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Maternal urinary iodine concentration in pregnancy and children's cognition: Results from an iodine-sufficient area

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CONTRIBUTORSHIP STATEMENT

Design: Jaddoe, Hofman, Verhulst, White, and Tiemeier

Acquisition of the data: Ghassabian, Alec Ross, and Tiemeier

Analysis of the data: Ghassabian and Tiemeier

Interpretation of the data: Ghassabian, Steenweg - de Graaff, Peeters, White, and Tiemeier

Drafting the article: Ghassabian and Tiemeier

Critical revision of the manuscript for important intellectual content: Ghassabian, Steenweg - de Graaff Peeters, Alec Ross, Jaddoe, Hofman, Verhulst, White, and Tiemeier

ABSTRACT

Background. 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.

Methods. In 1525 mother-child pairs in a Dutch birth cohort, we investigated the relation between maternal urinary iodine concentration (UIC)<150 μg/g creatinine, assessed <18 weeks gestation, and children's nonverbal IQ and language comprehension. Cognition was assessed during a visit to the research centre using Dutch test batteries when the children were six years.

Results. The median UIC was 296.5 μg/g creatinine (90% range 112.8-710.2). We found a relation between maternal low UIC and children's suboptimum nonverbal IQ (unadjusted *OR*=1.44, 95%*CI* 1.02-2.02). However, after adjustment for confounders, maternal low UIC was not associated with children's nonverbal IQ (adjusted *OR*=1.33, 95%*CI* 0.92-1.93). Similar results emerged in the analysis of language comprehension at six years.

Conclusion. 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 as to affect neurodevelopment. This may result from the Dutch iodine supplementation policy.

ARTICLE SUMMARY: 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 UIC<150 μg/g creatinine in early pregnancy.
- In this prospective study, there was no clear relation between maternal relatively low urinary iodine concentration and children's nonverbal IQ or language comprehension at age six years.
- Because 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 urinary iodine concentration and children's cognitive delay.
- The lack of a clear association with children's cognitive abilities likely reflects the policy of iodine supplementation in the Netherlands.

DATA SHARING STATEMENT

No additional data available.

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] Due to the supplementation of iodine to 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 higher requirement during pregnancy.[3] Guidelines recommend an almost 2-fold increase in dietary iodine intake during pregnancy to maintain optimal thyroid hormone production in both mother and foetus.[3,4] Randomized 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. in UK (*n*=1040) showed that the children born to mothers with mild-to-moderate iodine deficiency were at risk of impairments in nonverbal IQ and reading skills.[6] Similarly, in 228 mother-child pairs in Australia, Hynes et al. found a relation between maternal mild iodine deficiency and spelling errors in children.[7] Both UK and Australia are considered mild-to-moderate iodine deficient countries by International Council for Control of Iodine Deficiency Disorders (ICCIDD).[2] However, it is unclear if relatively low levels of iodine intake during pregnancy also occur in countries with optimal iodine status, which affect cognitive development in the offspring.

The goal of this study was to investigate 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).[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 intra-individual variability in iodine excretion, and provides an accurate estimate of iodine status in individuals.[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 foetal life onwards.[9] The Medical Ethics Committee of the Erasmus Medical Centre approved the study, and written informed consent was obtained from parents. 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. Urinary iodine concentration was assessed in 2251 pregnant women with singleton live birth. In this group, data on child cognitive measures were available in 1525 children at age six years. There were no differences in maternal iodine levels and demographics between mother-child pairs included in the analyses and those excluded because of missing data on child cognitive measures.

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 sulphuric acid) was added. Subsequently, ceri-ammonium sulfate was added, and color 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 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) urinary iodine concentration is recommended, as urinary iodine concentrations are influenced by recent iodine intake. For pregnant populations, the median urinary iodine levels of <150 μg/l are considered as insufficient, 150–49 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 nonverbal 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 visualization abilities), and Categories (assesses abstract reasoning abilities). Raw test scores were converted into nonverbal 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 nonverbal 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 breastfeeding 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 immunoelectrochemiluminesence 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. Maternal IQ was assessed during the child's visit to the research centre.

