

Maternal iodine status in a multi-ethnic UK birth cohort: Associations with child cognitive and educational development

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Abstract

Background: Maternal iodine requirements increase during pregnancy to supply thyroid hormones critical for fetal neurodevelopment. Iodine insufficiency may result in poorer cognitive or child educational outcomes but current evidence is sparse and inconsistent.

Objectives: To quantify the association between maternal iodine status and child educational outcomes.

Methods: Urinary iodine concentrations (UIC) and iodine/creatinine ratios (I:Cr) were measured in 6971 mothers at 26–28 weeks' gestation participating in the Born in Bradford cohort. Maternal iodine status was examined in relation to child school achievement (early years foundation stage (EYFS), phonics, and Key Stage 1 (KS1)), other learning outcomes, social and behavioural difficulties, and sensorimotor control in 5745 children aged 4–7 years.

Results: Median (interquartile range) UIC was 76 µg/L (46, 120), and I:Cr was 83 µg/g (59, 121). Overall, there was no strong or consistent evidence to support associations between UIC or I:Cr and neurodevelopmental outcomes. For instance, predicted EYFS and phonics scores (primary outcomes) at the 25th vs 75th I:Cr percentiles (99% confidence intervals) were similar, with no evidence of associations: EYFS scores were 32 (99% CI 31, 33) and 33 (99% CI 32, 34), and phonics scores were 34 (99% CI 33, 35) and 35 (99% CI 34, 36), respectively.

Conclusions: In the largest single study of its kind, there was little evidence of detrimental neurodevelopmental outcomes in children born to pregnant women with iodine insufficiency as defined by World Health Organization–outlined thresholds.

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Alternative functional biomarkers for iodine status in pregnancy and focused assessment of other health outcomes may provide additional insight.

KEYWORDS

born in Bradford, child development, cognition, deficiency, iodine, nutrition, pregnancy, pregnancy

1 | BACKGROUND

Iodine is an essential mineral required for thyroid hormone production, supporting normal metabolic processes throughout the life course.¹ During pregnancy, iodine demands increase to support normal fetal development and compensate for increased renal iodine clearance.² Because thyroid hormones are necessary for normal neuronal migration and myelination during brain development, severe maternal iodine deficiency can potentially hinder child growth and development, including psychomotor and neurological development.^{1,3} Irreversible mental retardation and neurological abnormalities can result from hypothyroxinaemia during critical developmental periods.²

Pregnant women in countries without iodisation or supplementation programmes are at particular risk of deficiency if they have low intakes of dairy, fish, or meat.⁴ Whilst improved general nutrition has resulted in a diminishing prevalence of iodine deficiency disorders in the UK and Western Europe,¹ iodine intake remains potentially inadequate, particularly in vulnerable groups. The World Health Organization defines iodine insufficiency in pregnant populations as median urinary iodine concentration (UIC) < 150 µg/L, with several studies reporting insufficient iodine status in pregnant women at this concentration, but there is little evidence for the functional importance of this threshold.^{1,5}

A small number of observational studies in developed countries have highlighted potential negative consequences of maternal

Synopsis

Study question

What is the association between maternal iodine status, child development, and educational outcomes?

What's already known

Maternal iodine requirements increase during pregnancy to supply thyroid hormones critical for fetal neurodevelopment. Severe iodine insufficiency may result in poorer cognitive outcomes but current evidence with mild-to-moderate insufficiency is sparse and inconsistent.

What this study adds

There was little evidence maternal iodine status was associated with poorer neurodevelopmental outcomes, or with important objective educational outcomes at ages 4-7.

iodine insufficiency for subsequent child cognition.⁶⁻¹⁴ In each case, associations were observed with only some outcome measures that were not consistent across studies. Furthermore, most previous work used existing WHO thresholds or assumed linear associations



to examine neurodevelopmental outcomes^{6-9,12,13} rather than exploring whether any thresholds exist for cognitive outcomes, or where they are. Further inconsistency was identified by a recent randomised controlled trial of iodine supplementation in mildly iodine-deficient pregnant women, which found no evidence of impact on offspring development at 5 years.¹⁵

This study therefore reports on maternal iodine concentrations during pregnancy using a large and well-characterised multi-ethnic cohort of British women, exploring the potential for threshold effects. We apply a comprehensive range of key neurodevelopmental domains in their offspring including objective measures of school achievement, standardised assessments of sensorimotor control and literacy, and teacher-reported assessments of emotional and behavioural development.

2 | METHODS

2.1 | Cohort selection

All babies born to women who agreed to participate in the Born in Bradford cohort study were eligible,¹⁶ recruiting 12 453 women with 13 963 pregnancies between 2007 and 2010. Spot urine samples were collected at 26-28 weeks' gestation from 6644 women (see Figure S1). The current study protocol has been registered at clinicaltrials.gov NCT03552341. The large study size provides sufficient power for detecting associations even of a potentially modest size (see protocol).

