

BMJ Open Maternal urinary iodine concentration in pregnancy and children's cognition: results from a population-based birth cohort in an iodine-sufficient area

Akhgar Ghassabian,^{1,2} Jolien Steenweg-de Graaff,^{1,2} Robin P Peeters,^{3,4} H Alec Ross,⁵ Vincent W Jaddoe,^{2,6,7} Albert Hofman,⁷ Frank C Verhulst,¹ Tonya White,^{1,8} Henning Tiemeier^{1,7,9}

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For numbered affiliations see end of article.

Correspondence to

Dr Akhgar Ghassabian;
a.ghassabian@erasmusmc.nl

ABSTRACT

Objective: Reports from populations with an insufficient iodine intake suggest that children of mothers with mild iodine deficiency during pregnancy are at risk for cognitive impairments. However, it is unknown whether, even in iodine-sufficient areas, low levels of iodine intake occur that influence cognitive development in the offspring. This study investigated the association between maternal low urinary iodine concentration (UIC) in pregnancy and children's cognition in a population-based sample from a country with an optimal iodine status (the Netherlands).

Setting and participants: In 1525 mother-child pairs in a Dutch multiethnic birth cohort, we investigated the relation between maternal UIC <150 µg/g creatinine, assessed <18 weeks gestation and children's cognition.

Outcomes measures: Non-verbal IQ and language comprehension were assessed during a visit to the research centre using Dutch test batteries when the children were 6 years.

Results: In total, 188 (12.3%) pregnant women had UIC <150 µg/g creatinine, with a median UIC equal to 119.3 µg/g creatinine. The median UIC in the group with UIC >150 µg/g creatinine was 322.9 µg/g and in the whole sample 296.5 µg/g creatinine. There was a univariate association between maternal low UIC and children's suboptimum non-verbal IQ (unadjusted OR=1.44, 95% CI 1.02 to 2.02). However, after adjustment for confounders, maternal low UIC was not associated with children's non-verbal IQ (adjusted OR=1.33, 95% CI 0.92 to 1.93). There was no relation between maternal UIC in early pregnancy and children's language comprehension at 6 years.

Conclusions: The lack of a clear association between maternal low UIC and children's cognition probably reflects that low levels of iodine were not frequent and severe enough to affect neurodevelopment. This may result from the Dutch iodine fortification policy, which allows iodised salt to be added to almost all processed food and emphasises the monitoring of iodine intake in the population.

Strengths and limitations of this study

- The present study is performed in 1525 mother-child pairs from a country with optimal iodine intake (the Netherlands).
- In total, 188 pregnant women (12.3%) had urinary iodine concentration (UIC) <150 µg/g creatinine in early pregnancy.
- In this prospective study, there was no clear relation between maternal relatively low UIC and children's non-verbal IQ or language comprehension at age 6 years.
- As mild iodine deficiency was not prevalent in our sample, it is possible that we did not have the power to detect a significant association between maternal low UIC and children's cognitive delay.
- The lack of a clear association with children's cognitive abilities most likely reflects the fortification policy in the Netherlands, which allows iodised salt to be added to almost all processed foods and emphasises the monitoring of iodine intake in the population.

INTRODUCTION

Iodine is an essential micronutrient required for thyroid hormone production. Severe iodine deficiency is one of the major preventable causes of mental retardation worldwide.¹ Owing to the iodine fortification of salt in many countries, severe iodine deficiency is a rare condition.² Nevertheless, mild-to-moderate iodine deficiency is still considered a major public health concern, even in some developed countries.²