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 were below 10% except for maternal psychopathology during pregnancy (17%), household income (17%), paternal education (32%), and child's history of breastfeeding (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 nonverbal 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 nonverbal IQ or language comprehension score in the lowest quartile of the sample (nonverbal IQ<93 and language comprehension score<0.77). Potential confounders were selected on the basis of background knowledge.[6,7,12] 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 breastfeeding at age six months, paternal age,

maternal body mass index (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.

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 four 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 1 Baseline characteristics (n=1525)

	Urinary Iodine Concentration (UIC) adjusted for creatinine levels		
	<150 μg/g	**>150 μg/g**	***p***
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	
Secondary	54.3	52.2	0.01
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	
Stopped when pregnant	8.5	10.8	0.24
Continued in pregnancy	12.9	16.1	
Household income			
<€1200	6.7	11.5	
>€1200 & <€2000	14.3	13.4	0.10
>€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
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, yr	33.5 (5.8)	31.9 (6.2)	<0.001
Education, %			
Primary	16.6	19.8	
Secondary	46.6	51.3	0.23
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	
Other Western	8.7	7.0	0.67
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
Breastfeeding 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.

Table 2 represents the association between maternal iodine status in pregnancy and children's cognition at age six years. After adjustment for possible confounders, we did not find a relation between maternal low UIC and children's nonverbal IQ or language comprehension.

Table 2 Maternal Urinary Iodine Concentration (UIC) adjusted for creatinine levels and children's nonverbal IQ and language comprehension at age 6 years.

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

Suboptimum nonverbal 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 breastfeeding at age six 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

DISCUSSION

The present study, performed in an iodine sufficient country, showed no clear relation between maternal low UIC in early pregnancy and children's nonverbal IQ or language comprehension at age six 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.[13] 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 multi-ethnic urban sample is iodine sufficient. Furthermore, many pregnant women of our sample may have been mostly iodine sufficient during the period of preconception or early postnatal phase, despite the fact that we observed a spot UIC lower than 150 μg/g creatinine in pregnancy. 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 child's neurodevelopment may be – to some extent – specific to verbal and reading abilities, and less apparent in nonverbal skills. In Generation R, we previously showed that low maternal UIC was related to poor working memory in children, but to not planning/organization.[14] However, the mechanisms through which mild iodine insufficiency influences child neurodevelopment 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). Because mild iodine deficiency is less 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. However, the observed effect sizes for low UIC in the present study

(e.g. *OR*=1.33, 95%*CI*: 0.92-1.92 for suboptimum nonverbal IQ) were very similar to those of the British study (*OR=1.*35, 95%*CI*: 0.93-1.94) 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 likely reflect the policy of iodine supplementation in the Netherlands. This suggests that iodine supplementation policies can prevent adverse neurodevelopmental outcomes in children.

ACKNOWLEDGEMENT

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What is already known on this subject?

Severe iodine deficiency, one of the major preventable causes of mental retardation worldwide, is a rare condition due to the supplementation of iodine to salt in many countries. Nevertheless, mild iodine deficiency is still considered a major public health concern, even in some developed countries. 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.

What this study adds?

The present study, performed in a country with optimal iodine intake, showed no clear relation between maternal relatively low urinary iodine concentration in early pregnancy and children's nonverbal IQ or language comprehension at age six years. The lack of a clear association with children's cognitive abilities likely reflects the policy of iodine supplementation in the Netherlands. This suggests that iodine supplementation policies can prevent adverse neurodevelopmental outcomes in children.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Cohort**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Done**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Done**
Objectives	3	State specific objectives, including any prespecified hypotheses **The goal of this study was to investigate 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).**
Methods		
Study design	4	Present key elements of study design early in the paper **Population-based birth cohort**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **In Rotterdam, the Netherlands** **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.** **Data on child cognitive measures were available in 1525 children at age six years.**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **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.** **At the age of six (mean age=6.0±0.3 years), the children were invited to visit the Generation R research centre.** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed **N/A** *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable

		Done
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). **Done** Describe comparability of assessment methods if there is more than one group **N/A**
Bias	9	Describe any efforts to address potential sources of bias **Done** **Potential confounders were selected on the basis of background knowledge.**
Study size	10	Explain how the study size was arrived at **In this group, data on child cognitive measures were available in 1525 children at age six years.** **Possible power problem is discussed:** **Because mild iodine deficiency is less 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. However, the observed effect sizes for low UIC in the present study (e.g. *OR*=1.33, 95%*CI*: 0.92-1.92 for suboptimum nonverbal IQ) were very similar to those of the British study (*OR=1*.35, 95%*CI*: 0.93-1.94) for the comparable measure but did not reach the significance level in either study.**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **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 nonverbal IQ or language comprehension score in the lowest quartile of the sample (nonverbal IQ<93 and language comprehension score<0.77).**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **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 nonverbal IQ and language comprehension scores.** **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 nonverbal IQ or language comprehension score in the lowest quartile of the sample.** **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 breastfeeding at age six months, paternal age, maternal body mass index (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.**

(*b*) Describe any methods used to examine subgroups and interactions

N/A

(*c*) Explain how missing data were addressed

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.

