Iodine deficiency in pregnant women living in the South-East of the UK: the influence of diet and nutritional supplements on iodine status

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Running title: Iodine deficiency in UK pregnant women.

Abbreviations: EAR: Estimated Average Requirement; FFQ: Food Frequency Questionnaire; RNI: Reference Nutrient Intake; UIC: Urinary Iodine Concentration; WHO: World Health Organisation.

Key words: Iodine, UK, pregnancy, diet
Abstract

Iodine is a key component of the thyroid hormones which are crucial for brain development. Pregnant women are vulnerable to iodine deficiency because their requirement for iodine is higher than that of non-pregnant adults. Data on the iodine status of UK pregnant women are sparse and there are no such data in the South East. One hundred pregnant women were recruited to a cross-sectional study at the Royal Surrey County Hospital, Guildford, at their first-trimester visit for an ultrasound scan. Participants provided a spot-urine sample (for the measurement of urinary iodine and creatinine concentrations) and 24-hour excretion of iodine was estimated from the urinary iodine-to-creatinine ratio. Women completed a general questionnaire and a food-frequency questionnaire. The median urinary iodine concentration (85·3 µg/l) indicated that the group was iodine deficient by WHO criteria. The median values of the iodine-to-creatinine ratio (122·9 µg/g) and of the estimated 24-hr iodine excretion (151·2 µg/day) were also suggestive of iodine deficiency. Urinary iodine concentration was significantly higher in women taking an iodine-containing prenatal supplement (n=42) than in those not taking such a supplement (P<0·001). In adjusted analyses, milk intake, maternal age and iodine-containing prenatal supplement use were positively associated with estimated 24-hour urinary iodine excretion. Our finding of iodine deficiency in these women gives cause for concern. We suggest that women of childbearing age and pregnant women should be given advice on how to improve their iodine status through dietary means. A national survey of iodine status in UK pregnant women is required.
Introduction

Iodine deficiency, once endemic in the UK, was eradicated by the concurrent increase in milk-
iodine concentration and milk consumption in the post-war years, though neither was aimed at
improving human iodine status\(^1\). From the 1960s, the UK was considered to be an iodine-
sufficient country, but data are now emerging that suggest that this may no longer be the case, at
least in women of childbearing age\(^2-5\) and pregnant women\(^6-8\); indeed the World Health
Organisation (WHO) now classifies the UK as mildly iodine deficient\(^9\).

Iodine is a key component of the thyroid hormones which are crucial for brain development,
particularly during gestation and early life\(^10\). The WHO iodine recommendation for pregnant
women is 250 µg/day which is considerably higher than the 150 µg/day recommendation for
adults. Pregnant women are vulnerable to iodine deficiency as the effects of in utero deficiency
on the developing fetus may have life-long consequences for the offspring. Severe iodine
deficiency during pregnancy is well-known to cause cretinism and severe mental retardation
\(^10\). We recently found mild-to-moderate iodine deficiency in a large UK cohort of pregnant women
and the children of those that had low iodine status in early pregnancy were more likely to have
significantly lower IQ and reading scores\(^11\).

Though it is vital that pregnant women meet their iodine requirements, this is not always
achieved even in developed countries such as the USA\(^{12,13}\). Strategies such as salt iodization
programmes that exist in many countries may provide enough iodine for adults but not
necessarily for pregnant women\(^14\). It is therefore important to monitor the iodine status of
pregnant women in a population; for this purpose, the WHO recommends collecting spot-urine
samples from a group of pregnant women and comparing the median urinary iodine concentration
(UIC) to the cut-off value for adequacy (150-249 µg/L)\(^15\).

The UK has never introduced a national iodine-fortification program to ensure adequate
population iodine intake, as has been done in many countries worldwide\(^10\). Furthermore, advice
to pregnant women from the UK Department of Health makes no mention of the need for iodine
in pregnancy nor does it list dietary sources\(^16\). Results from the National Diet and Nutrition
Survey (NDNS) suggest that milk (and milk products), fish and eggs are the main dietary sources
of iodine (estimated from food-diary analysis) in UK adults (17); certain groups of women may not consume these iodine-rich foods. Not all UK prenatal supplements contain iodine and, in contrast to the situation in the USA, Australia and New Zealand, there is no official recommendation for pregnant women to take an iodine supplement (18,19).

