Goitre prevalence and thyroid abnormalities at ultrasonography: a comparative epidemiological study in two regions with slightly different iodine status

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Summary

OBJECTIVE The association between severe iodine deficiency and endemic goitre is well established, but little information is available on the relation between milder degrees of iodine deficiency and goitre prevalence.

SUBJECTS In a comparative epidemiological study performed in two regions in Denmark, we examined 4649 subjects from the general population, women aged 18–65 years and men aged 60–65 years.

METHODS Ultrasonography and palpation of the thyroid was performed in all participants. Iodine excretion was measured in casual urine samples. Previous thyroid disease was detected by questionnaires, personal interviews and tracing of records.

RESULTS The median iodine excretion was 61 μg/l (mild iodine deficiency (ID)) and 45 μg/l (moderate ID) in the two regions. Median thyroid volume at ultrasonography was 11·9 ml (mild ID) and 13·6 ml (moderate ID), \( P < 0·001 \), and thyroid enlargement was found in 15·0% (mild ID) and 22·6% (moderate ID), \( P < 0·001 \). Goitre prevalence increased in both regions with age to the age group 40–45 years, but not after that age. Subjects who had moved from the moderate ID to the mild ID area had the same prevalence of thyroid enlargement as the subjects staying permanently in the mild ID area. Thyroid nodules at ultrasonography were found in 30% in both regions, but nodules were larger and more often palpable in the moderate ID area. Palpable goitre was found in 9·8% (mild ID) and 14·6% (moderate ID), \( P < 0·001 \). The greatest regional difference in thyroid abnormalities was found among men.

CONCLUSION Marked differences in the prevalence of thyroid abnormalities were found in these regions with modest differences in iodine excretion.

It has been known since the beginning of the 19th century that severe iodine deficiency leads to endemic goitre. Little is known, however, about the relation between iodine intake and thyroid abnormalities in the spectrum between clear iodine deficiency and iodine repletion. Thyroid volume and goitre prevalence (Hintze et al., 1991; Nygaard et al., 1993; Riehl et al., 1995; Aghini-Lombardi et al., 1999) and the occurrence of thyroid nodules (Carroll, 1982; Woestyn et al., 1985; Brander et al., 1991; Miki et al., 1993) have been studied in the general population. However, differences in selection and the age and sex of the investigated cohorts combined with the subjectivity of the ultrasonography and differences in ultrasonic equipment make comparisons biased and questionable. Further, genetic background and exposure to other goitrogens also play a role.

Thus, the minimal iodine intake of a population that will prevent iodine deficiency disorders remains to be established. This is still a matter of concern, as iodine deficiency disorders are abundant in many parts of the world including parts of Europe, and several reports have been published on side-effects of iodination programmes (Stanbury et al., 1998). Consequently, it is desirable that iodine intake is increased gradually and only to the level that is required to prevent iodine deficiency disorders (Laurberg, 1994).

We designed a comparative population study of goitre prevalence and thyroid abnormalities at ultrasonography in two regions in Denmark with presumed longstanding mild and moderate iodine deficiency (Pedersen et al., 1997; Knudsen et al., 1999a); differences mainly caused by different iodine content of tap water (Pedersen et al., 1999). This study precedes the onset of an iodination programme in Denmark and thereby also serves as first part of the monitoring of the iodination programme.
Subjects and methods

Subjects were invited from two urban areas in Denmark; the northern part of the municipality of Copenhagen and the central part of Aalborg, the fourth largest city in Denmark, situated in the north-western part of the country. These regions represent the mild iodine deficiency of east Denmark and the moderate iodine deficiency of the western part of Denmark (Pedersen et al., 1997; Knudsen et al., 1999a). Among inhabitants of Danish origin living in the two regions, all women aged 18–22, 25–30, 40–45 and 60–65 years and men aged 60–65 years were drawn from the civil registration system, in which all persons living in Denmark are registered by a unique 10-digit number. These 40 233 subjects were given random numbers within each group by help of a PC programme and invited in the order of the random numbers.

