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Iodine status of postpartum women and their infants in Australia after the introduction of mandatory iodine fortification

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Abstract

Mandatory I fortification in bread was introduced in Australia in 2009 in response to the re-emergence of biochemical I deficiency based on median urinary I concentration (UIC) <100 μg/l. Data on the I status of lactating mothers and their infants in Australia are scarce. The primary aim of this study was to assess the I status, determined by UIC and breast milk I concentration (BMIC), of breast-feeding mothers in South Australia and UIC of their infants. The secondary aim was to assess the relationship between the I status of mothers and their infants. The median UIC of the mothers (*n* 686) was 125 (interquartile range (IQR) 76–200) μg/l and median BMIC (*n* 538) was 127 (IQR 84–184) μg/l. In all, 38 and 36 % of the mothers had a UIC and BMIC below 100 μg/l, respectively. The median UIC of infants (*n* 628) was 198 (IQR 121–296) μg/l, and 17 % had UIC <100 μg/l. Infant UIC was positively associated with maternal UIC (β 0·26; 95 % CI 0·14, 0·37, $P<0·001$) and BMIC (β 0·85; 95 % CI 0·66, 1·04, $P<0·001$) at 3 months postpartum after adjustment for gestational age, parity, maternal secondary and further education, BMI category and infant feeding mode. The adjusted OR for infant UIC <100 μg/l was 6·49 (95 % CI 3·80, 11·08, $P<0·001$) in mothers with BMIC <100 μg/l compared with those with BMIC ≥100 μg/l. The I status of mothers and breast-fed infants in South Australia, following mandatory I fortification, is indicative of I sufficiency. BMIC <100 μg/l increased the risk of biochemical I deficiency in breast-fed infants.

Key words: Iodine: Urinary iodine concentration: Breast milk: Mothers: Infants

I is essential for the synthesis of thyroid hormones, which play a critical role in growth and development[1]. I deficiency is a common nutritional deficiency in both developed and developing countries. It is estimated that approximately 2 billion individuals world-wide are I deficient[2]. Furthermore, approximately 38 million newborns in developing countries[3] and over 24 million school-age children in Europe are classified as I deficient[4]. Severe I deficiency (defined as median urinary I concentration (UIC) <20 μg/l in a population) before birth and in early infancy can result in irreversible cognitive and physical deficits[5]. It is therefore important to ensure adequate I nutrition during this critical developmental period.

I deficiency has become a public health issue in Australia and mandatory I fortification was implemented in Australia in 2009 to address the re-emergence of I deficiency[6]. This strategy has led to improvement in the I status of the general population[7] but data on the I status of lactating mothers and their infants in Australia are scarce. Before the mandatory fortification, two small studies ($n \leq 50$) conducted in tertiary referral hospitals in Sydney reported I deficiency in lactating mothers in the early postpartum period[8,9], as indicated by a median UIC <100 μg/l[10]. There has been only one small study (*n* 60) assessing I status of lactating mothers following the introduction of mandatory I fortification in Australia. This study reported a median UIC of 123 μg/l (interquartile range (IQR) 71–236 μg/l)[11], indicating an improvement in I status of lactating women in Sydney, compared with the pre-fortification period. However, it did not meet the minimum sample size required to assess I status of populations (*n* 300) as suggested by the World Health Organization[12]. There are currently no studies with an adequate sample size that have determined the I status of lactating women and/or infants in Australia after mandatory I fortification.

Although UIC is the recommended biomarker for assessing the I status of populations it is not appropriate to use it as a marker of I status of individuals due to large day to day variation[12], breast milk I concentration (BMIC) may be a suitable marker of I status of exclusively breast-fed infants as breast milk is the sole source of dietary I for these infants.

Abbreviations: BMIC, breast milk I concentration; IQR, interquartile range; UIC, urinary I concentration.

