Original Article

Iodine status in pre-school children prior to mandatory iodine fortification in Australia

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Abstract

The iodine status of children between the ages of 5 and 15 years has been routinely assessed in many countries, but few studies have examined iodine status in pre-school children. We conducted a cross-sectional study of pre-school children living in Adelaide, South Australia, between 2005 and 2007. Children 1–5 years old were identified using a unique sampling strategy to ensure that the study population was representative. A 3-day weighed diet record, a blood sample and a urine sample were obtained from each child. The median urinary iodine concentration (UIC) of the children ($n = 279$) was $129 \mu\text{g L}^{-1}$, indicating iodine sufficiency (normal range: $100\text{--}199 \mu\text{g L}^{-1}$), but 35% of the children had a $\text{UIC} < 100 \mu\text{g L}^{-1}$. The median thyroglobulin concentration of children ($n = 217$) was $24 \mu\text{g L}^{-1}$ and thyroglobulin concentration declined with increasing age ($P = 0.024$). The mean daily iodine intake was $76 \mu\text{g}$. The intake of iodine was lower than expected and highlights difficulties in accurately assessing iodine intakes. Further studies are needed to monitor dietary changes and iodine status in this age group since the implementation of mandatory fortification of bread with iodised salt in Australia in 2009.

Keywords: iodine deficiency, urinary iodine concentration, thyroglobulin, children, Australia.

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Introduction

An adequate amount of iodine is required in the diet for the synthesis of the thyroid hormones triiodothyronine (T3) and thyroxine (T4), which, in turn, are needed for normal growth and mental development. Pregnancy is the most critical time for the development of the central nervous system because neurodevelopment is rapid during this period. The brain continues to develop after birth (Cameron 2008); hence, a good supply of thyroid hormones is needed throughout childhood for optimal neurodevelopment as well as normal growth and metabolism. Although the iodine status of children between the

ages of 5 and 15 years has been assessed in many countries, there are few studies worldwide that have measured the iodine status of pre-school children. The diets of young children typically contain only small quantities of iodine-rich foods, such as fish and seafood, and dietary guidelines for children in this age group often discourage the addition of salt (including iodised salt) to home-prepared and manufactured foods (National Health & Medical Research Council 2003). Given this, pre-school children could be at higher risk of iodine deficiency than school-aged children.

Australia has a history of iodine deficiency, particularly in the eastern and southern states. The

introduction of iodised salt and the use of iodophors in the dairy industry were attributed to eliminating iodine deficiency in the first half of the 20th century. However, in the late 1990s, Gunton *et al.* (1999) reported iodine deficiency in hospital patients in Sydney with similar findings observed in subsequent studies in pregnant women (Guttikonda *et al.* 2002; Burgess *et al.* 2007) and children (McDonnell *et al.* 2003; Hamrosi *et al.* 2005) in Melbourne and Tasmania. In 2003, a large study conducted by Li *et al.* of 8–10-year-old schoolchildren living in five mainland states confirmed mild iodine deficiency had re-emerged in the eastern states (Li *et al.* 2006). To our knowledge, there have been no studies that have investigated the iodine status of pre-school children in Australia, a subgroup of the population that is often overlooked.

The most commonly accepted method of assessing iodine status of a population is to determine the urinary iodine concentration (UIC) from a casual or spot urine sample, with a UIC > 100 $\mu\text{g L}^{-1}$, indicative of adequate iodine status. Although this cut-off has only been validated in school-aged children, it is still recommended for use in younger children (World Health Organization *et al.* 2007). In addition to UIC, the volume of the thyroid gland can be measured by ultrasonography, with a value >97th percentile indicating goitre, but there are no published reference values for thyroid volume in children under the age of 5 years (Zimmermann *et al.* 2001). In addition, there is a growing interest in the measurement of thyroglobulin (Tg), a sensitive biochemical index of iodine status (Vejbjerg *et al.* 2009) as serum Tg concentrations increase when the thyroid gland enlarges, but Tg has not been routinely reported in children. Using a

combination of biomarkers including UIC and Tg, this paper reports on the iodine status of pre-school children, who participated in a comprehensive survey assessing nutritional status in this age group from a representative sample of Australian children (Zhou *et al.* 2012).

