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)

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Summary

Background As a component of thyroid hormones, iodine is essential for fetal brain development. Although the UK has long been considered iodine replete, increasing evidence suggests that it might now be mildly iodine deficient. We assessed whether mild iodine deficiency during early pregnancy was associated with an adverse effect on child cognitive development.

Methods We analysed mother–child pairs from the Avon Longitudinal Study of Parents and Children (ALSPAC) cohort by measuring urinary iodine concentration (and creatinine to correct for urine volume) in stored samples from 1040 first-trimester pregnant women. We selected women on the basis of a singleton pregnancy and availability of both a urine sample from the first trimester (defined as ≤13 weeks' gestation; median 10 weeks [IQR 9–12]) and a measure of intelligence quotient (IQ) in the offspring at age 8 years. Women's results for iodine-to-creatinine ratio were dichotomised to less than 150 μg/g or 150 μg/g or more on the basis of WHO criteria for iodine deficiency or sufficiency in pregnancy. We assessed the association between maternal iodine status and child IQ at age 8 years and reading ability at age 9 years. We included 21 socioeconomic, parental, and child factors as confounders.

Findings The group was classified as having mild-to-moderate iodine deficiency on the basis of a median urinary iodine concentration of 91·1 μg/L (IQR 53·8–143; iodine-to-creatinine ratio 110 μg/g, IQR 74–170). After adjustment for confounders, children of women with an iodine-to-creatinine ratio of less than 150 μg/g were more likely to have scores in the lowest quartile for verbal IQ (odds ratio 1·58, 95% CI 1·09–2·30; p=0·02), reading accuracy (1·69, 1·15–2·49; p=0·007), and reading comprehension (1·54, 1·06–2·23; p=0·02) than were those of mothers with ratios of 150 μg/g or more. When the less than 150 μg/g group was subdivided, scores worsened ongoing from 150 μg/g or more, to 50–150 μg/g, to less than 50 μg/g.

Interpretation Our results show the importance of adequate iodine status during early gestation and emphasise the risk that iodine deficiency can pose to the developing infant, even in a country classified as only mildly iodine deficient. Iodine deficiency in pregnant women in the UK should be treated as an important public health issue that needs attention.

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Introduction

WHO considers iodine deficiency to be "the single most important preventable cause of brain damage" worldwide.[1] Although iodine deficiency is often thought to be a problem of developing countries, industrialised countries are not immune.[2] Indeed, concern is emerging that iodine deficiency might be widespread in the UK. This concern is based on results of a nationwide study of adolescent schoolgirls, which showed mild iodine deficiency in the UK[3] and confirmed findings of smaller UK studies of women of child-bearing age and pregnant women.[4–8]

Iodine deficiency was common in the UK until the 1960s,[9] but unlike many countries, an iodised-salt programme was not introduced to eradicate the deficiency. This absence of implementation was partly because the country experienced iodisation through an adventitious increase in the iodine content of milk as a result of changes in dairy farming after the 1930s.[9] The

apparent eradication of goitre, and reports from Total Diet Studies that iodine intake was more than adequate,[10] fostered the belief that the UK was iodine sufficient. Thus, by contrast with almost all other developed countries, no national surveys have been done to monitor iodine status in the UK population since the 1940s.[3,9]

Iodine deficiency has widespread implications because iodine is a key component of the thyroid hormones, which are crucial for brain and neurological development, particularly during gestation.[11] Although severe deficiency in pregnancy is well known to result in adverse childhood outcomes, such as cretinism and mental retardation,[11] less is known about the effects of mild-to-moderate deficiency.[12] At this deficiency level, only two small intervention studies have been done that have child cognitive outcomes, and although both have shown improvements with iodine supplementation in pregnancy, interpretation is restricted because the studies were neither randomised nor placebo controlled.[13]