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Previous studies in Iran have demonstrated a positive relationship between maternal BMIC and the UIC of their infants[13,14]. It has been suggested that a BMIC of at least 80–100 μg/l is required to ensure that full-term breast-fed infants received a sufficient supply of I to meet their I requirements[15,16]. Data on BMIC of lactating women in Australia are limited, with only one small study (*n* 50) reporting a median BMIC of 84 μg/l in mothers between 3 and 9 d postpartum, indicative of an inadequate I supply to meet the requirements of term infants[8]. This study was conducted before mandatory I fortification and collected from a convenience sample in a tertiary referral hospital in Sydney, Australia. Thus, the average BMIC of Australian women following the introduction of mandatory I fortification is unknown.

The primary aim of this study was to assess the I status of mothers and infants post-I fortification in Australia. The secondary aim was to examine the relationship between maternal UIC, BMIC and infant UIC.

Methods

Study design

This study was undertaken as part of a larger prospective cohort study which aimed to examine the relationship between maternal I intake in pregnancy and neurodevelopmental outcomes in the children at 18 months of age (Pregnancy I and Neurodevelopment in Kids)[17,18]. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and all procedures involving human subjects were approved by the Women's & Children's Health Network Human Research Ethics Committee (Ref: REC 1657/2/11 & REC 2230/12/15). Written informed consent was obtained from all participants.

Participants and recruitment

Healthy pregnant women (<20 weeks of gestation) were recruited from the antenatal clinics at the Women's and Children's Hospital and Flinders Medical Centre in Adelaide, South Australia between August 2011 and December 2012 and were followed up until 3 months after birth. Women with a history of thyroid disease, drug or alcohol abuse, who had a known fetal abnormality in their current pregnancy, or families in which English was not the primary language spoken at home were excluded.

Assessment of iodine status

UIC was assessed as a biomarker of I status of mothers and infants. A spot urine sample (10–20 ml) was collected from mothers and their infants at 3 months after birth (between September 2012 and October 2013) using a 70-ml sterilised pot (Southern Cross Scientific Ltd). The urine samples were stored at −20°C for subsequent batch analysis of UIC. UIC was measured using the WHO Method Two[12] in an Ensuring the Quality of Urinary Iodine Procedures program accredited laboratory at the University of Adelaide. The principle of this method is the colorimetric Sandell-Kolthoff reaction following ammonium persulfate digestion. The Seronorm™ Trace Elements Urine (SERO) was used as external standard and the results (mean) obtained by using this method was 285 (SD 12) μg/l compared with the certified value of 304 (SD 44) μg/l. The detection limit and reporting limit of the assay were 5·5 and 18·3 μg/l, respectively. Intra-assay and inter-assay CV were both <5 %.

BMIC was also determined as an additional biomarker of I status. A breast milk sample was collected from all breast-feeding mothers at the same time of the urine sample collection and using the same type of the container used for collecting urine. Mothers were instructed to collect 10–20 ml of the breast milk in the morning between 05.00 and 09.00 hours before the first feed. Breast milk samples were collected in either the study clinic or in the mother's home. If the sample was collected at home, mothers were instructed to freeze the samples in their home freezer until collection by study staff, whereas breast milk samples collected in the clinic were kept in the clinic freezer after collection. The samples were transported from the participant's home or the clinic to the laboratory within 4 d. The samples were kept frozen during transport using an insulated container with a freeze brick. All breast milk samples were then stored at −80°C until analysis. No I contamination was detected in any components used for urine and breast milk samples collection and analysis. I concentration in breast milk was determined using a modified method of the determination of I in food samples by Inductively Coupled Plasma MS after tetramethylammonium hydroxide extraction as described in detail previously[19]. Using this method, the results obtained for the external standard NIST 1549 milk powder (National Institute of Standard and Technology) was 3·38 (SD 0·02) mg/kg, which is the same as the certified value of 3·38 (SD 0·02) mg/kg. The method quantitative limit for human breast milk was 1·6 μg/l. The intra-assay and inter-assay CV were <1 and 3·5 %, respectively.