Iodine deficiency has been demonstrated in studies of pregnant women in Scotland (7), the North-East of England (6) and Cardiff (8) but these studies all have limitations: one was only published as an abstract (7), two were published prior to the updated WHO iodine requirements for pregnancy (6,7), and one reported iodine status of women recruited to a trial (8) who may not be representative of pregnant women in general. There are no data on the iodine status of pregnant women from the South-East of the UK nor any information on the dietary sources that contribute to iodine status in pregnant women as none of the previous studies collected dietary data. Furthermore there is no information on the effect of taking a UK prenatal iodine-containing supplement on iodine status. The current study therefore aimed to evaluate iodine status in pregnant women in the South East of the UK and to explore factors that influence iodine status at this critical life-stage. On the basis of the sparse UK literature, we hypothesised that women would be iodine deficient by WHO criteria.

**Experimental methods**

**Recruitment of subjects**

Pregnant women were recruited consecutively to a cross sectional study at the time of their first-trimester ultrasound scan (around 12 weeks’ gestation) at the Royal Surrey County Hospital, Guildford. Women were not eligible for inclusion if they had a history of thyroid disease or were taking thyroid medication. Owing to budget and time constraints, it was not possible to recruit throughout the year and a decision was made to recruit in the summer season only (July to September 2009). This removed the complication of straddling seasons as milk-iodine content shows a seasonal variation (1) that affects iodine status; other UK studies have found lower urinary iodine concentrations in samples collected in summer than in winter (4,20).

Participants were asked to provide a spot-urine sample at the ultrasound clinic; all clinics were conducted in the morning though timing of sample collection is unlikely to affect the
concentration of iodine or creatinine\textsuperscript{(21)}. They were also required to complete a short food-
frequency questionnaire (FFQ) and a general questionnaire that collected demographic and
nutritional information. One of the authors was present during the completion of the
questionnaire, giving an opportunity for clarification (for example the meaning of “iodised salt”).
The study was conducted according to the guidelines laid down in the Declaration of Helsinki
and all procedures involving human subjects were approved by the NRES Ethics Committee
(South East Coast – Surrey, ref 08/H1109/140) and the University of Surrey Ethics Committee
(ref EC/2009/39/FHMS). Written informed consent was obtained from all subjects.

Analysis of dietary intake and nutritional supplement use

The general questionnaire collected details on participant age, smoking status, time since a
previous delivery (birth in the last three years). It also collected information on whether the
participant was a vegetarian or vegan and whether or not she took a prenatal nutritional
supplement. The dose of iodine in the supplement, if any, was determined by conducting a shelf-
survey of prenatal supplements available in the UK in November 2009.

The 46-item semi-quantitative FFQ was designed to give detailed information only on foods that
were iodine-rich or with potential goitrogenic properties. It was not intended to calculate nutrient
intakes, rather to estimate the quantity of iodine-rich foods consumed (e.g. grams per week of
fish). The FFQ design was based on the FFQ used in the European Prospective Investigation of
Cancer (EPIC) study\textsuperscript{(22)}. There were nine frequency options for all foods except milk; in the
latter case, daily consumption had six frequency options. With the exception of eggs (kept as a
frequency coding), all other food items were recoded to estimated weekly intake (in grams).

Estimated intake was computed by combining information on number of weekly portions with
estimated food weights of each portion; medium portion sizes were used\textsuperscript{(23)} and an average
portion weight was computed for composite food groups, such as “white fish”. The coding of
weekly portions was based on that used for the FFQ completed by pregnant women in the Avon
Longitudinal Study of Parents and Children (ALSPAC)\textsuperscript{(24)}. The weekly portions were as follows:
0 = none/rarely, 0·5 = once a fortnight, 2 = one-to-four times per week, 5·5 = five-to-seven times
per week and 10 = more than once daily\textsuperscript{(24)}. 
The 46 food items were collapsed to seven food categories: (i) daily milk intake; (ii) seafood (total of processed fish, white fish, oily fish, shellfish and fish roe); (iii) meat and poultry (total of all processed meat, red meat and poultry); (iii) dairy products (total of all cream, yoghurts, butter and cheese); (iv) eggs (once/fortnight or less, once/week or more); (v) iodised salt; (vi) seaweed; (vii) goitrogens [total soy products (soy milk, tofu and other soy products), cruciferous vegetables (broccoli/kale/spring greens, cabbage, Brussels sprouts, cauliflower, turnip/swede, radish) and sweet potatoes]. For the purposes of statistical analyses, daily milk consumption was recoded as: (i) none, (ii) less than <140 mL, (iii) 140 to 280 mL and (iv) more than >280 mL.

Weekly estimated intake (in grams) of seafood, meat/poultry and dairy products was divided into tertiles. Consumption of seaweed and iodised salt was dichotomised into either “consumer” or “non-consumer” due to the low numbers of consumers (n = 13 and n = 4 respectively).