2.2 | Exposure

Participants provided urine samples after overnight fasting at routine antenatal clinics for oral glucose tolerance tests. Samples were centrifuged, aliquoted, and barcode-tagged before freezing and storage at -80°C at Bradford Royal Infirmary and subsequent transfer to Leeds Institute of Cardiovascular and Metabolic Medicine, University of Leeds. Urinary¹²⁷iodine concentration ($\mu\text{g/L}$) was estimated using inductively coupled plasma mass spectrometry (ICP-MS) (Thermo iCAP Q, Hemel Hempstead, UK). This methodology is accredited by the Centers for Disease Control and Prevention (CDC) Ensuring the Quality of Urinary Iodine Procedures (EQUIP) standardisation programme.¹⁷ To improve accuracy in measuring iodine status and account for urine dilution, we used the iodine-to-creatinine ratio (I:Cr), which has been shown to better reflect 24-hour urine excretion than UIC in pregnant women.¹⁸ A standard microplate assay utilising the Jaffe reaction was employed for evaluating creatinine concentrations. For inter-laboratory comparison, a subsample of the BiB urine samples were provided to the MRC Elsie Widdowson Laboratory, University of Cambridge, who conduct iodine analysis for the UK National Diet and Nutrition Survey (NDNS). Further details of laboratory methods are reported in Supplementary Methods.

2.3 | Outcomes

The primary outcomes were early years foundation stage (EYFS) profile (ages 4-5), phonics score (ages 5-6), and Key Stage 1 (KS1) school assessments (ages 6-7). These assessments are reported to the local authority and data routinely reported to BiB. Additional learning, behavioural and sensorimotor assessments were also conducted during EYFS (ages 4-5).¹⁹

The EYFS profile is a UK-wide, teacher-led, statutory evaluation of development in five prime areas of learning (personal, social, and emotional development, physical development, and communication and language) and two specific areas of learning (mathematics and literacy).²⁰ These are derived from assessments of achievement in 17 separate early learning goals (ELGs).²⁰ Children were scored as emerging (1), at expected standard (2) or exceeding standard (3) for each ELG, with total scores ranging from 17 to 51. Children were dichotomised as being "at or above the expected level" or "emerging," across all and within each domain.²⁰ The national EYFS assessment was updated in 2013, with scores being incomparable across pre- and post-2013 versions, leading to the exclusion of results from 303 children using the older version.

The phonics assessment focuses on reading of 20 real and 20 pseudo words. Where children repeated the test the next year, results from the first attempt were used. KS1 attainment is measured within key domains (English, Reading, Writing, Mathematics, and Science). The national KS1 assessment methods changed in 2016 during the study and results from the different versions were therefore analysed separately, with the KS1 "English" sub-assessment discontinued after 2016.

Further developmental outcomes were collected for a subgroup of children.²¹ Receptive vocabulary was assessed using the British Picture Vocabulary Scale (BPVS) (2nd Edition). Letter Identification used a sub-test of the Woodcock Reading Mastery Test battery. The Strengths and Difficulties Questionnaire (SDQ) assessed child mental health difficulties as a score out of 40, combining emotional and peer problems (internalising) with conduct and hyperactivity problems (externalising)²² (Web Appendix, p2).

Children's sensorimotor control was measured using the Clinical Kinematic Assessment Tool (CKAT), a tablet-based computerised assessment of children's uni-manual tracking, aiming, and steering performance (Supplementary Methods).

2.4 | Statistical analysis

To account for variation in urine dilution²³ the standardised measure of I:Cr was the primary exposure used, though UIC was also examined. Potential associations between iodine status and neurodevelopment were examined using multiple linear or logistic regression. All models used robust (Sandwich) estimates of variance, taking account of sibling clusters.²⁴

We examined evidence for non-linear associations by fitting restricted cubic splines with four knots placed at 5th, 35th, 65th, and

95th percentiles.²⁵ Adjusted predicted outcomes were plotted for a standard lower-risk cohort participant (primiparous, White ethnicity, English as the dominant language, employed and not materially deprived, non-smoker, non-alcohol drinker, no pregnancy complications, with mean BMI, age, and gestation). This was achieved by centring continuous covariates about the cohort mean and specifying the reference group for categorical variables. The Wald test was used to assess the overall contribution of iodine status to each model.

Adjustment for confounding was informed by a directed acyclic graph (Figure S2). All models were adjusted for potential confounders and competing exposures (Supplementary Methods): maternal age, socio-economic and educational status (Table S2), ethnicity, season, smoking in pregnancy, drinking alcohol in pregnancy, pregnancy complications (gestational diabetes, hypertension, pre-eclampsia), early pregnancy body mass index (BMI), parity, child's sex, length of gestation, and speaking English as an additional language.

To mitigate against multiple testing, 99% CIs were used throughout. Stata version 15.1 (StataCorp) was used for data preparation and analysis.

2.5 | Missing data

Information was incomplete for some covariates, ranging from <1% missing for ethnicity, between 3% and 7% for clinical complications such as pre-eclampsia, pregnancy-induced hypertension, pre-pregnancy hypertension, and gestational diabetes, and between 10% and 12% for smoking status, alcohol use, English as an additional language, socio-economic status and education, and BMI (Table S3). We imputed for missing covariates using multiple imputation by chained equations, with predictive mean matching for continuous variables and logistic regression for categorical variables. Separate imputation models were used for each outcome and exposure, including the outcome and all covariates in each imputation model, with 100 imputed datasets (Supplementary Methods).

2.6 | Sensitivity analysis

Sensitivity analysis was conducted to confirm no substantial differences with results from unimputed data. Sensitivity analyses were also conducted additionally adjusting for total fish intake, consuming five portions of fruit and vegetables per day, and having ever breastfed, available in a subsample of the cohort ($n = 2776$).