Pregnant women are particularly susceptible to iodine deficiency because of the higher requirement during pregnancy.³ Guidelines recommend an almost twofold increase in dietary iodine intake during pregnancy to maintain optimal thyroid hormone

production in the mother and the fetus.^{3 4} Randomised trials of iodine supplementation in pregnant women from regions with severe iodine deficiency confirmed the effect of maternal severe iodine deficiency on children's cognitive development.⁵ Recently, an observational study by Bath *et al*⁶ in UK (n=1040) showed that the children born to mothers with mild-to-moderate iodine deficiency were at risk of impairments in non-verbal IQ and reading skills. In this study, mild-to-moderate iodine deficiency was defined as having urinary iodine concentration (UIC) lower than 150 µg/g of creatinine on the basis of WHO criteria.³ Similarly, in 228 mother-child pairs in Australia, Hynes *et al*⁷ found a relation between maternal mild iodine deficiency (UIC<150 µg/L) and standardised academic test score, for example, spelling errors, in children. UK and Australia are considered mild-to-moderate iodine-deficient countries by the International Council for Control of Iodine Deficiency Disorders (ICCIDD).² However, it is unclear whether relatively low levels of iodine intake during pregnancy also occur in countries with optimal iodine status, which affects cognitive development in the offspring.

The goal of this study was to investigate the association between maternal low UIC in pregnancy and children's cognition in a population-based sample from a country with an optimal iodine status (the Netherlands).² UIC is a good marker of dietary iodine intake, and can be assessed reliably in spot urine samples at the population level.⁸ Adjustment of UIC for creatinine levels decreases the intraindividual variability in iodine excretion, and provides a more accurate estimate of iodine status in individuals compared to crude values.⁸

METHODS

Participants

This study was embedded within the Generation R Study, a population-based birth cohort in Rotterdam, the Netherlands, which follows children from fetal life onwards.⁹ In total, 7145 pregnant women were recruited in early pregnancy (gestational age <18 weeks). All women had a delivery date between April 2002 and January 2006. During early pregnancy, 2375 pregnant women provided urine samples. UIC was assessed in 2251 pregnant women with a singleton live birth. In this group, data on child cognitive measures were available in 1525 children at age 6 years. There was no difference in maternal iodine levels between mother-child pairs included in the analyses and those excluded because of missing data on child cognitive measures. Likewise, demographic characteristics including maternal age and education, household income or child's characteristics, such as gestational age at birth or ethnic background, did not differ between these two groups.

Measurements

During the first prenatal visit (mean gestational age=13.28 (1.85), range 6.07–17.93 weeks), maternal

urine samples were collected at random times during the day. Urinary iodine was measured by the ceri-arsenite reaction after digestion by means of ammonium persulfate. After brief centrifugation, sodium arsenite solution (0.1 mol/L in 1 mol/L of sulfuric acid) was added. Subsequently, ceri-ammonium sulfate was added, and colour was allowed to develop at 250°C over 60 min. Optical density was assessed at 405 nm. At a concentration of 1.7 µmol/L iodine, the within-assay coefficient of variation (CV) was 5.1% and the between-assay CV was 14.3%. To adjust for total urinary volume, we used the UIC adjusted for creatinine levels (UIC/creatinine). We defined low UIC as values <150 µg/g creatinine. To assess the iodine status of a population, the median (not the mean) UIC is recommended, as UICs are influenced by recent iodine intake. For pregnant populations, the median urinary iodine levels of <150 µg/L are considered as insufficient, 150–249 µg/L as adequate and >500 µg/L as excessive.³

At the age of six (mean age=6.0±0.3 years), the children were invited to visit the Generation R research centre. During this visit, children's non-verbal IQ and language comprehension were assessed using validated Dutch test batteries: two subtests of the Snijders-Oomen Niet-verbale intelligentie Test-Revisie (SON-R 2½–7) and the receptive subtest of the Taaltest voor Kinderen (TvK).^{10 11}

The subtests of SON-R 2½–7 were Mosaics (assesses spatial visualisation abilities), and Categories (assesses abstract reasoning abilities). Raw test scores were converted into non-verbal IQ scores using norms tailored to exact age. For the receptive subtest of the TvK, the children were given 26 test items, and for each item they had to choose the best picture that matched the given words. We added the total correct answers for each child and divided this sum by the total number of items answered, yielding a percentage correct score. The correlation between non-verbal IQ and language comprehension scores was $r=0.42$ ($p<0.001$).