(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed

There were no differences in maternal iodine levels and demographics between mother-child pairs included in the analyses and those excluded because of missing data on child cognitive measures.

Case-control study—If applicable, explain how matching of cases and controls was addressed

Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy

(*e*) Describe any sensitivity analyses

N/A

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **In total, 7145 pregnant women were recruited in early pregnancy (gestational age<18 weeks). During early pregnancy, 2375 pregnant women provided urine samples. Urinary iodine concentration was assessed in 2251 pregnant women with singleton live birth. In this group, data on child cognitive measures were available in 1525 children at age six years.**
		(b) Give reasons for non-participation at each stage **The reasons are given if known.**
		(c) Consider use of a flow diagram **Criteria for eligibility and exclusion at each stage are described in the text.**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Table 1**
		(b) Indicate number of participants with missing data for each variable of interest **The percentage of missing data for covariates were below 10% except for maternal psychopathology during pregnancy (17%), household income (17%), paternal education (32%), and child's history of breastfeeding (13%).**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **Table 1**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Table 2** **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 breastfeeding at age six months, paternal age, maternal body mass index (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.**
		(*b*) Report category boundaries when continuous variables were categorized **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 nonverbal IQ or language comprehension score in the lowest quartile of the sample (nonverbal IQ<93 and language comprehension score<0.77).**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **N/A**

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **N/A**
Discussion		
Key results	18	Summarise key results with reference to study objectives **The present study, performed in an iodine sufficient country, showed no clear relation between maternal low UIC in early pregnancy and children's nonverbal IQ or language comprehension at age six years. There are several possible explanations for this finding.**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Done**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Done**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Done**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Done in acknowledgement**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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

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

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ABSTRACT

Objectives. 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 multi-ethnic birth cohort, we investigated the relation between maternal UIC<150 *μ*g/g creatinine, assessed <18 weeks gestation, and children's cognition.

Outcomes measures. Nonverbal IQ and language comprehension was assessed during a visit to the research centre using Dutch test batteries when the children were six years.

Results. In total, 188 (12.3%) pregnant women had UIC<150 μg/g creatinine, with a median UIC equals 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 nonverbal IQ (unadjusted OR=1.44, 95%CI: 1.02-2.02). However, after adjustment for confounders, maternal low UIC was not associated with children's nonverbal IQ (adjusted *OR*=1.33, 95%*CI* 0.92-1.93). There was no relation between maternal UIC in early pregnancy and children's language comprehension at six years.

Conclusion. 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 as to affect neurodevelopment. This may result from the Dutch iodine fortification policy, which allows

adding iodized salt to almost all processed food and emphasizes the monitoring of iodine intake in the population.

ARTICLE SUMMARY: 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 UIC<150 μg/g creatinine in early pregnancy.
- In this prospective study, there was no clear relation between maternal relatively low urinary iodine concentration and children's nonverbal IQ or language comprehension at age six years.
- Because 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 urinary iodine concentration and children's cognitive delay.
- The lack of a clear association with children's cognitive abilities likely reflects fortification policy in the Netherlands, which allows adding iodized salt to almost all processed food and emphasizes 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] Due 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 higher requirement during pregnancy.[3] Guidelines recommend an almost 2-fold increase in dietary iodine intake during pregnancy to maintain optimal thyroid hormone production in both mother and foetus.[3,4] Randomized 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. in UK (*n*=1040) showed that the children born to mothers with mild-to-moderate iodine deficiency were at risk of impairments in nonverbal IQ and reading skills.[6] 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 World Health Organization criteria.[3] Similarly, in 228 mother-child pairs in Australia, Hynes et al. found a relation between maternal mild iodine deficiency (UIC<150 µg/L) and standardized academic test score, e.g. spelling errors, in children.[7] Both UK and Australia are considered mild-to-moderate iodine deficient countries by International Council for Control of Iodine Deficiency Disorders (ICCIDD).[2] However, it is unclear if relatively low levels of iodine intake during pregnancy also occur in countries with optimal iodine status, which affect 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 intra-individual 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 foetal life onwards.[9] The Medical Ethics Committee of the Erasmus Medical Centre approved the study, and written informed consent was obtained from parents. 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. Urinary iodine concentration was assessed in 2251 pregnant women with singleton live birth. In this group, data on child cognitive measures were available in 1525 children at age six 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 sulphuric acid) was added.