Other assessments

Socio-demographic characteristics of the mothers including age, gestational age, weight and height, parity, education level, employment, smoking and alcohol consumption status, were collected at study entry. Information on feeding mode (exclusively breast-feeding, partially breast-feeding or non-breast-feeding) at 3 months postpartum was collected by maternal report at the 3 month follow-up appointment. Women are recommended to take I supplements of 150 μg/d when planning pregnancy, during pregnancy and breast-feeding in Australia[20]. The information on I supplementation in lactation was not collected in the current study as the exposure variables in our study were maternal UIC and BMIC, not maternal I intake.

Statistical analysis

Normally distributed data are reported as means and standard deviations and non-normally distributed data are expressed as medians and IQR. The I status of the mothers and their infants was classified according to the WHO criteria: a median UIC <100 μg/l was considered indicative of I deficiency, whereas a median UIC ≥ 500 μg/l in mothers and a median UIC ≥300 μg/l in infants was considered indicative of excessive I intake[12]. A BMIC <100 μg/l was taken as indicative of an inadequate I supply to the infants[21].

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The percentage of mothers and infants with UIC below (<100 μg/l) or above (≥500 μg/l in mothers or ≥300 μg/l in infants) the WHO population thresholds were calculated as these thresholds are often reported in the literature. These thresholds should not be used to classify the I status of individuals as a single spot UIC is not an appropriate marker of individuals' I status due to the large day to day variation in UIC[12]. UIC was not normally distributed, thus quantile regression models, estimating the 50th centile (the median), were used to investigate the differences in UIC and BMIC between groups categorised by infant and maternal characteristics, that is infant sex, feeding mode and maternal BMI category. A quantile regression model was used to assess the relationships between maternal UIC (as the predictor) and infant UIC (as the outcome) with and without adjustment for covariates. Subgroup analysis was also performed in breast-feeding mothers and their children to assess the relationship between BMIC (as the predictor) and infant UIC (as the outcome). When UIC and BMIC were separated into two groups: <100 *v.* ≥100 μg/l, quantile regression models were also used to assess the differences in infant/maternal UIC and BMIC between these groups. Logistic regression models were used to estimate the OR of infants having a UIC <100 μg/l when their mothers had a UIC <100 μg/l or BMIC <100 μg/l. The OR of having a BMIC <100 μg/l when maternal UIC were <100 μg/l. Both unadjusted and adjusted analyses were performed. Covariates adjusted in all regression models including gestational age at study entry, parity, maternal completed secondary and further education, BMI category and feeding mode. Results from all models are reported as standardised regression coefficient (β) or OR as appropriate with 95 % CI.

Results

A total of 696 mothers and their infants who provided either maternal urine, breast milk and/or infant urine samples at 3 months postpartum were included in the study. Of these, urine samples were obtained from 686 (99 %) mothers and 628 (90 %) infants; and breast milk samples from 538 (95 %) of the 573 mothers who were still breast-feeding at 3 months postpartum. The socio-demographic characteristics of the mothers at enrolment are shown in Table 1. The percentages of infants who were exclusively breast-fed, partially breast-fed or exclusively formula fed at 3 months of age were 61, 18 and 21 %, respectively.

Iodine status of mothers at 3 months postpartum

The median UIC of mothers was 125 (IQR 76–200) μg/l; 38 % of mothers had UIC <100 μg/l, whereas 2 % had UIC ≥500 μg/l. The median BMIC was 127 (IQR 84–184) μg/l, with 36 % mothers having BMIC <100 μg/l. The median BMIC and percentage of mothers with BMIC <100 μg/l in the groups of mothers categorised by UIC <100 *v.* UIC ≥100 μg/l are shown in Table 2.