Subjects and methods

This was a cross-sectional study of a representative sample of children living in Adelaide, South Australia, conducted between September 2005 and July 2007. Demographic data, a 3-day weighed diet record, blood sample and urine sample were collected from each child. The study received ethical approval from the Human Research Ethics Committee at the Women's & Children's Health Network, Adelaide, South Australia. The nature of the study was fully explained to the caregivers of the children and informed written consent was obtained from all caregivers.

There were 2132 Census Collection Districts (CCD) in Adelaide, each containing 220 dwellings. Each CCD was assigned an Advantage–Disadvantage Index by the Australian Bureau of Statistics as an index of socioeconomic status (SES); these were stratified to low, medium and high SES. A stratified random sampling technique was used to select CCDs to obtain a representative population sample, using a door-knocking protocol (Karr *et al.* 1996; Soh *et al.* 2002). In brief, an address start point and direction was randomly determined for each identified CCD. From each start point, two trained research assistants knocked on the doors of households to identify if there was a child aged between 1 and 5 years in the

Key messages

- Pre-school children are often overlooked in surveys assessing iodine status, despite their relatively high dietary requirements for iodine.
- Our study indicates adequate iodine status in pre-school children prior to mandatory iodine fortification in Australia.
- Ongoing monitoring of the iodine status of children in Australia is needed to avoid excessive iodine intake with the advent of mandatory iodine fortification, which can also have adverse health consequences.
- The challenge in assessing iodine intakes is reliant on an appropriate method of dietary assessment and a food composition database that contains accurate iodine values.

household. If no one was home, households were visited up to three times on a different day (including a weekend day) and at different times from the previous visits. CCDs from each of the SES strata were visited according to the random selection until the required number of children ($n = 100$) from each SES strata was obtained. Children were excluded if they were diagnosed with congenital or metabolic disorders (e.g. diabetes mellitus, cystic fibrosis) that required specialised dietary intervention, or were hospitalised in the last 6 months before the study, or were immunosuppressed. If more than one child was eligible per household, the one with the earliest birth date was selected to participate in the study. Consenting families were asked to attend a clinical appointment with their child for assessment.

The weight and length/height of each child, wearing light clothing without shoes using standardised procedures (World Health Organization 2008), was measured during the clinical appointment. Weight-for-age (WAZ) and weight-for-height z -scores (WHZ) were calculated using WHO ANTHRO 2005 software version 3 (WHO, Geneva, Switzerland).

Parents were asked to complete the 3-day weighed record of their child's food intake on three consecutive days, including one weekend. Parents were given detailed instructions on how to complete the food record and were provided with sample food diaries as examples. Parents were supplied with a weighing scale and metric cups and spoons, and were asked to measure and record everything their child ate and drank during the study period, both at home and away from home. For dishes made at home, detailed recipes were obtained, and for commercially packed foods, brand name was recorded and packaging retained to check for nutritional composition. Parents were instructed to weigh and record the amount of food and drink served to the child as well record the weight of any uneaten food, which was subtracted from the served amount to obtain the actual amount eaten. Completed diet records were collected from homes and checked by a dietitian. Phone calls were made to clarify any ambiguities or missing information. Food records were entered and analysed using a dietary analysis package (FoodWorks Professional, Xyris Pty Ltd, Qld, Australia) with the NUTTAB 2006

database (Food Standards Australia New Zealand 2006) included in the software. Iodine contents of foods that are the main sources of dietary iodine in the diets of pre-school children, including eggs, dairy products and seafood were obtained from the NUTTAB 2006 database. Some foods such as biscuits and other non-core foods in the NUTTAB 2006 database did not contain iodine values and the iodine contents of these food items were substituted using values from the New Zealand Food Composition Database (Crop and Food Research 2006), an approach used by Food Standards Australia New Zealand to assess iodine intake of Australian for mandatory iodine fortification (Australian Institute of Health and Welfare 2011). For foods that were of a similar nature, the same iodine content was used for each food.