Further sensitivity analyses were conducted to assess robustness of results: (a) excluding extreme iodine concentrations >3 standard deviations (SD) from the mean on the log scale ($n = 42$), (b) excluding women with pregnancy complications (gestational diabetes, hypertension or pre-eclampsia ($n = 913$), and (c) excluding users of iodine-containing supplements ($n = 1040$). Evidence of effect-modification by ethnicity (White or Pakistani ethnic background), maternal socio-economic and education category (more deprived and less educated vs less deprived and more educated), or

child's sex, were formally tested by including an interaction term in the model (Supplementary Methods).

2.7 | Ethics approval

Ethical approval for BiB was granted by Bradford Research Ethics Committee (07/H1302/112).

3 | RESULTS

3.1 | Study participants

Of 12 453 women with 13 776 pregnancies recruited into the cohort, 6644 women (53%) provided 6977 urine samples at 26-28 weeks' gestation. In total, 6971 samples were successfully analysed for iodine and creatinine from 6639 women with 7013 children. Women who provided urine samples were broadly similar to those who did not (Table S4). The mean age of participants was 27 years (SD 6) and mean BMI was 26 kg/m² (SD 6) (Table 1). Maternal characteristics and child outcomes are presented by maternal urinary I:Cr in Tables 1 and 2. At least one outcome measure was collected or reported for 5745 (82%) children. Because of incomplete covariate data, subsequent results are based on the imputed datasets.

3.2 | Iodine status

The median (interquartile range (IQR)) UIC for all samples was 76 µg/L (45-120) with 29% below 50 µg/L (Table 1), characterising this population of pregnant women as iodine insufficient by WHO criteria.²⁶ In White European women, the median UIC (82 µg/L, IQR 49-127) was higher than women of Pakistani (73 µg/L, IQR 42-115), or other ethnic background (72 µg/L, IQR 42-111) (Table S5). Median (IQR) I:Cr was 83 µg/g (59-121) and women with lower I:Cr were more likely to have lower socio-economic and educational backgrounds (Table 1).

3.3 | National school assessments

There was some evidence of higher maternal I:Cr associated with higher total EYFS score for I:Cr less than approximately 150 µg/g, though wide confidence intervals allowed the possibility of no association (Figure 1A). For a typical mother with lower-risk characteristics (defined above) the EYFS scores (99% CIs) at the 25th (59 µg/g), 50th (83 µg/g), and 75th (121 µg/g) I:Cr percentiles were predicted to be 32 (99% CI 31, 33), 33 (99% CI 32, 34), and 33 (99% CI 32, 34) µg/g, respectively (Table S6). Sensitivity analyses using complete data only and excluding extreme I:Cr values ($n = 42$) yielded similar estimates (Table S6, Figure S3A,B). There was evidence for the association between I:Cr and EYFS score differed between boys and girls

TABLE 1 Maternal characteristics according to urinary iodine-to-creatinine ratio, n = 6971

	All participants	Maternal urinary iodine-to-creatinine ratio (fifths)				
		1–lower	2	3	4	5–higher
I:Cr (µg/g), median (range)	83 (1-2283)	45 (1-54)	64 (54-73)	83 (73-95)	111 (92-136)	174 (136-2283)
n	6971	1395	1394	1394	1394	1394
I:Cr (µg/g), geometric mean (99% CI)	86.1 (84.6, 87.6)	41.9 (41.1, 42.7)	63.7 (63.4, 64.1)	83.2 (82.8, 83.7)	111.7 (111.0, 112.5)	190.4 (186.2, 194.7)
I:Cr (µg/g), median (IQR)	83.1 (59.3, 121.0)	44.8 (37.6, 50.1)	64.0 (59.3, 68.7)	83.1 (77.8, 89.1)	110.8 (102.5, 121.0)	174.0 (151.5, 218.2)
UIC (µg/L), geometric mean (99% CI)	70.8 (69.2, 72.5)	41.1 (39.1, 43.2)	55.6 (53.1, 58.2)	72.5 (69.4, 75.7)	84.4 (80.9, 88.1)	127.6 (121.7, 133.7)
UIC (µg/L), median (IQR)	76.2 (44.7, 120.2)	46.6 (22.2, 71.2)	61.8 (36.3, 91.3)	80.9 (51.0, 114.2)	92.9 (55.4, 133.6)	137.8 (83.6, 207.9)
Age (y), mean (SD)	27.2 (5.6)	26.4 (5.5)	26.7 (5.5)	27.6 (5.6)	27.4 (5.7)	28.0 (5.5)
BMI (kg/m ²), mean (SD)	25.9 (5.5)	26.7 (5.9)	26.3 (5.6)	25.9 (5.5)	25.4 (5.0)	25.1 (5.1)
Educational achievement ¹ , n (%)						
<5 GSCE equivalent	1271 (18)	325 (23)	266 (19)	255 (18)	212 (15)	213 (15)
5 GSCE equivalent	1827 (26)	416 (30)	398 (29)	342 (25)	352 (25)	319 (23)
A-level equivalent	932 (13)	167 (12)	176 (13)	202 (14)	199 (14)	188 (13)
Higher than A level	1707 (24)	242 (17)	295 (21)	362 (26)	377 (27)	431 (31)
Don't know/other	1234 (18)	245 (18)	259 (19)	233 (17)	254 (18)	243 (17)
Socio-economic status						
Least deprived and most educated	1312 (21)	179 (15)	221 (18)	294 (24)	279 (23)	339 (27)
Employed and not materially deprived	1291 (21)	191 (16)	250 (20)	264 (21)	306 (25)	280 (22)
Employed and no access to money	961 (16)	184 (15)	213 (17)	183 (15)	189 (15)	192 (15)
Receiving benefits and not materially deprived	1174 (27)	430 (35)	362 (29)	304 (25)	284 (23)	294 (23)
Most economically deprived	954 (15)	240 (20)	191 (15)	192 (16)	181 (15)	150 (12)
Ethnic background, n (%)						
White European	3010 (43)	472 (34)	584 (42)	623 (45)	645 (47)	686 (49)
Pakistani	2946 (43)	678 (49)	626 (45)	573 (41)	560 (40)	509 (37)
Other (Black, Indian, mixed, other)	970 (14)	231 (17)	179 (13)	186 (13)	180 (13)	194 (14)
Speaks English as an additional language	2653 (43)	627 (51)	593 (47)	508 (41)	469 (37)	456 (37)
Health and lifestyle in pregnancy						
Complication in pregnancy ³ , n (%)	896 (13)	168 (12)	178 (13)	174 (12)	186 (13)	190 (14)
Drank any alcohol, n (%)	1323 (19)	217 (16)	269 (19)	291 (21)	265 (19)	281 (20)
Smoked, n (%)	1012 (15)	188 (13)	200 (14)	225 (16)	191 (14)	208 (15)
Used any supplements, n (%)	1398 (20)	120 (9)	167 (12)	255 (18)	320 (23)	536 (38)
Used iodine-containing supplement, n (%)	1040 (15)	65 (5)	106 (8)	178 (13)	235 (17)	456 (33)
White fish intake ² (g/d), mean (SD)	21.0 (26.9)	19.5 (28.1)	18.3 (24.0)	25.5 (29.5)	21.9 (26.8)	22.5 (25.7)
Oily fish intake ² (g/d), mean (SD)	1.4 (3.9)	1.1 (3.7)	1.0 (3.0)	1.4 (3.9)	1.9 (4.5)	1.8 (4.1)

