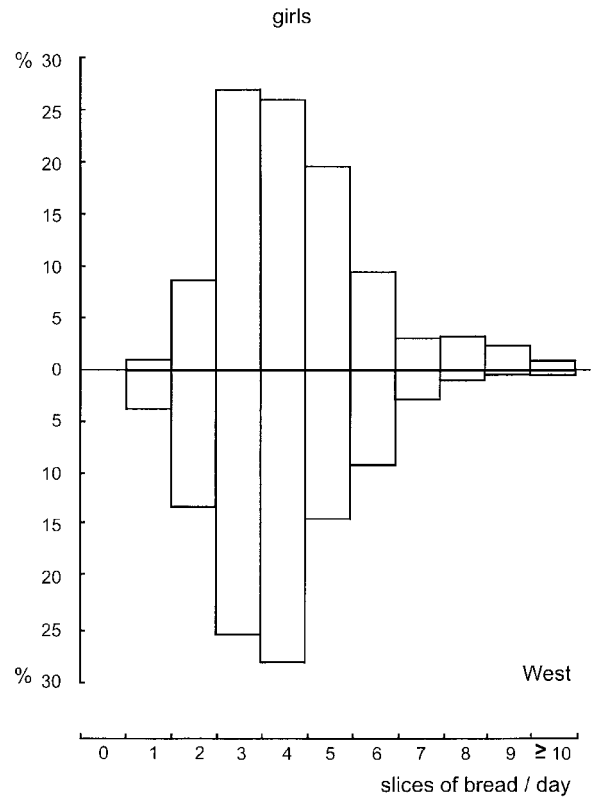
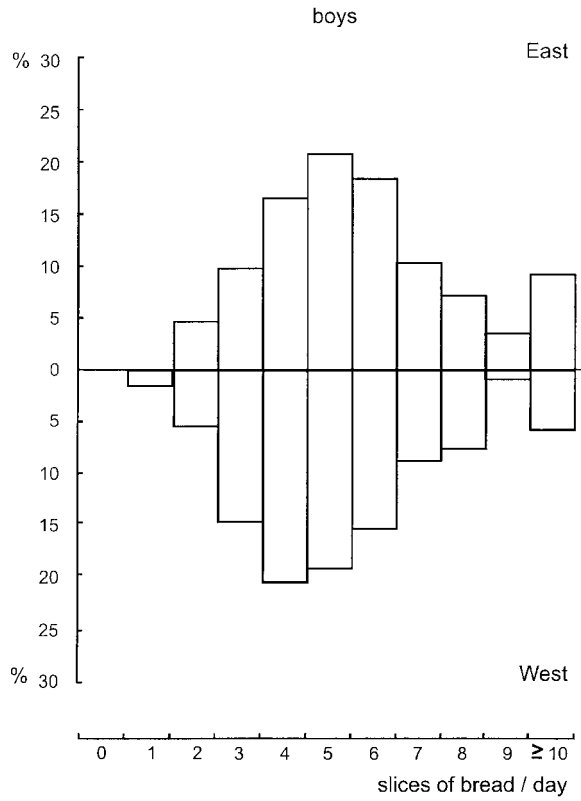
Discussion

Absence of iodine deficiency disorders

The present survey clearly indicates the absence of endemic goiter in The Netherlands according to WHO criteria (3, 4): the prevalence of goiter (grade I or higher by inspection and palpation) was <5%, the frequency of thyroid volume >97th centile by ultrasound was <5%, and the median urinary iodine concentration was >100 µg/l among the investigated

Table 4 Nutritional history of Dutch schoolchildren living in the eastern or western part of the country (differences between groups indicated by the chi-square test).

| | | Eastern region (%) | | Western region (%) | | All (%) | |
|-----------------|-------|--------------------|----|--------------------|----------|---------|----------|
| No iodized salt | Boys | 42.9] | NS | 51.1] | NS | 47.6] | NS |
| | Girls | 42.9] | | 44.9] | | 44.1] | |
| | All | 42.9 | | 47.6 | | 45.7 | |
| No milk | Boys | 3.4] | NS | 5.2] | P = 0.04 | 4.5] | P = 0.02 |
| | Girls | 5.7] | | 10.0] | | 8.2] | |
| | All | 4.6 | | 7.8 | | 6.5 | |
| No seafish | Boys | 29.9] | NS | 21.4] | P = 0.02 | 24.9] | P = 0.02 |
| | Girls | 34.7] | | 30.0] | | 32.0] | |
| | All | 32.6 | | 26.1 | | 28.8 | |



