Similarities and differences of dietary and other determinants of iodine status in pregnant women from three European birth cohorts.

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Abstract

Purpose: As a component of thyroid hormones, adequate iodine intake is essential during pregnancy for fetal neurodevelopment. Across Europe, iodine deficiency is common in pregnancy, but data are lacking on the predictors of iodine status at this life stage. We, therefore, aimed to explore determinants of iodine status during pregnancy in three European populations of differing iodine status.

Methods: Data were from 6566 pregnant women from three prospective population-based birth cohorts from the United Kingdom (ALSPAC, n=2852), Spain (INMA, n=1460), and the Netherlands (Generation R, n=2254). Urinary iodine-to-creatinine ratio (UI/Creat, µg/g) was measured in spot-urine samples in pregnancy (≤18-weeks gestation). Maternal dietary intake, categorised by food groups (g/day), was estimated from food-frequency questionnaires (FFQs). Multivariable regression models used dietary variables (energy-adjusted) and maternal characteristics as predictors of iodine status.

Results: Median UI/Creat in pregnant women of ALSPAC, INMA, and Generation R was 121, 151, and 210 µg/g, respectively. Maternal age was positively associated with UI/Creat in all cohorts ($P<0.001$), while UI/Creat varied by ethnicity only in Generation R ($P<0.05$). Of the dietary predictors, intake of milk and dairy products (per 100 g/day) was positively associated with UI/Creat in all cohorts [ALSPAC ($B=3.73$, $P<0.0001$); INMA ($B=6.92$, $P=0.002$); Generation R ($B=2.34$, $P=0.001$)]. Cohort-specific dietary determinants positively associated with UI/Creat included fish and shellfish in ALSPAC and INMA, and eggs and cereal/cereal products in Generation R.

Conclusions: The cohort-specific dietary determinants probably reflect not only dietary habits but iodine-fortification policies; hence public-health interventions to improve iodine intake in pregnancy need to be country-specific.

Introduction

Iodine is an essential component of the thyroid hormones which are important for optimal fetal and early postnatal neurodevelopment [1,2]. Mild-to-moderate maternal iodine deficiency in early pregnancy has been associated with suboptimal offspring cognitive outcomes [3–7]. The early stages of pregnancy mark the beginning of crucial fetal brain development processes such as neuron proliferation, migration, and differentiation [8]. Though these early processes are thyroid hormone-dependent, the fetal thyroid gland is not fully functional until 18-20 weeks, highlighting the importance of thyroid hormone supply from the mother. In this critical early period, the mother, therefore, needs sufficient iodine intake to maintain optimal thyroid function [1]. As a result of the increased demand for thyroid hormones and other physiological changes associated with pregnancy, pregnant women have a higher iodine requirement than the general population, putting them at greater risk of deficiency [9,10].

As more than 90% of the dietary iodine absorbed is excreted by the kidneys, urinary iodine concentration (UIC) is considered to be a good estimate of recent iodine intake at the population level [11]. In pregnant populations, iodine sufficiency is defined by a median UIC in the range of 150-249 µg/L, corresponding to the iodine intake of 250 µg/day recommended by the World Health Organisation (WHO) [12].

Determining the main food sources of iodine in pregnancy is essential, so that pregnant women can be given information on how to achieve adequate iodine nutrition. Although good food sources of iodine, such as milk, eggs, fish, and, in some countries, iodised salt, are well-known, the consumption patterns of these foods vary between and within populations, as does their iodine content (i.e., as a result of seasonal variation, agricultural practices, and differences in iodine content of soil and water) [13,14]. Consequently, some variation in the importance of different iodine food sources to population iodine status is expected between countries; hence universal dietary recommendations to increase iodine intake are unlikely to be appropriate.

Considering the negative consequences of iodine deficiency in pregnancy and the fact that many pregnant women worldwide are still iodine-deficient [15], achieving adequate iodine status in the pregnant population is of public-health importance. Data are, however, lacking on the determinants of iodine status in pregnancy in both deficient and sufficient areas; knowledge of such factors would help to identify women likely to have low iodine status.

This study aimed to explore the determinants of iodine status during early pregnancy in three European populations of differing iodine status. The objectives of the study were: (i) to establish whether iodine status during early pregnancy is associated with maternal socio-demographic, anthropometric, lifestyle factors, and pregnancy characteristics; (ii) to determine how maternal iodine status is influenced by dietary intake during pregnancy; (iii) to identify similarities and differences in the main determinants of iodine status between deficient and sufficient pregnant populations.

Methods

Study population

Data from three prospective population-based birth cohorts were used: (i) the Avon Longitudinal Study of Parents and Children (ALSPAC) in the United Kingdom (UK) [16,17]; (ii) Generation R in the Netherlands [18]; and (iii) INfancia y Medio Ambiente (INMA) in Spain [19]. In ALSPAC, 14541 pregnant women living in the former Avon area in the South West of England, with an expected delivery date between 1st April 1991 and 31st December 1992, were recruited. The study website contains details of all the data that are available through a fully searchable data dictionary and variable search tool [20]. In Generation R, 9778 mothers residing in Rotterdam with an expected delivery date from April 2002 to January 2006 were enrolled in the study. In total, 2150 pregnant women were recruited as part of the INMA Project from three regions in Spain (Valencia, Sabadell, and Gipuzkoa), in the period of November 2003 to January 2008.

Ethics

Ethical approval was obtained prior to recruitment from a number of bodies: the ALSPAC Ethics and Law Committee and the Local Research Ethics Committees (ALSPAC), the Medical Ethical Committee of the Erasmus Medical Centre (Generation R), the Ethical Committee of the Municipal Institute of Medical Investigation and the ethical committees of the hospitals involved in the studies (INMA). All participating women provided informed consent.

Selection criteria for the current study

Women were selected for the current study if they had at least one pre-existing measure of urinary iodine concentration in pregnancy [4,21,22] or urine samples available for iodine measurement, provided that the child had a measure of intelligence quotient (IQ) for ALSPAC and Generation R. In INMA, iodine was measured in all women with additional urine samples available, irrespective of child-IQ data.

Women with multiple pregnancies, in-vitro fertilisation, known thyroid disease, and/or use of thyroid-related medication were excluded (Fig. 1). We restricted analyses to measures from early pregnancy, the most critical time for iodine-dependent brain development [2,23]; hence, for this study, only samples collected ≤ 18 weeks' gestation were included.

Iodine measurements

Urinary iodine concentration (UIC, μg/L) was measured in spot-urine samples collected at a median (25-75th percentile) gestational age of 11.0 (8.0-15.0) weeks in ALSPAC, 13.1 (12.1-14.6) weeks in Generation R, and 13.0 (12.4-13.9) weeks in INMA. Gestational week was established using ultrasound examination (Generation R and INMA) or the date of the last menstrual period (ALSPAC). To adjust for variation in intra- and inter-individual daily

hydration status [24–27], iodine concentration was corrected by dividing by urinary creatinine concentration to give the iodine-to-creatinine ratio (UI/Creat, µg/g). Correcting UIC by use of urinary creatinine concentration reduces intra-individual variation [25], especially in cohorts of the same sex and age-range [i.e., our cohorts were all women of childbearing age (15-44 years)]. The iodine-to-creatinine ratio has previously been used in all three cohorts [4,7,21].

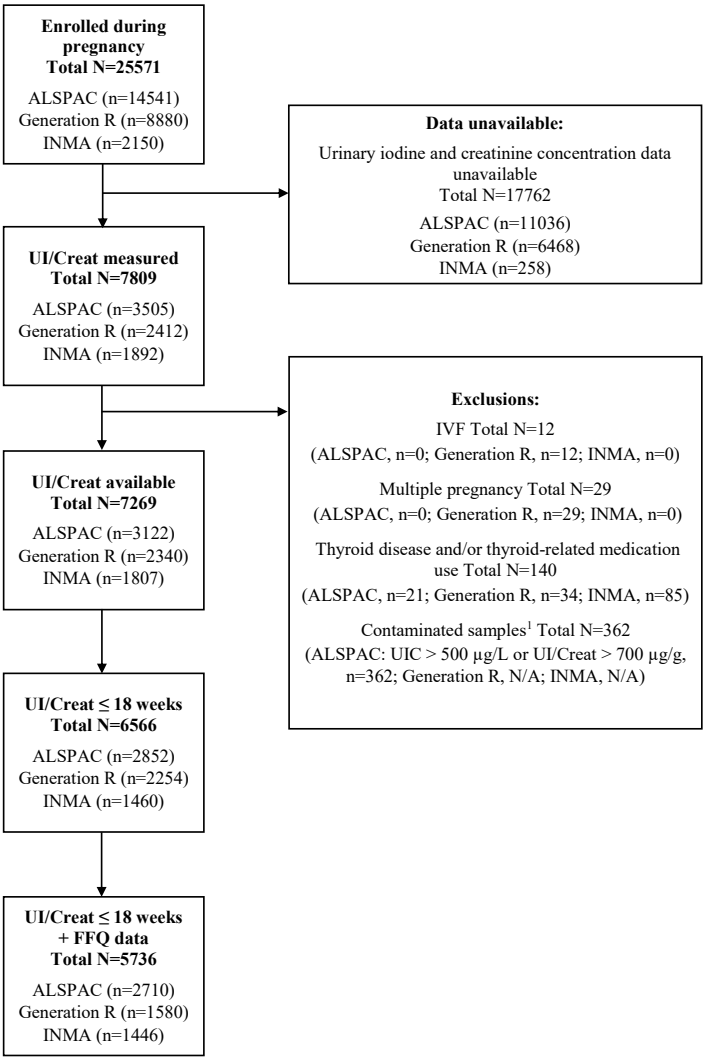

Fig. 1 Flow chart of the study population selection.

[a] Urine samples with UIC > 500 µg/L or UI/Creat > 700 µg/g were excluded only from the ALSPAC cohort, as there was a concern about contamination by the use of iodine-containing test strips (see methods). There was no such concern in Generation R and INMA; therefore, the exclusion criteria were not applicable to urine samples from these two cohorts. FFQ, food frequency questionnaire; IVF, in-vitro fertilisation; N/A, not applicable; UI/Creat, urinary iodine-to-creatinine ratio; UIC, urinary iodine concentration.

In each cohort, we reported both the median (25-75th percentile) UIC (µg/L) and UI/Creat (µg/g). The percentage with UI/Creat <150 µg/g was also reported; this cut-off was informed by the WHO threshold for adequacy in pregnancy (a median UIC ≥150 µg/L) [12] and, when corrected for creatinine concentration, has been used in previous research [4,6,7].

Laboratory analysis

Urinary creatinine concentration was determined by the Jaffe rate method in all cohorts. Urinary iodine concentration was determined as previously described in detail [4,22]; a brief description follows.