(Continues)

TABLE 1 (Continued)

	All participants	Maternal urinary iodine-to-creatinine ratio (fifths)				
		1—lower	2	3	4	5—higher
Total fish intake ² (g/d), mean (SD)	23.9 (29.5)	22.2 (31.2)	20.5 (26.2)	25.4 (31.8)	24.9 (29.2)	26.4 (28.3)
Eats 5 portions of fruit and vegetables per day ² , n (%)						
Always	441 (19)	77 (15)	87 (19)	96 (19)	95 (21)	86 (19)
Sometimes	1781 (75)	384 (76)	353 (76)	367 (74)	337 (73)	340 (76)
Never	154 (6)	44 (9)	26 (6)	34 (7)	27 (6)	23 (5)

Abbreviations: BMI, body mass index; CI, confidence intervals; GCSE, General Certificate of Secondary education; I:Cr, urinary iodine-to-creatinine ratio; IQR, interquartile range; SD, standard deviation; UIC, urinary iodine concentration.

¹UK-equivalent qualifications were calculated from detailed overseas qualifications. GCSEs are standard assessments at age approx. 16. A-level assessments indicate education to approx. age 18.

²Mean calculated from among those who were asked about diet in pregnancy (n = 2776).

³Gestational diabetes, hypertension, or pre-eclampsia.

($P_{\text{interaction}} = 0.005$) with a positive relationship in girls but an inverse relationship in boys (Figure S3C,D).

There was little evidence of an association between I:Cr and phonics scores (Figure 1B) or in subgroups (child's sex, ethnic group, or deprivation and educational group) (Figure S4), though the general trends were consistent with that seen with EYFS scores. Estimates were similar after excluding I:Cr outliers (n = 42) or mothers with complications in pregnancy (n = 913)(Figure S4A,B). There was no evidence of any association between I:Cr and achieving the EYFS or phonics standard (Figure 1C,D) or achieving the EYFS standard in any sub-domain (Figure S5).

Pre-2016 KS1 reading was the only KS1 test showing evidence of an association with maternal I:Cr (Figure 2A,B). For a typical mother with lower-risk characteristics (previously defined), the % achieving the pre-2016 KS1 reading standard (99% CIs) at the 25th, 50th, and 75th I:Cr percentiles were estimated as 85 (99% CI 70, 93), 87 (99% CI 73, 94), and 84 (99% CI 68, 93) $\mu\text{g/g}$, respectively (Table S6). There was no evidence that this association differed by child's sex, ethnic background, or maternal deprivation and education (Figure S6). For other KS1 assessments, the pre-2016 assessments for maths, science, and writing reflected the general trends seen with pre-2016 KS1 reading (Figure 2D,F,H), but wide confidence intervals included the possibility of no association. There was no evidence of any association with any of the post-2016 assessments (Figure 2C,E,G,I), sensitivity analyses, or of differences between subgroups (data not shown).

3.4 | Assessment for learning, sensorimotor control, and behavioural difficulties

SDQ scores (total, internalising and externalising) were not associated with I:Cr in any analyses (Figure S7A-C), nor when SDQ scores were dichotomised (SDQ score ≥ 12 , indicating slightly raised or high) (Figure S7D). There was some evidence that higher I:Cr predicted fewer difficulties in White Europeans than in children with

Pakistani ethnic backgrounds ($P_{\text{interaction}} = 0.005$) (Figure S8C,D), but no evidence of a difference between males and females ($P_{\text{interaction}} = 0.847$) (Figure S8A,B).