The median BMIC was higher in mothers with UIC ≥100 μg/l compared with those with UIC <100 μg/l, by 33 (95 % CI 18, 48) μg/l ($P<0·001$) before adjustment and by 39 (95 % CI 22, 55) μg/l ($P<0·001$) after the adjustment. Mothers with a UIC <100 μg/l were also more likely to have a BMIC <100 μg/l, compared with mothers with a UIC ≥100 μg/l, in both unadjusted and adjusted analysis (Table 2).

Table 1. Demographic characteristics of women at study entry (*n* 696) (Medians and interquartile ranges (IQR); numbers and percentages)

Characteristics	Median	IQR
Age (years)	33·0	33·0–36·0
Gestational age (weeks)	16·4	14·9–18·0
Parity ≥1		
n	315	
%	45·3	
Education		
Completed secondary school		
n	584	
%	83·9	
Completed further education		
n	363	
%	52·2	
BMI (kg/m^2)	24·9	22·5–28·1

The median UIC of mothers according to feeding mode are shown in Fig. 1. Median UIC of non-breast-feeding mothers was significantly higher than that of exclusively breast-feeding mothers after the adjustment for gestational age, parity, maternal secondary and further education, BMI categories and feeding mode ($P<0·01$). No difference in the median UIC was found between partially and exclusively breast-feeding mothers ($P>0·05$). There was no difference in the median BMIC between women with baseline BMI <25 kg/m^2 (123 (IQR 68, 188) μg/l) and those with BMI ≥25 kg/m^2 (126 (IQR 85, 222) μg/l). Unadjusted and adjusted estimates β and 95 % CI are shown in Table 3. Maternal UIC was positively associated with BMIC in both unadjusted (β 0·21 (95 % CI 0·17, 0·26), $P<0·001$) and adjusted analysis (β 0·27 (95 % CI 0·18, 0·35), $P<0·001$).

Iodine status of infants at 3 months of age

The median UIC of infants at 3 months was 198 (IQR 121–296) μg/l; 17 % of infants had UIC <100 μg/l, whereas 24 % had UIC ≥300 μg/l. Table 2 showed median UIC of infants and percentage of infants with UIC <100 μg/l according to maternal UIC and BMIC categories (<100 *v.* ≥100 μg/l).

The median UIC of male (*n* 347) and female infants (*n* 281) were 196 (IQR 120–293) and 201 (IQR 122–299) μg/l, respectively. Median UIC and IQR of infants according to feeding mode are shown in Fig. 1. No difference in the median UIC was found between male and female infants and between infants with different feeding modes, including exclusively breast-fed, partially breast-fed and exclusively formula fed in both adjusted and unadjusted analysis (Table 3).

The relationship between iodine status of mothers and their infants

Infant UIC were positively associated with maternal UIC with or without adjustment for gestational age, parity, maternal education, baseline BMI category and infant feeding mode (unadjusted β 0·22; 95 % CI 0·08, 0·36, $P=0·002$ and adjusted β 0·26; 95 % CI 0·14, 0·37, $P<0·001$). A similar relationship was also observed between infant UIC and BMIC in the subgroup of breast-fed infants in both unadjusted analysis (β 0·86; 95 % CI 0·65, 1·08,

Table 2. Median breast milk iodine concentration (BMIC) and infant urinary iodine concentration (UIC) according to maternal UIC and BMIC category(Medians and interquartile ranges (IQR); numbers and percentages)

	Maternal UIC <100 µg/l		Maternal UIC ≥100 µg/l		
	Median	IQR	Median	IQR	Adjusted *P**
BMIC (µg/l)	110	74, 155	143	98, 203	<0·001†
BMIC <100 µg/l					<0·001‡
n	104		87		
%	47		28		
Infant UIC (µg/l)	175	102, 262	207	128, 318	0·007†
Infant UIC <100 µg/l					0·023‡
n	59		50		
%	24		13		
	BMIC <100 µg/l		BMIC ≥100 µg/l		
Median infant UIC (µg/l)	132	84, 216	225	150, 353	<0·001†
Infant UIC <100 µg/l					<0·001‡
n	60		22		
%	34		7		

* Adjusted for gestational age at study entry, parity, maternal completed secondary and further education, BMI category and feeding mode.
† *P* value derived from quantile regression.
‡ *P* value derived from logistic regression.