Poor neurodevelopmental outcomes have been noted in children of pregnant women with mild thyroid hormone deficiency,[14] but because many of those studies did not measure maternal iodine status and were done in iodine-replete regions, the effect of mild-to-moderate iodine deficiency on cognition is relatively unexplored. Although evidence now suggests that iodine deficiency exists in the UK, no data are available for the effect of prenatal maternal iodine status on childhood cognition. Therefore, with samples and data from the Avon Longitudinal Study of Parents and Children (ALSPAC),[15] we investigated the association between maternal iodine status and child cognitive performance. Because thyroid hormone supply to the fetus during the first trimester is dependent entirely on the mother,[11] we postulated that women with low iodine status in early pregnancy would have children with poorer cognitive outcomes than would those of higher status. A previous ALSPAC study[16] showed a positive association between maternal seafood consumption and child intelligence quotient (IQ), which we suggest could at least partly have been driven by the high iodine content of seafood.

Methods

Study design and participants

ALSPAC methodology has been described elsewhere;[15] briefly, all pregnant women living in the former Avon area in southwest England, with an expected delivery date between April 1, 1991, and Dec 31, 1992, were eligible for inclusion. 14541 pregnant women were enrolled and 13988 children survived for at least 12 months. The study had the approval of the ALSPAC ethics and law committee and the local research ethics committees. We analysed a subsample of the ALSPAC cohort. Funds were available to measure iodine in roughly 1000 women. We selected 1040 women on the basis of a singleton pregnancy and the availability of both a urine sample from the first trimester (defined as ≤13 weeks' gestation; median 10 weeks [IQR 9–12]) and a measure of IQ in the offspring at age 8 years.

Procedures

We studied mother–child pairs by measuring iodine concentration (and creatinine to correct for urine volume) in stored spot-urine samples and investigating the association of these values to the child's IQ at age 8 years and reading ability at age 9 years. Urinary iodine is regarded as a good population biomarker of recent iodine intake because more than 90% of ingested iodine is excreted in the urine.[11] A median urinary iodine concentration of 150–249 μg/L in a population of pregnant women shows iodine adequacy.[1] For assessment of iodine status in individuals, several 24 h urine collections are ideal, but are impractical in large-scale studies.[11] Because ALSPAC had only spot-urine samples available, we reduced the intra-individual variation in daily urine volume by measuring urinary creatinine

concentration. Many investigators have shown that adjustment of urinary iodine concentration by urinary creatinine reduces the variability in iodine excretion when used in same-sex groups of a similar age,[17–19] and has a stronger correlation to measured 24 h urine volume than does iodine concentration.[20] Furthermore, the intra-individual coefficient of variation of the age-adjusted and sex-adjusted iodine-to-creatinine ratio is similar to that of the 24 h iodine excretion.[18] Thus, this adjusted ratio is more reliable than is urinary iodine concentration alone because creatinine accounts for individual hydration status.

Because our cohort were all women and of childbearing age (17–44 years), we used the iodine-to-creatinine ratio as a proxy for individual iodine status.[17–20] We measured iodine and creatinine concentrations in spot-urine samples collected in the first trimester and stored at –20°C. Prolonged frozen storage of urine samples does not affect iodine (Makhmudov A, Iodine Lab Workshop, Centers for Disease Control and Prevention, personal communication) or creatinine concentrations.[21]