Laboratory analysis

Urinary iodine concentration (UIC) was measured on a ThermoElemental X-Series ICP-MS (ThermoFisher Scientific, Hemel Hempstead, UK) in the Trace Element Laboratory at the University of Surrey. The samples were diluted with an alkaline diluent which was prepared by dissolving 3·32 g NH₄H₂PO₄ and 1·16 g (NH₄)₂H₂EDTA (Analar grade, Sigma-Aldrich, Dorset, UK) in deionised water, adding 10·0 mL ammonia solution (s.g. 0·88), and making up to 1000 mL with deionised water. 400 µL of each participant’s urine sample was made up to 10 mL with the alkaline diluent. Standard iodine solutions were prepared with potassium iodide solution (Analar grade, Romil Ltd, Cambridge, UK) for the construction of calibration curves. 400 µL of control urine was added to 400 µL of each standard in order to obtain matrix-matched standards.

An internal standard was added to all samples: Rhodium (¹⁰³Rh) and Iridium (¹⁹²Ir) (both SPEX Certiprep Ltd, Middlesex, UK) were made up in a working standard solution of 1 mg/L (ppm) in 1% v/v nitric acid (Trace analysis grade, Fisher Scientific). This solution was made up in a ratio of 1 in 10 with the diluent. 150 µL of this solution was added to every tube in the analysis. To evaluate the accuracy of the method, certified reference materials (CRM) were obtained through quality-assurance programme of the Centre for Disease Control (CDC), entitled ‘Ensuring the Quality of Urinary Iodine Procedures’ (EQUIP). Our observed mean values for the EQUIP CRMs were: 27·6 (SD 2·3, n=3) for U02 (certified mean 28·7 µg/L, range 20·1-37·3); 47·4 (SD 2·1, n=4) for U05 (certified mean 45·0 µg/L, range 31·5-58·5); 301·8 (SD 7·5, n=4) for U09.
(certified mean 296.3 µg/L, range 251.9-340.7); 9.6 (SD 0.8, n=2) for U10 (certified mean 12.2 µg/L, range 8.5-15.9). Urinary creatinine was measured in the Biochemistry Department at The Royal Surrey County Hospital on the ADVIA Chemistry System (Siemens Healthcare, Camberley, UK) by the Jaffe rate method.

Classification of iodine status

The UK Dietary Reference Values for iodine were published in 1991 and are outdated as they do not reflect the need for additional iodine during pregnancy\(^{(10,25)}\). For this study, we have therefore used the WHO criteria to assess iodine status in pregnancy\(^{(15)}\). The iodine status of the group was described by comparing the median UIC value to the WHO UIC cut-offs for iodine adequacy in pregnancy\(^{(15)}\). However, these cut-offs cannot be used to identify iodine deficiency in an individual owing to the large intra-individual variation in iodine excretion from day to day in a spot-urine sample; it is often incorrectly assumed that anyone with a UIC value from a spot-urine sample that is below the cut-off for adequacy (150 µg/L in the case of pregnancy) is iodine deficient which may well not be the case\(^{(10)}\).

By using urinary creatinine concentration in a spot-urine sample to correct urinary iodine concentration (UIC) for intra-individual variation in daily urine volume produced, we can more closely approach individual iodine status, especially when the age and sex of the individual is taken into account\(^{(26-28)}\). We have therefore reported iodine status in three ways: as the simple iodine concentration (µg/L), the iodine-to-creatinine ratio (µg/g) and as the estimated 24-hr excretion of iodine (µg/day). The 24-hr excretion of iodine was estimated by multiplying the iodine-to-creatinine ratio by the expected daily excretion of creatinine, which is 1.23 g/day\(^{(26)}\) for our cohort of women aged from 19 to 49 years [on the basis that the value for non-pregnant adults can be used as creatinine excretion is unaltered in pregnancy\(^{(29,30)}\)] . In order to explore relationships with participant characteristics (such as age) and dietary intake (estimated from the FFQ), we used the estimated 24-hr excretion of iodine for each participant as a proxy for individual iodine status, though we recognize the limitations of this method.

Statistical analysis
Urinary iodine concentration and the estimated 24-hr excretion of iodine were not normally distributed and therefore medians with the 25th and 75th percentiles are reported. The estimated 24-hr iodine excretion was log-transformed using the natural logarithm to allow parametric testing. Maternal age was recoded as a categorical variable: 19-34 years and 35-49 years. Independent t-tests or one-way ANOVA were used on the log-transformed data to compare two or two-or-more groups respectively. Spearman-rank correlation was used to explore relationships between continuous data.

