# **Iodine status of pregnant women with obesity from inner city populations in the United Kingdom**

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**Running title:** Iodine status of women with obesity during pregnancy

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# **Abstract**

**Background/Objectives:** Iodine is essential for foetal neurodevelopment and growth. Requirements increase in pregnancy to support increased thyroid hormone synthesis for maternal and foetal requirements, and for foetal transfer. Iodine deficiency in pregnancy is widely reported, and obesity has been associated with sub-optimal thyroid function. We evaluated iodine status and its relation with birthweight in a secondary analysis of pregnant women with obesity from multi-ethnic inner-city settings who participated in the UK Pregnancies Better Eating and Activity trial (UPBEAT).

**Subjects/Methods:** Iodine and creatinine concentrations were evaluated in spot urine samples in the second (15+0-18+6 weeks, n=954) trimester of pregnancy. We assessed iodine status as urinary iodine concentration (UIC) and urinary iodine-to-creatinine ratio (UI/Cr) and applied WHO/UNICEF/IGN population threshold of median UIC >150µg/L for iodine sufficiency. Relationships between iodine status and birthweight were determined using linear and logistic regression with appropriate adjustment, including for maternal BMI and gestational age.

**Results:** Median (IQR) UIC and UI/Cr in the second trimester of pregnancy was 147µg/L (99-257) and 97µg/L (59-165), respectively. An UI/Cr <150μg/g was observed in 70% of women. Compared to women with UI/Cr >150 µg/g, there was a trend for women with UI/Cr <150 µg/g to deliver infants with a lower birthweight (β= -60.0 g; 95% CI -120.9 to -1.01, *P*=0.05).

**Conclusions:** Iodine status of pregnant women with obesity from this cohort of UK women was suboptimal. Lower iodine status was associated with lower birthweight.

# **Introduction**

Maternal iodine requirements are higher in early pregnancy due to an increase in thyroid hormone synthesis, thyroid hormone transfer and iodine supply to the foetus, and in order to meet the increase in renal iodine clearance.1 The UK Reference Nutrient Intake (RNI) for iodine in adults is 140μg/day, with no incremental increase during pregnancy. However, the World Health Organization (WHO), the United Nations Children’s Fund (UNICEF) and the Iodine Global Network (IGN, formerly the ICCIDD, Iodine Council for the Control of Iodine Deficiency Disorders) recommend 250μg/day during pregnancy.2

As the foetus is dependent on thyroid hormones and a supply of iodine from the maternal circulation, an adequate iodine status during pregnancy is critical. Severe iodine deficiency can result in cretinism3 and mild to moderate deficiency before or during pregnancy can have an adverse effect on child neurodevelopment.4–7 Thyroid hormones play a central role in the developmental cycle including growth and development of the skeleton and peripheral tissues, and are linked to the actions of growth hormone and the insulin-like growth factors

(IGFs).8,9 There are reports that iodine insufficiency may affect foetal growth, however with little conformity between studies.10–17

Over 90% of dietary iodine is excreted in the urine andurinary iodine concentration (UIC) is a reliable indicator of recent iodine intake.18 A concentration lower than 150 μg/L is indicative of inadequate iodine status in a pregnant population according to WHO/UNICEF/IGN.2 The main sources of iodine for the UK adults are dairy products19 and the population is considered iodine sufficient,20 although using the WHO cut-off, evidence from across the UK and Northern Ireland suggests a risk of insufficiency in pregnancy.10,14,21–23 These findings are consistent with evidence from several other European countries demonstrating iodine insufficiency in pregnancy.24–29

In line with the rising global prevalence of obesity, increasing numbers of women with obesity in the UK are presenting for antenatal care.30 In a recent meta-analysis, obesity in non-pregnant populations was associated with an increased risk of hypothyroidism, which may itself predispose to weight gain.31 There is also some evidence that obesity is associated with a greater risk of iodine deficiency,32 however, the mechanism for this is unclear. The possible emergence of maternal iodine deficiency in Europe, together with recent UK data, highlights a need for further investigation of iodine status of UK pregnant women, including those who have obesity. To our knowledge, no previous studies have assessed iodine status in a population of pregnant women with obesity.

In this study, we assessed iodine status of pregnant women with obesity (BMI ≥30 kg/m2) by evaluation of urinary iodine and creatinine in participants from the UK Pregnancies Better Eating and Activity Trial (UPBEAT).33 We also evaluated the relationship between iodine status and birthweight.