We measured ^{127}iodine at the Trace Element Unit, Southampton General Hospital (Southampton, UK), with a dynamic reaction cell inductively-coupled plasma mass spectrometer (SCIEX Perkin-Elmer, Beaconsfield, UK) against a urine calibration curve spiked with 0, 50, 100, 200, and 400 μg/L iodine (potassium iodide, British Drug Houses [BDH], Poole, UK). Samples for the calibration, test, and quality control were diluted 1:14 with diluent (0·3% triton, 0·3% ammonia, 0·001 mol/L EDTA [edetic acid] diammonium salt, and 0·01 mol/L ammonium phosphate; all BDH, Poole). Tellurium (Fisher Scientific, Loughborough, UK) was added as an internal standard. Samples were measured in duplicate. We verified the accuracy of results with the certified reference material seronorm trace elements urine (Nycomed, Norway; certified iodine content 304 μg/L [range 270–338]) and internal quality-control samples D (target value 35·5 μg/L, range 33–38) and E (120 μg/L, 115–125). Observed values were 299 μg/L (SD 14·5, n=229) for the certified reference material, 35·8 μg/L (1·3, n=136) for sample D, and 121 (2·6, n=125) for sample E. Within-run precision gave a relative SD of 2·8% at 36 μg/L, 1·9% at 120 μg/L, and 2·2% at 300 μg/L. Between-run precision gave a relative SD of 2·1% at 36 μg/L, 1·6% at 120 μg/L, and 3·8% at 300 μg/L. Limit of detection was 1 μg/L. We measured urinary creatinine with the UniCel DxC Synchron clinical system analyser (Beckman Coulter, High Wycombe, UK) by the Jaffe rate method.

Outcomes

Child IQ at age 8 years had been assessed in the ALSPAC clinic in 7408 children (56% of the eligible children of the total cohort) with use of an abbreviated form of the Wechsler Intelligence Scale for Children,[22] as previously described.[16] At age 9 years, trained psychologists assessed children's reading speed, accuracy, and comprehension

with the Neale Analysis of Reading Ability.[23] Additionally, children were asked to read real words and a reading score was derived as the sum of correct responses.[24] We defined suboptimum outcomes in any of these measures as scores in the bottom quartile.

Statistical analysis

With no official criteria for iodine adequacy in individuals, we used WHO population criteria for pregnancy[1] to dichotomise maternal urinary iodine-to-creatinine ratio as 150 µg/g or more (ie, sufficient) or less than 150 µg/g (ie, deficient). We did additional supplementary analyses by dividing women in the less than 150 µg/g category into those with iodine concentrations less than 50 µg/g (ie, severe) and those with concentrations of 50–150 µg/g (ie, mild-to-moderate).[12] We used logistic regression to assess the association between maternal iodine status and risk of suboptimum child cognition, with women in the 150 µg/g or more group as the reference category. We used linear regression and independent t tests to investigate the association with the full range of scores for IQ and reading. We compared categorical variables with χ^2 tests.

Because cognitive development is affected by a range of factors we controlled for various potential confounders. These confounders were mostly from self-completed questionnaires and consisted of 14 categorical variables and seven continuous measures. Covariates in the analysis were maternal age at delivery, mother's parenting score (seven-factor measure of cognitive stimulation at 6 months of age), home observation for measurement of environment (HOME) score (six-factor measure of the emotional and cognitive environment at 6 months of age),[25] the family adversity index (18-factor measure of hardship during pregnancy),[26] life-event score (exposure to 41 stressful events during pregnancy), and intakes of omega-3 fatty acids (from seafood) and iron estimated from the Food Frequency Questionnaire, which was completed at 32 weeks' gestation.[27] The appendix has details of mother's parenting, HOME and life-event scores, and the family adversity index. The 14 categorical variables comprised three groups: (1) child factors (sex, birthweight [<2500 g or ≥2500 g], preterm birth [<37 weeks or ≥37 weeks], breastfeeding [none or some], and ethnic origin [white or non-white]); (2) maternal factors (smoking status [non-smoker, smoked before pregnancy but not at 18 weeks' gestation, or smoking at 18 weeks' gestation], alcohol intake [non-consumer, consumed alcohol before pregnancy but not at 18 weeks' gestation, or consumed alcohol at 18 weeks' gestation], parity [zero, one, two or more], maternal depression since birth [yes or no], and use of fish-oil supplements during pregnancy [yes or no]); and (3) markers of socioeconomic status (maternal and paternal education [low=no qualifications, certificate of secondary education, or vocational, medium=O level, and high=A level or degree]), housing status [owned or mortgaged, private

rented, or council rented], and crowding [≤one person or >one person per room]). We included iron intake because of its association with thyroid function.[11] We included estimated intake of omega-3 fatty acid (from seafood) because of previous associations noted between seafood intake and IQ in ALSPAC.[15]