ALSPAC: urinary iodine concentration was measured as ^{127}I at the Trace Element Unit, Southampton General Hospital, on a dynamic reaction cell inductively coupled plasma mass spectrometer (NexION 300D Perkin-Elmer, Beaconsfield). The accuracy of the results was verified using the certified reference material (CRM) Seronorm urine Levels 1 and 2 (Nycomed, Norway), and accuracy was also monitored by measurement of EQUIP samples at regular intervals throughout the analysis. Within-run precision gave a relative standard deviation (RSD) of 0.8% at 42 µg/L, 2.5% at 84 µg/L, 0.6% at 149 µg/L, and 2.0% at 297 µg/L. Between-run precision was 8.7% RSD at 42 µg/L, 6.5% at 84 µg/L, 7.2% at 149 µg/L, and 6.8% at 297 µg/L.

Generation R: urinary iodine concentration was measured in Radboud University Medical Centre, Nijmegen, the Netherlands, by the Sandell-Kolthoff method. Iodine calibration was performed using the CRM Seronorm urine Levels 1 and 2 (Nycomed, Norway) and four EQUIP samples that were certified for urinary iodine concentration (Centers for Disease Control and Prevention, USA). At a level of 216 µg/L, the within-assay precision was 5.1% RSD and the between-assay precision was 14.3% RSD (n= 30).

INMA: urinary iodine concentration was measured at the Public Health Laboratory Standards, Basque Government Department of Health, Spain (*Acreditation LE/1108 with ISO 15189 for Clinical Laboratories, National Acreditation Entity*), using a paired-ion reversed-phase, high-performance liquid chromatography with electrochemical detection at a silver-working electrode (Waters Chromatography, Milford, MA). The accuracy of the results was verified using the CRM Seronorm urine Levels 1 and 2 (Nycomed, Norway) and internal quality control samples. Within-run precision was 4.5% RSD at 50 µg/L, 3.2% at 100 µg/L, and 2.0% at 300 µg/L. Between-run precision was 7.9% RSD at 50 µg/L, 3.5% at 100 µg/L, and 2.5 % at 300 µg/L.

In ALSPAC, there was concern that some urine samples had been contaminated by the use of iodine-containing test strips [28], and therefore, samples with UIC >500 µg/L and/or UI/Creat >700 µg/g were excluded (n=412, 11.8%). These cut-offs were based on previous information from ALSPAC and from other studies of UK pregnant women [4,29,30]. Some ALSPAC women had multiple urine samples and in cases, where one sample was contaminated, the results from the next available uncontaminated sample were used (n=50).

Dietary assessment

Maternal diet in all cohorts was assessed using a food-frequency questionnaire (FFQ). This was administered in late pregnancy in ALSPAC (at 32 weeks) and in early pregnancy in Generation R and INMA (at the same time as urine sampling). The FFQ was unquantified in ALSPAC, but was semi-quantitative (SFFQ) in Generation R and INMA. The FFQ was self-administered in ALSPAC and Generation R, and administered by trained interviewers in INMA.

ALSPAC: Detailed information about the design of the questionnaire can be found elsewhere [31,32]. Briefly, women were asked to indicate how frequently "nowadays" they consumed 43 food groups and individual foods with five predefined frequency categories, ranging from "never or rarely" to "more than once a day". Portion sizes were not included in the questionnaire.

Generation R: SFFQ in Generation R represented an adapted version of a validated SFFQ in elderly subjects [33]. In summary, it contained a list of 293 foods and asked about frequency of consumption in the past three months, mostly, therefore, reflecting the first trimester. Questions about portion size, estimated using food photographs or Dutch household measures, methods of preparation, and additions to foods were also included [3,34]. The food list had previously been reduced to 17 main food groups [35], based on the European Prospective Investigation into Cancer and Nutrition SOFT classification (EPIC-SOFT) [36].

INMA: SFFQ was based on an expanded adaptation of a 61-item SFFQ by Willet and colleagues [37] that was developed and validated [38,39]. To summarise, women were asked how often, on average, they had consumed a specified standard portion of 100 food items in early pregnancy (since their last menstrual period until the time of the interview at ~12 weeks), using nine frequency categories, ranging from "never or less than once a month" to "six or more times per day".

For the current study, in each cohort, food intake (g/day) was calculated by multiplying the frequency of consumption by an average standard portion (for the ALSPAC FFQ) or a specified portion (for the SFFQ in Generation R and INMA) of that food. Foods were then classified into food groups and the amounts of individual food items consumed were summed accordingly. To facilitate comparison between cohorts, the classification of food groups used in Generation [36] was used as a template. This required the formation of new food groups in ALSPAC, while the pre-existing food groups were used in Generation R and INMA, with some minor modifications to make them comparable. The definitions of food groups in the individual cohorts are shown in Supplemental Table 1. Separate information about the consumption of table salt and use of iodine-fortified table salt was collected only in the INMA cohort.

Iodine supplement use

Detailed data on the use of potassium iodide and/or iodine-containing multivitamin/mineral supplements during pregnancy were collected only in INMA. For this analysis, we used data on iodine supplements from pre-pregnancy until the end of the first trimester, expressed as mean iodine intake from supplements. In our ALSPAC sample, only two women took a kelp supplement and one took a potassium-iodide supplement; they were excluded from the analysis. Data on the use of iodine-containing multivitamin supplements from preconception until enrolment (at time of urine sample collection) were available only for a sub-set of our Generation R sample (n=381); women who took an iodine-containing supplement (n=345) were excluded in sensitivity analyses.

Maternal and pregnancy characteristics

Information on pregnancy characteristics, anthropometrics, socio-demographic, and environmental exposures was collected by means of questionnaires or extracted from obstetric medical records. Discrete variables were re-categorised, where possible, to facilitate comparisons between cohorts. Exposure factors in these analyses can be classified into three groups: (i) maternal factors: maternal age (ALSPAC: at last menstrual period; Generation R, INMA: at urine collection); pre-pregnancy body mass index (BMI, kg/m^2); ethnicity (ALSPAC: White/non-white; Generation R: Dutch/non-Dutch, where non-Dutch = Indonesian, Cape Verdean, Moroccan, Dutch Antilles, Surinamese, Turkish, other non-Western, Asian, other Western; INMA: Spanish/non-Spanish, where non-Spanish = Latin American, European, others); parity (zero, one, two or more); smoking status (never smoked, smoked initially or until pregnancy was known, continued smoking); and alcohol consumption during pregnancy (yes/no); (ii) markers of socio-economic status: education level (ALSPAC: low = no qualification, certificate of secondary education, or vocational; medium = O level or A level; high = a degree; Generation R: low = no education or primary; medium = secondary phase 1 and 2; high = higher phase 1 and 2; INMA: low = no education, unfinished primary, or primary; medium = secondary; high = university degree); monthly net household income (Generation R: low <€1200, medium = €1200-2200, high >€2200); home ownership (ALSPAC: owned/mortgaged, private/other rented, council rented); crowding index (ALSPAC: ≤1 person per room, +1 person per room); family adversity index [ALSPAC: 18-item measure of hardships during pregnancy [40], categorised into: no adversities, mild (0-2), severe (≥3) [41]]; life event score (ALSPAC: exposure to stressful situations during pregnancy); marital status (ALSPAC: never married, married, other; Generation R: unmarried/married); and living with father's child/partner (ALSPAC, INMA: yes/no); and (iii) child factors: child's sex (male/female).

Statistical analyses

To study the associations of maternal characteristics and diet with iodine status, we used UI/Creat as a measure of individual iodine status. UI/Creat was not normally distributed

but right-skewed. To meet parametric-test assumptions, UI/Creat was transformed using the natural logarithm. Outliers were assessed by visual inspection of box-plots. We assessed non-linearity of the associations of each continuous independent variable with UI/Creat by adding their squared term to the regression models, and also by plotting each potential determinant variable against UI/Creat and comparing the fit (R^2) of a linear *vs.* quadratic function through the data points.

Multiple linear regression models with log-transformed UI/Creat as the dependent variable were performed for each cohort using two models: Model 1 included maternal and pregnancy factors, markers of socio-economic status and child's sex as independent variables; Model 2 included variables from Model 1 plus dietary intake of food groups.

Analyses of the dietary influences on UI/Creat (Model 2) were also adjusted for estimated energy intake (kcal/day). Effect estimates (unstandardised B coefficients) for food groups were expressed per 100 g and also per portion (g). The increase in the geometric mean of UI/Creat per 100 g and per portion increase in intake and its 95% confidence interval (CI) were calculated by back-transformation [exponentiation (EXP)] of the effect estimates and 95% CIs from logarithmic scale. The following formulae were used for the back-transformations: effect estimate per 100 g = EXP (intercept + *B* * 100) – EXP (intercept); lower 95% CI = EXP [intercept + (*B* * 100) – (1.96 * standard error of estimate (SEE) *100)] – EXP (intercept); and upper 95% CI = EXP [intercept + (*B* * 100) + (1.96 * SEE * 100)] – EXP (intercept). For calculations per portion size, the multiplication by 100 in the formulae is replaced with the portion size (g) for each food group accordingly. When calculating the effect estimates from Model 2, all categorical covariates were set to their reference group and the continuous covariates gestational week, maternal age, BMI, and energy intake were centered to their means.

We conducted four types of sensitivity analyses: (i) under-reporting: to account for potential under-reporting of energy intake in Model 2, in all cohorts, we excluded women with energy intakes below the 5th percentile; (ii) iodine supplements: we adjusted Model 2 for iodine-supplement use in INMA (as the only cohort with complete iodine-supplement data) and excluded iodine-supplement-users in Generation R (as data were available only for a sub-set of the sample); (iii) gestational age: as the median gestational week at urine sampling was later in INMA and Generation R than in ALSPAC, we performed sensitivity analyses to test the associations with iodine status in the first trimester, using samples collected up to 13 weeks; and (iv) covariate creatinine-adjustment method: since age, BMI, and ethnicity are known predictors of urinary creatinine concentration [42] and urinary creatinine can also vary during gestation [43], this could result in spurious associations of these variables with the ratio of UI/Creat; we, therefore, performed sensitivity analyses for these variables (BMI, age, ethnicity, and gestational age) using Model 1 and 2 with the (natural) log-transformed UIC (µg/L) unadjusted for creatinine as our dependent variable and added creatinine concentration as a separate independent variable to the models. This method has been recommended previ-

ously [42] and ensures that UIC is adjusted for dilution by creatinine concentration, while the associations of the other variables with UIC are independent of urinary creatinine.

All analyses were conducted using multiply-imputed data to account for missing data on socio-demographic variables. Multiple imputation was performed using the automatic method in SPSS. A total of 20 datasets were generated and analysed using standard multiple imputation procedures [44]. Detailed information about the imputed variables is provided in the Electronic Supplementary Material. Missing FFQ data were not imputed, as diet has a wide inter-person variability hence imputation of dietary data would not be sufficiently accurate. All statistical analyses were performed with IBM SPSS Statistics version 24.0 (IBM Corp., Armonk, NY, USA). Values were considered statistically significant at $P<0.05$.