The examinations took place in the period 10 March 1997 to 1 June 1998, and 9274 subjects were invited; 403 subjects were impossible to contact due to change of address or death. The number of subjects invited in each group was adjusted throughout the period to obtain the same number of participants in each age and sex group. All examinations were conducted independently in the two regions by two teams comprising a doctor, a sonographer and a secretary. All information and procedures including ultrasonography were standardized before the examination (Knudsen et al., 1999b) and identical equipment was used. The participants were invited by letter, and in case of no response, a further letter was sent. If there was no response after two letters or the subject refused to participate, a short questionnaire was sent. In order to evaluate a possible selection bias, thyroid relevant information on all invited participants was sought in the National Patient Register, where information on all operations and diagnoses at discharge from somatic hospitals in Denmark has been registered since 1977. In both regions the participation rate was significantly higher in the group of women aged 40–45 years compared to the other groups (Table 1).

The participants answered questionnaires concerning previous thyroid disease, smoking habits and medication before attending the investigation. This was detailed in an interview, and if there was still uncertainty, medical records were traced.

An ultrasonographic examination of the thyroid was performed as previously described (Knudsen et al., 1999b) with a Sonoline Versa Pro 7.5-MHz 70 mm linear transducer (Siemens, Germany), effective length 62 mm. Thyroid volume was calculated as maximal length × width × depth × π/6 of each lobe. Thyroid enlargement was defined as a thyroid volume exceeding 18 ml for women and 25 ml for men, which corresponds to mean ± 3 SD in iodine sufficient populations (Gutekunst et al., 1988). The number of distinct nodules > 5 mm in diameter and the diameter of each nodule were registered; in case of more than three nodules in a lobe, only the three largest were registered. Thyroid volume, the number of distinct nodules, and the size of the nodules have previously been shown to be valid for comparison between the two observers from each region with minimal inter observer variation (Knudsen et al., 1999b). A physical examination of the neck was performed without knowledge of the result of the ultrasonography, and goitre was classified according to WHO criteria (Delange, 1994).

Spot urine samples were collected during the time interval 0800–1900 hours and analysed for iodine concentration for 4592 subjects (98.8%). The urine samples were digested by alkaline ashing and analysed by the Ce/As method for iodine content as previously described (Wilson & Van Zyl, 1967; Laurberg, 1987). The analytical sensitivity of the assay was 2–3 μg/l; within-run coefficient of variation was 2.1% and between-run coefficient of variation 2.7%. The median iodine excretion was 53 μg/l in Aalborg and 68 μg/l in Copenhagen; after exclusion of subjects taking individual iodine supplementation the figures were 45 μg/l and 61 μg/l, respectively. According to criteria outlined by WHO (Delange, 1994), the Aalborg area is moderately iodine-deficient and the Copenhagen area mildly iodine-deficient.

The study was approved by the regional Ethics Committee in Copenhagen and Northern Jutland and all participants gave written informed consent.

Statistics

All data processing was done with the SPSS 8.0 software (SPSS Inc., Chicago, IL, USA). Non-parametric tests were used for the analysis of thyroid volume data, as the distribution of thyroid volumes was skewed towards higher values. Pearson χ² tests

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**Table 1** Participation rates and smoking habits in the two regions in Denmark. Five subjects did not report smoking habits