Multiple linear regression [using General Linear Model (GLM) in SPSS] was used to evaluate associations between dietary and demographic factors and the (log-transformed) estimated 24-hr iodine excretion; variables that were significantly related to estimated 24-hr iodine excretion in the unadjusted analyses were entered into the model. The model was then used for calculation of estimated geometric means (with their 95% CI) of estimated 24-hr iodine excretion for each category of milk intake; the geometric means were computed by back transformation of the adjusted means and 95% CI of the log transformed estimated 24-hr iodine excretion variable. Significance was set at $P<0.05$ and analyses were conducted using the Statistical Package for Social Sciences (version 19.0; SPSS, Inc., Chicago, USA).

**Results**

During the defined study period (July to September 2009), 100 women were recruited to the study. The mean age (SD) of the women was 32.4 (4.7) years with a range of 19-47 years. The median urinary iodine concentration was 85.3 µg/L, classifying this group of pregnant women as mildly-to-moderately iodine deficient (15,31) (Table 1). The median iodine-to-creatinine ratio (122.9 µg/g) was also low and the median estimated 24-hr excretion of iodine (151.2 µg/day) was considerably below the value that would be expected (i.e. 225 µg) if 250 µg iodine (the dietary requirement for pregnant women) were consumed/day of which 90% was excreted.

Describing the prevalence of iodine deficiency within our cohort is challenging. Many authors report the percentage of values below the WHO cut-off of 150 µg/L, which in our study would be 76% (or 67% if using the iodine-to-creatinine ratio with a cut-off of 150 µg/g). However, this may over-estimate the extent of deficiency; strictly speaking, the EAR, not the RNI should be
used to report the prevalence of deficiency of a nutrient in a population \(^{(32)}\). Hence it may be more correct to report the percentage with values below the Estimated Average Requirement (EAR), which we estimate to be 180 µg/day (calculated by converting the pregnancy RNI of 250 µg/day to an EAR using the published RNI-to-EAR conversion factor for iodine of 1.4 \(^{(32)}\)). Therefore the expected value in a 24-hr urine excretion would be approximately 160 µg/day (assuming a 90% excretion of the EAR of 180 µg/day). By these calculations, 53% (n=53) of the women in our study had an estimated 24-hr iodine excretion value below the EAR.

**Participant characteristics and iodine status**

Table 2 shows the effect of participant characteristics on maternal iodine status. There was no significant difference in iodine excretion by smoking status, consumption of a vegetarian diet (there were no vegans) or time since last birth (Table 2). Estimated 24-hr iodine excretion was significantly higher in women over 35 years than in women aged 19-34 years \((P = 0.01\); Table 2). We explored the relationship between maternal age and urinary creatinine excretion to investigate whether the higher iodine status at older age was explained by lower creatinine excretion \(^{(33)}\); we did find a significant negative correlation between maternal age and urinary creatinine concentration \((r = -0.21, P = 0.01\)). To test whether older women consumed more iodine-rich foods, we explored correlations between dietary food groups and maternal age and found a positive association with seafood \((r = 0.22, P = 0.03\) and cheese \((r=0.30, P = 0.003\) (data not shown).

**Use of an iodine-containing nutritional supplement**

Seventy-five participants (75%) were taking a nutritional supplement at the time of recruitment (including single folic-acid supplements); 51 (51%) women were taking a multivitamin or mineral supplement but only 42 (42%) were using a prenatal vitamin and mineral formulation that contained iodine. The median content of iodine in the supplements reported by the participants was 140 µg/dose (range 75 -150 µg). The iodine status of women who took an iodine-containing supplement was significantly higher than that of those who did not take such a supplement; this relationship was demonstrated both by the simple iodine-concentration measure \((P < 0.0001\)) and by the estimated 24-hr iodine excretion \((P < 0.0001\); Table 2). Figure 1 shows our result in comparison with the WHO recommended levels for a population of pregnant...
women (15). The median urinary-iodine concentration of women taking an iodine-containing supplement (111 µg/L) was closer to the WHO adequate range for pregnant women (150-249 µg/L) than that of women not taking such a supplement (61 µg/L), which was close to the severe-deficiency level (≤50 µg/L) (31).

**Dietary influences on iodine status**

Iodised salt was rarely or never used by 96% of the women and there was no significant difference in iodine excretion between consumers and non-consumers (Table 3). There was no difference in iodine status between consumers (n=13) and non-consumers of seaweed \( (P = 0.23; \text{data not shown}) \). Weekly estimated intake of goitrogens or meat and poultry was not significantly associated with iodine excretion (Table 3). Although iodine excretion was higher in the top than in the bottom tertile of dairy intake (Table 3), the difference was not significant \( (P = 0.10) \).