Results

Sample characteristics

After exclusions, the final study population comprised 6566 pregnant women: 2852 from ALSPAC, 2254 from Generation R, and 1460 from INMA (Fig. 1). Descriptive statistics of mothers by cohort are shown in Table 1. Maternal age varied across cohorts, with women in ALSPAC having a lower mean ± standard deviation (SD) age than women in INMA [28.7 (±4.5) vs. 31.4 (±4.1) years, respectively]. Median BMI was within the healthy range in all cohorts (Table 1). The majority of mothers defined themselves as White in ALSPAC (98.2%), Spanish in INMA (91.8%), while slightly more than half of the women in Generation R said they were non-Dutch (51.4%). Most women were nulliparous and non-smokers, with similar proportions between cohorts.

Iodine status

The median UI/Creat (25-75th percentile) was 121 (81-193) µg/g in women from the UK (62.8% <150 µg/g), 151 (96-255) µg/g in women from Spain (49.5% <150 µg/g), and 210 (140-303) µg/g in women from the Netherlands (28.8% <150 µg/g) (Table 2).

Association with socio-demographic and lifestyle factors

In multivariable models (adjusted Models 1 and 2), gestational week of urine sample, maternal age, and BMI were associated with UI/Creat in all three cohorts. Gestational week at urine sampling (≤18 weeks) was positively associated with UI/Creat in ALSPAC ($B=0.051$, $P<0.0001$) but not in the other two cohorts (Table 3). However, in sensitivity analyses restricted to samples collected up to 13 weeks, there was an association of gestational week with UI/Creat in all three cohorts (ALSPAC: $B=0.029$, $P<0.001$, n=1951; Generation R: $B=0.031$, $P=0.049$, n=1094; INMA: $B=0.079$, $P=0.045$, n=747) with a larger effect size in Generation R and INMA than in the analyses up to 18 weeks. In the sensitivity analysis

using covariate creatinine-adjustment, the results for the association of gestational week up to 18 weeks with UIC did not substantially differ from those with UI/Creat in ALSPAC and INMA, while in Generation R, the effect size was higher, reaching statistical significance (Supplemental Table 3).

There was a positive association of maternal age with UI/Creat (ALSPAC: B=0.014, P<0.0001; Generation R: B=0.018, P<0.0001; INMA: B=0.020, P=0.0001). After further adjusting for maternal diet and energy intake estimated from the FFQs (Model 2), the effect size of age was attenuated by 16-30% across cohorts, but remained statistically significant (Table 3). The positive association with age remained in all cohorts, except in Model 2 for ALSPAC, when using the covariate creatinine-adjustment method of UIC (Supplemental Table 3).

There was a negative association of BMI with UI/Creat (ALSPAC: B= -0.013, P=0.0001; Generation R: B= -0.011, P<0.0001; INMA: B= -0.013, P=0.005), which, after adjustment for maternal diet and energy intake remained statistically significant (Table 3, Model 2). However, BMI was not associated with UIC (μg/L) with the covariate creatinine-adjustment method in Generation R and INMA but remained negatively associated with UIC in ALSPAC, though with a lower effect size (Supplemental Table 3).

Cohort-specific socio-demographic and lifestyle factors were identified as determinants of iodine status. In Generation R, maternal ethnicity and smoking were associated with UI/Creat (Table 3). Compared to the Dutch women, Moroccan, Turkish and other non-Western women had a higher UI/Creat, whereas Surinamese and those from the Dutch Antilles had a lower UI/Creat. Some of these effects were attenuated after accounting for maternal diet in Model 2 (Table 3). Similarly to UI/Creat, UIC (with covariate creatinine-adjustment) also differed by ethnicity; Moroccan, Turkish and other non-Western women still had a significantly higher UIC than the Dutch, while the UICs of Surinamese and Dutch Antilles women did not significantly differ from those of the Dutch women (Supplemental Table 3). Generation R women who reported smoking vs. those who never smoked had a lower UI/Creat, which remained statistically significant after adjustment for maternal diet (Table 3, Model 1 and 2). In ALSPAC, family adversity index (severe *vs.* none; B= -0.100, P=0.016), and marital status (married vs. never-married; B=0.095, P=0.015) were associated with UI/Creat, even after adjusting for maternal diet (Table 3). Results for all predictors included in the multivariable models are presented in Supplemental Table 2.

Dietary influences on iodine status

As not all women with urinary iodine measurements before 18 weeks had also completed an FFQ, numbers for these analyses were lower for all cohorts (Fig. 1): ALSPAC (n=2710), Generation R (n=1580), INMA (n=1446). Descriptive statistics of dietary intakes of food groups for pregnant women in each cohort are presented in Supplemental Table 4.

Table 1 Descriptive statistics [a] of the study population by cohort.

Sample characteristics	ALSPAC (n=2852)	Generation R (n=2254)	INMA (n=1460)
Maternal factors			
Age [b,c] (years), mean (±SD)	28.7 (±4.5)	29.9 (±5.0)	31.4 (±4.1)
Pre-pregnancy BMI (kg/m^2), median (IQRs) [c]	22.3 (20.5 - 24.6)	23.5 (21.5 - 26.4)	22.5 (20.8 - 25.0)
Ethnicity [d], n (%)			
Reference group	2800 (98.2)	1095 (48.6)	1340 (91.8)
Non-white	52 (1.8)	N/A	N/A
Non-Dutch	N/A	1159 (51.4) [e]	N/A
Non-Spanish	N/A	N/A	120 (8.2)
Parity [c], n (%)			
0	1354 (47.5)	1279 (56.7)	806 (55.2)
1	965 (33.8)	665 (29.5)	544 (37.3)
≥ 2	533 (18.7)	310 (13.8)	110 (7.5)
Smoking status, n (%)			
Never smoked	2169 (76.1)	1671 (74.2)	1020 (69.9)
Stopped smoking	333 (11.7)	211 (9.3)	187 (12.8)
Continued smoking	350 (12.2)	372 (16.5)	253 (17.3)
Alcohol consumption, n (%)			
No	1350 (47.4)	1458 (64.7)	1330 (91.1)
Yes	1502 (52.6)	796 (35.3)	130 (8.9)
Markers of socio-economic status			
Education level, n (%)			
Low	576 (20.2)	247 (11.0)	337 (23.1)
Medium	1780 (62.4)	995 (44.1)	581(39.8)
High	496 (17.4)	1012 (44.9)	542 (37.1)
Net household income (€ per month), n (%)			
Low < €1200	N/A	492 (21.8)	N/A
Medium €1200-2200	N/A	597 (26.5)	N/A
High > €2200	N/A	1165 (51.7)	N/A
Home ownership, n (%)			
Owned/mortgaged	2425 (85.0)	N/A	N/A
Private/other rented	236 (8.3)	N/A	N/A
Council rented	191 (6.7)	N/A	N/A
Crowding index, n (%)			
≤ 1 person per room	2747 (96.3)	N/A	N/A
+ 1 person per room	105 (3.7)	N/A	N/A
Family adversity index, n (%)			
None 0	1395 (48.9)	N/A	N/A
Mild 1-2	1124 (39.4)	N/A	N/A
Severe > 3	333 (11.7)	N/A	N/A

Table 1 Descriptive statistics [a] of the study population by cohort. (continued)

Sample characteristics	ALSPAC (n=2852)	Generation R (n=2254)	INMA (n=1460)
Life event score, median (IQRs)	3.0 (2.0 - 5.0)	N/A	N/A
Marital status, n (%)			
Never-married	355 (12.5)	1136 (50.4)	N/A
Married	2357 (82.6)	1118 (49.6)	N/A
Other [f]	140 (4.9)	N/A	N/A
Living with a partner, n (%)			
Yes	2720 (95.4)	N/A	1445 (99.0)
No	132 (4.6)	N/A	15 (1.0)
Child factors			
Child's sex [c], n (%)			
Male	1405 (49.3)	1147 (50.9)	737 (50.5)
Female	1447 (50.7)	1107 (49.1)	723 (49.5)

[a] Data presented as mean (±SD) for continuous normally distributed variables, median (IQRs) for continuous non-normally distributed variables and n (%) for categorical variables.

[b] Maternal age at urine sample collection, except in ALSPAC (age at last menstrual period).

[c] Data were not imputed, due to no missing values for age (in ALSPAC, Generation R), pre-pregnancy BMI (INMA), parity (Generation R) and child's sex (ALSPAC). The rest of the data are shown after imputation of the missing values (see methods).

[d] ALSPAC (Reference group=White); Generation R (Reference group=Dutch, Non-Dutch=Indonesian, Cape Verdean, Moroccan, Dutch Antilles, Surinamese, Turkish, Other non-Western, Asian, or other Western, see Table 3); INMA (Reference group=Spanish, Non-Spanish=Latin American, European, or Others).

[e] Non-Dutch group in Generation R presented in detail in Table 3.

[f] ALSPAC (Other=widowed, divorced, or separated).

Abbreviations: BMI, body mass index; IQRs, interquartile ranges; N/A, data not available or not applicable; SD, standard deviation.

Table 2 Urinary iodine status in early pregnancy (≤ 18 gestational weeks) expressed as UIC, UI/Creat and proportion of mothers with UI/Creat below 150 µg/g.

	ALSPAC (n=2852)	Generation R (n=2254)	INMA (n=1460)
Gestational age at urine sampling, weeks [a]	11.0 (8.0 - 15.0)	13.1 (12.1 - 14.6)	13.0 (12.4 - 13.9)
Urinary iodine concentration (UIC), µg/L [a]	95 (56 - 151)	165 (94 - 277)	130 (76 - 219)
Iodine-to-creatinine ratio (UI/Creat), µg/g [a]	121 (81 - 193)	210 (140 - 303)	151 (96 - 255)
UI/Creat < 150 µg/g, n (%)	1792 (62.8)	650 (28.8)	723 (49.5)

Abbreviations: UI/Creat, urinary iodine-to-creatinine ratio; UIC, urinary iodine concentration.

[a] Data presented as median (25^{th} - 75^{th} percentiles).

Table 3 Determinants [a] of urinary iodine-to-creatinine ratio measured at ≤ 18 gestational weeks, statistically significant in at least one cohort.