**Materials/Subjects and Methods**

**Study Design and Participants**

This study utilised participant samples and data collected in the UPBEAT trial, the methods of which have been previously reported.34 Briefly, UPBEAT was a multicentre, randomised controlled trial of a behavioural intervention addressing diet and physical activity versus standard antenatal care in women with obesity living in eight inner-city UK locations during pregnancy. The intervention aimed to prevent gestational diabetes mellitus and reduce the incidence of large-for-gestational-age infants in 1555 women. Women randomised to the intervention group participated in a behavioural intervention of diet and physical activity advice, which aimed to reduce dietary glycaemic load and saturated fat intake while increasing physical activity and being more active in daily life. All women attended antenatal appointments according to local health care provision at their study centres. For those randomised to standard care, no additional information was provided. The intervention did not influence the primary outcomes of the incidence of gestational diabetes mellitus or large-for-gestational-age infants.33

Women over 16 years with a body mass index (BMI) ≥30kg/m2, singleton pregnancy and gestational age between 15+0 and 18+6 weeks were invited to participate. Women were excluded if they were unwilling or unable to give informed consent, if they had pre-existing diabetes, hypertension, renal disease, systemic lupus erythematous, antiphospholipid syndrome, sickle cell disease, thalassemia, celiac disease, currently prescribed metformin, or current psychosis. Women were also excluded if they had a clinical diagnosis of thyroid disease. At the first appointment, written informed consent was obtained from participating women. NHS Research Ethics Committee approval was obtained in all centres (UK IRAS integrated research application system; reference 09/H0802/5), and the UPBEAT study was registered under ISRCTN89971375.

**Data and Sample Collection**

Women provided spot urine samples at three study visits. For the purposes of this investigation we included all women who provided sufficient urine samples at the first study visit before allocation to treatment groups (second trimester; 15+0-18+6 weeks’ gestation, n=954). Urine was stored at -80°C until analysis. Urine samples were aliquoted prior to using dipsticks to measure proteinuria.

On enrolment to the study, social, demographic, anthropometric and biochemical data were collected from all participants. Information recorded included age (years), BMI (kg/m2), gestational age (weeks), ethnicity (Black, White, Asian, other), parity (nulliparous, multiparous), smoking status (smoker, ex-smoker, non-smoker), living in a deprived area (Index of multiple deprivation; scores were calculated for the region of residence, and assessed as quintiles), prenatal or other multivitamin use and years in education. Iodine content of any multivitamins was not ascertained. Maternal anthropometric measurements collected included sum of skinfold thicknesses (mm) and mid-arm circumference (cm). A food frequency questionnaire (FFQ) collected information on the dietary intake of the participants and dietary patterns were derived using factor analysis which yielded four distinct dietary patterns; ‘Fruit and vegetables’, ‘African/Caribbean’, ‘Processed’ and ‘Snacks’, which have been previously described.35 Biochemical measures assessed from blood samples at enrolment included triglycerides, LDL cholesterol and HDL cholesterol.

**Birthweight**

Birthweight was recorded at delivery. Low birthweight (g) was defined as <2.5kg, small-for-gestational age (SGA) was defined as ≤10th customised birthweight centile for gestational age, adjusted for maternal height and weight, ethnic origin, parity, and sex of the baby.

**Laboratory analysis**

Urinary iodine concentration (UIC) was measured using the Sandell-Kolthoff reaction36 (Affinity Biomarker Labs, London, UK). The inter-assay coefficient of variation (CV) for urinary iodine was <10% and the intra-assay CV <9%. Urinary creatinine was assessed to account for differences in hydration and was measured by the ADVIA 1800 Chemistry System (Siemens, UK) using the Jaffe method.37 The intra-assay and inter-assay CVs for urinary creatinine were <3% and ≤4%, respectively.

**Statistical analysis**

Data were tested for normality using the Kolmogorov Smirnov test. Data are presented as mean (standard deviation), frequency (percentage) or median (interquartile range) as appropriate.

Maternal iodine status in the sample population isreported as median UIC (μg/L) and iodine-to-creatinine ratio (UI/Cr) (μg/g) to correct for hydration effects38 and to permit comparison with previous UK studies.7,29,39 Creatinine excretion has been shown to be relatively constant during gestation.40

Habitual insufficient population iodine status was determined using the WHO/UNICEF/IGN threshold for a pregnant women of UIC <150 μg/L,2 and UI/Cr <150 μg/g. We used UI/Cr to examine the association between iodine intake, maternal characteristics and gestational outcomes. For UI/Cr and maternal characteristics, we used linear regression with log transformed UI/Cr*.* Variables with *P*<0.20 in the unadjusted analyses were entered into a general linear model and adjusted for maternal age, BMI, ethnicity, education, living in a deprived area, parity and smoking status. Linear regression was used to investigate the association between UI/Cr as a continuous variable and birthweight while logistic regression was performed to examine the relationship between UI/Cr and binary outcomes (LGA and SGA). UI/Cr was additionally stratified into two iodine status groups; UI/Cr ≥150 μg/g (“iodine sufficient”) and UI/Cr <150 μg/g (“iodine insufficient”). The reference group was UI/Cr ≥150 μg/g. The models were adjusted for maternal age, ethnicity, BMI, parity, socioeconomic status, smoking, treatment allocation and infant sex. Gestational age at delivery was additionally included as a covariate when assessing the association between UI/Cr and birthweight.

Statistical analysis was carried out using Stata version 15.0 (StataCorp, College Station, Texas, US). Significance was set at *P*<0.05.

**Results**

Urine samples were available from 954 women in the second trimester of pregnancy. Five women who experienced pregnancy/infant loss were excluded (total study sample n=949). The characteristics of the women are presented in **Table 1**. The mean (SD) age of the women was 30.6 (5.6) years and the median (IQR) BMI was 35.2 (32.8-38.5) kg/m2. The majority of women were of white ethnicity (67%) and 44% lived in the most deprived area according to the quintiles of Index of Multiple Deprivation. The majority were non-smokers in the index pregnancy (70%).