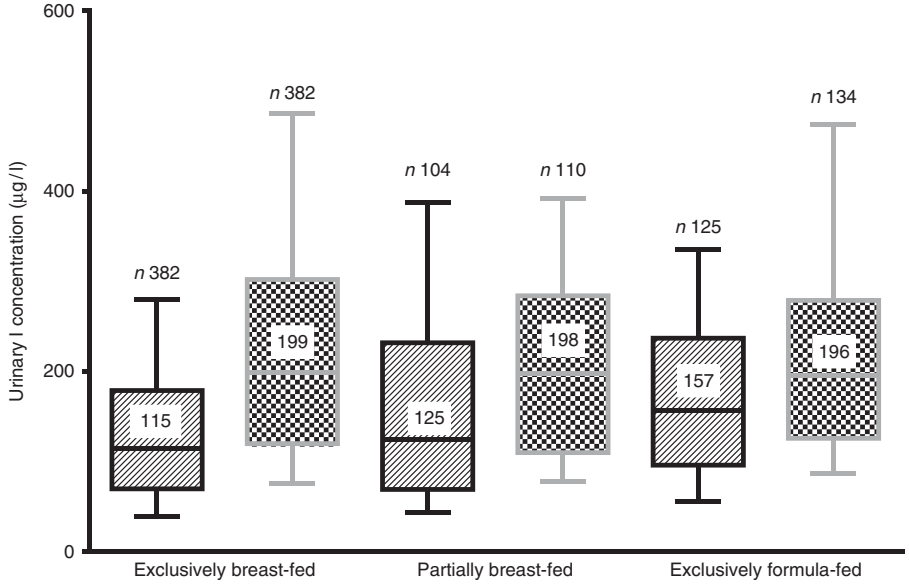

Fig. 1. Urinary iodine concentration of mothers (▨) and infants (▩) according to feeding mode.

P < 0·001) and adjusted analysis (adjusted for gestational age, parity, maternal completed secondary and further education, BMI category and feeding mode) (*β* 0·85; 95 % CI 0·66, 1·04, *P* < 0·001).

The median UIC of infants whose mothers had UIC ≥100 µg/l was 32 (95 % CI 7, 57) µg/l (*P* = 0·013) higher than infants whose mothers had UIC <100 µg/l. A similar finding was observed (32 (95 % CI 9, 56) µg/l (*P* = 0·007) higher) after adjustment for gestational age, parity, maternal secondary and further education, baseline BMI category, and infant feeding mode. When the data of breast-fed infants were analysed separately, the median UIC of infants whose mothers had a BMIC ≥100 µg/l was 93 (95 % CI 61, 125) µg/l (*P* < 0·001) higher than infants whose mothers with BMIC <100 µg/l in unadjusted analysis, and 87 (95 % CI 61, 114) µg/l (*P* < 0·001) higher in adjusted analysis.

Infants of mothers with UIC <100 µg/l were more likely to have UIC <100 µg/l compared with infants born to mothers with UIC ≥100 µg/l before and after the adjustment for gestational age, parity, mothers completed secondary and further education, baseline BMI category and feeding mode (Table 3). Infants of mothers with BMIC <100 µg/l were more likely to have a UIC <100 µg/l than infants of mothers with BMIC ≥100 µg/l in both unadjusted and adjusted analysis (Table 3).