We used three models to adjust the analysis for potential confounders: model one included three variables related to maternal iodine status (maternal age, stressful life-event scores, and maternal education); model two included 15 additional confounders (alcohol intake, breastfeeding, crowding, ethnic origin of the child, family adversity during pregnancy, fish-oil supplements during pregnancy, sex, HOME score, housing status, intake of omega-3 fatty acids from seafood, intake of iron estimated from the Food Frequency Questionnaire, mother's parenting score, parity, paternal education, and smoking status) that were significantly related to at least one cognitive outcome in this cohort; and model three included three additional confounders (birthweight, maternal depression since birth, and preterm birth) that were potentially on the causal pathway. We used these three models in the regression analysis for each cognitive outcome.

	Urinary iodine-to-creatinine ratio		p value
	<150 µg/g (n=646)	≥150 µg/g (n=312)	
Age of mother (years)	29·3 (4·4)	30·3 (4·5)	0·001*
Life-event scores	3·31 (2·34)	3·68 (2·62)	0·03*
Maternal education	..	..	0·002†
Low	133 (21%)	42 (14%)	..
Medium	249 (39%)	109 (35%)	..
High	263 (41%)	161 (52%)	..

Data are mean (SD) or n (%). *Independent t test. †Linear-trend test in cross tabulation analysis.

Table 1: Association between confounders and maternal iodine status

	Urinary iodine-to-creatinine ratio		p value*
	<150 µg/g	≥150 µg/g	
IQ at age 8 years			
Verbal	186/646 (29%)	61/312 (20%)	0·002
Performance	184/646 (28%)	70/312 (22%)	0·05
Total	177/646 (27%)	65/312 (21%)	0·03
Reading at age 9 years			
Words read per minute	170/611 (28%)	62/293 (21%)	0·03
Accuracy	178/612 (29%)	55/283 (19%)	0·001
Comprehension	182/612 (30%)	62/293 (21%)	0·007
Reading score	164/618 (27%)	54/293 (18%)	0·007

Data are n/N (%). Suboptimum outcome defined as scores in the bottom quartile. IQ=intelligence quotient. *χ^2 test comparing proportion of suboptimum cognitive outcomes between the less than 150 µg/g group and the 150 µg/g or more group.

Table 2: Proportion of children classified as having suboptimum outcomes by maternal iodine status (unadjusted)

	Unadjusted			Adjusted model one			Adjusted model two			Adjusted model three		
	OR (95% CI)	p value	n	OR (95% CI)	p value	n	OR (95% CI)	p value	n	OR (95% CI)	p value	n
IQ at age 8 years												
Verbal	1·66 (1·20–2·31)	0·002	958	1·46 (1·04–2·05)	0·03	945	1·68 (1·16–2·42)	0·006	901	1·58 (1·09–2·30)	0·02	880
Performance	1·38 (1·00–1·89)	0·05	958	1·26 (0·91–1·75)	0·16	945	1·26 (0·89–1·76)	0·19	901	1·22 (0·86–1·72)	0·27	880
Total	1·43 (1·04–1·98)	0·03	958	1·27 (0·91–1·78)	0·16	945	1·40 (0·98–2·02)	0·07	901	1·35 (0·93–1·94)	0·11	880
Reading at age 9 years												
Words read per minute	1·44 (1·03–2·00)	0·03	904	1·26 (0·89–1·78)	0·18	893	1·26 (0·87–1·80)	0·22	855	1·20 (0·83–1·74)	0·33	838
Accuracy	1·78 (1·26–2·50)	0·001	905	1·57 (1·10–2·24)	0·01	894	1·71 (1·17–2·50)	0·005	856	1·69 (1·15–2·49)	0·007	839
Comprehension	1·58 (1·13–2·19)	0·007	905	1·39 (0·99–1·97)	0·06	894	1·54 (1·07–2·21)	0·02	856	1·54 (1·06–2·23)	0·02	839
Reading score	1·60 (1·13–2·26)	0·008	911	1·41 (0·98–2·02)	0·06	900	1·47 (1·00–2·15)	0·05	862	1·47 (1·00–2·16)	0·05	844