Information on birth date, sex and birth weight was obtained from registries. Gestational age at birth was established using an ultrasound examination during pregnancy. Birth order, parental age and education, marital status, ethnicity, household income and history of smoking, as well as child's history of breast feeding, were assessed by questionnaires. Child's ethnic background was defined based on the country of birth of both parents. Maternal education was defined by the highest completed education. Maternal smoking was assessed at enrolment and in mid and late pregnancy. Maternal weight and length were measured at enrolment and were used to calculate body mass index (BMI). In early pregnancy, maternal folate concentrations were analysed in plasma samples by using an immunoelectrochemiluminescence assay on the Architect System (Abbott Diagnostics BV). We used the Brief Symptom Inventory, a validated self-report questionnaire, to measure maternal psychopathology during pregnancy. In early pregnancy, maternal thyroid

parameters (thyroid stimulating hormone (TSH) and free thyroxine) were measured in the blood.¹² Maternal non-verbal IQ was assessed during the child's visit to the research centre, using a computerised version of the Ravens Advanced Progressive Matrices Test, set I.¹³

Statistical analyses

Mother-child pairs with data on UIC and one or more cognitive measures were included in the analyses. The percentage of missing data for covariates was below 10% except for maternal psychopathology during pregnancy (17%), household income (17%), paternal education (32%) and child's history of breast feeding (13%). Missing values were imputed using multiple imputations. Thirty copies of the original data set were generated with missing values replaced by values randomly generated from the predictive distribution, on the basis of the correlation between the variables.

Maternal low UIC during early pregnancy was the determinant in all analyses. We used linear regression to examine the relation between maternal low UIC and children's non-verbal IQ and language comprehension scores. Language comprehension scores were log transformed to meet the assumption of normality. To facilitate the interpretation of findings, we also used logistic regression to explore whether maternal low UIC was related to the odds of having a non-verbal IQ or language comprehension score in the lowest quartile of the sample (non-verbal IQ < 93 and language comprehension score < 0.77). Potential confounders were selected on the basis of background knowledge.^{6, 7} The relation between maternal UIC and children's cognition was examined in three steps: *model 1*, univariate association; *model 2*, adjusted for the child's sex and age, and maternal age and education; *model 3*, additionally adjusted for a child's ethnic background, birth order, history of breast feeding at age 6 months, paternal age, maternal BMI, maternal history of smoking, maternal IQ, marital status, paternal education, maternal psychopathology in pregnancy, maternal folate concentration in early pregnancy, household income and time of urine sampling in pregnancy. We additionally adjusted the models for maternal thyroid parameters.

RESULTS

Our results showed that Generation R participants were iodine sufficient, with median UIC = 229.6 µg/L (90% range 55.2–732.6; iodine to creatinine ratio 296.5 µg/g creatinine (90% range 112.8–710.2)). In total, 188 pregnant women (12.3%) had UIC < 150 µg/g creatinine; only 4 pregnant women had UIC < 50 µg/g creatinine. Iodine status of the mother in pregnancy was associated with maternal age, BMI, education, psychopathology scores in pregnancy, marital status and plasma folate levels in pregnancy (table 1).

Table 2 represents the association between maternal iodine status in pregnancy and children's cognition at

age 6 years. After adjustment for possible confounders, we did not find a relation between maternal low UIC and children's non-verbal IQ or language comprehension. Additional adjustment of the models for maternal thyroid parameters did not change the results (*B* additionally adjusted for maternal TSH = -0.87, 95% CI -3.32 to 1.45; *B* additionally adjusted for maternal free thyroxine = -0.86, 95% CI -3.19 to 1.47).