Determinants	ALSPAC (n=2852)						Generation R (n=2254)						INMA (n=1460)					
	Adjusted Model 1 [b]			Adjusted Model 2 [c]			Adjusted Model 1 [b]			Adjusted Model 2 [c]			Adjusted Model 1 [b]			Adjusted Model 2 [c]		
	n	*B*	*P*	*n*	*B*	*P*	*n*	*B*	*P*	*n*	*B*	*P*	*n*	*B*	*P*	*n*	*B*	*P*
Gestational age at urine sampling, weeks	2852	0.051	<0.001	2710	0.052	<0.001	2254	0.007	0.300	1580	0.011	0.133	1460	0.004	0.755	1446	-0.009	0.513
Age [d], years	2852	0.014	<0.001	2710	0.010	0.002	2254	0.018	<0.001	1580	0.015	<0.001	1460	0.020	<0.001	1446	0.014	0.008
Pre-pregnancy BMI, kg/m^2	2852	-0.013	<0.001	2710	-0.012	<0.001	2254	-0.011	<0.001	1580	-0.013	<0.001	1460	-0.013	0.005	1446	-0.010	0.033
Family adversity index																		
None 0	1395	Ref.		1334	Ref.		N/A	.	.	.	.	.	N/A	.	.	.	.	.
Mild 1-2	1124	-0.007	0.765	1069	-0.003	0.906	N/A	.	.	.	.	.	N/A	.	.	.	.	.
Severe > 3	333	-0.100	0.016	307	-0.086	0.046	N/A	.	.	.	.	.	N/A	.	.	.	.	.
Marital status																		
Never-married	355	Ref.		320	Ref.		1136	Ref.		825	Ref.		N/A	.	.	.	.	.
Married	2357	0.095	0.015	2269	0.119	0.003	1118	0.030	0.285	755	0.044	0.168	N/A	.	.	.	.	.
Other [e]	140	0.028	0.666	121	0.051	0.447	N/A	.	.	.	.	.	N/A	.	.	.	.	.
Ethnicity [f]																		
Reference group	2800	Ref.		2674	Ref.		1095	Ref.		930	Ref.		1340	Ref.		1328	Ref.	
Non-white	52	-0.018	0.851	36	0.043	0.676	N/A	.	.	.	.	.	N/A	.	.	.	.	.
Non-Dutch:	N/A	.	.	.	.	.							N/A	.	.	.	.	.
- *Indonesian*	N/A	.	.	.	.	.	72	-0.047	0.494	58	-0.081	0.286	N/A	.	.	.	.	.
- *Cape Verdean*	N/A	.	.	.	.	.	87	-0.013	0.848	41	0.065	0.502	N/A	.	.	.	.	.
- *Moroccan*	N/A	.	.	.	.	.	165	0.255	<0.001	72	0.182	0.028	N/A	.	.	.	.	.
- *Dutch Antilles*	N/A	.	.	.	.	.	65	-0.174	0.025	37	-0.225	0.031	N/A	.	.	.	.	.
- *Surinamese*	N/A	.	.	.	.	.	196	-0.115	0.017	111	-0.160	0.014	N/A	.	.	.	.	.
- *Turkish*	N/A	.	.	.	.	.	226	0.391	<0.001	103	0.360	<0.001	N/A	.	.	.	.	.
- *Other, non-Western*	N/A	.	.	.	.	.	107	0.157	0.011	53	0.125	0.137	N/A	.	.	.	.	.
- *Asian*	N/A	.	.	.	.	.	32	0.091	0.383	19	0.028	0.835	N/A	.	.	.	.	.

- Other, Western	N/A	.	.	.	.	.	209	0.052	0.228	156	0.062	0.213	N/A	.	.	.	.	.
Non-Spanish	N/A	.	.	.	.	.	N/A	.	.	.	.	.	120	-0.016	0.810	118	-0.003	0.961
Smoking status																		
Never smoked	2169	Ref.		2077	Ref.		1671	Ref.		1202	Ref.		1020	Ref.		1011	Ref.	
Stopped smoking	333	-0.003	0.943	312	-0.010	0.797	211	-0.093	0.035	147	-0.121	0.020	187	-0.060	0.296	186	-0.060	0.287
Continued smoking	350	0.018	0.620	321	0.060	0.116	372	-0.008	0.831	231	0.049	0.296	253	-0.001	0.990	249	0.020	0.707

[a] Effect estimates (*B*=unstandardised regression coefficient) and *P*-values from multiple linear regression models performed for each cohort with (natural) log-transformed iodine-to-creatinine ratio (UI/Creat) as the dependent variable and maternal characteristics and dietary intakes as independent variables (for full models, see footnotes b and c). Reported *B* coefficients represent the change in the mean (natural) log of UI/Creat per unit increase in the continuous independent variables and for each category compared to the reference for the categorical independent variables.

[b] Adjusted Model 1 (adjusted for maternal and pregnancy characteristics); ALSPAC (R^2=0.123, $P < 0.0001$): gestational age (weeks), age (years), pre-pregnancy BMI (kg/m^2), ethnicity, parity, smoking status, alcohol consumption, education, home ownership, crowding index, family adversity index, life event score, marital status and child's sex; Generation R (R^2=0.086, $P < 0.0001$): gestational age (weeks), age (years), pre-pregnancy BMI (kg/m^2), ethnicity, parity, smoking status, alcohol consumption, education, net household income, marital status and child's sex; INMA (R^2=0.021, $P < 0.0001$): gestational age (weeks), age (years), pre-pregnancy BMI (kg/m^2), ethnicity, parity, smoking status, alcohol consumption, education, living with a partner and child's sex .

[c] Adjusted Model 2 (adjusted for maternal and pregnancy characteristics + dietary intakes); ALSPAC (R^2=0.147, $P < 0.0001$): Model 1 + energy intake (kcal/day) + intake of vegetables (g/day), fruit (g/day), nuts and seeds (g/day), potatoes (g/day), legumes (g/day), cereals and cereal products (g/day), cakes, confectionery and added sugar (g/day), added fats (g/day), milk and dairy products (g/day), meat and meat products (g/day), eggs (g/day), fish and shellfish (g/day), processed and fried foods (g/day), non-alcoholic beverages (g/day), miscellaneous (g/day); Generation R (R^2=0.091, $P < 0.0001$): Model 1 + energy intake (kcal/day) + intake of vegetables (g/day), fruit (g/day), nuts and seeds (g/day), potatoes (g/day), legumes (g/day), cereals and cereal products (g/day), cakes, confectionery and added sugar (g/day), added fats (g/day), milk and dairy products (g/day), meat and meat products (g/day), eggs (g/day), fish and shellfish (g/day), condiments and seasoning (g/day), processed and fried foods (g/day), non-alcoholic beverages (g/day), alcoholic beverages (g/day), miscellaneous (g/day); INMA (R^2=0.060, $P < 0.0001$): Model 1 + energy intake (kcal/day) + intake of vegetables (g/day), fruit (g/day), nuts and seeds (g/day), potatoes (g/day), legumes (g/day), cereals and cereal products (g/day), cakes, confectionery and added sugar (g/day), added fats (g/day), milk and dairy products (g/day), meat and meat products (g/day), eggs (g/day), fish and shellfish (g/day), condiments and seasoning (e.g., salt) (g/day), processed and fried foods (g/day), non-alcoholic beverages (g/day), alcoholic beverages (g/day).

[d] Maternal age at urine sample collection, except in ALSPAC (age at last menstrual period).

[e] ALSPAC (Other=widowed, divorced, or separated).

[f] ALSPAC (Reference group=White); Generation R (Reference group=Dutch, Non-Dutch=Indonesian, Cape Verdean, Moroccan, Dutch Antilles, Surinamese, Turkish, Other non-western, Asian, or Other western); INMA (Reference group=Spanish, Non-Spanish=Latin American, European, or Others).

Abbreviations: BMI, body mass index; N/A, data not available or not applicable; Ref, reference category; UI/Creat, urinary iodine-to-creatinine ratio.

Table 4 Multivariable associations of food group intakes estimated from FFQ (per portion size, g) [a] with urinary iodine-to-creatinine ratio measured at ≤ 18 gestational weeks, statistically significant in at least one cohort.

Food group	Standard portion (g) [a]	Description [a]	ALSPAC (n=2710)		Generation R (n=1580)		INMA (n=1446)	
			B (95% CI) [b]	*P* [c]	*B* (95% CI) [b]	*P* [d]	*B* (95% CI) [b]	*P* [e]
Fruit	80 g	*a portion '5-a-day'*	2.22 (0.47, 4.03)	0.012	0.90 (-0.90, 2.75)	0.328	-3.51 (-7.16, 0.20)	0.064
Nuts and seeds	30 g	*a handful*	5.08 (-0.63, 11.53)	0.083	12.92 (4.83, 21.73)	0.001	18.63 (-10.61, 52.17)	0.223
Cereals and cereal products	36 g	*a medium slice of bread*	0.51 (-0.33, 1.36)	0.238	4.25 (2.23, 6.31)	<0.001	0.07 (-5.12, 5.40)	0.978
Cakes, confectionery and added sugar	50 g	*a chocolate bar*	2.39 (0.25, 4.63)	0.028	2.64 (-1.13, 6.57)	0.172	-9.19 (-22.95, 5.59)	0.217
Added fats	10 g	*spread on a slice of bread*	1.12 (-0.14, 2.41)	0.082	2.70 (0.39, 5.08)	0.022	-4.19 (-11.03, 2.89)	0.243
Milk and dairy products	200 g	*a glass of milk*	7.77 (5.65, 9.99)	<0.001	4.74 (2.01, 7.56)	0.001	14.07 (5.07, 23.45)	0.002
Meat and meat products	130 g	*a medium portion chicken breast*	1.65 (-2.96, 6.78)	0.497	3.75 (-5.35, 13.87)	0.433	-41.48 (-63.44, -16.20)	0.002
Eggs	50 g	*an average egg*	2.64 (-0.60, 6.12)	0.112	28.10 (12.27, 46.47)	<0.001	39.69 (-6.67, 96.68)	0.099
Fish and shellfish	120 g	*a medium cod fillet*	6.18 (1.07, 11.87)	0.016	2.42 (-19.04, 30.69)	0.845	34.08 (3.28, 69.37)	0.029
Condiments and seasoning (e.g., salt) [f]	5 g	*a level teaspoon (WHO)* [g]	N/A	.	1.34 (-1.50, 4.29)	0.359	214.41 (56.88, 465.35)	0.003

[a] Portion sizes are based on Food Standard Agency (1998) Food Portion Sizes (3ed.) London: TSO.

[b] Effect estimates (*B*=unstandardised regression coefficient) represent the actual change in the geometric mean of UI/Creat (µg/g) associated with a portion size increase in intake of a food group. *B* coefficients and their 95% CIs are calculated by back-transformation from logarithmic scale (see methods). Values are adjusted for dietary intake of other food groups, energy intake and other potential confounders (for full models, see Table 3, footnote c). When calculating the *B* coefficients all categorical covariates were set to their reference group and the continuous covariates gestational age, maternal age, pre-pregnancy BMI and energy intake were centred to their means.

[c] *P*-value adjusted for energy (kcal/day) + gestational age (weeks), age (years), pre-pregnancy BMI (kg/m^2), ethnicity, parity, smoking status, alcohol consumption, education, home ownership, crowding index, family adversity index, life event score, marital status and child's sex (R^2=0.147, $P < 0.0001$).

[d] *P*-values adjusted for energy (kcal/day) + gestational age (weeks), age (years), pre-pregnancy BMI (kg/m^2), ethnicity, parity, smoking status, alcohol consumption, education, net household income, marital status and child's sex (R^2=0.091, $P < 0.0001$).

[e] *P*-values adjusted for energy (kcal/day) + gestational age (weeks), age (years), pre-pregnancy BMI (kg/m^2), ethnicity, parity, smoking status, alcohol consumption, education, living with a partner and child's sex (R^2=0.060, $P < 0.0001$).