Suboptimum outcome defined as scores in the bottom quartile. We used maternal iodine status 150 μg/g or more as the reference group. OR=odds ratio. IQ=intelligence quotient.

Table 3: Risk of suboptimum outcomes in children according to urinary iodine-to-creatinine ratio (<150 μg/g vs ≥150 μg/g), unadjusted and adjusted for potential confounders
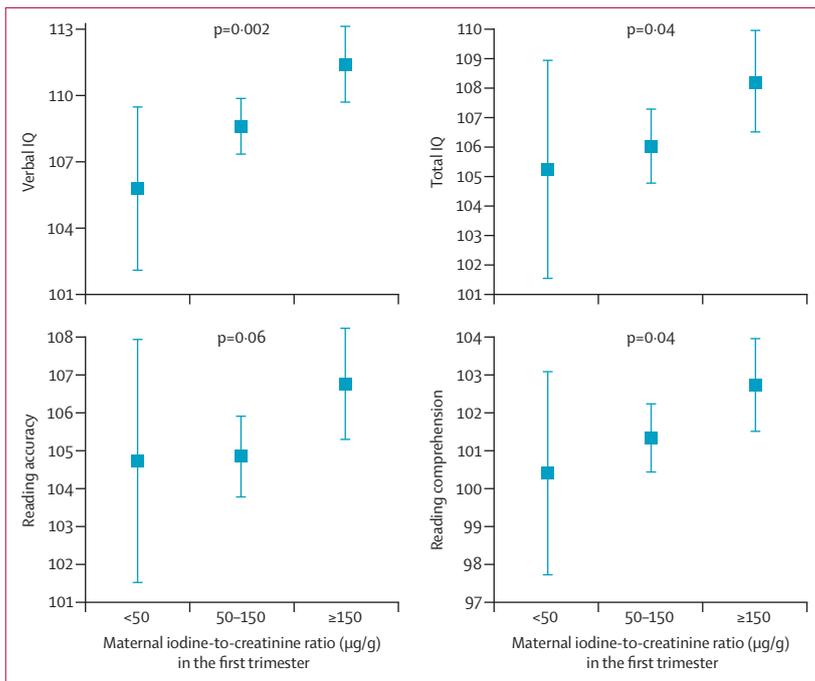

Figure: **Means (95% CIs) for child cognitive outcomes according to maternal iodine status in the first trimester**
Values are adjusted for the effect of confounders (model three). Child verbal and total IQ were assessed at age 8 years and reading accuracy and comprehension at age 9 years. IQ=intelligence quotient.

We compared women in the final analysis of this study with the remainder of those from ALSPAC (appendix). The study sample had markers of higher socioeconomic status (eg, maternal and paternal education, housing status, reduced smoking and crowding), fewer non-white children and low-birthweight babies, a higher proportion of breastfeeding, and higher parenting and HOME scores than did the remainder of the ALSPAC cohort. These differences are probably attributable to drop-out from ALSPAC of those in low socioeconomic groups,[28] because we selected women on the basis of outcome data

when the child was aged 8 years. p values were not adjusted for multiple testing. We did analyses with SPSS (version 19.0).