There was no evidence of any association between I:Cr and letter identification, receptive vocabulary, or sensorimotor control (Figure S9). In sensitivity analyses, additionally adjusting for diet (fruit, vegetable, and fish intake) or breast feeding gave similar estimates (data not shown). Iodine measured as UIC rather than I:Cr was not found to be associated with any outcomes (Table S6).

4 | COMMENT

4.1 | Principal findings

In this UK cohort, where dietary fortification or supplementation of iodine was not routine, there was little evidence of associations between iodine status measured at 26-28 weeks' gestation and most child educational, learning, or sensorimotor assessments at ages 4-7 years. The single exception to this was in just one of nine KS1 outcomes (pre-2016 KS1 reading). However, whilst uncertain, trends in EYFS scores, phonics, and pre-2016 KS1 assessments were all consistent and there was some evidence of modest positive associations between I:Cr and the EYFS, phonics, and SDQ scores in some sensitivity analyses and subgroups.

4.2 | Strengths of the study

Key strengths in our methodology include objective national measures of educational achievement (outcomes) and robust sample analysis using CDC-endorsed and validated urinary iodine assessment methods (exposure).¹⁷ We also corrected UIC for creatinine concentrations to account for important differences in urine dilution.¹⁸ Our modelling of potential non-linear associations permits identification of any important I:Cr thresholds,

TABLE 2 Child characteristics and cognitive outcomes according to maternal urinary iodine-to-creatinine ratio, n = 7013 children

	All participants	Maternal urinary iodine-to-creatinine ratio (fifths)				
		1—lower iodine	2	3	4	5—higher iodine
I:Cr (µg/g), median (range)	83 (1-2283)	45 (1-54)	64 (54-73)	83 (73-95)	111 (92-136)	174 (136-2283)
n	7013	1401	1401	1401	1401	1401
Sex (male), n (%)	3594 (51)	688 (49)	712 (51)	731 (52)	732 (52)	731 (52)
Early years foundation stage [n = 5383]						
Total points, all sub-domains (range 17-51), median (IQR) ¹	34 (28-37)	34 (27-36)	34 (28-36)	34 (29-37)	34 (28-37)	34 (29-37)
At expected/exceeded level for all sub-domains, n (%)	3031 (56)	605 (55)	604 (54)	612 (58)	614 (58)	596 (58)
Phonics assessment in year 1						
Total score (range 0-40), median (IQR) ¹ [n = 5468]	37 (33-39)	36 (33-38)	37 (33-39)	37 (33-39)	37 (33-39)	37 (34-39)
Achieved the standard (32/40), n (%) [n = 5587]	4424 (79)	887 (78)	894 (78)	874 (80)	903 (80)	866 (80)
Key Stage 1, pre 2016 (achieved standard), n (%) ³ [n = 1317]						
English	1032 (78)	214 (74)	203 (77)	219 (83)	194 (78)	202 (80)
Writing	888 (67)	196 (68)	177 (68)	190 (72)	156 (63)	169 (67)
Maths	1024 (78)	220 (76)	196 (75)	217 (82)	197 (79)	194 (77)
Reading	1038 (79)	214 (74)	205 (78)	220 (83)	195 (79)	204 (81)
Science	1148 (87)	245 (84)	230 (88)	231 (88)	219 (88)	223 (88)
Key Stage 1, from 2016 (achieved standard), n (%) ³ [n = 4162]						
Writing	2963 (71)	591 (71)	602 (70)	587 (72)	607 (71)	576 (72)
Maths	3190 (77)	627 (75)	658 (76)	626 (77)	645 (76)	634 (79)
Reading	3149 (76)	618 (74)	651 (75)	625 (77)	642 (75)	613 (77)
Science	3389 (81)	662 (79)	696 (81)	680 (84)	683 (80)	668 (84)
Strengths and Difficulties Questionnaire [n = 1019]						
Total difficulty score (range 0-40), median (IQR) ²	5 (2-9)	5 (2-9)	4 (2-8)	4 (2-8)	4 (2-9)	5 (2-9)
Close to average (0-11), n (%)	864 (85)	209 (80)	182 (88)	173 (86)	156 (85)	144 (86)
Slightly raised (12-15), n (%)	108 (11)	38 (15)	14 (7)	23 (11)	19 (10)	14 (8)
High or very high (16-40), n (%)	47 (5)	13 (5)	10 (5)	6 (3)	9 (5)	9 (5)
Letter identification score, mean (SD) ¹ [n = 1421]	106.8 (12.9)	105.5 (12.7)	106.3 (13.0)	107.7 (13.1)	106.5 (12.1)	108.4 (13.2)
British Picture Vocabulary Scale, mean (SD) ¹ [n = 1439]	101.0 (16.3)	99.2 (14.3)	100.2 (14.9)	101.0 (16.7)	101.9 (19.1)	103.5 (16.7)
CKAT scores [n = 1426]						
Overall standardised score, mean (SD) ¹	99.5 (10.8)	99.8 (10.6)	99.2 (10.8)	99.1 (10.5)	99.7 (10.7)	99.9 (11.3)
Tracking without guide: root mean square, median (IQR) ²	14.1 (10.1-21.7)	14.2 (10.0-22.3)	14.0 (10.3-21.0)	14.4 (10.4-23.6)	13.3 (10.1-19.8)	14.1 (9.7-21.2)
Tracking with guideline: root mean square, median (IQR) ²	20.8 (12.7-36.1)	20.4 (12.2-35.3)	20.5 (12.4-34.3)	22.8 (13.1-39.0)	19.4 (13.3-37.4)	20.9 (12.8-35.8)
Aiming: path length time (s), median (IQR) ²	2.0 (1.7-2.3)	2.0 (1.7-2.2)	2.0 (1.7-2.3)	1.9 (1.7-2.3)	2.0 (1.8-2.3)	1.9 (1.7-2.3)
Steering: path accuracy (mm), median (IQR) ²	2.1 (1.7-2.7)	2.1 (1.7-2.8)	2.1 (1.7-2.9)	2.0 (1.6-2.6)	2.1 (1.7-2.7)	2.1 (1.7-2.7)