A non-fasting blood sample was obtained from each child via venipuncture by a trained paediatric phlebotomist. Blood samples were processed within 3 h of collection and serum samples were stored at -80°C before being couriered with dry ice to the analytical laboratory for testing. The concentration of serum Tg was determined using a radioimmunoassay by EndoLab, Christchurch Hospital, Christchurch. The Tg assay has an analytical detection limit of $0.1 \mu\text{g L}^{-1}$ and accuracy was checked using CRM 457 (Institute for Reference Materials and Measurement, Geel, Belgium). The inter-assay coefficients of variation (CVs) were 25% at $0.2 \mu\text{g L}^{-1}$, 8% at $40.4 \mu\text{g L}^{-1}$ and 5% at $333 \mu\text{g L}^{-1}$. Intra-assay CVs were 5% at $0.2 \mu\text{g L}^{-1}$, 2% at $40.4 \mu\text{g L}^{-1}$ and 2% at $333 \mu\text{g L}^{-1}$. Samples were screened for serum antibodies to Tg (TgAb) as these antibodies can interfere with serum Tg determination.

During the clinical appointment, the parents of toilet-trained children were asked to take children to the toilet and collect a sample of urine. For children who were not toilet-trained, a urine sample was collected via a paediatric collection bag (Liberty, Implex Pty Ltd, Heathcare SA, Australia) *in situ*. If a urine sample was unable to be obtained during the clinical appointment, parents were instructed to collect a urine sample at home and place the sample in a fridge, which was collected within 3 weeks. For all children, 5–10 mL of urine was then decanted into a 50-mL

Table 1. Urinary iodine concentration (UIC) and thyroglobulin (Tg) concentration

Age (month)	UIC ($\mu\text{g L}^{-1}$)				Tg ($\mu\text{g L}^{-1}$)	
	<i>n</i>	Median (IQR)	% children with UIC < 100 $\mu\text{g L}^{-1}$	% children with UIC > 300 $\mu\text{g L}^{-1}$	<i>n</i>	Median (IQR)
12–24	77	144 (78, 256)	31	17	54	26 (19, 39)
>24–36	68	122 (68, 231)	46	13	48	23 (17, 36)
>36–48	69	126 (71, 184)	39	10	58	24 (16, 33)
>48–60	65	130 (103, 176)	25	2	57	20 (14, 31)
Total	279	129 (78, 202)	35	11	217	24 (16, 35)

IQR, interquartile range.

sterilised urine collection container and stored at -20°C until analysis.

Urine samples were sent by courier to the Department of Human Nutrition, University of Otago, and analysed (YZ) using a modification of the method of Pino *et al.* (1998). A certified urine standard sample (Seronom, Sero AS, Asker, Norway) and an internal pooled urine sample were included with each batch of urine samples in the analysis. The mean concentration of Seronom was $139 \mu\text{g L}^{-1}$ [95% confidence interval (CI): 133, $145 \mu\text{g L}^{-1}$] compared with the certified value of $141 \mu\text{g L}^{-1}$ (95% CI: 132, $150 \mu\text{g L}^{-1}$). The coefficients of variation for the Seronom and pooled urine sample were 4.2% ($n = 74$) and 4.7% ($n = 70$), respectively.

Stata 11.1 (STATA Corporation, College Station, TX, USA) was used for statistical analyses. Children were divided into four age groups: 12–24 months, >24–36 months, >36–48 months and >48–60 months for all analyses. Descriptive statistics, including median and interquartile range (IQR), were used to summarise UIC and Tg. UIC was log-transformed to improve normality for subsequent statistical analyses. Univariate regression was conducted to assess the association between UIC and age, gender, WHZ, SES, total energy intake and iodine intake. Any variable with a $P < 0.20$ in the univariate model was included in the multivariate model to examine predictors of UIC. Univariate regression was also undertaken to identify food groups that contributed to iodine intake, and those food groups with a $P < 0.20$ were included in the multivariate model. Tests were two-sided and statistical significance was set at $P < 0.05$.