DISCUSSION

Convincing evidence from randomised controlled trials in severe iodine-deficient countries has shown the effectiveness of iodine fortification policies or supplementation in pregnant women. However, the existing evidence on the effectiveness of intervention in mild-to-moderate iodine-deficient areas is very limited with regard to an improvement in neurocognitive outcomes in children.¹⁴ The present study, performed in an iodine-sufficient country, showed no clear relation between maternal low UIC in early pregnancy and children's non-verbal IQ or language comprehension at age 6 years. There are several possible explanations for this finding. First, this study was performed in the Netherlands, which has a population with an adequate dietary iodine intake.¹⁵ Also, the median UIC in Generation R participants was much higher than the values reported in pregnant women of other populations (median UIC in this study = 296.5 µg/g creatinine, median UIC in the British study = 110 µg/g creatinine).^{6, 7} Even the median UIC levels in the 'low' group of Generation R (median = 119.3 µg/g creatinine) was higher than the median UIC in the total sample of previous studies. These levels document that the Generation R multiethnic urban sample is iodine sufficient. Furthermore, many pregnant women in our sample may have been mostly iodine sufficient during the period of preconception or early post-natal phase, despite the fact that we observed a spot UIC lower than 150 µg/g creatinine in pregnancy. A single measurement of urinary iodine is a good reflection of iodine status of a population, but may not necessarily reflect the iodine status of the individual. A second possible explanation is that the effect of iodine deficiency on a child's neurodevelopment may, to some extent, be specific to verbal and reading abilities, and less apparent in non-verbal skills. In the Generation R Study, we previously showed that low maternal UIC was related to poor working memory in children, but not to planning/organisation.¹⁶ The absence of any relation between maternal low iodine and cognitive aspects of executive function, in particular planning/organisation, is in line with the findings of the present study. The mechanisms through which mild iodine insufficiency influences other aspects of child neurodevelopment, such as working memory, are not clear. Third, despite a larger sample size compared to the British or Australian studies, the present study had a smaller group of women with UIC < 150 µg/g creatinine (188 women in the present study and 646 women in the British study). As mild iodine deficiency is less prevalent in

Table 1 Baseline characteristics (n=1525)

	UIC adjusted for creatinine levels		p Value
	<150 µg/g	>150 µg/g	
Maternal characteristics			
Age at enrolment, years	30.8 (4.6)	28.6 (5.3)	<0.001
Body mass index at enrolment	24.4 (4.3)	25.3 (5.1)	0.01
Education, %			
Primary	18.2	27.5	0.01
Secondary	54.3	52.2	
Higher education	27.5	20.3	
Psychopathology score in pregnancy	0.14 (0.00–1.02)	0.21 (0.02–1.31)	<0.001
Smoking, %			
Never	78.6	73.1	0.24
Stopped when pregnant	8.5	10.8	
Continued in pregnancy	12.9	16.1	
Household income			
<€1200	6.7	11.5	0.10
>€1200 and <€2000	14.3	13.4	
>€2000	79.0	75.1	
Marital status, married/with partner %	90.4	78.9	<0.001
Folate concentration in early pregnancy, nmol/L	19.2 (9.2)	17.2 (8.2)	0.004
Free thyroxine in early pregnancy, pmol/L	15.28 (0.22)	14.94 (0.09)	0.15
Thyroid stimulating hormone in early pregnancy, mU/L	1.44 (0.08)	1.56 (0.04)	0.20
Maternal IQ score	97 (79–113)	97 (80–113)	0.14
UIC adjusted for creatinine	322.9 (168.6–732.2)	119.3 (65.5–147.1)	<0.001
Gestational age at urine sampling	13.1 (10.5–16.8)	12.9 (10.2–16.5)	0.55
Paternal characteristics			
Age at enrolment, years	33.5 (5.8)	31.9 (6.2)	<0.001
Education, %			
Primary	16.6	19.8	0.23
Secondary	46.6	51.3	
High	36.8	28.9	
Child characteristics			
Age at visit, years	5.9 (0.2)	5.9 (0.2)	1.00
Sex, boy %	48.8	49.5	0.87
First born %	59.1	62.0	0.44
Ethnic background %			
Dutch	57.5	57.2	0.67
Other Western	8.7	7.0	
Non-Western	33.8	35.8	
Birth weight	3441 (521)	3419 (493)	0.60
Gestational age at birth	40.3 (37.4–42.1)	40.3 (37.2–41.9)	0.90
Breast feeding at 6 months, yes	35.6	26.7	0.03
IQ scores at 6 years	102 (15)	100 (16)	0.12
Language comprehension score at 6 years	0.85 (0.62–0.96)	0.85 (0.61–0.96)	0.87