Abbreviations: CI, confidence intervals; CKAT, Clinical Kinematic Assessment Tool; IQR, interquartile range; SD, standard deviation.

¹Higher scores represent better attainment or more advanced understanding.

²Higher scores represent more difficulty or slower and less accurate kinematic ability.

³The KS1 standard before 2016 is defined as "Working securely at level 2B or beyond." From 2016, the standard is defined as "Working at the expected standard or beyond."

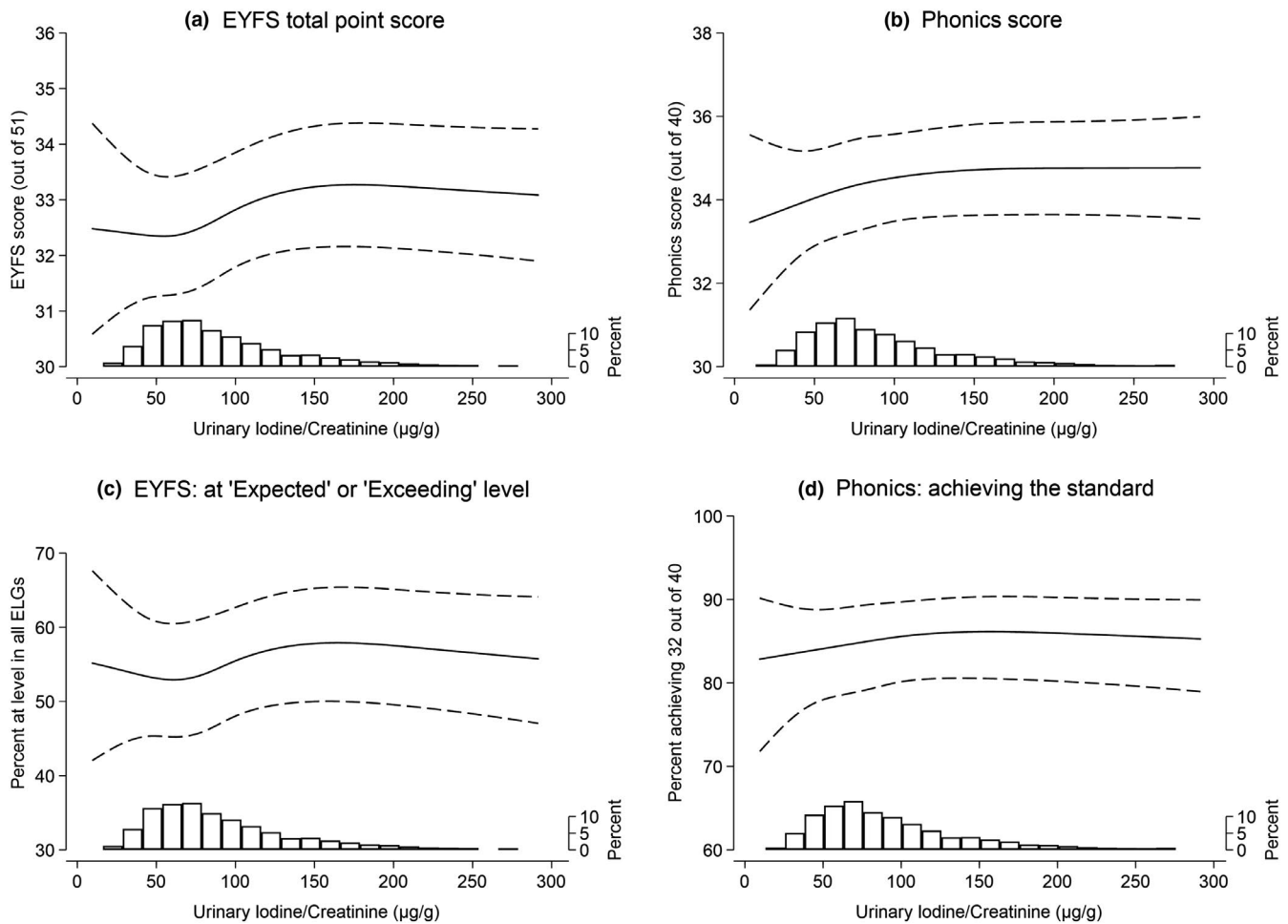


FIGURE 1 Estimated scores and the estimated % of children achieving the EYFS and phonics standards across the range of maternal urinary I:Cr concentrations. Histograms illustrate the distribution of iodine concentrations, and although the figures are curtailed at 300 $\mu\text{g/g}$, the splines (solid line) and 99% CIs (dashed lines) were drawn using data from all participants. Splines were drawn after adjustment for maternal age, ethnic group, season, socio-economic status, BMI, parity, smoking, alcohol, complications in pregnancy, gestation length, child's sex, and speaking English as an additional language. The spline position in these figures illustrates the predicted estimate for typical participants (primiparous, White ethnic background, do not speak English as an additional language, "Employed and not materially deprived," did not smoke, drink, or experience complications in pregnancy, and have average BMI, age, and gestation length). ELG, early learning goals; EYFS, early years foundation stage

though we did not observe any consistent evidence of a threshold effect in this setting. Further strengths include a population with comparatively low iodine status for a developed country allowing a wide range of iodine exposure, and from a multi-ethnic community allowing a wide range of dietary intakes. Our findings support the suggestion that people from South Asian backgrounds are more likely to have insufficient iodine.