Discussion

Our study is the first prospective cohort study to simultaneously assess I status of both mothers and their infants in Australia after the introduction of mandatory I fortification. The median UIC of

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Table 3. Infant urinary iodine concentrations (UIC), maternal UIC and breast milk iodine concentration (BMIC) according to infant sex, feeding mode and BMI category
(Standardised regression coefficients (*β*) and 95 % confidence intervals; odds ratios and 95 % confidence intervals)

	Unadjusted analysis			Adjusted analysis*		
Models	*β*	95 % CI	*P*	*β*	95 % CI	*P*
Maternal UIC by feeding mode			0·006			0·007
Non-breast-feeding *v.* breast-feeding	42	16, 68	0·001	44	16, 71	0·002
Partially breast-feeding *v.* exclusively breast-feeding	12	−17, 41	0·422	7	−25, 39	0·685
BMIC by BMI category (≥25 *v.* <25 kg/m^2)	2	−14, 18	0·801	−5	−21, 11	0·547
Infant UIC by feeding mode			0·985			0·926
Non-breast-fed *v.* breast-fed	−3	−37, 31	0·862	3	−28, 34	0·851
Partially breast-fed *v.* exclusively breast-fed	−1	−37, 35	0·956	−5	−40, 30	0·769
Infant UIC by infant sex (female *v.* male)	5	−21, 31	0·703	13	−11, 37	0·293
	OR	95 % CI		OR	95 % CI	
Infant UIC <100 µg/l by maternal UIC <100 µg/l	2·25	1·11, 4·56	0·025	2·27	1·12, 4·60	0·023
Infant UIC <100 µg/l by BMIC <100 µg/l	6·49	3·80, 11·08	<0·001	6·49	3·80, 11·08	<0·001
Maternal UIC <100 µg/l by BMIC <100 µg/l	2·28	1·59, 3·27	<0·001	2·43	1·66, 3·59	<0·001

* Adjusted for gestational age at study entry, parity, maternal completed secondary and further education, BMI category and feeding mode.

both mothers and infants were indicative of I sufficiency in this study population, which should not be interpreted to indicate that all participants are I sufficient as a single spot UIC cannot be used to define I status of individuals[12]. The present study also provides the first data on BMIC of lactating women in South Australia post-fortification, and suggests that, on average, their breast milk provides an adequate I supply to meet the requirement of full term breast-fed infants at 3 months of age.

The median UIC of lactating women in our study, the largest Australian study conducted to date, is consistent with a small study (*n* 60) conducted in Illawarra region of Australia post-fortification[11] indicating an I sufficient status of lactating women. Our study is the first to report I status of Australian infants following the introduction of mandatory I fortification. Our finding of adequate I status in both mothers and infants are in agreement with a national I survey conducted in 2011–2012, which showed that child-bearing aged women and school-age children in South Australia were I sufficient post-fortification[7]. We found, however, that mothers with UIC <100 µg/l were more likely to produce breast milk containing I <100 µg/l and their infants had a higher risk of I deficiency. Although the median UIC of breast-fed infants whose mothers had BMIC <100 µg/l was considered I sufficient, the risk of these infants having a UIC <100 µg/l were six times higher compared with breast-fed infants whose mothers had a BMIC ≥100 µg/l. This suggests that I intake of breast-fed infants may be suboptimal if maternal BMIC is <100 µg/l. These findings highlight the importance of achieving and maintaining an I sufficient status during lactation in order to ensure sufficient I supply to their breast-fed infants.

The positive association between maternal and infant UIC in our study is consistent with previous reports[22,23], but there is little evidence on the relationship between maternal BMIC and UIC. The only study in Australia that examined this relationship[8] was conducted before the mandatory I fortification, and showed no correlation between maternal BMIC and UIC. However, the study was only conducted on a small sample (*n* 50) and may not have adequate power to detect the association. The current study is the first to investigate the relationship between maternal UIC/BMIC and infant UIC in Australia, and has demonstrated that both maternal UIC and BMIC measured at 3 months postpartum were positively associated with infant UIC at this same time point. Furthermore, our results suggest that BMIC is a better predictor of infant UIC compared with maternal UIC as reflected by a stronger association between BMIC and infant UIC and a larger effect size of BMIC on infants UIC from the regression analysis.