By contrast, intake of milk, eggs and seafood were positively associated with estimated 24-hr iodine excretion (Table 3). The difference in iodine status between the categories of milk consumption was highly significant \( (P = 0.007) \) and *post hoc* tests showed that women who did not consume milk had significantly lower iodine excretion than those consuming more than approximately 280 mL per day \( (P = 0.008) \). One woman reported consuming up to approximately 570 mL of goats’ milk per day; she was an outlier with an estimated 24-hr iodine excretion of 1414.0 µg/g. The estimated 24-hr iodine excretion differed significantly between tertiles of seafood intake \( (P = 0.04) \) and the *post-hoc* test showed that iodine excretion was significantly lower in the bottom than the top tertile \( (P = 0.03; \text{Table 3}) \). Iodine excretion differed significantly with frequency of egg consumption \( (P = 0.04) \); higher iodine excretion was associated with a greater frequency of weekly egg consumption (Table 3).

In the adjusted analysis (that included significant variables from univariate analyses), the only factors significantly associated with estimated 24-hr iodine excretion were categories of milk consumption \( (P = 0.002) \), use of an iodine supplement \( (P < 0.0001) \) and maternal age \( (P = 0.007) \). There were no significant interactions between variables. The model explained 31.1% of the variance in estimated 24-hr iodine excretion \( (\text{adjusted } R^2 = 0.311) \); milk explained 15.1% (partial eta squared = 0.151), iodine-supplement use 14.5% (partial eta squared = 0.145) and
maternal age 7.8% (partial eta squared = 0.078) of the variance. Egg ($P = 0.24$) and seafood intake ($P = 0.42$) were not significantly associated with iodine excretion in the adjusted model. When all other factors were controlled for, there remained evidence of a trend of increasing estimated 24-hr iodine excretion with increasing daily milk consumption (Figure 2).

Discussion

Our results support our hypothesis that pregnant women in the South-East of the UK would have inadequate iodine status as the median UIC classified the women as mildly-to-moderately iodine deficient. Our results, together with those from earlier UK studies, suggest that UK pregnant women are not meeting the higher iodine requirements of pregnancy; this may be having a negative effect on fetal brain development. Indeed the level of deficiency found in our current study (median UIC 85.3 µg/L) is similar to that in an Australian study (in women recruited prior to mandatory iodine-fortification of bread in 2009) and in our own recent UK study (median UIC 81 µg/L and 91.1 µg/L respectively); those studies found associations between iodine status in pregnancy and poorer cognition (IQ, reading ability and spelling) in the child up to the age of nine years.

As we only collected one urine sample from each woman, we cannot accurately describe the prevalence of iodine deficiency in our study; ideally, multiple urine samples from each woman should be collected in order to adjust the iodine concentration distribution for intra-individual variation. However, while recognising the limitation that one urine sample from each woman may not reflect usual iodine status, we feel that reporting the percentage of women below the EAR threshold (53%) is a more accurate reflection of the extent of iodine deficiency than by the traditional approach of reporting the percentage below the WHO cut-off (150 µg/L) (which reflects the RNI for pregnancy). In our opinion, the methodology for the use of the EAR cut-point method during pregnancy needs further development.

We found that maternal age was positively associated with estimated 24-hr iodine excretion. There are two potential explanations for this: (i) older women consume more iodine-rich foods and, (ii) urinary creatinine excretion decreases with age (which we found), thus increasing the iodine-to-creatinine ratio. Data from the 2000/01 Adult National Diet and Nutrition Survey
(NDNS) suggests an increased dietary iodine intake with advancing age, as older women had a significantly higher iodine intake (estimated from food-diaries) than younger women\textsuperscript{(17)}.

Women who reported taking an iodine-containing supplement had a significantly higher iodine status than those who did not take such a supplement, which is consistent with other research findings in Europe\textsuperscript{(35-37)} and New Zealand\textsuperscript{(38)}. Health authorities in America, Australia and New Zealand recommend that all pregnant (and lactating) women should take a supplement containing 150 µg/d of iodine during pregnancy\textsuperscript{(18,19)}. There are just two trials that supplemented pregnant women with iodine in regions of mild-to-moderate iodine deficiency\textsuperscript{(39,40)}; while these suggest a benefit for child cognition, further good-quality evidence from a randomised controlled trial is needed. In our study we have no data on maternal or neonatal thyroid function or on long-term cognitive outcomes in the offspring that would support benefit [or indeed lack of harm\textsuperscript{(41,42)}] of initiating iodine supplementation in pregnancy. Despite the fact that 51% of women in our study were taking a prenatal multivitamin and mineral supplement, only 42% were taking a supplement that contained iodine – a reflection of the fact that, at the time, only 67% of UK prenatal supplements contained iodine and that there is no official UK advice to take an iodine supplement during pregnancy. A higher percentage of women in our study were taking an iodine-containing supplement than were women in the US\textsuperscript{(43,44)}, Switzerland\textsuperscript{(45)}, New Zealand\textsuperscript{(38)} or Australia\textsuperscript{(46)}. Most UK pregnant women are unaware of the need for iodine\textsuperscript{(47)} so the presence of iodine in the supplement is unlikely to influence choice but the leading UK prenatal supplement brand does contain iodine. In addition, Surrey is an affluent area\textsuperscript{(48)} and therefore supplement use may be higher than in other, less affluent, UK regions\textsuperscript{(49)}.