Role of the funding source
Neither the Waterloo Foundation nor Wassen International had any role in study design, data collection, data analysis, data interpretation, or writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
Because of concern that some urine samples might have been contaminated with test strips containing iodine,[29] we excluded from the analysis 77 women with urinary iodine concentrations of more than 500 μg/L. This cutoff was based on results from both our own, and other studies, of pregnant women in the UK.[7,8] Additionally, we excluded four women who reported taking thyroid hormone drugs, and one woman with inconsistent laboratory measurements of iodine, leaving 958 women for analysis. The median urinary iodine concentration was 91·1 μg/L (IQR 53·8–143; iodine-to-creatinine ratio 110 μg/g, IQR 74–170), classifying this group as having mild-to-moderate iodine deficiency.[1,12] 646 (67%) women had a ratio of less than 150 μg/g, indicating insufficient iodine intake. None of the women reported use of iodine or seaweed (an iodine source) supplements during pregnancy. Maternal education, age, and life-event scores were significantly associated with maternal iodine status (table 1). The appendix shows results for other confounders not significantly associated with iodine status. A higher proportion of children born to women with an iodine status of less than 150 μg/g had suboptimum cognitive outcomes than did those born to women in the 150 μg/g or more group (table 2).

Table 3 shows results for the three models with different numbers of confounders. Odds ratios (ORs) were not greatly changed between the unadjusted and the three adjusted models, although there was some attenuation in effect sizes (roughly 15% for significant outcomes) and this finding, combined with attrition in the numbers of participants, reduced the statistical significance for an association (table 3). We noted significant associations for verbal IQ, reading accuracy, and reading comprehension, with a marginal association for reading score; there was slightly stronger evidence for effects on reading accuracy than on other outcomes with the fully adjusted model (model three; table 3). Although we defined suboptimum IQ as the bottom quartile of scores, the risk of low verbal IQ with maternal iodine status less than 150 μg/g was greater when an IQ less than 85 was used as the cutoff value (OR 2·69, 95% CI 1·21–5·98; adjusted model three), suggesting that iodine deficiency is more strongly associated with low-end IQ scores.

When we subdivided the deficient category, scores worsened ongoing from the 150 μg/g or more group, to the 50–150 μg/g group, to the less than 50 μg/g group for both IQ and reading (figure). Children of mothers with an iodine status between 50 μg/g and 150 μg/g had a significantly increased risk of suboptimum outcomes for verbal IQ, and reading accuracy and comprehension compared with those of mothers with a status of 150 μg/g or more (table 4). Although the effect sizes were larger for children of mothers with an iodine-to-creatinine ratio of less than 50 μg/g, the low numbers of participants in this group probably explains the non-significance. After controlling for all 21 confounders, we noted a significant trend towards a lower risk of suboptimum classification with increasing maternal iodine status for verbal IQ, reading accuracy, and reading score (table 4).

When we assessed cognitive scores as continuous variables, children born to mothers in the 150 μg/g or more group had higher scores for all cognitive outcomes than did those born to mothers in the less than 150 μg/g group (appendix). For example, mean total IQ was 108·5 (SD 15·0) in the 150 μg/g and more group and 105·1 (15·9) in the less than 150 μg/g group (p=0·02). This association was attenuated after we controlled for potential confounders, but evidence of significantly higher scores was shown for verbal and total IQ and reading accuracy in children born to mothers in the 150 μg/g and more group (appendix).

Although the confounders we chose are typical of those included in our other studies,[15] we did a sensitivity analysis by including factors from 6 months to 8 years that could affect cognition; our conclusions were unchanged (data not shown). We also did a sensitivity analysis with iodine-to-creatinine ratio as a continuous variable, for which results were similar (data not shown). We tested all two-way interactions between the iodine variable (<150 μg/g or ≥150 μg/g) and confounders (with our primary outcome of total IQ as