4.3 | Limitations of the data

There are limitations in assessing iodine status from single spot urine samples, including high day-to-day variation in iodine intake not reflecting a usual iodine status,²⁷ any rapid changes during pregnancy or brief periods of insufficiency. However, this method is widely used in population studies and is considered sufficient for characterising iodine status in populations.²⁶

Furthermore, urinary iodine excretion has been found to reflect recent iodine intake²⁷ and all samples in this study were collected after overnight fasting and at a similar time of day. Urine samples were unavailable for a proportion of mothers, and there was incomplete follow-up for some developmental outcomes. However, this was mostly because of funding constraints rather than non-response, and women providing samples were similar to those who did not, so unlikely to introduce bias. Our multi-ethnic community may not be representative of the UK, but this affords a range of exposures providing greater opportunity to identify associations with lower maternal iodine status as well as high.

4.4 | Interpretation

Other cohorts previously reported evidence for associations between low iodine status and poorer neurodevelopmental

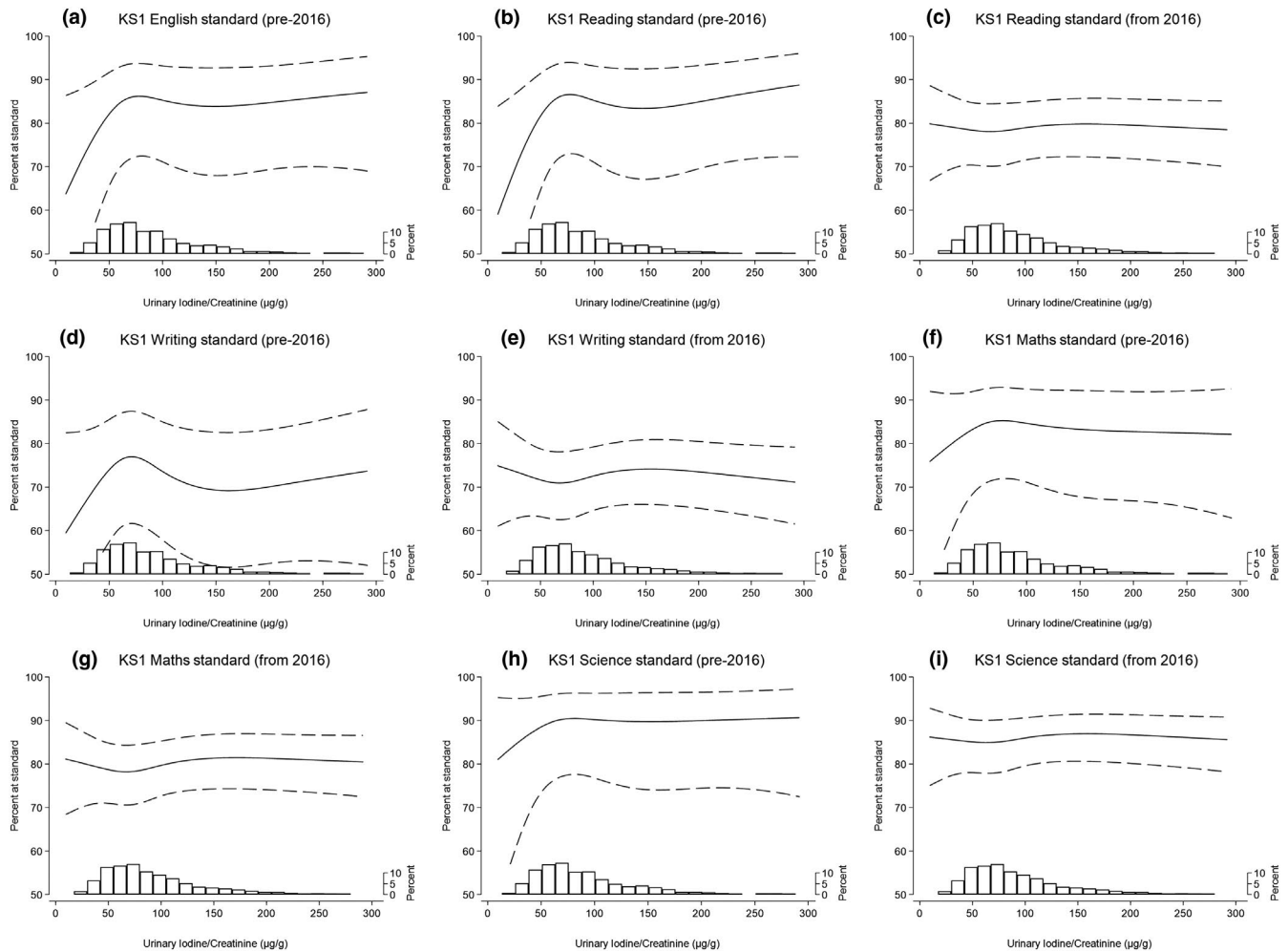


FIGURE 2 Estimated % of children achieving the Key Stage 1 standards across the range of maternal I:Cr concentrations. Adjustments and figure details are as in Figure 1. The KS1 standard before 2016 is defined as 'Working securely at level 2B or beyond'. From 2016 the standard is defined as "Working at the expected standard or beyond"