The finding that a higher intake of milk was related to a higher urinary iodine excretion is consistent with studies in pregnancy in other countries\textsuperscript{(35,43,50,51)}. Our results suggest that women consuming more than approximately 280 mL of milk per day had an iodine status greater than the cut-off for iodine adequacy in pregnancy, even after adjusting for other factors. However, it needs to be remembered that this milk-volume figure relates to intake of summer milk (as we recruited over the summer) which has a lower iodine content than winter milk. The inaccuracies of a food frequency questionnaire for collecting dietary-intake data should also be kept in mind.
We have shown a positive association between frequency of egg intake and maternal iodine status, although significance disappeared in the adjusted analysis. This is in contrast to the findings of the UK study of iodine status of teenage schoolgirls, which surprisingly found that a high intake of eggs was associated with low urinary iodine excretion\(^{(4)}\) though we have previously suggested that failings in the FFQ in that study (ambiguous and unquantified frequency options) resulted in spurious associations\(^{(52)}\). Iodine status was higher in women in the top tertile of fish intake, but the relationship was no longer significant when adjusted for other dietary factors. Seafood intake also failed to show associations with the iodine status of pregnant women in Spain\(^{(35,53)}\) and teenage girls in the UK\(^{(4)}\). The lack of a strong relationship between fish intake and iodine status (compared to the relationship with milk intake, despite its lower iodine concentration) may be explained by the insensitivity of an FFQ (see limitations) and the relatively poor consumption of fish by many UK women\(^{(49)}\). The fact that such a low percentage of pregnant women in our study reported the use of iodised salt may reflect its poor availability in UK supermarkets\(^{(54)}\).

Our study was limited by the relatively small sample size; however, a study of adults has estimated that 100 spot-urine samples (if corrected to estimate 24-hour iodine excretion) are sufficient to give a population estimate of urinary iodine excretion (within a 95% confidence interval) with a precision of \(\pm 10\%\)\(^{(55)}\). Nevertheless, the stratified analyses in our study (e.g. by age or dietary pattern) are based on a small sample size and therefore the results should be treated with caution. The other major limitation of the study is the fact that recruitment was conducted only in the summer months and in only one region of the UK (Surrey). Given the known seasonal variation in the iodine content of dairy products\(^{(1)}\), it is likely that our study represents a worst-case scenario. On the other hand, Surrey being an affluent county, the women in this study are likely to have higher socio-economic status than those in many other UK regions. Thus results may be biased towards higher iodine status as the intake of iodine-rich foods, particularly fish, may be greater in more affluent women. A large multi-centre study is needed to provide a more comprehensive view of the iodine status of UK pregnant women as Surrey women may not be representative of UK women in general. The evaluation of the impact of diet on iodine status is limited by the inherent limitations of a FFQ. It is perhaps unsurprising that some dietary items failed to show associations with iodine status given that iodine excretion reflects recent (previous
24 to 48 hours) dietary-iodine intake\cite{28}, and FFQs evaluate intake over a longer time period. Thus consumption of foods consumed regularly, such as milk, is more likely to affect the iodine concentration of a spot-urine sample than are food items with irregular and low consumption within the cohort, such as fish; this is likely to be especially true in studies with small sample sizes, such as ours. We are aware that there are limitations of using a single spot-urine sample for individual iodine status assessment and although we have attempted to overcome some of these limitations by use of the age-and-sex adjusted iodine-to-creatinine ratio, this method still has limitations\cite{27}; future studies might explore the use of body weight for further adjustment of the iodine-to-creatinine ratio and the collection of repeated urine samples for measurement of iodine status in the same individual\cite{27}.