[f] In INMA this food group also includes iodised salt. Separate information about the consumption of table salt and use of iodine-fortified table salt was collected only in the INMA cohort.

[g] Maximum daily salt intake, as recommended by WHO (5 g/day salt, or 2 g/day Sodium).

Abbreviations: BMI, body mass index; 95% CI, confidence interval; FFQ, food frequency questionnaire; N/A, data not available; UI/Creat, urinary iodine-to-creatinine; WHO, World Health Organisation.

"Milk and dairy products" was the only food group positively associated with UI/Creat in all three cohorts: ALSPAC (B=3.73, P<0.0001); Generation R (B=2.34, P=0.001); INMA (B=6.92, P=0.002) (Supplemental Table 5). Based on the fully-adjusted models, one-portion increase in consumption of milk and dairy products (e.g., a glass of milk, 200 g) [45] was associated with a 5-14 µg/g increase in the geometric mean of UI/Creat (Table 4). Intake of "fish and shellfish" was positively associated with UI/Creat in pregnant women in Spain (INMA) and the UK (ALSPAC), though the effect size per 100 g was more than five times larger in INMA women (B=28.04, P=0.029 vs. B=5.10, P=0.017).

Cohort-specific dietary determinants were also identified (Table 4). In ALSPAC, consumption of fruit (P=0.012), cakes and confectionery (P=0.028) were positively associated with UI/Creat. Intake of cereals and cereal products (P<0.0001), eggs (P=0.0001), nuts and seeds (P=0.001), and added fat (P=0.022) were all positively associated with UI/Creat in Generation R. Higher salt intake (including iodised salt) (per 1 g) was associated with higher UI/Creat (P=0.003), while increasing meat intake was associated with lower UI/Creat (P=0.002) in INMA.

Excluding women with extremely low energy intakes (< 5th percentile) did not considerably change our results, except for small changes in INMA where the association between fish intake and UI/Creat was borderline significant but the effect size remained relatively unchanged (*data not shown*). In INMA, mean daily iodine-supplement intake was an important determinant of UI/Creat (Standardised B=0.235, P<0.0001). Adjusting for iodine-supplement use in INMA attenuated the result for maternal age (B=0.012, P=0.018), but did not change the rest of the results substantially (*data not shown*). In Generation R, the exclusion of iodine-supplement users resulted in higher effect estimates for some ethnic groups (e.g., Moroccan, Turkish and other Western); the associations between intake of non-alcoholic and alcoholic beverages and UI/Creat reached statistical significance but the effect sizes remained unchanged; the rest of the results remained relatively unchanged (*data not shown*).

Discussion

In this study of pregnant women, several dietary (milk and dairy products) and maternal factors (maternal age, BMI, gestational week) were associated with UI/Creat across all cohorts in adjusted models. Furthermore, important cohort-specific dietary determinants were identified, such as fish intake in ALSPAC (UK), egg and cereal/cereal product intake in Generation R (Netherlands), and fish, salt, and meat intake in INMA (Spain).

The population of pregnant women from the Netherlands was iodine-sufficient, while populations from the UK and Spain were mildly-to-moderately deficient. It should be noted that the ALSPAC median-UIC value, although from samples that are nearly 25 years old,

is almost identical to the UK value from the 2017 Global Scorecard for Iodine Nutrition in pregnant women, i.e., 95 µg/L vs. 99 µg/L [15].

The differences in iodine status between the countries may be partly explained by differing use of iodised salt. The iodised salt penetration rate in households and the food industry (e.g., bread-making) in the Netherlands has been estimated as 60% and 70%, respectively, while a 16% penetration rate has been reported in Spanish households [46]. By contrast, iodisation of salt was never common in the UK [47], and even nowadays, its availability is very limited (21.5%); furthermore, the iodine concentration of the major UK brand is low [48].

Association with socio-demographic and lifestyle factors

Gestational week of urine samples was positively associated with a UI/Creat in ALSPAC but not in the other cohorts. This may be because ALSPAC samples were collected at an earlier gestational age than in the other cohorts; if the greatest increase in urinary iodine excretion is in the first weeks of pregnancy, the effect of gestational age may be attenuated in later samples (i.e., up to 18 weeks as in our study). Indeed, in sensitivity analyses, when we restricted analysis to samples collected up to 13 weeks, the effect size was higher in the other two cohorts. The positive association between gestational week of urine sample with UI/Creat in early pregnancy could be attributed to an increase in glomerular filtration rate and subsequent renal iodine loss in early pregnancy [49,50], though data are conflicting as studies report both an increase and a decrease in the UI/Creat [51–54]. As urinary iodine excretion in early vs. late pregnancy stages might be higher as a result of increased renal clearance of iodine, using early measurement to assess status might overestimate true intake [55]. Creatinine clearance has also been shown to vary during gestation [43], which could have biased our results when using UI/Creat. However, gestational week was also positively associated with UIC (µg/L) alone when including creatinine separately in the model.

In all three cohorts, BMI was negatively associated with UI/Creat. In a study in non-pregnant adults [56], creatinine clearance was positively associated with BMI, independent of adiposity, and a positive association with lean thigh-tissue area was reported; this suggests that the association of creatinine with BMI might be explained by lean body mass. The negative association between BMI and UI/Creat that we report may therefore be partly explained by the use of creatinine adjustment and may highlight potential issues with the use of this measure of iodine status [42,57]. Indeed, in sensitivity analysis, we did not find an association of BMI with UIC alone in two of the cohorts when we adjusted for creatinine by including it as a covariate in the model instead of using the ratio of UI/Creat.

There was a positive association of maternal age with UI/Creat in all cohorts. Age was still significantly associated with UI/Creat after adjustment for dietary intake though the effect size was attenuated; it was further reduced when iodine-supplement use in INMA was accounted for, suggesting that some of the effect of age could be explained by diet and supplement use in older women. Similarly to BMI, age is a known predictor of urinary creatinine [42]. However,

in sensitivity analysis when adjusting for creatinine separately in the model, unlike BMI, age remained positively associated with UIC but with a lower effect size.

The iodine status of pregnant women from the Netherlands varied by ethnic origin, with higher iodine status in Moroccan, Turkish and other non-Western women, and lower iodine status in Surinamese and Dutch Antilles women, even after adjusting for socio-demographic factors. Variation in diet may partially explain these differences as some of the effect estimates were attenuated when adjusting for dietary intake. Alternatively, there may be genetic variability in iodine or creatinine clearance [42,58]. Indeed, we found that when using UIC and adjusting for urinary creatinine separately in the model, UIC varied similarly to UI/Creat between the ethnic groups though some of the associations were attenuated and were no longer significant (e.g., for Surinamese and Dutch Antilles women). It should be noted that numbers in some of these ethnic-group categories were relatively small (n<100). Ethnicity was not significantly associated with iodine status in ALSPAC or INMA, but this may reflect the small sample sizes of other ethnic groups in these cohorts. Ethnic differences in iodine status could help to identify subgroups at high-risk for iodine insufficiency; in countries with a large proportion of diverse ethnic groups, culturally-specific approaches to improve dietary adequacy may be more suitable than a single solution for the whole population.

Dietary influences on iodine status

The only food group that was positively associated with UI/Creat in all three cohorts was "milk and dairy products", demonstrating their significant role as an important dietary determinant of iodine status in pregnancy. This finding is consistent with the results of other studies in European pregnant women, i.e., Norway [59,60], Iceland [61], Italy [62], Spain [63], and the UK [52,64], as well as studies of pregnant women in Australia [65].

Based on our model, a portion of "milk and dairy products" equivalent to a glass of milk (200 g) was associated with 5 to 14 µg/g increase in UI/Creat across cohorts. The effect sizes for milk differed between cohorts; the highest effect size was in Spain, while the lowest was in the Netherlands. This is in line with the milk-iodine concentration in each country (i.e., ~26 µg in Spain [66], ~15 µg in the Netherlands [67], and 15 µg in the UK in 1990/1991 [68]). The results might be different if repeated now as the iodine concentration in UK milk is higher than estimated when ALSPAC women were recruited in 1990/1991, i.e., 427 vs. 150 µg/kg [68,69].

Consumption of eggs and fish were positively associated with UI/Creat, though not consistently across the cohorts; the association with egg intake was statistically significant only in the Netherlands, while intake of fish and shellfish was associated with UI/Creat only in Spain and the UK. The effect size for eggs was higher than that expected, given their iodine content, but similar to values reported previously [60]. These higher values may reflect the consumption of eggs with salt in the Netherlands, which is likely to be iodised. An average portion of fish (120 g) was associated with some 6 to 34 µg/g increase in UI/Creat, across cohorts. Variation in the effect size could partly reflect the variability in average fish consumption, particularly

of white fish, which is a good iodine source [70] (e.g., pregnant women in Spain consumed a higher amount of white fish daily than did women in the UK). The wide CIs around the estimates probably relate to the variability in fish-iodine concentration [14] (i.e., the proportion of oily fish in the food group has a much lower iodine concentration [70]) and to the irregular nature of fish consumption which may not be captured by a spot-UI/Creat.

Consumption of cereals and cereal products was a statistically significant determinant of UI/Creat only in the Netherlands; this association is probably driven by consumption of bread which is made with iodised salt in the Netherlands [71], whereas without iodised salt, bread has a low iodine concentration and was not found to be a predictor of iodine status in the UK or Spanish cohorts. Intake of iodised table salt was measured only in pregnant women from Spain; 1 g of salt was associated with around 32 μg/g increase in UI/Creat. Both of these results suggest that iodised salt consumed either discretionarily (e.g., as table salt in Spain), or as part of processed foods (e.g., in bread in the Netherlands) is an important dietary determinant of iodine status. We observed the highest UI/Creat in the Netherlands, followed by Spain, and the lowest in the UK, suggesting that iodised-salt use might be a key dietary factor with large influence on iodine status.

Surprisingly, meat intake was negatively associated with UI/Creat in the Spanish cohort, even after controlling for socio-demographic variables. Higher urinary creatinine concentrations have been reported in individuals with a high-meat diet, which may account for the lower ratio [72,73].

Some of our other food-group associations are difficult to explain and may be chance findings, e.g., the positive association with fruit, and cakes/confectionary in the UK. However, fruit intake was also associated with urinary iodine excretion in Norwegian pregnant women [59] and the finding might warrant further investigation.

Although we have observed significant increases in UI/Creat, the effect sizes were relatively small and the total explained variance in UI/Creat (R^2) was low. This is probably explained by the large day-to-day variability in iodine intake which cannot be captured in a single spot-urine sample and the measurement errors of dietary assessment methods in capturing habitual iodine intake. Moreover, as a result of the physiological changes occurring during gestation (e.g., increased renal iodine clearance), pregnancy may not represent a steady state of iodine metabolism (intake vs. excretion) [10].