Results

A total of 13 272 households were visited from 54 CCDs and 9464 households answered the door. There were 573 eligible children from the 54 CCDs visited and 300 children, 100 children from each SES strata, consented to take part in the survey. Diet records were obtained from 297 children; however, 8 were excluded because the child was still breastfed and it was not possible to estimate the quantity of breast milk consumed. Urine was collected from 279 children and serum samples were available for Tg determination from 217 children. There were complete data on dietary intake, UIC and Tg for 202 children. Of these children, 96% were born in Australia, 48% were first born, 52% were boys, and their mean (standard deviation) was 0.54 (0.98) for WAZ and 0.71 (0.99) for WHZ, respectively. There were no significant differences between children with or without complete data with regard to gender ($P = 0.547$), SES ($P = 0.680$) and UIC ($P = 0.453$).

The median UIC (IQR) for the children was 129 (78–202) $\mu\text{g L}^{-1}$, 35% of children had a UIC below $100 \mu\text{g L}^{-1}$ and 11% had a UIC above $300 \mu\text{g L}^{-1}$ (Table 1), which indicates that these children were iodine sufficient and iodine intake was adequate but not excessive (World Health Organization *et al.* 2007). Univariate and multivariate linear regression found that only dietary iodine was significantly associated with UIC (Table 2), such that every 10 μg increase in the intake of dietary iodine increased UIC by 4%. The median (IQR) Tg concentration was 24 (16, 35) $\mu\text{g L}^{-1}$ and 96% (208/217) of children had a Tg concentration $>10 \mu\text{g L}^{-1}$. Tg concentration declined with increasing

Table 2. Variables associated with urinary iodine concentration in linear regression analyses

Variable	Univariate analysis		Multivariate analysis	
	Ratio* (95% CI)	P-value	Ratio* (95% CI)	P-value
Age (year)	1.00 (0.99, 1.06)	0.423	NA	
Socioeconomic status	1.00 (0.89, 1.13)	0.958	NA	
Energy (kJ)	1.00 (0.99, 1.00)	0.215	NA	
Weight-for-height z-score	1.04 (0.94, 1.14)	0.473	NA	
Gender	0.83 (0.68, 1.00)	0.055	0.86 (0.71, 1.04)	0.112
Dietary iodine (10 µg)	1.04 (1.01, 1.07)	0.013	1.04 (1.00, 1.07)	0.026

CI, confidence interval; NA, not applicable. *Ratio of geometric means from log-transformed data.

age ($P = 0.025$) (Table 1). Only one child tested positive for Tg-Ab.

The mean daily energy intake of the children was 5142 (95% CI: 4992–5293) kJ and energy intakes increased with age ($P < 0.001$) as follows: 4421 (95% CI: 4187, 4656) kJ day⁻¹ for 12–24 months; 5051 (95% CI: 4787, 5315) kJ day⁻¹ for >24–36 months; 5264 (95% CI: 4969, 5559) kJ day⁻¹ for >36–48 months; and 6029 (95% CI: 5734, 6324) kJ day⁻¹ for >48–60 months. The energy contribution as a percentage from carbohydrate, fat and protein was 49% (95% CI: 48, 50), 34% (95% CI: 33, 35) and 17% (95% CI: 17, 18), respectively. The mean daily iodine intake was 76 (95% CI: 73, 80) µg and iodine intakes declined with age ($P = 0.003$) as follows: 84 (95% CI: 76, 90) µg for 1–2 years; 78 (95% CI: 71, 85) µg for 2–3 years; 71 (95% CI: 64, 78) µg for 3–4 years; and 71 (95% CI: 63, 78) µg for 4–5 years. The main sources of dietary iodine in the diet of these children were dairy products (28.4%) and bakery products (22.0%).

Discussion

This is the first study to assess the iodine status of pre-school children in Australia and one of a handful of studies worldwide involving this age group (Delange *et al.* 2001; Pouessel *et al.* 2003; Heydon *et al.* 2009). The median UIC of 129 µg L⁻¹ and less than 50% (i.e. 35%) of children with UIC < 100 µg L⁻¹ indicates adequate iodine status in these children according to the WHO/UNICEF/ICCIDD criteria. The iodine status of a representative sample of Australian school children aged 8–10 years old living in the same state (i.e. South Australia) was reported to

be 101 µg L⁻¹ (Li *et al.* 2006). The higher UIC observed in our children may reflect higher dairy product consumption in younger children, a variable found to be significantly associated with UIC. The consumption of dairy products has been shown to decline with age in Australian children (Department of Health and Aging *et al.* 2008).