<table>
<thead>
<tr>
<th></th>
<th>Copenhagen</th>
<th>Aalborg</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td>Invited</td>
<td>5209</td>
<td>4065</td>
<td>9274</td>
</tr>
<tr>
<td>Full participation</td>
<td>5209</td>
<td>4065</td>
<td>9274</td>
</tr>
<tr>
<td>Total</td>
<td>2429 (46.6%)</td>
<td>2220 (54.6%)</td>
<td>4649 (50.1%)</td>
</tr>
<tr>
<td>Women</td>
<td>1936 (48.4%)</td>
<td>1776 (54.1%)</td>
<td>3712 (50.9%)</td>
</tr>
<tr>
<td>Men</td>
<td>493 (40.7%)</td>
<td>444 (57.2%)</td>
<td>937 (47.1%)</td>
</tr>
<tr>
<td>Short questionnaire</td>
<td>1406 (27.0%)</td>
<td>1079 (26.5%)</td>
<td>2485 (26.8%)</td>
</tr>
<tr>
<td>No response</td>
<td>1372 (26.3%)</td>
<td>768 (18.9%)</td>
<td>2139 (23.1%)</td>
</tr>
<tr>
<td>Tobacco smoking</td>
<td>994 (41.0%)</td>
<td>725 (32.7%)</td>
<td>1719 (37.0%)</td>
</tr>
<tr>
<td>Women</td>
<td>779 (40.2%)</td>
<td>562 (31.7%)</td>
<td>1341 (40.5%)</td>
</tr>
<tr>
<td>Men</td>
<td>215 (43.9%)</td>
<td>163 (36.7%)</td>
<td>378 (36.1%)</td>
</tr>
</tbody>
</table>

The participation rate as well as smoking habits differ significantly between the two regions (P < 0.001; Pearson χ²)

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were used for the analyses of dichotomous variables. For the analyses of the differences in the relation between variables between the regions, interaction terms in logistic regression analysis was used; for instance in the nonresponder data, the term ‘region×participation’ was used to assess any differences in selection bias between the two regions. Level of significance was set to 5%. Where data are presented for age groups, it has been tested in a logistic regression analysis if differences in age profiles within the groups might account for the differences.

Results

Previously diagnosed goitre

Previously diagnosed nontoxic goitre was reported by 179 participants in the questionnaires. After the interviews – and in 16 ambiguous cases after tracing medical records – 63 of the 179 cases were re-classified as the diagnosis was incorrect and further 62 cases of nontoxic goitre were identified. Thus, previously diagnosed nontoxic goitre was found in 76 participants (3.1%) in the mild ID area and in 102 participants (4.6%) in the moderate ID area (\(P<0.009\), Pearson \(\chi^2\)). This difference was mainly due to a much higher frequency of goitre in the elderly women from the moderate ID area (Table 2).

Goitre prevalence and iodine status

Goitre

Overall 9.8% in the mild ID area and 14.6% in the moderate ID area (\(P<0.001\)) had a goitre minimum grade 1a (palpable and enlarged, but not visible thyroid gland) at the clinical examination (Table 2). For minimum grade 1b the percentages were 2.5% and 3.9% (\(P=0.008\)) and for grade 2 or 3 1.1% and 1.2% (\(P=0.65\)).

Nodules

The prevalence of distinct thyroid nodules with a diameter of minimum 10 mm was similar in the two regions (Table 3). Minor differences in the distribution between the groups in the two regions were found, as solitary thyroid nodules were more prevalent among women aged 18–22 years in the mild ID area, whereas multiple nodules were more prevalent among the men aged 60–65 years in the moderate ID area. The prevalence of thyroid nodules in subjects with thyroid enlargement was 67% among women aged 40–45 years and 89% in women aged 60–65 years. Using cut-off values for thyroid nodules of 5, 10 or 20 mm the overall prevalence of nodules were 28.7%, 17.3% and 5.0%, but the relation between the regions were the same with all criteria.

The size of the nodules differed between the regions (Table 4); the median nodule diameter was 9.3 mm in the mild ID area and 10.5 mm in the moderate ID area (\(P<0.001\), Mann–Whitney). Nodules were also more often palpable in the

Table 2  Goitre and thyroid volume in two areas with mild (Copenhagen, \(n=2429\)) or moderate (Aalborg, \(n=2220\)) iodine deficiency (ID). Except for previous goitre diagnosis, subjects previously treated for thyroid disease were excluded (240 subjects). Thyroid volumes are given as medians. Thyroid enlargement was defined as a volume exceeding 18 ml for women and 25 ml for men (Gutekunst et al., 1988) and palpable goitre was defined as a palpable and enlarged thyroid (minimum WHO grade 1 A)