Numbers are mean (SD) for variables with normal distribution, median (90% range) for not normally distributed variables and percentages for categorical variables.

UIC, urinary iodine concentration.

our sample, it is possible that we did not have the power to detect a significant association between maternal low UIC and children's cognitive delay. However, the observed effect sizes for low UIC in the present study (eg, OR=1.33, 95% CI 0.92 to 1.92 for suboptimum non-verbal IQ) were very similar to those of the British study (OR=1.35, 95% CI 0.93 to 1.94) for the comparable measure but did not reach the significance level in either study.

The infrequent occurrence of maternal low UIC during pregnancy and the lack of a clear association

with children's cognitive abilities most likely reflect the Dutch government's iodine fortification policy, which allows iodised salt to be added to almost all processed food and emphasises the monitoring of iodine intake in the population. In case of non-optimal intake at the population level, governmental measures are taken to boost the supply of iodine in the population.¹⁵ This suggests that iodine fortification programmes can prevent adverse neurodevelopmental outcomes in children.

Table 2 Maternal UIC adjusted for creatinine levels and children's non-verbal IQ and language comprehension at age 6 years

Determinant: UIC<150 µg/g	Non-verbal IQ (n=1450)		Language comprehension (n=1319)	
	Score B (95% CI), p value	Suboptimum (n=351) OR (95% CI), p value	Score B (95% CI), p value	Suboptimum (n=323) OR (95% CI), p value
Model 1	-2.16 (-4.52 to 0.19), 0.07	1.44 (1.02 to 2.02), 0.04	-0.01 (-0.03 to 0.02), 0.67	1.03 (0.71 to 1.51), 0.86
Model 2	-0.65 (-2.93 to 1.63), 0.58	1.21 (0.85 to 1.73), 0.30	0.01 (-0.01 to 0.03), 0.44	0.85 (0.57 to 1.27), 0.42
Model 3	-0.86 (-3.10 to 1.38), 0.45	1.33 (0.92 to 1.92), 0.13	0.004 (-0.02 to 0.03), 0.72	0.82 (0.56 to 1.19), 0.82

Suboptimum non-verbal IQ: score in the lowest quartile (IQ scores <93).

Language score was log-transformed to satisfy the assumption of normality.

Suboptimum language comprehension: scores in the lowest quartile (language comprehension scores <0.77).

Model 1: unadjusted.

Model 2: adjusted for child's sex and age at the time of cognitive assessment, maternal age and maternal educational levels.

Model 3: adjusted for child's sex and age at the time of cognitive assessment, ethnic background, birth order and history of breast feeding at age 6 months, and parental age at the time of pregnancy, maternal body mass index, maternal history of smoking, maternal IQ, marital status, parental educational levels, maternal psychopathology in pregnancy, maternal folate concentration in early pregnancy, household income and time of urine sampling in pregnancy.

UIC, urinary iodine concentration.