In conclusion, we have demonstrated iodine deficiency in pregnant women in the South East of the UK – a cause for concern given the need for adequate iodine for fetal brain development\cite{10}. Intake of milk and iodine-containing supplements were the most important predictors of iodine status in UK pregnant women. Women who follow the current Government generic pregnancy healthy eating advice to consume 2-3 portions of dairy products per day, together with the recommended 1-2 portions of fish per week, should receive an adequate supply of iodine. However, for women who do not consume these iodine-rich foods, an appropriate prenatal iodine-containing supplement is probably appropriate (although kelp supplements should be avoided); indeed in this study we have shown that the use of such a supplement was associated with higher iodine status. Ensuring adequate iodine intake is likely to be particularly important prior to pregnancy to ensure that stores of iodine are optimized so that there is no shortfall in early gestation\cite{42,56}. The dietary advice to UK pregnant women needs to be revised to explain why increased iodine intake during pregnancy is important and good dietary sources should be clearly signposted.

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Conflicts of interest
We declare that we have no conflict of interest.

Authorship
S.C.B, J.W and M.P.R designed the study. S.C.B recruited the participants, facilitated with laboratory analysis, conducted the statistical analysis and prepared the first draft of the manuscript. A.W and A.T developed the laboratory method and completed the laboratory analysis. S.C.B. and M.P.R wrote the manuscript. All authors approved the final manuscript.


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Table 1 Iodine status of pregnant women from the South-East of the UK (n=100), reported as iodine concentration (µg/L), iodine-to-creatinine ratio (µg/g) and estimated 24-hr excretion (µg/day)*

<table>
<thead>
<tr>
<th></th>
<th>Median</th>
<th>25th, 75th percentile</th>
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<tbody>
<tr>
<td>Iodine concentration (µg/L)</td>
<td>85·3</td>
<td>39·6, 145·5</td>
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<tr>
<td>Iodine-to-creatinine ratio (µg/g)</td>
<td>122·9</td>
<td>79·5, 163·6</td>
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<tr>
<td>Estimated 24-hr iodine excretion (µg/day)*</td>
<td>151·2</td>
<td>97·8, 201·2</td>
</tr>
</tbody>
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*Age-and-sex adjusted iodine-to-creatinine ratio on the basis of an expected daily urinary creatinine excretion of 1.23 g/day\(^{(26)}\).
Table 2 Estimated 24-hr iodine excretion* (µg/day) according to participant characteristics

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Number (%)</th>
<th>Estimated 24-hr iodine excretion (µg/day)*</th>
<th>Median</th>
<th>25th, 75th percentile</th>
<th>P value†</th>
<th>Adjusted P value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td>19-34</td>
<td>66 (66)</td>
<td>131·8</td>
<td>86·3 - 198·5</td>
<td>0·01</td>
<td>0·007</td>
<td></td>
</tr>
<tr>
<td>35-49</td>
<td>34 (34)</td>
<td>178·1</td>
<td>134·1 - 241·3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoking status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-smoker</td>
<td>95 (95)</td>
<td>154·9</td>
<td>97·1 - 201·4</td>
<td>0·57</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td>5 (5)</td>
<td>118·7</td>
<td>88·9 - 202·3</td>
<td>0·57</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Time since last gave birth (in last three years)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 1 year</td>
<td>4 (4)</td>
<td>84·2</td>
<td>71·8 - 338·0</td>
<td>0·86</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>&lt; 2 years</td>
<td>24 (24)</td>
<td>158·4</td>
<td>92·9 - 195·6</td>
<td>0·86</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>&lt; 3 years</td>
<td>13 (13)</td>
<td>133·0</td>
<td>94·1 - 258·8</td>
<td>0·86</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>No birth in past 3 yrs</td>
<td>59 (59)</td>
<td>154·9</td>
<td>105·4 - 227·4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vegetarian status</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Omnivore</td>
<td>94 (94)</td>
<td>151·2</td>
<td>96·4 - 202·2</td>
<td>0·89</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Vegetarian§</td>
<td>5 (5)</td>
<td>139·2</td>
<td>94·4 - 293·0</td>
<td>0·89</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Use of iodine-containing supplement</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>42 (42)</td>
<td>183·6</td>
<td>132·9 - 294·7</td>
<td>&lt;0·0001</td>
<td>&lt;0·0001</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>58 (58)</td>
<td>124·9</td>
<td>82·0 - 175·6</td>
<td>0·007</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Age-and-sex adjusted iodine-to-creatinine ratio on the basis of an expected daily urinary creatinine excretion of 1.23 g/day.
†P value for comparison between groups from independent t-test or ANOVA conducted on log-transformed estimated 24-hr iodine excretion data; ‡adjusted P value from General Linear Model with variables: maternal age, supplement use, milk, seafood and egg intake; N/A: Variable not entered into multivariate analyses; §one women was classified as a pescatarian but was excluded from statistical analysis that compared vegetarians and omnivores.
Table 3  Estimated 24-hr iodine excretion* (µg/day) according to maternal diet