**Iodine status**

The median (IQR) UIC and UI/Cr in the second trimester of pregnancy were 147µg/L (IQR 99-257 µg/L) and 97µg/g (IQR 59-165µg/g), respectively. An UI/Cr <150μg/g was observed in 70% of women **(Table 2)**.

**Association with maternal variables**

In univariate models, age, BMI, smoking, education, multivitamin use and following a ‘Processed’ dietary pattern were associated with UI/Cr **(Table 3)**. Maternal age and education were positively associated with UI/Cr which was robust to adjustment for confounders (all *P*<0.05) and there was a positive relationship between UI/Cr and HCL cholesterol in the unadjusted model. There was a negative association between UI/Cr and BMI, smoking, multivitamin use and the ‘Processed’ dietary pattern in univariate models. Women who reported not taking multivitamins and those who followed a ‘Processed’ dietary pattern had poorer UI/Cr, which was robust to adjustment for confounders (both *P*<0.05).

**Association with birthweight and duration of gestation**

**Table 4** shows the association between UI/Cr and birthweight and birthweight centiles. There was a significant positive association between UI/Cr and birthweight which was robust to adjustment for confounders (β= 50.72g; 95%CI 15.26 to 86.18, *P*=0.01). There was a trend for women with inadequate iodine status to deliver an infant with a lower birthweight (β= -59.95g; 95%CI -120.91 to -1.01, *P*=0.05).

**Discussion**

This study has shown sub-optimal iodine status amongst multi-ethnic pregnant women with obesity living in inner city areas in the UK. The median UIC and UI/Cr demonstrate that iodine intakes in this cohort of pregnant women in the second trimester may be habitually below recommendations.2 These results are consistent with recent studies in BMI heterogeneous pregnant women in European countries that have also used UI/Cr to assess iodine status.14,23,24,39,41

The UK population has generally been considered to be iodine sufficient; however, a 2009 study in UK schoolgirls aged 14-15 years reported that approximately half were mildly iodine deficient.42 Our finding of inadequate iodine status in a group of UK pregnant women with obesity living in inner-city sites supports a growing body of evidence of iodine deficiency in UK pregnant women, adding to data from SW England,7,22 SE England,43 Central England,41 NE England,44 Northern Ireland,23 Wales45 and in geographically divergent sites.10 Despite these observations, Department of Health recommendations set in 1992 have not changed.19,46 Further, though prenatal supplements containing iodine are available, not all contain iodine and their use is unsystematic.47 Universal salt iodisation is a cost-effective mass fortification strategy that has been successfully applied in many countries globally. When iodised to recommended concentrations, iodised salt adequately supplies the needs of pregnant women.48

Though we saw a trend between iodine intakes and BMI in our unadjusted model, the finding of suboptimal iodine status in a cohort of pregnant women with obesity may be particularly important as there is evidence that obesity is associated with iodine deficiency.32 Individuals with obesity may be particularly vulnerable to insufficiencies in micronutrient intakes, the aetiology of which may be multifactorial including inadequate dietary intakes (“hidden hunger”) or biological factors associated with obesity such as alterations in micronutrient metabolism.49,50 Poorer quality diets have been reported in pregnant women with an increased BMI,51–53 which may result in inadequate micronutrient intake. Indeed, our observation that women who followed a ‘Processed’ dietary pattern, characterised by chocolate, crisps, potatoes, processed meat/meat products, squash and fizzy drinks35 had poorer iodine status, highlights the importance of the provision of healthy eating advice to pregnant women with obesity to optimise micronutrient intakes. This finding is supported by a recent qualitative study in the UK which reported that awareness and knowledge of iodine was low among pregnant women. Women were not aware of the importance of iodine, sources of iodine or iodine intake recommendations and described dietary advice as confusing, focusing largely on foods to avoid, supplements and selected nutrients not including iodine.54

Our study found evidence of an association between iodine status and birthweight. Our findings are consistent with a systematic review16 in weight-heterogenous women and evidence from observational studies that maternal iodine status is related to birthweight.11,12,15 Similar to our findings, in a cohort study in Bangladesh, Rydbeck *et al*. reported a positive association between maternal UIC and birthweight which increased by 9.3g (95% CI: 2.9, 16) for each 0.1mg/L increase in maternal UIC.15 Alvarez-Pedrerol *et al.* found that Spanish pregnant women with a third trimester UIC below 50µg/l had infants with a lower birthweight than women with a UIC 50-149µg/l.12 Snart *et al.*, in 6,637 UK pregnant women, found that for typical women, the birthweight centile at the 25th UI/Cr percentile (59µg/g) was 2.7 percentage points lower than that at the 75th UI/Cr percentile (121µg/g) (99%CI 0.8, 4.6).41 In contrast, two other UK studies reported no association between UIC or UI/Cr and birthweight.10,14 Well-designed trials examining the association between iodine repletion and growth are sparse.16 Further research in adequately powered studies is warranted in order to clarify the association between iodine status and foetal growth, especially given the critical role of iodine in early life development.