Subsequently, ceri-ammonium sulfate was added, and color 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 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) urinary iodine concentration is recommended, as urinary iodine concentrations 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 nonverbal 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 visualization abilities), and Categories (assesses abstract reasoning abilities). Raw test scores were converted into nonverbal 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 nonverbal 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 breastfeeding 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 immunoelectrochemiluminesence 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 nonverbal IQ was assessed during the child's visit to the research center, using a computerized 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 were below 10% except for maternal psychopathology during pregnancy (17%), household income (17%), paternal education (32%), and child's history of breastfeeding (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 nonverbal 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 nonverbal IQ or language comprehension score in the lowest quartile of the sample (nonverbal 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 breastfeeding at age six months, paternal age, maternal body mass index (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 four 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 1 Baseline characteristics (n=1525)

	Urinary Iodine Concentration (UIC) adjusted for creatinine levels		
	<150 μg/g	**>150 μg/g**	***p***
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	
Secondary	54.3	52.2	0.01
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	
Stopped when pregnant	8.5	10.8	0.24
Continued in pregnancy	12.9	16.1	
Household income			
<€1200	6.7	11.5	
>€1200 & <€2000	14.3	13.4	0.10
>€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, yr	33.5 (5.8)	31.9 (6.2)	<0.001
Education, %			
Primary	16.6	19.8	
Secondary	46.6	51.3	0.23
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	
Other Western	8.7	7.0	0.67
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
Breastfeeding 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.

Table 2 represents the association between maternal iodine status in pregnancy and children's cognition at age six years. After adjustment for possible confounders, we did not find a relation between maternal low UIC and children's nonverbal 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, 1.45; *B* additionally adjusted for maternal free thyroxine=-0.86, 95%*CI*: -3.19, 1.47).

Table 2 Maternal Urinary Iodine Concentration (UIC) adjusted for creatinine levels and children's nonverbal IQ and language comprehension at age 6 years.

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

Suboptimum nonverbal 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 breastfeeding at age six 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

DISCUSSION

Convincing evidence from randomized 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 nonverbal IQ or language comprehension at age six 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 multi-ethnic urban sample is iodine sufficient. Furthermore, many pregnant women of our sample may have been mostly iodine sufficient during the period of preconception or early postnatal phase, despite the fact that we observed a spot UIC lower than 150 μg/g creatinine in pregnancy. 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 child's neurodevelopment may be – to some extent – specific to verbal and reading abilities, and less apparent in nonverbal skills. In the Generation R Study, we previously showed that low maternal UIC was related to poor working memory in children, but to not planning/organization.[16] The absence of any relation between maternal low iodine and cognitive aspects of executive function, in particular planning/organization, 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 *μ*g/g creatinine (188 women in the present study and 646 women in the British study). Because mild iodine deficiency is less 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. However, the observed effect sizes for low UIC in the present study (e.g. *OR*=1.33, 95%*CI*: 0.92-1.92 for suboptimum nonverbal IQ) were very similar to those of the British study (*OR=1.*35, 95%*CI*: 0.93-1.94) 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 likely reflect the Dutch government's iodine fortification policy, which allows adding iodized salt to almost all processed food and emphasizes 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.

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CONTRIBUTORSHIP STATEMENT

Design: Jaddoe, Hofman, Verhulst, White, and Tiemeier

Acquisition of the data: Ghassabian, Alec Ross, and Tiemeier

Analysis of the data: Ghassabian and Tiemeier

Interpretation of the data: Ghassabian, Steenweg - de Graaff, Peeters, White, and Tiemeier

Drafting the article: Ghassabian and Tiemeier

Critical revision of the manuscript for important intellectual content: Ghassabian, Steenweg - de Graaff Peeters, Alec Ross, Jaddoe, Hofman, Verhulst, White, and Tiemeier

COMPETING OF INTEREST

The authors have nothing to disclose.