<table>
<thead>
<tr>
<th>Food group</th>
<th>Estimated 24-hr iodine excretion (µg/day)*</th>
<th>P value†</th>
<th>Adjusted P value‡</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Median, 25th, 75th percentile</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Daily milk intake (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>None (n = 7)</td>
<td>83·4</td>
<td>0·007</td>
<td>0·002</td>
</tr>
<tr>
<td>&lt; 140 mL (n = 24)</td>
<td>132·1</td>
<td>0·10</td>
<td>N/A</td>
</tr>
<tr>
<td>140-280 mL (n = 41)</td>
<td>156·6</td>
<td>0·04</td>
<td>0·42</td>
</tr>
<tr>
<td>&gt;280 mL (n = 28)</td>
<td>171·4</td>
<td>0·54</td>
<td>N/A</td>
</tr>
<tr>
<td>Dairy produce intake per week (g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bottom tertile (0-406g)</td>
<td>139·1</td>
<td>0·75</td>
<td>N/A</td>
</tr>
<tr>
<td>Middle tertile (406-829g)</td>
<td>130·6</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Top tertile (830g+)</td>
<td>173·6</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Seafood intake per week (g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bottom tertile (0-238)</td>
<td>133·0</td>
<td>0·04</td>
<td>0·24</td>
</tr>
<tr>
<td>Middle tertile (239-401)</td>
<td>157·5</td>
<td>0·54</td>
<td>N/A</td>
</tr>
<tr>
<td>Top tertile (402+)</td>
<td>165·8</td>
<td>0·97</td>
<td>N/A</td>
</tr>
<tr>
<td>Meat and poultry intake per week (g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bottom tertile (0-628)</td>
<td>140·6</td>
<td>0·04</td>
<td>0·24</td>
</tr>
<tr>
<td>Middle tertile (629-821)</td>
<td>154·9</td>
<td>0·97</td>
<td>N/A</td>
</tr>
<tr>
<td>Top tertile (822+)</td>
<td>167·8</td>
<td>0·75</td>
<td>N/A</td>
</tr>
<tr>
<td>Egg consumption (n)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Once/fortnight or less (n=32)</td>
<td>118·7</td>
<td>0·04</td>
<td>0·24</td>
</tr>
<tr>
<td>Once/week or more (n=68)</td>
<td>165·8</td>
<td>0·54</td>
<td>N/A</td>
</tr>
<tr>
<td>Goitrogen intake per week (g)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bottom tertile (0-333)</td>
<td>147·7</td>
<td>0·97</td>
<td>N/A</td>
</tr>
<tr>
<td>Middle tertile (334-640)</td>
<td>158·4</td>
<td>0·75</td>
<td>N/A</td>
</tr>
<tr>
<td>Top tertile (641+)</td>
<td>137·6</td>
<td>0·97</td>
<td>N/A</td>
</tr>
<tr>
<td>Iodised salt use</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes (n = 4)</td>
<td>184·0</td>
<td>0·75</td>
<td>N/A</td>
</tr>
<tr>
<td>No (n = 96)</td>
<td>151·2</td>
<td>0·04</td>
<td>0·24</td>
</tr>
</tbody>
</table>
*Age-and-sex adjusted iodine-to-creatinine ratio on the basis of an expected daily urinary creatinine excretion of 1.23 g/day.

†Results from ANOVA on log-transformed estimated 24-hr iodine excretion.

‡ Adjusted $P$ value from General Linear Model (GLM) with variables: maternal age, supplement use, milk, seafood and egg intake. N/A: Variable not entered into multivariate analyses.
Figure 1 Iodine status of women by use of iodine-containing supplements. UIC significantly higher in women taking an iodine-containing supplement ($P<0.0001$) than in non-users (analysis on log-transformed data).

Figure 2 Adjusted geometric means (95% CI) of estimated 24-hr iodine excretion (computed by back-transformation of the log-transformed 24-hr iodine excretion) by maternal milk intake [variables included in the model: frequency of egg intake, maternal age (yrs), use of iodine-containing supplement, tertiles of weekly seafood intake (g)]. Dashed line represents the expected value (225 µg) in a 24-hr iodine excretion if 250 µg iodine (the dietary requirement for pregnant women) were consumed/day of which 90% was excreted.
WHO (2007) adequate range for population median iodine concentration in pregnancy

** $P < 0.001$
Daily maternal milk intake

Geometric mean (95% CI) estimated 24-hr iodine excretion (µg/g)

- None
- Less than <140 mL
- 140-280 mL
- More than 280 mL

- Estimated values for each category are shown with error bars representing the 95% confidence interval.