	50 μg/g vs ≥150 μg/g		50–150 μg/g vs ≥150 μg/g		Trend	
	OR (95% CI)	n	OR (95% CI)	n	p value	n
IQ at age 8 years						
Verbal	1·93 (1·00–3·73)	65	1·55 (1·06–2·26)	526	0·01	880
Performance	1·35 (0·71–2·56)	65	1·20 (0·85–1·71)	526	0·25	880
Total	1·52 (0·79–2·93)	65	1·33 (0·92–1·92)	526	0·11	880
Reading at age 9 years						
Words per min	1·50 (0·76–2·95)	59	1·18 (0·81–1·71)	505	0·22	838
Accuracy	1·71 (0·84–3·50)	59	1·69 (1·15–2·50)	506	0·02	839
Comprehension	1·30 (0·64–2·63)	59	1·56 (1·07–2·27)	509	0·07	839
Reading score	2·20 (1·17–4·36)	59	1·41 (0·95–2·08)	512	0·02	844

Suboptimum outcome defined as scores in the bottom quartile. Results are from logistic regression with model three (21 confounder variables). We used maternal iodine-to-creatinine ratio of 150 μg/g or more as the reference group. OR=odds ratio. IQ=intelligence quotient.

Table 4: Risk of suboptimum outcomes in children according to urinary iodine-to-creatinine ratio when the less than 150 μg/g group was divided into less than 50 μg/g and 50–150 μg/g

the dependent variable); these were null (Bonferroni correction; data not shown).

Discussion

The data support our hypothesis that inadequate iodine status during early pregnancy is adversely associated with child cognitive development. Irrespective of the method of statistical testing, our findings were robust. Low maternal iodine status was associated with an increased risk of suboptimum scores for verbal IQ at age 8 years, and reading accuracy, comprehension, and reading score at age 9 years, even after adjustment for many potential confounders. Furthermore, our results suggest a worsening trend in cognitive outcome with decreasing maternal iodine status. Our sizeable study adds to the sparse scientific literature describing the possible in-utero effects of mild-to-moderate iodine deficiency. We have shown that risk of suboptimum cognitive scores in children is not confined to mothers with very low iodine status (ie, <50 μg/g), but that iodine-to-creatinine ratios of 50–150 μg/g (which would suggest mild-to-moderate deficiency[12]) are also associated with heightened risk. Although there are studies that link child cognition to mildly compromised maternal thyroid function,[14] these do not imply an effect of mild-to-moderate iodine deficiency as such, because thyroid function is affected by factors other than iodine intake.

In view of our results, the association between maternal seafood intake and child IQ in a previous study[15] of ALSPAC might have been wholly or partly due to the high iodine content of seafood. Maternal seafood intake of 340 g or less per week was associated with an increased risk of the child's verbal IQ score being in the bottom quartile compared with an intake of more than 340 g per week; these findings are in line with our results. The suggestion in that study was that long-chain omega-3 fatty acids from fish caused this effect, but because we included these fatty acids as a confounder in our analyses,

Panel: Research in context

Systematic review

We searched PubMed with the terms "iodine", "deficiency", "pregnancy", "cognition", and "UK" up to October, 2012. We established that no UK data were available for the effect of maternal iodine status in pregnancy on child cognitive development. Few studies exist from countries with mild-to-moderate iodine deficiency that have data for child cognitive outcome. The Avon Longitudinal Study of Parents and Children (ALSPAC) resource[15] provided an opportunity to investigate this association in a cohort of UK women.

Interpretation

Our study is the first to show an association between mild-to-moderate maternal iodine deficiency in UK pregnant women and impaired cognitive outcomes in their children at ages 8–9 years. Iodine deficiency in pregnant women in the UK should be treated as an important public health issue that needs attention.

they are unlikely to be solely responsible for the effects of seafood on brain development.