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DATA SHARING STATEMENT

No additional data available.

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What is already known on this subject?

Severe iodine deficiency, one of the major preventable causes of mental retardation worldwide, is a rare condition due to the iodine fortification of salt in many countries. Nevertheless, mild iodine deficiency is still considered a major public health concern, even in some developed countries. 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.

What this study adds?

The present study, performed in a country with optimal iodine intake, showed no clear relation between maternal relatively low urinary iodine concentration in early pregnancy and children's nonverbal IQ or language comprehension at age six years. The lack of a clear association with children's cognitive abilities likely reflect the Dutch iodine fortification policy, which allows adding iodized salt to almost all processed food and emphasizes the monitoring of iodine intake in the population. In case of non-optimal intake, measures would be taken to boost the supply of iodine in the population.This suggests that iodine fortification programmes can prevent adverse neurodevelopmental outcomes in children.

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

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COMPETING OF INTEREST

The authors have nothing to disclose.

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DATA SHARING STATEMENT

No additional data available.

ABSTRACT

Objectives. 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 multi-ethnic birth cohort, we investigated the relation between maternal UIC<150 *μ*g/g creatinine, assessed <18 weeks gestation, and children's cognition.

Outcomes measures. Nonverbal IQ and language comprehension was assessed during a visit to the research centre using Dutch test batteries when the children were six years.

Results. In total, 188 (12.3%) pregnant women had UIC<150 μg/g creatinine, with a median UIC equals 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 nonverbal IQ (unadjusted OR=1.44, 95%CI: 1.02-2.02). However, after adjustment for confounders, maternal low UIC was not associated with children's nonverbal IQ (adjusted *OR*=1.33, 95%*CI* 0.92-1.93). There was no relation between maternal UIC in early pregnancy and children's language comprehension at six years.

Conclusion. 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 as to affect neurodevelopment. This may result from the Dutch iodine fortification policy, which allows

adding iodized salt to almost all processed food and emphasizes the monitoring of iodine intake in the population.

ARTICLE SUMMARY: 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 UIC<150 μg/g creatinine in early pregnancy.
- In this prospective study, there was no clear relation between maternal relatively low urinary iodine concentration and children's nonverbal IQ or language comprehension at age six years.
- Because 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 urinary iodine concentration and children's cognitive delay.
- The lack of a clear association with children's cognitive abilities likely reflects fortification policy in the Netherlands, which allows adding iodized salt to almost all processed food and emphasizes 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] Due 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 higher requirement during pregnancy.[3] Guidelines recommend an almost 2-fold increase in dietary iodine intake during pregnancy to maintain optimal thyroid hormone production in both mother and foetus.[3,4] Randomized 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. in UK (*n*=1040) showed that the children born to mothers with mild-to-moderate iodine deficiency were at risk of impairments in nonverbal IQ and reading skills.[6] 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 World Health Organization criteria.[3] Similarly, in 228 mother-child pairs in Australia, Hynes et al. found a relation between maternal mild iodine deficiency (UIC<150 µg/L) and standardized academic test score, e.g. spelling errors, in children.[7] Both UK and Australia are considered mild-to-moderate iodine deficient countries by International Council for Control of Iodine Deficiency Disorders (ICCIDD).[2] However, it is unclear if relatively low levels of iodine intake during pregnancy also occur in countries with optimal iodine status, which affect 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 intra-individual 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 foetal life onwards.[9] The Medical Ethics Committee of the Erasmus Medical Centre approved the study, and written informed consent was obtained from parents. 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. Urinary iodine concentration was assessed in 2251 pregnant women with singleton live birth. In this group, data on child cognitive measures were available in 1525 children at age six 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 sulphuric acid) was added.