Although large studies in adults in a number of countries, including Germany (*n* 6978) and China (*n* 26 773) have reported lower UIC in females compared with males[24,25], whether this is the case in infants is less clear. We found no difference in median UIC at 3 months of age between male and female infants, similar to studies in Iran (*n* 147)[26] and France (*n* 95)[27] in infants under 12 months of age. Another large study of 16 481 Chinese infants, however, reported that the median UIC of female infants was significantly lower than males[28], but the magnitude of difference was small, at 6 µg/l. Whether there are differences in I metabolism, I status and I requirement between male and female infants remains unclear, but if they do exist, they are probably small and unlikely to be clinically important.

Maternal overweight and obesity have been associated with an increased risk of a number of micronutrient deficiencies[29]. I is a key component of thyroid hormone which regulates metabolic rate. There is limited evidence suggesting an association between thyroid hormone concentrations and markers of metabolic health including BMI and insulin sensitivity in adults[30]. In the current study, we saw no differences in BMIC at 3 months postpartum between overweight/obese mothers and normal weight mothers categorised based on BMI at study entry, and the median BMIC in both groups were higher than the cut-off of 100 µg/l, indicative of adequate I level to meet the I requirements of their infants. It is important to note that the BMI of the women in this study was determined from weight and height collected at study entry (<20 weeks of gestation), and subsequent weight changes during pregnancy/lactation

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may also have the potential to impact on BMIC. Thus, further studies in which I status/BMIC and maternal weight are assessed at multiple time-points before and after pregnancy are required to more clearly delineate if overweight or obese may have a negative impact on maternal/infant I status and BMIC.

The current study provides the first data regarding I nutrition status of infants in Australia with different feeding modes. Our finding is consistent with the results of a previous study conducted in USA, which also showed no difference in median UIC between exclusively breast-fed, partially breast-fed and exclusively formula fed infants <3 months of age[31]. Although there appeared to be no impact of feeding mode on infant UIC in this population with adequate I status, we found that mothers who were exclusively breast-feeding had a lower median UIC than women who were not breast-feeding reflecting the higher I requirements in breast-feeding women. In addition, mothers who breast-fed their infants were more likely to have a UIC <100 μg/l than non-breast-feeding mothers. Whether breast-feeding has a short-term impact on UIC or long-term impact on thyroid function of the mother is still unclear, and it will be important to assess whether there are differences in maternal thyroid function between breast-feeding and non-breast-feeding women in future studies.

Recently it was reported that the BMIC of lactating women increased and reached the peak levels at 6 h after the administration of 600 μg KI[32]. BMIC was reported to be higher in the foremilk and the mid-feed milk compared with the hindmilk[33] and declined as lactation progressed in the first 6 months[34]. However, for practical and logistical reasons, only foremilk samples were collected from the participants in the early morning. Therefore, further studies in which multiple samples are collected at different stages of lactation and from different breast milk fractions will be important. Furthermore, we did not collect data on I intake or use of I supplements at 3 months' postpartum in the present study. Therefore, whether I fortification alone or coupled with I supplements improved I status and BMIC of lactating mothers in Australia is unclear. Women in our study were recruited from two major maternal hospitals in Adelaide, South Australia, however, families where English was not spoken at home were not eligible to take part in the study. Consequently, our results may not be generalisable to mothers and children from a non-English-speaking background.

In conclusion, our findings indicate that the I status of lactating mothers and their infants in South Australia is sufficient post mandatory I fortification. However, I intake of breast-fed infants may be suboptimal if maternal BMIC is <100 μg/l.

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The author contributions are as follows: S. J. Z and M. M. designed and managed the study with input from S. S. and P. R.; D. C. recruited the participants, collected the breast milk and urine samples, D. H. performed breast milk and urine analysis and drafted the manuscript with contributions from all authors. R. G. and B. M. supervised the analysis of breast milk and urine samples. All authors reviewed and approved the manuscript submitted.

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Supplementary material

For supplementary material/s referred to in this article, please visit https://doi.org/10.1017/S0007114517001775

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