Strengths and limitations

Strengths of our study include the large sample size, the inclusion of pregnant women from three geographically and culturally different populations. Furthermore, we explored associations with the entire range of food groups, rather than focusing on a few groups or isolated foods as in previous studies [62,63]. However, our study also has a number of limitations. Firstly, the use of an FFQ for measuring diet and the use of spot-urine samples for estimating individual iodine intake have their methodological disadvantages [24–26,74]. Although we only had

spot-urine samples which might not reflect individual iodine intake or status, we used UI/Creat which has been shown as a valid alternative to the 24-hour urinary iodine excretion when used in homogenous population groups [75]. Although urinary iodine concentration was measured in three different laboratories using different assays, each laboratory ensured accuracy by use of certified reference materials. Exploring associations between data from an FFQ and spot-UI/Creat can also be problematic, as an FFQ is designed to measure habitual diet [76], whereas a spot-urine sample reflects iodine intake in the last 24-48 hours [11]; this may be reflected in the more consistent association between UI/Creat and intake of daily food items (e.g., milk) than those infrequently consumed (e.g., fish). However, our large cohort sample size would have helped to overcome this limitation to some extent. Second, it should be noted that in ALSPAC there was a time difference in the administration of the FFQ (at 32 weeks) and urine-sample collection (≤18 weeks); hence the FFQ might not reflect diet during early pregnancy. Third, although we harmonised the classification of foods into food groups, there were some differences in the foods included in each group which may explain variation in effect sizes between cohorts (i.e., in ALSPAC the dairy food group included milk and cheese, while in INMA and Generation R, ice cream, yoghurt, cream were also included). Fourth, we had incomplete, or no, data on iodine supplement use in two of the cohorts (Generation R and ALSPAC), which could be an important determinant that we were unable to evaluate; however this is unlikely to be a limitation in ALSPAC as it is unlikely that women would have taken an iodine-containing supplement in the early 1990s. Finally, we measured urinary iodine only in women with available child IQ data in two of the cohorts which might have created bias.

Conclusion

Various maternal characteristics and dietary habits were associated with UI/Creat in pregnancy, some of which were population-specific. For that reason, universal interventions and dietary recommendations to improve the iodine intake of pregnant women might not be appropriate; a country-specific approach needs to be adopted. Between countries, but also within countries with a large proportion of different ethnic groups, culturally-specific recommendations are probably necessary. Achieving and maintaining iodine sufficiency in populations require monitoring dietary determinants of iodine status so that appropriate action can be taken, where necessary.

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Supplementary material

ALSPAC

For the women in the analysis (n=2852), there were 2.6% missing values in total (n=1263) and 19.3% of the cases (n=550) had at least one missing value. Data were imputed for 12 out of the 15 variables used in the analysis, including pre-pregnancy BMI (n=250), ethnicity (n=96), parity (n=134), smoking status (n=51, smoking status variable was made from two imputed smoking variables with n=102 missing values in total), alcohol consumption (n=101, alcohol consumption variable was made from two imputed variables with n=159 missing values in total), education level (n=86), home ownership (n=72), crowding index (n=94), family adversity index (n=30), life event score (n=96), marital status (n=47), and living with a partner (n=97). Data were not imputed for gestational age, maternal age and child's sex due to no missing values.

Generation R

For the women in the analysis (n=2254), there were 5.5% missing values in total (n=1369) and 31.7% of the cases (n=715) had at least one missing value. Data were imputed for nine out of 11 variables, including gestational age (n=1), pre-pregnancy BMI (n=12), ethnicity (n=71), smoking status (n=248), alcohol consumption (n=254), education level (n=149), net household income (n=479), marital status (n=154), and child's sex (n=1). Data were not imputed for maternal age and parity due to no missing values.

INMA

For the women in the analysis (n=1460), there were 1.1% missing values in total (n=154) and 5.8% of the cases (n=84) had at least one missing value. Data were imputed for nine out of ten variables, including gestational age (n=4), maternal age (n=4), ethnicity (n=3), parity (n=2), smoking status (n=44), alcohol consumption (n=56), education level (n=5), living with a partner (n=1), and child's sex (n=35). Data were not imputed for pre-pregnancy BMI due to no missing values.

Supplemental Table 1 Overview of the classification of foods into food groups by cohort.

Food group	ALSPAC	Generation R	INMA
Vegetables	green leafy vegetables (e.g., cabbage), other green vegetables (e.g., leeks), carrots, other root vegetables (e.g., turnip), salad vegetables (e.g., tomatoes)	leafy (e.g., spinach), root (e.g., carrots), cabbage, mixed salad vegetables, mushrooms, allium (e.g., onion, garlic), stems and sprouts (e.g., asparagus), fruiting (e.g., tomatoes)	leafy (e.g., spinach), root (e.g., carrots), cruciferous (e.g., broccoli), salad vegetables (e.g., lettuce), allium (e.g., onions, leek, garlic), fruiting (e.g., tomatoes, aubergines, peppers)
Fruit	fresh fruit (e.g., apple, grapes, banana)	fresh fruit (e.g., apple, grapes, banana), olives	fresh fruit (e.g., apple, grapes, banana)
Nuts and seeds	nuts, tahini	nuts, seeds, nut spread	almonds, peanuts, hazelnuts, pine nuts
Potatoes	chips, roast potatoes, boiled/ mashed/ jacket potatoes	potatoes and other tubers (does not include potato crisps)	fried, boiled/roasted potatoes, potato crisps
Legumes	pulses (e.g., lentils, chickpeas), baked beans, peas, sweetcorn, broad beans	dried lentils, beans and peas	lentils, chickpeas, beans
Cereals and cereal products	breakfast cereals (e.g., oats, cornflakes, bran cereals), pasta, rice, bread, crispbreads, pizza	breakfast cereals, pasta, rice, bread, pretzels, crispbreads, pizza, flour and thickeners	breakfast cereals, pasta, rice, bread, boiled corn
Cakes, confectionery and added sugar	cakes or buns, biscuits, chocolate bars (e.g., Mars), chocolate (e.g., dairy milk), sweets (e.g., toffees), pudding (e.g., cheesecake, mousse), sugar	cakes, pastries, biscuits, candy bars, chocolate, non- chocolate sweets (e.g., toffees) jam, honey, sugar, ice cream, syrups, water ice	cakes, pastries, biscuits, chocolate, jams, honey, sugar
Added fats	animal fats (e.g., butter, ghee), vegetable oils and spreads (e.g., olive oil)	animal fats (e.g., butter),vegetable oils (e.g., olive oil), spreads and margarines	animal fats (e.g., butter), vegetable oils and spreads (e.g., olive oil)
Milk and dairy products	milk, cheese	milk, milk drinks, evaporated milk, yoghurt, fresh cheese (e.g., cottage cheese), cheese, milk puddings (e.g., mouse, cream base), cream	fresh milk, condensed milk, yoghurt, cheese, custard, ice cream, cream
Meat and meat products	red meat, poultry, offal (e.g., liver), processed meat (e.g., sausages, burgers, bacon), pies and pasties (e.g., meat pies)	red meat, poultry, offal (e.g., liver), processed meat (e.g., sausage, pate)	red meat, white meat (e.g., chicken), offal (e.g., liver), processed meat (e.g., sausages, pate, bacon)
Eggs	eggs, quiche	eggs	eggs

Supplemental Table 1 Overview of the classification of foods into food groups by cohort. (continued)

Food group	ALSPAC	Generation R	INMA
Fish and shellfish	white fish (e.g., cod), oily fish (e.g., salmon), shellfish (e.g., prawns)	white fish (e.g., cod), oily fish (e.g., salmon), shellfish (e.g., prawns), processed fish (e.g., fish fingers)	boiled/fried/ grilled white fish (e.g., cod), boiled/ fried/ grilled oily fish (e.g., salmon), seafood and shellfish (e.g., oysters, clams, lobster)
Condiments and seasoning	N/A	seasonings (e.g., salt, herbs, spices)	salt, including iodised salt
Processed and fried foods *(e.g., sauces, soups, fried foods, crisps)*	fried food (e.g., bacon, eggs, egg fried fish), crisps	sauces (e.g., tomato, dressings, mayonnaise), soups, bouillons	vegetable soups, tomato sauce, chicken croquettes, pizza
Non-alcoholic beverages *(excluding coffee and tea)*	tinned juice (e.g., tomato juice), pure fruit juice, soft drinks	fruit and vegetable juices, soft drinks, isotonic drinks, water	fruit juice, soft drinks, non-alcoholic beer, tap water, bottled water
Alcoholic beverages	N/A	wine, beer, liquors and spirits	wine, beer, liquors and spirits
Miscellaneous *(e.g., soy products, diet foods and sweeteners)*	soy products (e.g., TVP, vegeburgers), bean curd (e.g., tofu)	diet products, soy products, artificial sweeteners	N/A

Abbreviations: N/A, data not available; TVP, texturised vegetable protein.

Supplemental Table 2 Determinants [a] of urinary iodine-to-creatinine ratio measured at ≤ 18 gestational weeks by cohort.

	ALSPAC (n=2852)			Generation R (n=2254)			INMA (n=1460)		
Determinants	*n*	*B* (95% CI)	*P* [b]	*n*	*B* (95% CI)	*P* [b]	*n*	*B* (95% CI)	*P* [b]
Maternal factors									
Gestational age at urine sampling, weeks	2852	0.051 (0.046, 0.057)	<0.001	2254	0.007 (-0.006, 0.019)	0.300	1460	0.004 (-0.023, 0.032)	0.755
Age [c], years	2852	0.014 (0.008, 0.020)	<0.001	2254	0.018 (0.012, 0.024)	<0.001	1460	0.020 (0.010, 0.030)	<0.001
Pre-pregnancy BMI, kg/m^2	2852	-0.013 (-0.019, -0.007)	<0.001	2254	-0.011 (-0.017, -0.006)	<0.001	1460	-0.013 (-0.022, -0.004)	0.005
Ethnicity [d]									
Reference group	2800	Ref.		1095	Ref.		1340	Ref.	
Non-white	52	-0.018 (-0.203, 0.168)	0.851	N/A	.	.	N/A	.	.
Non-Dutch	N/A	.	.	1159	(see separate table) e		N/A	.	.
Non-Spanish	N/A	.	.	N/A	.	.	120	-0.016 (-0.150, 0.118)	0.810
Parity									
0	1354	Ref.		1279	Ref.		806	Ref.	
1	965	0.032 (-0.021, 0.085)	0.232	665	-0.001 (-0.057, 0.056)	0.982	544	-0.029 (-0.110, 0.052)	0.481
≥ 2	533	0.040 (-0.029, 0.108)	0.254	310	-0.041 (-0.123, 0.041)	0.327	110	-0.128 (-0.276, 0.020)	0.090
Smoking status									
Never smoked	2169	Ref.		1671	Ref.		1020	Ref.	
Stopped smoking	333	-0.003 (-0.075, 0.070)	0.943	211	-0.093 (-0.179, -0.007)	0.035	187	-0.060 (-0.172, 0.052)	0.296
Continued smoking	350	0.018 (-0.055, 0.092)	0.620	372	-0.008 (-0.083, 0.066)	0.831	253	-0.001 (-0.105, 0.104)	0.990
Alcohol consumption									
No	1350	Ref.		1458	Ref.		1330	Ref.	
Yes	1502	-0.006 (-0.052, 0.040)	0.795	796	-0.002 (-0.059, 0.055)	0.954	130	-0.051 (-0.181, 0.079)	0.442