Important associations between iodine status and social and demographic factors were identified in this study. Older and more educated women, who may have better quality diets,55,56 had better iodine status as assessed using UI/Cr, in agreement with previous reports.29,57 Iodine supplement use in pregnant women is positively associated with iodine status23 and in the present study we found multivitamin use to be related UI/Cr, adding to the evidence that supplements may be an important source of iodine for pregnant women, although information on specific iodine containing supplements was not available in this study.

Strengths of this study include the large sample size and the inclusion of a cohort of solely pregnant women with a BMI of ≥30 kg/m2. UPBEAT included women from geographically different regions in the UK who were socially and ethnically diverse. 43.6% of our sample lived in areas with a high index of multiple deprivation. Due to the extensive data collection in UPBEAT, some potential determinants of iodine status could be explored.

The study had several limitations. Spot-urine samples may not reflect individual iodine status, although UI/Cr has been shown to be a good alternative to 24-h urine iodine excretion.58 We did not collect data specifically on iodine supplement use or whether multivitamins contained iodine. Iodine was assessed in women taking part in a clinical trial, which may have introduced selection bias.Thyroid hormones were not assessed in this study, therefore maternal thyroid function and its relationship with birthweight could not be examined, however a low UI/Cr has been previously associated with a rise in TSH.59 Finally, though a strength of our study, generalisability of our results is limited since the sample includes obese pregnant women only.

In conclusion, this study has identified that UK pregnant women with obesity have inadequate iodine status. The results of this study add to the increasing evidence that iodine deficiency is widespread in UK pregnant women. As there is presently no iodine fortification programme in the UK nor is iodine supplementation in pregnancy recommended, the implementation of routine dietary advice to improve iodine nutrition of UK pregnant women should be considered by public health agencies. Our finding that lower iodine status associates with lower birthweight adds to the existing evidence, however, given the small number of studies that have examined this relationship, further research is merited.

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**Conflict of Interest**

KMG has received reimbursement for speaking at conferences sponsored by companies selling nutritional products, and is part of an academic consortium that has received research funding from Abbott Nutrition, Nestec, BenevolentAI Bio Ltd. and Danone. The other authors report no potential conflicts of interest.

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**Author contributions**

ACF and JF conceived of the study. ACF, JF, CG and AB designed the study. KVD and ACF analysed the data. JF, KVD, SLW and AF interpreted the data. JF, KVD and ACF wrote the manuscript.

LP, JHL, KMG contributed to data interpretation and provided feedback on the manuscript.

All authors have read and approved the final manuscript.

**References**

1 Glinoer D. The regulation of thyroid function during normal pregnancy: importance of the iodine nutrition status. *Best Pract Res Clin Endocrinol Metab* 2004; **18**: 133–52.

2 WHO. UNICEF & ICCIDD assessment of iodine deficiency disorders and monitoring their elimination. Geneva (Switzerland): WHO; 2007. .

3 Zimmermann MB, Jooste PL, Pandav CS. Iodine-deficiency disorders. *Lancet (London, England)* 2008; **372**: 1251–62.

4 Hynes KL, Otahal P, Hay I, Burgess JR. Mild iodine deficiency during pregnancy is associated with reduced educational outcomes in the offspring: 9-year follow-up of the gestational iodine cohort. *J Clin Endocrinol Metab* 2013; **98**: 1954–62.

5 Markhus MW, Dahl L, Moe V, Abel MH, Brantsæter AL, Øyen J *et al.* Maternal Iodine Status is Associated with Offspring Language Skills in Infancy and Toddlerhood. *Nutrients* 2018; **10**. doi:10.3390/nu10091270.

6 Robinson SM, Crozier SR, Miles EA, Gale CR, Calder PC, Cooper C *et al.* Preconception Maternal Iodine Status Is Positively Associated with IQ but Not with Measures of Executive Function in Childhood. *J Nutr* 2018; **148**: 959–966.

7 Bath SC, Steer CD, Golding J, Emmett P, Rayman MP. Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). *Lancet (London, England)* 2013; **382**: 331–7.

8 Robson H, Siebler T, Shalet SM, Williams GR. Interactions between GH, IGF-I, glucocorticoids, and thyroid hormones during skeletal growth. *Pediatr Res* 2002; **52**: 137–147.

9 Zimmermann MB. The role of iodine in human growth and development. *Semin Cell Dev Biol* 2011; **22**: 645–652.

10 Snart CJP, Keeble C, Taylor E, Cade JE, Stewart PM, Zimmermann M *et al.* Maternal Iodine Status and Associations with Birth Outcomes in Three Major Cities in the United Kingdom. *Nutrients* 2019; **11**: 1–12.

11 Charoenratana C, Leelapat P, Traisrisilp K, Tongsong T. Maternal iodine insufficiency and adverse pregnancy outcomes. *Matern Child Nutr* 2016; **12**: 680–7.

12 Alvarez-Pedrerol M, Guxens M, Mendez M, Canet Y, Martorell R, Espada M *et al.* Iodine levels and thyroid hormones in healthy pregnant women and birth weight of their offspring. *Eur J Endocrinol* 2009; **160**: 423–9.