Subsequently, ceri-ammonium sulfate was added, and color 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 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) urinary iodine concentration is recommended, as urinary iodine concentrations 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 nonverbal 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 visualization abilities), and Categories (assesses abstract reasoning abilities). Raw test scores were converted into nonverbal 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 nonverbal 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 breastfeeding 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 immunoelectrochemiluminesence 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 nonverbal IQ was assessed during the child's visit to the research center, using a computerized 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 were below 10% except for maternal psychopathology during pregnancy (17%), household income (17%), paternal education (32%), and child's history of breastfeeding (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 nonverbal 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 nonverbal IQ or language comprehension score in the lowest quartile of the sample (nonverbal 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 breastfeeding at age six months, paternal age, maternal body mass index (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 four 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 1 Baseline characteristics (n=1525)

	Urinary Iodine Concentration (UIC) adjusted for creatinine levels		
	<150 μg/g	**>150 μg/g**	***p***
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	
Secondary	54.3	52.2	0.01
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	
Stopped when pregnant	8.5	10.8	0.24
Continued in pregnancy	12.9	16.1	
Household income			
<€1200	6.7	11.5	
>€1200 & <€2000	14.3	13.4	0.10
>€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, yr	33.5 (5.8)	31.9 (6.2)	<0.001
Education, %			
Primary	16.6	19.8	
Secondary	46.6	51.3	0.23
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	
Other Western	8.7	7.0	0.67
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
Breastfeeding 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.

Table 2 represents the association between maternal iodine status in pregnancy and children's cognition at age six years. After adjustment for possible confounders, we did not find a relation between maternal low UIC and children's nonverbal 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, 1.45; *B* additionally adjusted for maternal free thyroxine=-0.86, 95%*CI*: -3.19, 1.47).

Table 2 Maternal Urinary Iodine Concentration (UIC) adjusted for creatinine levels and children's nonverbal IQ and language comprehension at age 6 years.

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

Suboptimum nonverbal 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 breastfeeding at age six 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

DISCUSSION

Convincing evidence from randomized 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 nonverbal IQ or language comprehension at age six 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 multi-ethnic urban sample is iodine sufficient. Furthermore, many pregnant women of our sample may have been mostly iodine sufficient during the period of preconception or early postnatal phase, despite the fact that we observed a spot UIC lower than 150 μg/g creatinine in pregnancy. 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 child's neurodevelopment may be – to some extent – specific to verbal and reading abilities, and less apparent in nonverbal skills. In the Generation R Study, we previously showed that low maternal UIC was related to poor working memory in children, but to not planning/organization.[16] The absence of any relation between maternal low iodine and cognitive aspects of executive function, in particular planning/organization, 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 *μ*g/g creatinine (188 women in the present study and 646 women in the British study). Because mild iodine deficiency is less 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. However, the observed effect sizes for low UIC in the present study (e.g. *OR*=1.33, 95%*CI*: 0.92-1.92 for suboptimum nonverbal IQ) were very similar to those of the British study (*OR=1*.35, 95%*CI*: 0.93-1.94) 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 likely reflect the Dutch government's iodine fortification policy, which allows adding iodized salt to almost all processed food and emphasizes 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.

ACKNOWLEDGEMENT

The Generation R Study is conducted by the Erasmus Medical Centre in close collaboration with the Municipal Health Service Rotterdam area, Rotterdam, the Rotterdam Homecare Foundation, Rotterdam and the Stichting Trombosedienst & Artsenlaboratorium Rijnmond (STAR-MDC), Rotterdam. We gratefully acknowledge the contribution of children and parents, general practitioners, hospitals, midwives and pharmacies in Rotterdam. The work of Dr Tiemeier and Dr Ghassabian was supported by a research grant from the European Community's 7th Framework Programme (FP7/2008–2013) under grant agreement 212652 (NUTRIMENTHE project, "The Effect of Diet on the Mental Performance of Children").

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What is already known on this subject?

Severe iodine deficiency, one of the major preventable causes of mental retardation worldwide, is a rare condition due to the iodine fortification of salt in many countries. Nevertheless, mild iodine deficiency is still considered a major public health concern, even in some developed countries. 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.

What this study adds?

The present study, performed in a country with optimal iodine intake, showed no clear relation between maternal relatively low urinary iodine concentration in early pregnancy and children's nonverbal IQ or language comprehension at age six years. The lack of a clear association with children's cognitive abilities likely reflect the Dutch iodine fortification policy, which allows adding iodized salt to almost all processed food and emphasizes the monitoring of iodine intake in the population. In case of non-optimal intake, measures would be taken to boost the supply of iodine in the population.This suggests that iodine fortification programmes can prevent adverse neurodevelopmental outcomes in children.