Supplemental Table 2 Determinants [a] of urinary iodine-to-creatinine ratio measured at ≤ 18 gestational weeks by cohort. (continued)

	ALSPAC (n=2852)			Generation R (n=2254)			INMA (n=1460)		
Determinants	*n*	*B* (95% CI)	*P* [b]	*n*	*B* (95% CI)	*P* [b]	*n*	*B* (95% CI)	*P* [b]
Markers of socio-economic status									
Education level									
Low	576	Ref.		247	Ref.		337	Ref.	
Medium	1780	0.005 (-0.056, 0.066)	0.869	995	-0.077 (-0.165, 0.012)	0.089	581	-0.016 (-0.112, 0.079)	0.736
High	496	0.026 (-0.055, 0.107)	0.531	1012	-0.057 (-0.159, 0.045)	0.272	542	0.089 (-0.013, 0.190)	0.088
Net household income (€ per month)									
Low < €1200	N/A	.	.	492	Ref.		N/A	.	.
Medium €1200-2200	N/A	.	.	597	0.022 (-0.063, 0.108)	0.606	N/A	.	.
High > €2200	N/A	.	.	1165	0.089 (-0.001, 0.179)	0.054	N/A	.	.
Home ownership									
Owned/mortgaged	2425	Ref.		N/A	.	.	N/A	.	.
Private/other rented	236	-0.037 (-0.126, 0.053)	0.422	N/A	.	.	N/A	.	.
Council rented	191	-0.032 (-0.136, 0.072)	0.547	N/A	.	.	N/A	.	.
Crowding index									
≤ 1 person per room	2747	Ref.		N/A	.	.	N/A	.	.
+ 1 person per room	105	0.134 (-0.006, 0.274)	0.060	N/A	.	.	N/A	.	.
Family adversity index									
None 0	1395	Ref.		N/A	.	.	N/A	.	.
Mild 1-2	1124	-0.007 (-0.056, 0.041)	0.765	N/A	.	.	N/A	.	.
Severe > 3	333	-0.100 (-0.182, -0.018)	0.016	N/A	.	.	N/A	.	.
Life event score	2852	0.007 (-0.001, 0.015)	0.097	N/A	.	.	N/A	.	.

Supplemental Table 2 Determinants [a] of urinary iodine-to-creatinine ratio measured at ≤ 18 gestational weeks by cohort. (continued)

	ALSPAC (n=2852)			Generation R (n=2254)			INMA (n=1460)		
Determinants	*n*	*B* (95% CI)	*P* [b]	*n*	*B* (95% CI)	*P* [b]	*n*	*B* (95% CI)	*P* [b]
Marital status									
Never-married	355	Ref.		1136	Ref.		N/A	.	.
Married	2357	0.095 (0.018, 0.171)	0.015	1118	0.030 (-0.025, 0.086)	0.285	N/A	.	.
Other [f]	140	0.028 (-0.097, 0.153)	0.666	N/A	.	.	N/A	.	.
Living with a partner									
Yes	N/A	.	.	N/A	.	.	1445	Ref.	
No	N/A	.	.	N/A	.	.	15	-0.233 (-0.598, 0.131)	0.209
Child factors									
Child's sex									
Male	1405	Ref.		1147	Ref.		737	Ref.	
Female	1447	-0.025 (-0.070, 0.019)	0.261	1107	-0.026 (-0.073, 0.021)	0.278	723	-0.014 (-0.087, 0.058)	0.700

[a] Effect estimates (*B*=unstandardized regression coefficient), their 95% CIs and *P*-values from multiple linear regression models performed for each cohort with (natural) log-transformed iodine-to-creatinine ratio (UI/Creat) as the dependent variable and maternal characteristics as independent variables (for full models, see footnote b). Reported *B* coefficients represent the change in the mean (natural) log of UI/Creat per unit increase in the continuous independent variables and for each category compared to the reference for the categorical independent variables.

[b] *P*-values from adjusted Model 1 (adjusted for maternal and pregnancy characteristics); ALSPAC (R^2=0.123, $P < 0.0001$): gestational age (weeks), age (years), pre- pregnancy BMI (kg/m^2), ethnicity, parity, smoking status, alcohol consumption, education, home ownership, crowding index, family adversity index, life event score, marital status and child's sex; Generation R (R^2=0.086, $P < 0.0001$): gestational age (weeks), age (years), pre-pregnancy BMI (kg/m^2), ethnicity, parity, smoking status, alcohol consumption, education, net household income, marital status and child's sex; INMA (R^2=0.021, $P < 0.0001$): gestational age (weeks), age (years), pre- pregnancy BMI (kg/m^2), ethnicity, parity, smoking status, alcohol consumption, education, living with a partner and child's sex.

[c] Maternal age at urine sample collection, except in ALSPAC (age at last menstrual period).

[d] ALSPAC (Reference group=White); Generation R (Reference group=Dutch, Non-Dutch=Indonesian, Cape Verdean, Moroccan, Dutch Antilles, Surinamese, Turkish, Other non-western, Asian, or Other western); INMA (Reference group=Spanish, Non-Spanish=Latin American, European, or Others).

[e] Non-Dutch group in Generation R presented in detail in Table 3.

[f] ALSPAC (Other=widowed, divorced, or separated).

Abbreviations: BMI, body mass index; 95% CI, confidence interval; N/A, data not available or not applicable; Ref, reference category; UI/Creat, urinary iodine-to-creatinine ratio.

Supplemental Table 3 Determinants [a] of urinary iodine concentration measured at ≤ 18 gestational weeks by cohort.

	ALSPAC (n=2852)						Generation R (n=2254)						INMA (n=1460)					
	Adjusted Model 1 [b]			Adjusted Model 2 [c]			Adjusted Model 1 [b]			Adjusted Model 2 [c]			Adjusted Model 1 [b]			Adjusted Model 2 [c]		
Determinants	*n*	*B*	*P*	*n*	*B*	*P*	*n*	*B*	*P*	*n*	*B*	*P*	*n*	*B*	*P*	*n*	*B*	*P*
Gestational age at urine sampling, weeks	2852	0.033	<0.001	2710	0.034	<0.001	2254	0.014	0.020	1580	0.021	0.004	1460	0.009	0.516	1446	-0.007	0.605
Age [d], years	2852	0.009	0.002	2710	0.006	0.063	2254	0.011	<0.001	1580	0.010	0.009	1460	0.019	<0.001	1446	0.013	0.008
Pre-pregnancy BMI, kg/m^2	2852	-0.009	0.004	2710	-0.009	0.008	2254	-0.003	0.279	1580	-0.004	0.192	1460	-0.007	0.113	1446	-0.002	0.650
Family adversity index																		
None 0	1395	Ref.		1334	Ref.		N/A	.	.	.	.	.	N/A	.	.	.	.	.
Mild 1-2	1124	-0.025	0.309	1069	-0.020	0.423	N/A	.	.	.	.	.	N/A	.	.	.	.	.
Severe > 3	333	-0.112	0.008	307	-0.101	0.019	N/A	.	.	.	.	.	N/A	.	.	.	.	.
Marital status																		
Never-married	355	Ref.		320	Ref.		1136	Ref.		825	Ref.		N/A	.	.	.	.	.
Married	2357	0.044	0.257	2269	0.078	0.054	1118	0.034	0.208	755	0.042	0.179	N/A	.	.	.	.	.
Other [e]	140	-0.015	0.815	121	0.009	0.889	N/A	.	.	.	.	.	N/A	.	.	.	.	.
Ethnicity [f]																		
Reference group	2800	Ref.		2674	Ref.		1095	Ref.		930	Ref.		1340	Ref.		1328	Ref.	
Non-white	52	0.048	0.611	36	0.109	0.284	N/A	.	.	.	.	.	N/A	.	.	.	.	.
Non-Dutch:	N/A	.	.	.	.	.							N/A	.	.	.	.	.
- *Indonesian*	N/A	.	.	.	.	.	72	-0.012	0.861	58	-0.026	0.725	N/A	.	.	.	.	.
- *Cape Verdean*	N/A	.	.	.	.	.	87	0.061	0.370	41	0.150	0.112	N/A	.	.	.	.	.
- *Moroccan*	N/A	.	.	.	.	.	165	0.286	<0.001	72	0.242	0.003	N/A	.	.	.	.	.
- *Dutch Antilles*	N/A	.	.	.	.	.	65	-0.064	0.393	37	-0.117	0.245	N/A	.	.	.	.	.
- *Surinamese*	N/A	.	.	.	.	.	196	-0.046	0.327	111	-0.024	0.698	N/A	.	.	.	.	.
- *Turkish*	N/A	.	.	.	.	.	226	0.323	<0.001	103	0.308	<0.001	N/A	.	.	.	.	.
- *Other, non-Western*	N/A	.	.	.	.	.	107	0.125	0.034	53	0.054	0.502	N/A	.	.	.	.	.

Supplemental Table 3 Determinants [a] of urinary iodine concentration measured at ≤ 18 gestational weeks by cohort. (continued)

	ALSPAC (n=2852)						Generation R (n=2254)						INMA (n=1460)					
	Adjusted Model 1 [b]			Adjusted Model 2 [c]			Adjusted Model 1 [b]			Adjusted Model 2 [c]			Adjusted Model 1 [b]			Adjusted Model 2 [c]		
Determinants	*n*	*B*	*P*	*n*	*B*	*P*	*n*	*B*	*P*	*n*	*B*	*P*	*n*	*B*	*P*	*n*	*B*	*P*
-*Asian*	N/A	.	.	.	.	.	32	0.062	0.544	19	0.022	0.863	N/A	.	.	.	.	.
-*Other, Western*	N/A	.	.	.	.	.	209	0.023	0.575	156	0.050	0.297	N/A	.	.	.	.	.
Non-Spanish	N/A	.	.	.	.	.	N/A	.	.	.	.	.	120	0.007	0.909	118	0.032	0.627
Smoking status																		
Never smoked	2169	Ref.		2077	Ref.		1671	Ref.		1202	Ref.		1020	Ref.		1011	Ref.	
Stopped smoking	333	-0.008	0.825	312	-0.015	0.686	211	-0.078	0.065	147	-0.120	0.016	187	-0.097	0.077	186	-0.096	0.076
Continued smoking	350	0.005	0.896	321	0.034	0.380	372	0.021	0.557	231	0.039	0.385	253	-0.015	0.765	249	0.010	0.838

[a] Effect estimates (*B*=unstandardised regression coefficient) and *P*-values from multiple linear regression models performed for each cohort with (natural) log-transformed urinary iodine concentration (UIC) as the dependent variable and maternal characteristics and dietary intakes as independent variables (for full models, see footnotes b and c). All models were additionally adjusted for urinary creatinine concentration (UCreat, g/L). Reported *B* coefficients represent the change in the mean (natural) log of UIC per unit increase in the continuous independent variables and for each category compared to the reference for the categorical independent variables.