The overall concentration of Tg in these children (24 µg L⁻¹) and the 26 µg L⁻¹ observed in 12–24 months old was lower than a median Tg of 35 µg L⁻¹ reported in 12–24-month-old Canadian children, a population classified as iodine sufficient (Djemli *et al.* 2004). There are no recommended cut-offs for Tg to classify iodine status of children. However, the normal reference range for Tg concentration in children 5–14 years old is 4–40 µg L⁻¹ (Zimmermann *et al.* 2003). A low UIC (i.e. <100 µg L⁻¹) can increase thyroid volume and subsequently the concentration of Tg. A median UIC < 100 µg L⁻¹ and a median Tg concentration >10 µg L⁻¹ have both been set as indicators of iodine deficiency (World Health Organization *et al.* 2001). As these indices have only been validated in school-aged children, this may explain the discrepancy between a median UIC that classifies the children in our study as iodine sufficient, but a Tg concentration that categorises the children as iodine deficient. We did find that Tg concentration declined with age and a similar finding has been observed in Canadian children aged 0–17 years (Djemli *et al.* 2004). If Tg concentration is to be used as an index of iodine status, the development of age-specific cut-offs to categorise iodine status is needed.

It is difficult to accurately assess iodine intake and, as a result, few studies have measured iodine intakes

Table 3. Comparison of iodine content ($\mu\text{g}/100\text{ g}$) of selected foods using different national food composition databases*

	New Zealand 2006	Australia 2006	Australia 2007	Australia 2010	UK 2002
Milk	8.6	13.3	22.6	23.4	31.0
Yoghurt	3.0	12.0	12.0	12.5	63.0
Cheese	5.5	17.4	17.4	24.4	39.0
Egg	51.9	21.6	36.6	47.3	53.0
Beef	1.0	1.4	3.3	2.6	14.0
Carrot	0.3	0.0	0.5	0.0	2.0
Tomato	0.1	0.1	0.6	0.1	2.0
Potato	0.3	0.0	0.4	0.5	33.0
Banana	0.1	0.0	0.5	0.4	8.0
Apple	0.2	0.0	0.5	0.0	NA
Pasta	1.5	2.3	2.3	3.4	36.0
Bread	0.6	1.2	2.5	48.0	6.0

NA, Not available. *Foods matched for description, energy content, preparation and method of cooking.

for a number of reasons. Firstly, the contribution of iodine from iodised salt, used at the table or in cooking, is difficult to estimate. Secondly, many national food composition databases (e.g. the United States) do not include information on the iodine content of foods. Thirdly, even within the same country, varying soil iodine contents, practices in food processing (i.e. use of iodates in bread or iodophors in the dairy industry) and animal rearing (i.e. use of iodised salt licks or iodine supplemented feeds) can result in fluctuations in the iodine content of foods. The children in this study had energy intakes that met recommendations for this age group (Department of Health and Aging *et al.* 2006) and the percent of total energy from macronutrients were within the acceptable macronutrient distribution range (Institute of Medicine 2005). The iodine intake, however, was lower than the 2007 Australian Children's Nutrition Survey, the only other Australian study that has assessed iodine intake of pre-school Australian children; the survey reported that 24–36-month-old children had an iodine intake of $126\text{ }\mu\text{g day}^{-1}$ (Department of Health and Aging *et al.* 2008); however, no biomarkers of iodine status were included in the 2007 Survey. The discrepancy in iodine intake between our study and that reported in the 2007 Children's Nutrition Survey is likely due to a number of factors. The different dietary assessment methodologies between the 2007 Children's Nutrition Survey (24-h recall) and our study (3-day weighed food record) may partly contribute to the discrepancy