<table>
<thead>
<tr>
<th>Group</th>
<th>Previous goitre diagnosis</th>
<th>Thyroid volume</th>
<th>Thyroid enlargement</th>
<th>Palpable goitre</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild ID</td>
<td>Moderate ID</td>
<td>Mild ID</td>
<td>Moderate ID</td>
</tr>
<tr>
<td>Women, 18–22 years</td>
<td>0.4%</td>
<td>0.2%</td>
<td>9.6 ml</td>
<td>10.3 ml</td>
</tr>
<tr>
<td>Women, 25–30 years</td>
<td>0.8%</td>
<td>1.1%</td>
<td>10.7 ml</td>
<td>12.1 ml</td>
</tr>
<tr>
<td>Women, 40–45 years</td>
<td>6.3%</td>
<td>6.5%</td>
<td>12.7 ml</td>
<td>14.2 ml</td>
</tr>
<tr>
<td>Women, 60–65 years</td>
<td>7.3%</td>
<td>13.3%</td>
<td>12.4 ml</td>
<td>14.8 ml</td>
</tr>
<tr>
<td>Men, 60–65 years</td>
<td>1.2%</td>
<td>2.3%</td>
<td>15.8 ml</td>
<td>19.5 ml</td>
</tr>
</tbody>
</table>
moderate ID area than in the mild ID area ($P = 0.02$ for interaction in logistic regression analysis).

**Subjects with change in residence**

A subset of the subjects investigated had moved between the regions. In the youngest group, 71 subjects had lived almost their entire lives (>15 years) in the moderate ID area, but now lived in the mild ID area. Their median thyroid volume was 9.5 ml compared to 9.6 ml for the rest of that age group in the mild ID area ($P = 0.74$, Mann–Whitney) and 10.3 ml in the moderate ID area ($P = 0.048$). In total 228 subjects had lived more than half of their lives in the moderate ID area, but now lived in the mild ID area. Their thyroid volumes were similar to those of the rest of the subjects from the mild ID area. Correspondingly, 77 subjects participated in the moderate ID area but had lived more than half of their lives in the mild ID area. Their thyroid volumes were significantly lower than those of the remaining group from the moderate ID area ($P < 0.001$).

**Data validation**

Data from the National Patient Register showed a significant selection bias regarding previous thyroid disease in this cohort, as odds ratio between participants and nonparticipants for goitre operation was 3.6 (95% confidence interval 2.1–6.0), for goitre diagnosis 2.6 (1.5–4.5), and for thyroid dysfunction 2.0 (1.3–3.2). These odds ratios were similar in the two regions. Self reported thyroid disease among participants and responders to the short questionnaire also indicated bias as odds ratio for self-reported goitre was 2.4 (1.6–3.5), whereas no significant differences were found for self-reported hypo- or hyperthyroidism. Again the relation was the same in the two regions.

**Discussion**

In this study we demonstrate that modest differences in iodine intake may lead to marked differences in goitre prevalence even in a presumably genetically homogeneous population. By using a comparative design with identical procedures and equipment and thorough evaluation of the inter observer variation of the ultrasonography (Knudsen et al., 1999b), we have obtained valid data for a direct comparison of prevalences of thyroid volumes and thyroid enlargement. A 50% higher prevalence of goitre or thyroid enlargement was found in the moderately