13 León G, Murcia M, Rebagliato M, Álvarez-Pedrerol M, Castilla AM, Basterrechea M *et al.* Maternal thyroid dysfunction during gestation, preterm delivery, and birthweight. The Infancia y Medio Ambiente Cohort, Spain. *Paediatr Perinat Epidemiol* 2015; **29**: 113–22.

14 Torlinska B, Bath SC, Janjua A, Boelaert K, Chan S-Y. Iodine Status during Pregnancy in a Region of Mild-to-Moderate Iodine Deficiency is not Associated with Adverse Obstetric Outcomes; Results from the Avon Longitudinal Study of Parents and Children (ALSPAC). *Nutrients* 2018; **10**: 1–13.

15 Rydbeck F, Rahman A, Grandér M, Ekström E-C, Vahter M, Kippler M. Maternal Urinary Iodine Concentration up to 1.0 mg/L Is Positively Associated with Birth Weight, Length, and Head Circumference of Male Offspring. *J Nutr* 2014; **144**: 1438–1444.

16 Farebrother J, Naude CE, Nicol L, Sang Z, Yang Z, Jooste PL *et al.* Effects of iodized salt and iodine supplements on prenatal and postnatal growth: A systematic review. *Adv Nutr* 2018; **9**. doi:10.1093/advances/nmy009.

17 Nazeri P, Shab-Bidar S, Pearce EN, Shariat M. Do maternal urinary iodine concentration or thyroid hormones within the normal range during pregnancy affect growth parameters at birth? A systematic review and meta-analysis. *Nutr Rev* 2020; **0**: 1–17.

18 Zimmermann MB. Methods to assess iron and iodine status. *Br J Nutr* 2008; **99 Suppl 3**: S2-9.

19 Bath SC, Rayman MP. Iodine deficiency in the UK: An overlooked cause of impaired neurodevelopment? *Proc Nutr Soc* 2013; **72**: 226–235.

20 National Diet and Nutrition Survey. NDNS: Results from Years 7 and 8. Public Health England. 2018.

21 Bath SC, Rayman MP. A review of the iodine status of UK pregnant women and its implications for the offspring. *Environ Geochem Health* 2015; **37**: 619–29.

22 Knight BA, Shields BM, He X, Pearce EN, Braverman LE, Sturley R *et al.* Iodine deficiency amongst pregnant women in South-West England. *Clin Endocrinol (Oxf)* 2017; **86**: 451–455.

23 McMullan P, Hamill L, Doolan K, Hunter A, McCance D, Patterson C *et al.* Iodine deficiency among pregnant women living in Northern Ireland. *Clin Endocrinol (Oxf)* 2019; : 0–2.

24 Dahl L, Wik Markhus M, Sanchez PVR, Moe V, Smith L, Meltzer HM *et al.* Iodine Deficiency in a Study Population of Norwegian Pregnant Women-Results from the Little in Norway Study (LiN). *Nutrients* 2018; **10**: 1–14.

25 Henjum S, Aakre I, Lilleengen AM, Garnweidner-Holme L, Borthne S, Pajalic Z *et al.* Suboptimal Iodine Status among Pregnant Women in the Oslo Area, Norway. *Nutrients* 2018; **10**: 1–14.

26 Granfors M, Andersson M, Stinca S, Åkerud H, Skalkidou A, Poromaa IS *et al.* Iodine deficiency in a study population of pregnant women in Sweden. *Acta Obstet Gynecol Scand* 2015; **94**: 1168–74.

27 Aguayo A, Grau G, Vela A, Aniel-Quiroga A, Espada M, Martul P *et al.* Urinary iodine and thyroid function in a population of healthy pregnant women in the North of Spain. *J Trace Elem Med Biol* 2013; **27**: 302–6.

28 Limbert E, Prazeres S, São Pedro M, Madureira D, Miranda A, Ribeiro M *et al.* Iodine intake in Portuguese pregnant women: results of a countrywide study. *Eur J Endocrinol* 2010; **163**: 631–5.

29 Dineva M, Rayman MP, Levie D, Guxens M, Peeters RP, Vioque J *et al.* Similarities and differences of dietary and other determinants of iodine status in pregnant women from three European birth cohorts. *Eur J Nutr* 2019. doi:10.1007/s00394-019-01913-w.

30 Devlieger R, Benhalima K, Damm P, Van Assche A, Mathieu C, Mahmood T *et al.* Maternal obesity in Europe: where do we stand and how to move forward?: A scientific paper commissioned by the European Board and College of Obstetrics and Gynaecology (EBCOG). *Eur J Obstet Gynecol Reprod Biol* 2016; **201**: 203–8.

31 Song R, Wang B, Yao Q, Li Q, Jia X, Zhang J. The Impact of Obesity on Thyroid Autoimmunity and Dysfunction: A Systematic Review and Meta-Analysis. *Front Immunol* 2019; **10**: 1–11.