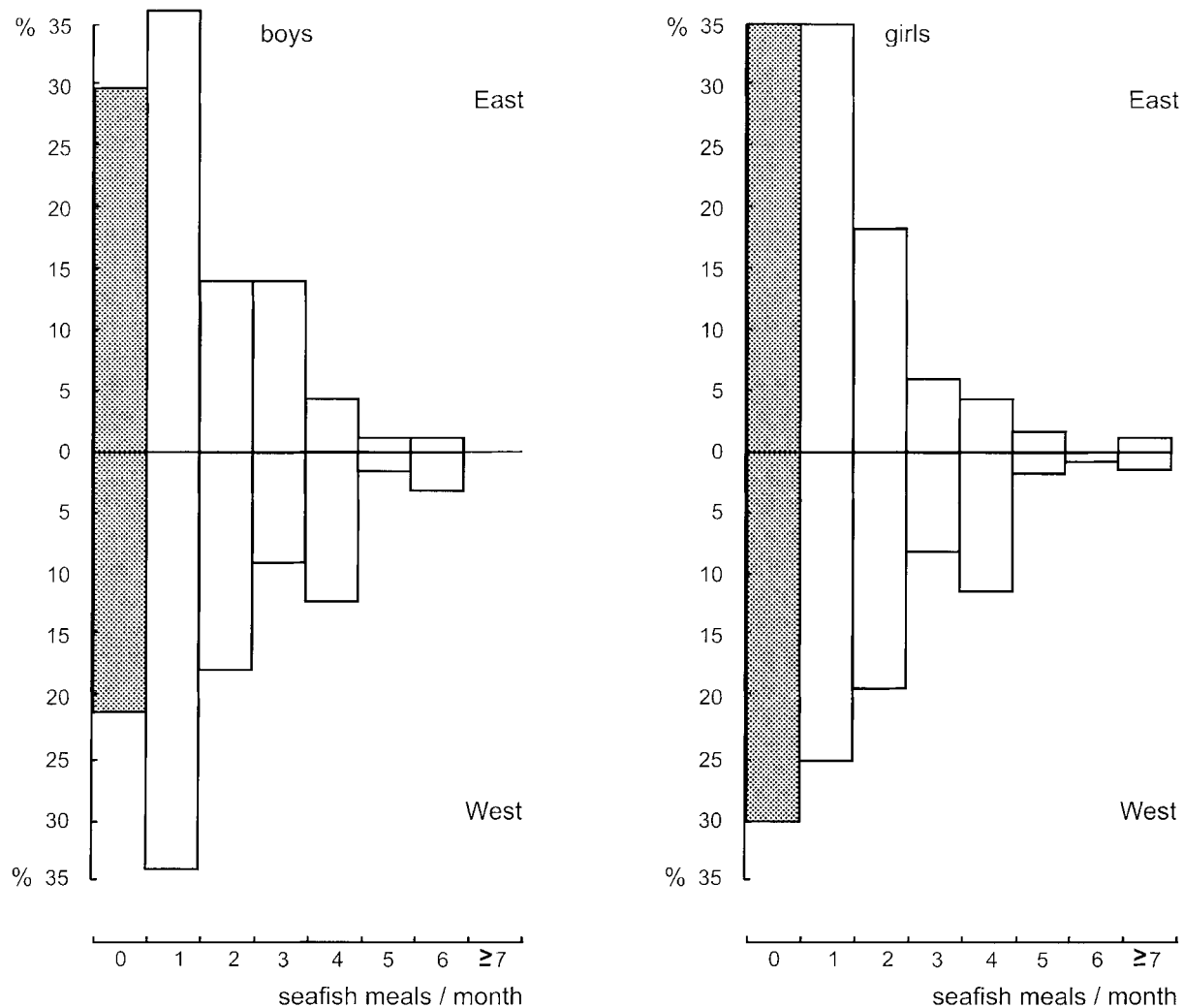


Figure 3 Frequency histograms of bread, milk and seafish consumption of Dutch schoolchildren living in the eastern or the western area. No regional differences were found in either boys or girls in bread and milk consumption, but seafish consumption was higher in the west, both in boys ($P = 0.047$) and in girls ($P = 0.003$).

schoolchildren. The conclusion is supported by a median urinary iodine level of $>50 \mu\text{g/l}$ in Dutch newborns (10). In fact, urinary iodine excretion in the present study (median $15.3 \mu\text{g/dl}$), in Dutch newborns (median $126 \mu\text{g}/24 \text{ h}$) (10) and in Dutch healthy adults (median $135 \mu\text{g}/24 \text{ h}$) (11) are well above the threshold values for iodine deficiency, indicating an absence of iodine deficiency in The Netherlands.