<table>
<thead>
<tr>
<th>Group</th>
<th>Solitary</th>
<th></th>
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<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mild ID</td>
<td>Moderate ID</td>
<td>$\chi^2$</td>
<td>Mild ID</td>
<td>Moderate ID</td>
<td>$\chi^2$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women, 18–22 years</td>
<td>2.2%</td>
<td>0.4%</td>
<td>$P = 0.02$</td>
<td>1.2%</td>
<td>0.2%</td>
<td>$P = 0.07$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women, 25–30 years</td>
<td>2.7%</td>
<td>2.0%</td>
<td>$P = 0.50$</td>
<td>2.7%</td>
<td>1.8%</td>
<td>$P = 0.36$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women, 40–45 years</td>
<td>7.2%</td>
<td>10.6%</td>
<td>$P = 0.11$</td>
<td>16.6%</td>
<td>13.5%</td>
<td>$P = 0.30$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women, 60–65 years</td>
<td>9.4%</td>
<td>11.9%</td>
<td>$P = 0.34$</td>
<td>29.7%</td>
<td>26.9%</td>
<td>$P = 0.54$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men, 60–65 years</td>
<td>7.3%</td>
<td>8.3%</td>
<td>$P = 0.39$</td>
<td>11.4%</td>
<td>16.6%</td>
<td>$P = 0.02$</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>5.6%</td>
<td>6.3%</td>
<td>$P = 0.33$</td>
<td>11.5%</td>
<td>11.0%</td>
<td>$P = 0.69$</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 3** Prevalence of nodules ≥ 10 mm in diameter in the thyroid by ultrasonography in a cohort from two areas with mild (Copenhagen, $n = 2315$) or moderate (Aalborg, $n = 2094$) iodine deficiency (ID). Subjects previously treated for thyroid disease were excluded. Pearson $\chi^2$ test for the comparison of the prevalences between the regions.

<table>
<thead>
<tr>
<th></th>
<th>Mild ID</th>
<th></th>
<th></th>
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<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>5–10 mm</td>
<td>10–20 mm</td>
<td>&gt;20 mm</td>
<td>5–10 mm</td>
<td>10–20 mm</td>
<td>&gt;20 mm</td>
<td>5–10 mm</td>
<td>10–20 mm</td>
</tr>
<tr>
<td>Solitary nodules</td>
<td>58.3%</td>
<td>33.0%</td>
<td>8.7%</td>
<td>53.8%</td>
<td>33.2%</td>
<td>12.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Multiple nodules</td>
<td>28.9%</td>
<td>50.3%</td>
<td>20.9%</td>
<td>21.4%</td>
<td>54.4%</td>
<td>24.1%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>42.2%</td>
<td>42.5%</td>
<td>15.4%</td>
<td>37.4%</td>
<td>44.0%</td>
<td>18.6%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 4** Size of the thyroid nodules identified at ultrasonography of a cohort from two areas with mild or moderate iodine deficiency. The total number of subjects with thyroid nodules was 683 in the mild ID area and 582 in the moderate ID area. Subjects previously treated for thyroid disease were excluded. In case of multiple nodules, the diameter of the largest nodule was registered.
iodine-deficient region compared to the mildly iodine-deficient region. Previous thyroid operations and previous goitre diagnosis at the National Patient Register were also more frequent in the moderate ID area, and a marked difference was found in all age groups. Differences in smoking habits did not contribute to these regional differences; on the contrary, the presented difference may be slightly underestimated, as the prevalence of smoking was highest in the mild ID area.

The participation rate was only 50%, a trend that is found in most studies of the general population in the past years. We do have, however, self-reported data on another 26% of the subjects and data from the National Patient Register on all subjects in the cohort; therefore a possible selection bias can be taken into consideration. An over-representation of subjects with a known goitre was found in the examined part of the cohort compared to nonresponders, leaving estimates of previous thyroid disease among the participants which may be 30–40% higher than in the entire cohort. Our data on goitre and thyroid enlargement, on the other hand, should be only slightly biased, as few of the identified cases had any awareness of a possible goitre beforehand. Most important is the fact that the bias towards subjects with previous thyroid disease participating with a higher rate was equal in the two regions; consequently, the different participation rates do not impose bias and the comparisons within the study are fully valid.

The evaluation of self-reported nontoxic goitre demonstrated that prevalences based entirely on questionnaires may be severely biased. After interviews and tracing of medical records, one third of the self-reported cases were disregarded but the same number of cases identified in addition.