Author affiliations

¹Department of Child and Adolescent Psychiatry, Erasmus Medical Centre – Sophia Children's Hospital, Rotterdam, The Netherlands

²The Generation R Study Group, Erasmus Medical Centre, Rotterdam, The Netherlands

³Department of Internal Medicine, Erasmus Medical Centre, Rotterdam, The Netherlands

⁴Rotterdam Thyroid Centre, Erasmus Medical Centre, Rotterdam, The Netherlands

⁵Department of Laboratory Medicine, Radboud University Nijmegen Medical Centre, Nijmegen, The Netherlands

⁶Department of Paediatrics, Erasmus Medical Centre – Sophia Children's Hospital, The Netherlands

⁷Department of Epidemiology, Erasmus Medical Centre, Rotterdam, The Netherlands

⁸Department of Radiology, Erasmus Medical Centre, Rotterdam, The Netherlands

⁹Department of Psychiatry, Erasmus Medical Centre, Rotterdam, The Netherlands

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Competing interests None.

Ethics approval The Medical Ethics Committee of the Erasmus Medical Centre approved the study, and written informed consent was obtained from parents.

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REFERENCES

- Zimmermann MB, Jooste PL, Pandav CS. Iodine-deficiency disorders. *Lancet* 2008;372:1251–62.
- Pearce EN, Andersson M, Zimmermann MB. Global iodine nutrition: where do we stand in 2013? *Thyroid* 2013;23:523–8.
- Stagnaro-Green A, Abalovich M, Alexander E, *et al.* Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid* 2011;21:1081–125.
- De Groot L, Abalovich M, Alexander EK, *et al.* Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2012;97:2543–65.
- Zhou SJ, Anderson AJ, Gibson RA, *et al.* Effect of iodine supplementation in pregnancy on child development and other clinical outcomes: a systematic review of randomized controlled trials. *Am J Clin Nutr* 2013;98:1241–54.
- Bath SC, Steer CD, Golding J, *et al.* 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* 2013;382:331–7.
- Hynes KL, Otahal P, Hay I, *et al.* 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.
- Vejbjerg P, Knudsen N, Perrild H, *et al.* Estimation of iodine intake from various urinary iodine measurements in population studies. *Thyroid* 2009;19:1281–6.
- Jaddoe VW, van Duijn CM, Franco OH, *et al.* The Generation R Study: design and cohort update 2012. *Eur J Epidemiol* 2012;27:739–56.
- Tellegen PJ, Winkel M, Wijnberg-Williams B, *et al.* *Snijders-Oomen niet-verbale intelligentietest: SON-R 2 ½-7*. Amsterdam: Boom Testuitgevers, 2005.
- Van Bon WHJ. *Taaltests voor kinderen*. Lisse: Swets & Zeitlinger, 1982.
- Ghassabian A, Bongers-Schokking JJ, Henrichs J, *et al.* Maternal thyroid function during pregnancy and behavioral problems in the offspring: the Generation R Study. *Pediatr Res* 2011;69:454–9.
- Prieler J. *Raven's advanced progressive matrices*. Vol 24. Mödling, Austria: Schufried, 2003.
- Taylor PN, Okosieme OE, Dayan CM, *et al.* Therapy of endocrine disease: impact of iodine supplementation in mild-to-moderate iodine deficiency: systematic review and meta-analysis. *Eur J Endocrinol* 2014;170:R1–15.
- National Institute for Public Health and the Environment. The iodine intake of children and adults in the Netherlands: results of the Dutch National Food Consumption Survey 2007–2010. 2012. <http://www.>



rivm.nl/en/Documents_and_publications/Scientific/Reports/2012/april/The_iodine_intake_of_children_and_adults_in_the_Netherlands_Results_of_the_Dutch_National_Food_Consumption_Survey_2007_2010 (accessed 5 Mar 2014).

16. van Mil NH, Tiemeier H, Bongers-Schokking JJ, *et al.* Low urinary iodine excretion during early pregnancy is associated with alterations in executive functioning in children. *J Nutr* 2012;142:2167–74.