as 24-h recalls have been shown to overestimate energy intake of infants and toddlers compared with 3-day weighed food records (Fisher *et al.* 2008). We did not collect information on iodised salt use in cooking or at the table, which may have also contributed to the lower iodine intake; however, widespread use of iodised salt was uncommon in Australia at the time of study. In addition, the NUTTAB 2006 Australian food composition database, the most up-to-date database available at the time of the study, was used to determine iodine intakes in our study, while the 2007 Children's Nutrition Survey used a modified food composition database specifically developed for use in the 2007 Survey. Furthermore, in some instances, foods missing from the 2006 Australian food composition database were replaced with foods from the 2006 New Zealand food composition database, which typically would have lower iodine content because New Zealand has lower soil iodine content than mainland Australia. A comparison of the same foods in 2006, 2007 and 2010 Australian databases shown in Table 3 illustrates how national databases can change with regard to iodine contents in food within the same country (Food Standards Australia New Zealand 2006, 2007, 2010), but also highlights the differences in iodine contents of foods between countries including New Zealand (Crop and Food Research 2006) and the UK (Food Standards Agency 2002).

In response to concerns about the re-emergence of iodine deficiency in Australia, the addition of iodised

salt to most commercial bread products became mandatory in 2009. Australian pre-school children consume $\sim 60\text{--}80\text{ g day}^{-1}$ of bread and bread products (Australian Bureau of Statistics 1999). We estimate that the consumption of fortified bread would increase the median UIC in these pre-school children from ~ 130 to $\sim 160\text{ }\mu\text{g L}^{-1}$, still within the $100\text{--}199\text{ }\mu\text{g L}^{-1}$ range considered a safe, adequate intake of iodine. However, we also estimate that bread fortification will increase the percentage of children with $\text{UIC} > 300\text{ }\mu\text{g L}^{-1}$, a level associated with excessive intake of iodine, from $\sim 10\%$ to $\sim 14\%$ in this study population. Thus, the addition of iodine to foods in Australia needs to be monitored, as there is a growing evidence that iodine excess (i.e. $\text{UIC} > 300\text{ }\mu\text{g L}^{-1}$) can be also associated with adverse health effects such as hypothyroidism (Laurberg *et al.* 2006). The tolerable upper limit (UL) intake for iodine in Australia is $200\text{ }\mu\text{g day}^{-1}$ for 1–3-year-old children and $300\text{ }\mu\text{g day}^{-1}$ for 4–8-year-old children (Department of Health and Aging *et al.* 2006). Concern that some children would exceed the UL was the primary reason that iodine fortification was limited to breads rather than being added to a number of other staple foods (Food Standards Australia New Zealand 2008).

The strengths of this study were the use of a door-knocking strategy to identify a representative sample of children, and the collection of both biochemical and dietary measures of iodine status. Based on UIC, these pre-school children had adequate iodine status, and the accompanying Tg data provide information on Tg concentration in iodine sufficient pre-school children for future reference. The iodine intake of the children was lower than expected and highlights the inherent difficulties in assessing dietary iodine, particularly with regard to the iodine content of foods in food composition databases. Despite this limitation, it is important to measure iodine intakes in order to identify foods and food groups that are good sources of iodine in the diets of pre-school children, as changes in dietary patterns do occur, which may impact on iodine status. The mandatory fortification of bread with iodised salt means that bread and bread products are now likely to make the largest contribution to total iodine intakes in pre-school children. Further studies are needed to monitor dietary

changes and iodine status in this age group since the implementation of mandatory fortification.

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Conflicts of interest

RG (ID: 519324) and MM (ID: 565000) were supported by a National Health & Medical Research Council Senior Research Fellowship. SJZ, SS and YZ have no conflict of interest. RG has been serving on the scientific advisory boards for Nestle and Fonterra. MM has been serving on the scientific advisory boards for Nestle, Fonterra and Nutricia. Associated honoraria for MM and RG are paid to their institutions to support conference travel and continuing education for postgraduate students and early career researchers.

Contributions

SS, SJZ, RG and MM designed the study; SJZ and MM conducted the study; YZ and SS analysed the urine iodine concentration and assessed iodine intake; SS drafted the manuscript; and all authors read and approved the final manuscript.

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