Iodine deficiency has been shown in UK schoolgirls[3] and in pregnant women in the past decade;[6–8] however, this is the first study to show that the extent of UK iodine deficiency is associated with adverse childhood outcomes (panel). Although our results are from a study started 21 years ago, they are applicable to the present UK situation because the level of iodine deficiency recorded is similar to that in a recent study of UK pregnant women.[8] Maternal iodine deficiency in pregnancy might have been overlooked as a preventable cause of developmental delay in UK children; poorer cognitive development can set children on a trajectory for poorer school attainment, examination grades, and employment opportunities. At the population level, even a slightly lower than average IQ affects economic success and productivity: a one-point increase in a nation's average IQ has been associated with a persistent 0·11% annual increase in gross domestic product per person.[30]

In the early 1990s, pregnant women and the health professionals advising them would have been unaware of the need for additional iodine beyond the 140 µg per day recommended for adults, with no separate recommendation for pregnancy.[31] Unsurprisingly therefore, these women, from a region that was part of the old UK goitre belt,[9] are deficient by WHO criteria that recommend an iodine intake of 250 µg per day in pregnancy.[1] The fact that UK guidelines for iodine intake in pregnancy have not been revised in line with those of other authorities is more surprising,[1,14,32] and might explain the absence of such advice on government websites.[33] The scarcity of dietary guidance and the fact that the UK has not adopted a national salt-iodisation programme means that iodine intake is left entirely to chance through individual food choices.

Our study has several limitations. First, because it is observational, residual confounding by factors that we either have not measured or not considered is a possibility; however, adjustment for up to 21 variables mostly made little difference to overall effect sizes. We did not control for potential iodine deficiency in the child, but this deficiency is likely to be less of an issue than in pregnancy because the iodine requirement in childhood is substantially lower (90–120 µg per day vs 250 µg per day[1]) and more likely to be met by children's high consumption of milk, the major UK iodine source. Furthermore, because milk intake in the 1990s was higher than in the present day, risk of deficiency in childhood would have been lower.[3] Second, use of one spot-urine sample has limitations for measurement of iodine status in an individual.[11,17,18] However, we minimised these limitations by correcting for urinary volume with use of iodine-to-creatinine ratio (although we appreciate that this adjustment also has limitations[18]) and by broad grouping of women into two categories of iodine status, effectively giving two populations and reducing the effect of any misclassification of status. Third, measurement of iodine status at one timepoint in pregnancy might not represent dietary iodine intake during the entire pregnancy and does not give specific information about maternal thyroid function, of which we have no measure. Fourth, the potential iodine contamination of some urine samples might have masked low values; however, this contamination would have moved iodine values to the 150 µg/g or more group and would thus have weakened effects by causing results to move towards the null. Fifth, selective drop-out might have biased results (because we selected women on the basis of child-outcome measures at 8 years), although epidemiological associations are less susceptible to this form of bias than are prevalence estimates.[28] The size of our study was constrained by funding and should be extended to include a greater number of mother–child pairs from ALSPAC, which would increase power to investigate a wide range of neurological outcomes associated with iodine deficiency. Furthermore, iodine status should be investigated at different gestational ages because deficiency during late gestation might affect other outcomes, such as hearing.[11]

Iodine has not been part of the public health agenda in the UK for the past 50 years; iodine requirements for pregnancy and lactation are outdated, population monitoring has been absent, and advice to pregnant women has not included information about iodine intake. With no official guidance, UK women of childbearing age should ensure that iodine requirements are met, ideally before conception to optimise thyroidal stores,[11] and deficiency should be avoided during pregnancy and lactation. Although kelp supplements are a source of iodine, they should be avoided because their iodine concentration is inconsistent[14] and often very high;[34] excessive maternal iodine intake can have adverse consequences for the mother and fetus.

Because of the observational nature of our study, our findings need to be replicated by others. Evidence from a randomised placebo-controlled trial of the effect of

iodine supplementation in pregnancy on child cognition is needed from regions of mild-to-moderate iodine deficiency because existing evidence from trials in such regions is weak;[13] we, and others, hope to run such a trial in the UK. In view of our findings, we support the call by Vanderpump and colleagues[3] for an urgent review of the UK iodine situation.

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