measures, but findings are not consistent across different studies using similar outcomes, or across different outcomes within the same study.^{7,9-11} Whilst there remains insufficient evidence of any strong associations within our cohort, our findings are more consistent with studies suggesting weak associations in more literacy-based outcomes, language, verbal IQ, and reading, rather than numeracy or motor skills.^{6,7,9-11} Some of the inconsistencies reported across studies may in part reflect different iodine measures. 24-hour urinary iodine excretion is the gold standard measure for iodine status but may not be feasible in large cohort studies, with spot sample UIC and I/Cr measures preferred. I/Cr minimises the variations caused by urine volume differences and dilution in pregnancy, and better reflects 24-hour iodine excretion and circulating iodine levels during pregnancy and postpartum.^{23,28} UIC may also increase the apparent prevalence of iodine deficiency compared with I/Cr measurement.¹⁸

Of existing comparable studies reporting urinary iodine status in pregnancy and neurodevelopmental outcomes in children, this is the largest single cohort by some margin.^{6-11,13,14} Several other

UK-based studies in pregnant women have also suggested iodine insufficiency according to WHO criteria,²⁶ but the BiB cohort had lower iodine status than most (Table S1). This provided a wider range of lower levels of exposure over which to detect any trends and allows the BiB cohort to contribute further to the evidence base.

Despite plausible mechanistic evidence for associations between maternal iodine status, thyroid hormones, and fetal neurodevelopment,²⁹ the evidence from our cohort of mothers does not provide strong evidence to support the hypothesis that insufficient iodine in pregnancy results in substantive adverse educational and cognitive outcomes in the child, within the observed range of mild-to-moderate iodine insufficiency.

It is not possible to identify whether any differences observed between boys and girls (EYFS) are because of biological differences provoking gendered behaviour patterns, or whether different expectations are responsible.³⁰ Previous research using measures such as IQ tests aim to predict future educational outcomes. Whilst it can be argued that IQ tests may be more sensitive, we argue that it

is ultimately educational outcomes that matter more to the future potential of the individual child and for the nation. We therefore consider it a strength to have linked and reported actual national measures of educational achievement rather than proxy measures. The phonics and KS1 tests are substantively objective assessments, less vulnerable to response bias, which may otherwise account for the observed differences.

The association between higher maternal I:Cr and higher probability of achieving pre-2016 KS1 reading standards was not seen in with the post-2016 assessment, despite a larger sample of children, possibly reflecting different assessment criteria. Evidence for associations between I:Cr and raised SDQ scores was inconsistent across analyses and ethnic groups. It is possible that the SDQ score is more sensitive at higher values, or the subjective nature of the assessment may allow some unconscious bias, leading to differences between ethnic groups. Additionally, despite carefully controlling for important potential confounders, we cannot rule out the potential for residual confounding.

The absence of consistent and strong associations may reflect a relatively small contribution of maternal iodine to overall child neurodevelopment compared with other influences, such as child diet, and environmental or social factors. Alternatively, there may be misclassification of outcomes or measurement error in assessments or other measurement error in estimating iodine concentration from a single spot urine sample, though all samples were handled consistently and ICP-MS used throughout. Iodine at 26-28 weeks' gestation may be outside of a critically important time window,¹⁴ with a previous meta-analysis reporting associations between verbal IQ, but not non-verbal, with iodine status in first trimester.¹⁴ However, there is evidence that maternal iodine status does not change markedly through pregnancy,^{31,32} so women with lower iodine status in mid-pregnancy were also likely to have lower iodine status earlier in pregnancy, and any impact of changes would be smoothed somewhat by any storage in the thyroid. It may also be that urinary iodine is not the most sensitive marker of any risk from iodine inadequacy.¹

5 | CONCLUSIONS

In a population with relatively low iodine intake, maternal iodine status at 26-28 weeks' gestation was not consistently associated with most educational, learning, behavioural, or sensorimotor outcomes in the majority of children aged 4-7 years. Whilst some previous studies have found evidence for associations,^{6,7,9-11} findings have been inconsistent both within, and across, studies. Our study suggests caution when linking non-severe iodine insufficiency and neurodevelopmental outcomes. Despite this, there remains scope for examining maternal iodine levels before conception and changes throughout pregnancy in such contexts, and the relationship with objectively measured and specific neurodevelopmental outcomes in children. Identification of additional biomarkers that better characterise and accurately measure longer-term iodine status in

individuals, alongside exploration of timing of samples, may also resolve inconsistencies in the evidence.

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DATA AVAILABILITY STATEMENT

Born in Bradford welcome collaboration with other researchers. Requests for existing data and biological samples will be reviewed, prioritised, and authorised by the BiB Executive Group. Potential collaborators should complete an outline proforma available on the Born in Bradford website (borninbradford.nhs.uk) and submit to the BiB Director.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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