STROBE Statement—checklist of items that should be included in reports of observational studies

	Item No	Recommendation
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract **Cohort**
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found **Done**
Introduction		
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported **Done**
Objectives	3	State specific objectives, including any prespecified hypotheses **The goal of this study was to investigate 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).**
Methods		
Study design	4	Present key elements of study design early in the paper **Population-based birth cohort**
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection **In Rotterdam, the Netherlands** **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.** **Data on child cognitive measures were available in 1525 children at age six years.**
Participants	6	(*a*) *Cohort study*—Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up **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.** **At the age of six (mean age=6.0±0.3 years), the children were invited to visit the Generation R research centre.** *Case-control study*—Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study*—Give the eligibility criteria, and the sources and methods of selection of participants
		(*b*) *Cohort study*—For matched studies, give matching criteria and number of exposed and unexposed **N/A** *Case-control study*—For matched studies, give matching criteria and the number of controls per case
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable

		Done
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). **Done** Describe comparability of assessment methods if there is more than one group **N/A**
Bias	9	Describe any efforts to address potential sources of bias **Done** **Potential confounders were selected on the basis of background knowledge.**
Study size	10	Explain how the study size was arrived at **In this group, data on child cognitive measures were available in 1525 children at age six years.** **Possible power problem is discussed:** **Because mild iodine deficiency is less 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. However, the observed effect sizes for low UIC in the present study (e.g. *OR*=1.33, 95%*CI*: 0.92-1.92 for suboptimum nonverbal IQ) were very similar to those of the British study (*OR=1*.35, 95%*CI*: 0.93-1.94) for the comparable measure but did not reach the significance level in either study.**
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why **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 nonverbal IQ or language comprehension score in the lowest quartile of the sample (nonverbal IQ<93 and language comprehension score<0.77).**
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding **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 nonverbal IQ and language comprehension scores.** **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 nonverbal IQ or language comprehension score in the lowest quartile of the sample.** **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 breastfeeding at age six months, paternal age, maternal body mass index (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.**

(*b*) Describe any methods used to examine subgroups and interactions

N/A

(*c*) Explain how missing data were addressed

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.

(*d*) *Cohort study*—If applicable, explain how loss to follow-up was addressed

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.

Case-control study—If applicable, explain how matching of cases and controls was addressed

Cross-sectional study—If applicable, describe analytical methods taking account of sampling strategy

(*e*) Describe any sensitivity analyses

N/A

Continued on next page

Results		
Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed **In total, 7145 pregnant women were recruited in early pregnancy (gestational age<18 weeks). During early pregnancy, 2375 pregnant women provided urine samples. Urinary iodine concentration was assessed in 2251 pregnant women with singleton live birth. In this group, data on child cognitive measures were available in 1525 children at age six years.**
		(b) Give reasons for non-participation at each stage **The reasons are given if known.**
		(c) Consider use of a flow diagram **Criteria for eligibility and exclusion at each stage are described in the text.**
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders **Table 1**
		(b) Indicate number of participants with missing data for each variable of interest **The percentage of missing data for covariates were below 10% except for maternal psychopathology during pregnancy (17%), household income (17%), paternal education (32%), and child's history of breastfeeding (13%).**
		(c) *Cohort study*—Summarise follow-up time (eg, average and total amount)
Outcome data	15*	*Cohort study*—Report numbers of outcome events or summary measures over time **Table 1**
		Case-control study—Report numbers in each exposure category, or summary measures of exposure
		Cross-sectional study—Report numbers of outcome events or summary measures
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included **Table 2** **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 breastfeeding at age six months, paternal age, maternal body mass index (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.**
		(*b*) Report category boundaries when continuous variables were categorized **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 nonverbal IQ or language comprehension score in the lowest quartile of the sample (nonverbal IQ<93 and language comprehension score<0.77).**
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period **N/A**

Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses **N/A**
Discussion		
Key results	18	Summarise key results with reference to study objectives **The present study, performed in an iodine sufficient country, showed no clear relation between maternal low UIC in early pregnancy and children's nonverbal IQ or language comprehension at age six years. There are several possible explanations for this finding.**
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias **Done**
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence **Done**
Generalisability	21	Discuss the generalisability (external validity) of the study results **Done**
Other information		
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based **Done in acknowledgement**

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.