32 Lecube A, Zafon C, Gromaz A, Fort JM, Caubet E, Baena JA *et al.* Iodine Deficiency Is Higher in Morbid Obesity in Comparison with Late After Bariatric Surgery and Non-obese Women. *Obes Surg* 2015; **25**: 85–89.

33 Poston L, Bell R, Croker H, Flynn AC, Godfrey KM, Goff L *et al.* Effect of a behavioural intervention in obese pregnant women (the UPBEAT study): a multicentre, randomised controlled trial. *lancet Diabetes Endocrinol* 2015; **3**: 767–77.

34 Briley AL, Barr S, Badger S, Bell R, Croker H, Godfrey KM *et al.* A complex intervention to improve pregnancy outcome in obese women; the UPBEAT randomised controlled trial. *BMC Pregnancy Childbirth* 2014; **14**: 74.

35 Flynn AC, Seed PT, Patel N, Barr S, Bell R, Briley AL *et al.* Dietary patterns in obese pregnant women; Influence of a behavioral intervention of diet and physical activity in the UPBEAT randomized controlled trial. *Int J Behav Nutr Phys Act* 2016; **13**: 1–12.

36 Sandell EB, Kolthoff IM. Micro determination of iodine by a catalytic method. *Mikrochim Acta* 1937; **1**: 9–25.

37 GR H. Natu re 0-1 1125. 1953; **559**: 4364.

38 Middleton DRS, Watts MJ, Lark RM, Milne CJ, Polya DA. Assessing urinary flow rate, creatinine, osmolality and other hydration adjustment methods for urinary biomonitoring using NHANES arsenic, iodine, lead and cadmium data. *Environ Heal A Glob Access Sci Source* 2016; **15**: 1–13.

39 Bath SC, Furmidge-Owen VL, Redman CW, Rayman MP. Gestational changes in iodine status in a cohort study of pregnant women from the United Kingdom: season as an effect modifier. *Am J Clin Nutr* 2015; **101**: 1180–7.

40 Gallery EDM, Ross M, Gyory AZ. 24-Hour Urinary Creatinine Excretion Is Not Altered in Human Pregnancy. *Hypertens Pregnancy* 1996; **15**: 257–261.

41 Snart C, Threapleton D, Keeble C, Taylor E, Waiblinger D, Reid S *et al.* Maternal iodine status, intrauterine growth, birth outcomes and congenital anomalies in a UK birth cohort. *BMC Med* 2020; : 1–11.

42 Vanderpump MPJ, Lazarus JH, Smyth PP, Laurberg P, Holder RL, Boelaert K *et al.* Iodine status of UK schoolgirls: A cross-sectional survey. *Lancet* 2011; **377**: 2007–2012.

43 Bath SC, Walter A, Taylor A, Wright J, Rayman MP. Iodine deficiency in pregnant women living in the South East of the UK: The influence of diet and nutritional supplements on iodine status. *Br J Nutr* 2014; **111**: 1622–1631.

44 Kibirige MS, Hutchison S, Owen CJ, Delves HT. Prevalence of maternal dietary iodine insufficiency in the north east of England: Implications for the fetus. *Arch Dis Child Fetal Neonatal Ed* 2004; **89**: 436–439.

45 Pearce EN, Lazarus JH, Smyth PPA, He X, Dall’Amico D, Parkes AB *et al.* Perchlorate and thiocyanate exposure and thyroid function in first-trimester pregnant women. *J Clin Endocrinol Metab* 2010; **95**: 3207–3215.

46 The Scientific Advisory Committee. Sacn Statement on Iodine and Health. 2014; : 1–44.

47 Vitamin supplementation in pregnancy. *Drug Ther Bull* 2016; **54**: 81–84.

48 Dold S, Zimmermann MB, Jukic T, Kusic Z, Jia Q, Sang Z *et al.* Universal salt iodization provides sufficient dietary iodine to achieve adequate iodine nutrition during the first 1000 days: A cross-sectional multicenter study. *J Nutr* 2018; **148**: 587–598.

49 Agarwal S, Reider C, Brooks JR, Fulgoni VL. Comparison of Prevalence of Inadequate Nutrient Intake Based on Body Weight Status of Adults in the United States: An Analysis of NHANES 2001–2008. *J Am Coll Nutr* 2015; **34**: 126–134.

50 García OP, Long KZ, Rosado JL. Impact of micronutrient deficiencies on obesity. *Nutr Rev* 2009; **67**: 559–572.

51 Rifas-Shiman SL, Rich-Edwards JW, Kleinman KP, Oken E, Gillman MW. Dietary quality during pregnancy varies by maternal characteristics in Project Viva: a US cohort. *J Am Diet Assoc* 2009; **109**: 1004–11.

52 Tsigga M, Filis V, Hatzopoulou K, Kotzamanidis C, Grammatikopoulou MG. Healthy Eating Index during pregnancy according to pre-gravid and gravid weight status. *Public Health Nutr* 2011; **14**: 290–296.

53 Moran LJ, Sui Z, Cramp CS, Dodd JM. A decrease in diet quality occurs during pregnancy in overweight and obese women which is maintained post-partum. *Int J Obes (Lond)* 2013; **37**: 704–11.