One of the main findings of our survey is that endemic goiter no longer existed in the eastern region of the country. Indeed, thyroid volume and urinary iodine concentration were not different between the eastern and western regions. It is difficult to explain the discrepancy with the high goiter rate observed in the east in 1985–1986 (2). Goiter prevalence at that time in the eastern town of Doetinchem was 20% for boys and 33% for girls, the mean urinary iodine

excretion was 133 and 122 $\mu\text{g/l/g}$ creatinine for boys and girls respectively, and the mean bread consumption was 6.7 and 3.9 slices daily for boys and girls respectively. Iodine excretion and bread consumption are comparable to the figures obtained in Doetinchem in the present survey. It might be that the goiter prevalence in 1985–1986 has been overestimated, as misclassification of thyroid size by inspection and palpation can be rather high (3, 12, 13).

The reference values of thyroid volume of Dutch schoolchildren (Fig. 1) are slightly lower than those obtained in the European ThyroMobil study which was restricted to the age group of 6–15 years (9). As the urinary iodine excretion in the Netherlands was the highest of the four countries that were selected for the determination of these normative thyroid volumes, it follows that even small differences in what is

considered an adequate iodine intake affect thyroid size. Recently, still lower reference values have been reported from other iodine-sufficient areas (14). Inter-observer variation in the assessment of thyroid volume by ultrasound is likely involved (15–17). Nevertheless, the accuracy of the data for Dutch schoolchildren is strengthened by the close agreement in thyroid volumes between the age group of 18 years in the present survey (12.1 ml in boys and 8.9 ml in girls) and Dutch healthy adults in a previous independent investigation (12.7 ml in males and 8.7 ml in females) (11).

Dietary habits

Although urinary iodine excretion was not different between the eastern and the western part of The Netherlands, differences in dietary habits were noted. Bread consumption was similar in both regions, but milk consumption was slightly higher in the east and seafood consumption was higher in the west. The contribution of iodized table salt to the daily iodine intake is probably small: daily intake of table salt is about 1 g for adults (18), and ioduria is similar in those using iodized salt (containing about 20 µgI/g) and those using non-iodized salt (2).

From the dietary habits we calculated the daily iodine intake, assuming an average iodine content of 20 µg per slice of bread (2), 58 µg per liter of milk (18), 280 µg per seafood meal (taking 1120 µg/kg seafood as the average of a variety of fishes, and 250 g as the average meal size) (19), and 20 µg/g iodized table salt with an average consumption of 1 g/day (18). To this was added a fixed amount of 30 µg I/day derived from other food sources, according to a Dutch Market Basket study mainly due to the presence of the iodine-containing dye erythrosine in sugar and sweets (18). Taking into account the sex-specific figures for consumption of iodized salt, bread, milk and seafood (Table 4 and Fig. 3), we calculated the average iodine intake for boys and girls respectively as follows: 10.5 and 11.2 µg (iodized salt), 100 and 80 µg (bread), 23.8 and 15.2 µg (milk), 7 and 6.4 µg (seafood), 30 and 30 µg (other sources), amounting to 171 µg/day for boys and 143 µg/day for girls. These figures are in good agreement with the measured urinary iodine concentrations of 16.7 µg/dl in boys and 14.5 µg/dl in girls. The sex difference in urinary iodine excretion is well known (3, 20). In our study the higher ioduria in boys (by 28 µg/day as calculated from dietary habits or by 2.2 µg/dl as measured in the urine) is due to an extra consumption of one slice of bread (20 µg) and one-seventh of a liter of milk (8.3 µg) per day as compared with girls. Bread consumption remains the main source of dietary iodine in The Netherlands, whereas the contribution of iodized salt and seafood is limited.

The effect of puberty

We studied schoolchildren up to the age of 18, a wider age range than in most previous studies. This allowed us to assess the effect of puberty. In The Netherlands, the average onset of puberty is at 11 years. Peak height velocity coincides in girls with Tanner stage M3P3 at the age of 11.7 years, and in boys with Tanner stage P4G4 at the age of 14.0 years (21). The sudden increase of thyroid volume in boys between 13 and 14 years and in girls between 11 and 12 years is therefore most likely related to the pubertal development (Fig. 2). The earlier puberty in girls explains their larger thyroid volume at the age of 12–13 years. In a study of Swiss schoolchildren aged 6–12 years, thyroid volume in girls is larger than in boys at the age of 12 (15); a study from Slovakia reports a larger volume in boys as of the age of 16 (22). The effect of puberty is not self-evident from the curves of the European ThyroMobil study (9), probably because the age range was only 6–15 years, the data were smoothed and/or because a difference in the age of onset of puberty exists between the various countries. Boys have a larger thyroid volume than girls as of the age of 14 in our study, and maintain this preponderance in adult life (11). This sex difference remains if thyroid volumes are expressed as a function of BSA (Fig. 2); thus, the larger thyroid volume of older boys and adults is not simply due to the greater height and weight of men relative to women. The greater lean body mass of males as compared with females is the most likely explanation for the sex difference (23).

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