A distinct difference in thyroid volumes was found between the regions. In a previous comparative study in two regions with iodine sufficiency and iodine deficiency median thyroid volumes of 9.1 and 17.0 ml, respectively, were found (Gutekunst et al., 1986). The volumes in the two regions in this study were in-between with 11.9 and 13.6 ml, though iodine status in Germany is similar to that in Denmark. Also in Germany, mean thyroid volumes in comparable groups were reported in the range from 13.3 to 27.5 ml (Riehl et al., 1995), and median volumes of 13.6 ml for women and 19.8 ml for men were reported in another German study (Struve & Hinrichs, 1989). In iodine sufficiency in the Netherlands, a median volume of 9.8 ml was reported (Berghout et al., 1989). In other studies, median volumes of 16 and 19 ml in mild ID areas (Hegedus et al., 1983; Nygaard et al., 1993). These varying estimates even from areas with the same iodine status emphasize that ecological comparisons are hampered by inter-observer variation, differences in methodology and different age and sex composition of the cohorts, and underline the advantage of comparative studies.

When iodine supplementation is implemented, thyroid enlargement is readily reversible in children (Hintze et al., 1988; Vermiglio et al., 1989; Aghini et al., 1997; Liesenkotter et al., 1997). This is confirmed in the present study by the low thyroid volumes among young subjects, who grew up in the moderate ID area and only lived for a few years in the region with only mild ID. Even in the elderly subjects who moved from the moderate ID area to the mild ID area or in the opposite direction, thyroid volume was similar to that of the subjects living all their life in the mild ID area. This indicates that goitre induced by iodine deficiency is widely reversible in all these age groups, and suggests that the exposure to life-long iodine deficiency is required for the development of iodine deficiency dependent goitre, at least in areas with only mild iodine deficiency.

We demonstrate a parallel increase in thyroid volume, thyroid enlargement and goitre at the clinical examination in females in both our regions from the age group 18–22 years to the age group 40–45 years, but after that no further increase was seen. This may suggest disappearance of a drive for thyroid growth at menopause. Such a mechanism is in accordance with the general difference in the prevalence of goitre between women and men, which is presumably caused by hormonal differences; the specific cause of the sex difference is not known in detail, but at least part of the explanation may be an oestrogen-induced down-regulation of the sodium/iodide symporter (Furlanetto et al., 1999). Another explanation for the age differences could be a cohort effect, this being a cross-sectional study. It was surprising that thyroid enlargement was almost as common among elderly men as among elderly women and that the most marked differences between the regions were found in the group of elderly men. The explanation for the pronounced difference in men might be that for women other, as yet mostly unknown, risk factors for developing thyroid disease play an important role, whereas men exhibit the pure iodine-induced goitre.

The prevalence of thyroid nodules in previous studies did not show any obvious relation to iodine status (Carroll, 1982; Woestyn et al., 1985; Brander et al., 1991; Miki et al., 1993; Nygaard et al., 1993), though Gutekunst et al. (1986) found a higher prevalence of nodules in the iodine deficient area in their comparative study. Correspondingly, no overall difference in the prevalence of nodules was found between the regions, though multinodular thyroid glands were significantly more prevalent in moderate ID than in mild ID among men. Other regional differences were detected, however, as nodules were larger and more often palpable in the moderate ID region. In spite of the comparison of the performance of the two observers showing agreement regarding the detection of nodules (Knudsen et al., 1999b), it is difficult to exclude a slight inter-observer bias in the detection of small nodules between the regions. To minimize such a bias, a cut-off for the diameter of
the nodules in the analyses was set to 10 mm, although nodules were registered from a diameter of 5 mm; this limit should also be more clinically relevant. It is possible, however, that the aetiology of nodules differs in the two regions, explaining the difference in the appearance of the nodules and favouring growth and clinical detection in the moderate ID region. Autoimmunity-induced thyroid abnormalities may for instance be more prevalent in areas with less iodine deficiency (Laurberg et al., 1998; Knudsen et al., 1999a; Tsatsoulis et al., 1999).

In conclusion this comparable population-based study demonstrated marked regional differences in thyroid size and goitre prevalence, probably conditional on minor differences in iodine intake. The findings suggest that a considerable reduction in iodine deficiency disorders might be obtained by a modest increase of iodine intake in a population.

Acknowledgements
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