54 Bouga M, Lean MEJ, Combet E. Iodine and pregnancy-a qualitative study focusing on dietary guidance and information. *Nutrients* 2018; **10**. doi:10.3390/nu10040408.

55 K. N, P. E, I. R. Dietary patterns in pregnancy and associations with socio-demographic and lifestyle factors. *Eur J Clin Nutr* 2008; **62**: 471–479.

56 Brantsæter AL, Haugen M, Samuelsen SO, Torjusen H, Trogstad L, Alexander J *et al.* A Dietary Pattern Characterized by High Intake of Vegetables, Fruits, and Vegetable Oils Is Associated with Reduced Risk of Preeclampsia in Nulliparous Pregnant Norwegian Women. *J Nutr* 2009; **139**: 1162–1168.

57 Fuse Y, Shishiba Y, Irie M. Gestational changes of thyroid function and urinary iodine in thyroid antibody-negative Japanese women. *Endocr J* 2013; **60**: 1095–106.

58 Knudsen N, Christiansen E, Brandt-Christensen M, Nygaard B, Perrild H. Age- and sex-adjusted iodine/creatinine ratio. A new standard in epidemiological surveys? Evaluation of three different estimates of iodine excretion based on casual urine samples and comparison to 24h values. *Eur J Clin Nutr* 2000; **54**: 361–363.

59 Moreno-Reyes R, Glinoer D, Van Oyen H, Vandevijvere S. High prevalence of thyroid disorders in pregnant women in a mildly iodine-deficient country: a population-based study. *J Clin Endocrinol Metab* 2013; **98**: 3694–3701.

**Tables (titles and legends)**

**Table 1 Maternal characteristics of the UPBEAT participants included in this analysis**

|  |  |
| --- | --- |
|  | **Study sample (n=949)** |
| **Age (years)1** | 30.6 (5.6) |
| **Body mass index (kg/m2)2** | 35.2 (32.8-38.5) |
| **Ethnicity3** |  |
| White | 636 (67) |
| Black | 200 (21.1) |
| Asian | 61 (6.4) |
| Other | 52 (5.5) |
| **Index of multiple deprivation3** |  |
| 1 (least deprived) | 42 (4.4) |
| 2 | 70 (7.4) |
| 3 | 111 (11.7) |
| 4 | 311 (32.9) |
| 5 (most deprived) | 412 (43.6) |
| **Parity3** |  |
| Multiparous | 517 (54.5) |
| **Smoking3** |  |
| Current | 61 (6.4) |
| Ex-smoker | 223 (23.5) |
| Non-smoker | 665 (70.1) |
| **Education (years)1** | 14.74 (2.9) |
| **Multivitamin use3** | 510 (58.8) |

Values are mean (SD)1, median (IQR)2 or number (%)3.

**Table 2 Urinary iodine concentration and iodine-to-creatinine ratio in the second trimester of pregnancy**

|  |  |
| --- | --- |
|  | **Second trimester** |
|  | **(15+0-18+6 weeks’ gestation)** |
|  | **(n=949)** |
| **Urinary iodine concentration (µg/L)1** | 147 (99-257) |
| **Iodine-to-creatinine ratio1 (UI/Cr) (µg/g)2** | 97 (59-165) |
| <150µg/g | 665 (70) |

Values are median (interquartile range)1 or number (%)2.

**Table 3 Determinants of iodine-to-creatinine ratio assessed in the second trimester of pregnancy (15-18+6 weeks’ gestation).**