[b] Adjusted Model 1 (adjusted for maternal and pregnancy characteristics); ALSPAC (R^2=0.424, $P < 0.0001$): gestational age (weeks), age (years), pre-pregnancy BMI (kg/m2), ethnicity, parity, smoking status, alcohol consumption, education, home ownership, crowding index, family adversity index, life event score, marital status, child's sex, UCreat (g/L) and UCreat^2; Generation R (R^2=0.525, $P < 0.0001$): gestational age (weeks), age (years), pre-pregnancy BMI (kg/m^2), ethnicity, parity, smoking status, alcohol consumption, education, net household income, marital status, child's sex, UCreat (g/L) and UCreat^2; INMA (R^2=0.193, $P < 0.0001$): gestational age (weeks), age (years), pre-pregnancy BMI (kg/m^2), ethnicity, parity, smoking status, alcohol consumption, education, living with a partner, child's sex, UCreat (g/L) and UCreat^2.

[c] Adjusted Model 2 (adjusted for maternal and pregnancy characteristics + dietary intakes); ALSPAC (R^2=0.443, $P < 0.0001$): Model 1 + energy intake (kcal/day) + intake of vegetables (g/day), fruit (g/day), nuts and seeds (g/day), potatoes (g/day), legumes (g/day), cereals and cereal products (g/day), cakes, confectionery and added sugar (g/day), added fats (g/day), milk and dairy products (g/day), meat and meat products (g/day), eggs (g/day), fish and shellfish (g/day), processed and fried foods (g/day), non-alcoholic beverages (g/day), miscellaneous (g/day); Generation R (R^2=0.548, $P < 0.0001$): Model 1 + energy intake (kcal/day) + intake of vegetables (g/day), fruit (g/day), nuts and seeds (g/day), potatoes (g/day), legumes (g/day), cereals and cereal products (g/day), cakes, confectionery and added sugar (g/day), added fats (g/day), milk and dairy products (g/day), meat and meat products (g/day), eggs (g/day), fish and shellfish (g/day), condiments and seasoning (g/day), processed and fried foods (g/day), non-alcoholic beverages (g/day), alcoholic beverages (g/day), miscellaneous (g/day); INMA (R^2=0.227, $P < 0.0001$): Model 1 + energy intake (kcal/day) + intake of vegetables (g/day), fruit (g/day), nuts and seeds (g/day), potatoes (g/day), legumes (g/day), cereals and cereal products (g/day), cakes, confectionery and added sugar (g/

day), added fats (g/day), milk and dairy products (g/day), meat and meat products (g/day), eggs (g/day), fish and shellfish (g/day), condiments and seasoning (e.g., salt) (g/day), processed and fried foods (g/day), non-alcoholic beverages (g/day), alcoholic beverages (g/day).

[d] Maternal age at urine sample collection, except in ALSPAC (age at last menstrual period).

[e] ALSPAC (Other=widowed, divorced, or separated).

[f] ALSPAC (Reference group=White); Generation R (Reference group=Dutch, Non-Dutch=Indonesian, Cape Verdean, Moroccan, Dutch Antilles, Surinamese, Turkish, Other non- western, Asian, or Other western); INMA (Reference group=Spanish, Non-Spanish=Latin American, European, or Others).

Abbreviations: BMI, body mass index; N/A, data not available or not applicable; Ref, reference category; UCreat, urinary creatinine concentration; UCreat^2, squared urinary creatinine concentration; UIC, urinary iodine concentration.

Supplemental Table 4 Descriptives of dietary intakes of food groups (g/day) and energy intake (kcal/day) estimated from FFQ by cohort.

	ALSPAC (n=2710)	**Generation R (n=1580)**	**INMA (n=1446)**
Food group (grams/day) [a]	*Mean (±SD)*	*Mean (±SD)*	*Mean (±SD)*
Vegetables	117 (±64)	144 (±64)	220 (±114)
Fruit	100 (±56)	171 (±116)	320 (±200)
Nuts and seeds	3 (±7)	17 (±12)	6 (±9)
Potatoes	98 (±49)	52 (±43)	63 (±37)
Legumes	54 (±32)	4 (±7)	38 (±25)
Cereals and cereal products	195 (±79)	195 (±71)	184 (±77)
Cakes, confectionery and added sugar	80 (±55)	98 (±56)	44 (±36)
Added fats	19 (±11)	25 (±14)	23 (±15)
Milk and dairy products	391 (±155)	412 (±251)	444 (±233)
Meat and meat products	71 (±40)	78 (±43)	116 (±50)
Eggs	21 (±18)	11 (±10)	20 (±9)
Fish and shellfish	35 (±30)	14 (±13)	69 (±36)
Condiments and seasoning (e.g., salt, iodised salt)	N/A	6 (±5)	0.3 (±0.4)
Processed and fried foods (e.g., sauces, soups, fried foods, crisps)	8 (±8)	100 (±90)	101 (±66)
Non-alcoholic beverages (excluding coffee and tea) [b]	175 (±83)	940 (±550)	1488 (±494)
Alcoholic beverages	N/A	6 (±17)	3 (±13)
Miscellaneous (e.g., soy products, diet foods and sweeteners)	2 (±9)	6 (±20)	N/A
Energy, kcal/day	1743 (±459)	2076 (±520)	2083 (±532)

[a] Dietary intake of food groups presented as mean (±SD) grams per day, energy intake presented as mean (±SD) kcal per day.

[b] Food group also includes water in INMA and Generation R (but not in ALSPAC).

Abbreviations**:** FFQ, food frequency questionnaire; N/A, data not available; SD, standard deviation.

Supplemental Table 5 Multivariable associations of food group intakes estimated from FFQ (per 100 g/day) [a] with urinary iodine-to-creatinine ratio measured at ≤ 18 gestational weeks by cohort.

	ALSPAC (n=2710)		Generation R (n=1580)		INMA (n=1446)	
Food group intakes (per 100 g/day) [a]	*B* (95% CI) [b]	*P* [c]	*B* (95% CI) [b]	*P* [d]	*B* (95% CI) [b]	*P* [e]
Vegetables	0.24 (-1.51, 2.06)	0.791	-0.76 (-4.78, 3.46)	0.719	0.48 (-7.07, 8.31)	0.903
Fruit	2.79 (0.59, 5.09)	0.012	1.13 (-1.12, 3.45)	0.328	-4.38 (-8.91, 0.26)	0.064
Nuts and seeds	19.30 (-2.05, 51.25)	0.083	51.07 (17.18, 96.03)	0.001	68.80 (-33.30, 230.33)	0.223
Potatoes	2.66 (-0.20, 5.71)	0.069	5.92 (-1.17, 13.61)	0.104	-16.46 (-36.05, 5.36)	0.134
Legumes	2.33 (-1.33, 6.29)	0.219	16.98 (-17.38, 68.39)	0.384	28.00 (-5.39, 66.86)	0.105
Cereals and cereal products	1.42 (-0.92, 3.88)	0.238	12.32 (6.34, 18.69)	<0.001	0.21 (-13.90, 15.34)	0.978
Cakes, confectionery and added sugar	4.90 (0.50, 9.73)	0.028	5.36 (-2.24, 13.64)	0.172	-17.98 (-43.38, 11.33)	0.217
Added fats [a]	0.11 (-0.01, 0.24)	0.082	0.27 (0.04, 0.50)	0.022	-0.42 (-1.13, 0.29)	0.243
Milk and dairy products	3.73 (2.74, 4.74)	<0.001	2.34 (1.00, 3.70)	0.001	6.92 (2.52, 11.41)	0.002
Meat and meat products	1.27 (-2.30, 5.13)	0.497	2.87 (-4.14, 10.49)	0.433	-32.71 (-50.77, -12.58)	0.002
Eggs	5.44 (-1.18, 13.06)	0.112	65.32 (26.28, 117.87)	<0.001	86.92 (-13.13, 238.12)	0.099
Fish and shellfish	5.10 (0.89, 9.70)	0.017	2.01 (-16.18, 24.91)	0.845	28.04 (2.73, 56.38)	0.029
Condiments and seasoning (e.g., salt) [a,f]	N/A	.	0.27 (-0.30, 0.84)	0.359	31.69 (10.31, 55.16)	0.003
Processed and fried foods (e.g., sauces, soups, fried foods, crisps)	0.85 (-12.40, 19.47)	0.915	1.88 (-0.98, 4.83)	0.199	0.00 (-11.26, 11.91)	0.999
Non-alcoholic beverages (excluding coffee and tea)	0.62 (-0.71, 1.99)	0.367	0.40 (-0.07, 0.87)	0.099	-1.46 (-3.05, 0.13)	0.072
Alcoholic beverages	N/A	.	13.86 (-1.99, 32.66)	0.090	-34.72 (-85.12, 36.20)	0.297
Miscellaneous (e.g., soy products, diet foods and sweeteners)	14.61 (-0.70, 35.22)	0.063	8.13 (-4.77, 23.06)	0.230	N/A	.

[a] Added fats and salt intakes expressed per 1 g/day.

[b] Effect estimates (*B*=unstandardized regression coefficient) represent the actual change in the geometric mean of UI/Creat (µg/g) associated with 100 g increase in intake of a food group. *B* coefficients and their 95% CIs are calculated by back-transformation from logarithmic scale (see methods). Values are adjusted for dietary intake of other food groups, energy intake and other potential confounders (for full models, see Table 3, footnote c). When calculating the *B* coefficients, all categorical covariates were set to their reference group and the continuous covariates gestational age, maternal age, pre-pregnancy BMI and energy intake were centred to their means.

[c] *P*-value adjusted for energy (kcal/day) + gestational age (weeks), age (years), pre-pregnancy BMI (kg/m^2), ethnicity, parity, smoking status, alcohol consumption, education, home ownership, crowding index, family adversity index, life event score, marital status and child's sex (R^2=0.147, $P < 0.0001$).

[d] *P*-values adjusted for energy (kcal/day) + gestational age (weeks), age (years), pre-pregnancy BMI (kg/m^2), ethnicity, parity, smoking status, alcohol consumption, education, net household income, marital status and child's sex (R^2=0.091, $P < 0.0001$).

[e] *P*-values adjusted for energy (kcal/day) + gestational age (weeks), age (years), pre-pregnancy BMI (kg/m^2), ethnicity, parity, smoking status, alcohol consumption, education, living with a partner and child's sex (R^2=0.060, $P < 0.0001$).

[f] In INMA this food group also includes iodised salt. Separate information about the consumption of table salt and use of iodine-fortified table salt was collected only in the INMA cohort.

Abbreviations: BMI, body mass index; 95% CI, confidence interval; FFQ, food frequency questionnaire; N/A, data not available; UI/Creat, urinary iodine-to- creatinine ratio.

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