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Maternal characteristics** | **n** | **Unadjusted β-Coefficient** | ***P*** | **n** | **Adjusted β-Coefficient** | ***P*** |
|  |  | **(95%CI)** |  |  | **(95%CI)** |  |
|  |  |  |  |  |  |  |
| **Age (years)** | **949** | **0.03 (0.02 to 0.04)** | **<0.001** | **946** | **0.03 (0.02 to 0.04)** | **<0.001** |
| **Body mass index (kg/m2)** | 949 | -0.01 (-0.02 to -0.0001) | 0.05 | 946 | -0.01 (-0.02 to 0.0003) | 0.06 |
| **Sum of skinfold thicknesses (mm)** | 937 | -0.001 (-0.003 to 0.001) | 0.4 |  | NA | NA |
| **Mid-arm circumference (cm)** | **943** | **-0.004 (-0.02 to 0.008)** | **0.5** |  | **NA** | **NA** |
| **Ethnicity** |  |  |  |  |  |  |
| White |  | Reference | 1 |  | NA | NA |
| Black |  | 0.004 (-0.12 to 0.13) |  |  |  |  |
| Asian |  | -0.003 (-0.21 to 0.21) |  |  |  |  |
| Other |  | 0.03 (-0.19 to 0.26) |  |  |  |  |
| **Index of multiple deprivation** | **946** |  |  |  |  |  |
| 1 (least deprived) |  | **0.14 (-0.12 to 0.39)** | **0.6** |  | NA | NA |
| 2 |  | 0.05 (-0.15 to 0.25) |  |  |  |  |
| 3 |  | 0.12 (-0.05 to 0.28) |  |  |  |  |
| 4 |  | 0.003 (-0.12 to 0.12) |  |  |  |  |
| 5 (most deprived) |  | Reference |  |  |  |  |
| **Parity** | **949** |  |  |  |  |  |
| Nulliparous |  | -0.03 (-0.13 to 0.08) | 0.6 |  | NA | NA |
| Multiparous |  | Reference |  |  |  |  |
| **Smoking** | **949** |  |  | **946** |  |  |
| Current |  | -0.30 (-0.51 to -0.09) | 0.01 |  | -0.13 (-0.34 to 0.08) | 0.5 |
| Ex-smoker |  | -0.07 (-0.20 to 0.05) |  |  | -0.04 (-0.16 to 0.09) |  |
| Never |  | Reference |  |  |  |  |
| **Education (years)** | **949** | **0.03 (0.02 to 0.05)** | **<0.001** | **946** | **0.02 (0.002 to 0.04)** | **0.03** |
| **Multivitamin use** | 868 |  |  |  |  |  |
| Yes |  | Reference | <0.001 | 865 |  | 0.01 |
| No |  | -0.20 (-0.31 to -0.09) |  |  | -0.16 (-0.26 to -0.05) |  |
| **Biochemical measures** |  |  |  |  |  |  |
| Triglycerides | 908 | -0.07 (-0.15 to 0.01) | 0.08 | 905 | -0.06 (-0.14 to 0.03) | 0.2 |
| LDL cholesterol | 908 | -0.02 (-0.09 to 0.04) | 0.5 |  | NA | NA |
| HDL cholesterol | 908 | 0.11 (0.02 to 0.20) | 0.01 | 905 | 0.07 (-0.02 to 0.16) | 0.1 |
| **Dietary patterns** |  |  |  |  |  |  |
| Fruit and vegetable | 628 | 0.02 (-0.05 to 0.09) | 0.5 |  | NA | NA |
| African/ Caribbean | 628 | 0.06 (-0.01 to 0.13) | 0.07 | 627 | 0.07 (-0.003 to 0.14) | 0.06 |
| Processed | 628 | -0.2 (-0.29 to -0.11) | <0.001 | 627 | -0.14 (-0.24 to -0.05) | 0.003 |
| Snacks | 628 | -0.02 (-0.09 to 0.04) | 0.5 |  | NA | NA |

Model 2 (adjusted) was adjusted for maternal age, BMI, ethnicity, education, living in a deprived area, parity and smoking status.

**Table 4 Association between iodine-to-creatinine ratio and birthweight**

|  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  |  |  |  | **Model 1 (unadjusted)** | | |  | **Model 2 (adjusted)** | | |
|  | **UI/Cr <150μg/g** | **UI/Cr ≥150μg/g** |  | **n** | **β-Coefficient (95% CI) /Odds ratio** | ***P*** |  | **n** | **β-Coefficient (95% CI) /Odds ratio** | ***P*** |
|  |  |  |  |  |  |  |  |  |  |  |
| **Categorical UI/Cr** | | | | | | | | | | |
| **Birthweight (g)** | 3455.8 (546.6) | 3535.7 (504.7) |  | 935 | -79.89 (-154.85 to -4.92) | 0.04 |  | 932 | -59.95 (-120.91 to 1.01) | 0.05 |
| **Small for gestational agea** (≤10th customised centile) | 77 (11.7) | 23 (8.2) |  | 935 | 1.48 (0.91 to 2.41) | 0.1 |  | 932 | 1.60 (0.97 to 2.66) | 0.07 |
| **Low birthweight (<2500g)a** | 21 (3.2) | 3 (1.08) |  | 935 | 3.04 (0.90 to 10.28) | 0.07 |  | 932 | 3.23 (0.65 to 15.99) | 0.15 |
|  |  |  |  |  |  |  |  |  |  |  |
| **Continuous UI/Cr** | | | | | | | | | | |
| **Birthweight (g)b** |  |  |  | 935 | 68.95 (25.85 to 112.06) | 0 |  | 932 | 50.72 (15.26 to 86.18) | 0.01 |
| **Small for gestational agea** (≤10th customised centile) |  |  |  | 935 | 0.78 (0.59 to 1.02) | 0.07 |  | 932 | 0.78 (0.58 to 1.04) | 0.09 |
| **Low birthweight (<2500g)a** |  |  |  | **935** | **0.50 (0.28 to 0.89)** | **0.02** |  | **932** | **0.48 (0.20 to 1.15)** | **0.1** |

Model 1 (unadjusted): association between iodine-to-creatinine ratio [adequate (UI/Cr ≥150 μg/g) vs. inadequate (UI/Cr <150 μg/g] and birth outcomes. Reference group women with UI/Cr ≥150 μg/g). Model 2 (adjusted): association between iodine-to-creatinine ratio [adequate (UI/Cr ≥150 μg/g) vs. inadequate (UI/Cr <150 μg/g] and birth outcomes. Reference group women with UI/Cr ≥150 μg/g, adjusted for age, ethnicity, BMI, parity, socioeconomic status, smoking, treatment allocation and infant sex. aodds ratio, badjusted for age, ethnicity, BMI, parity, socioeconomic status, smoking, treatment allocation, infant sex and gestational age at delivery