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# Low Urinary Iodine Excretion during Early Pregnancy Is Associated with Alterations in Executive Functioning in Children[1–3]

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## Abstract

The rare but deleterious effects of severe iodine deficiency during pregnancy on cognitive functioning of children are well known. Reports on possible associations between mild-to-moderate maternal iodine deficiency and child development, however, are scarce. In a population-based cohort we examined the association between maternal urinary iodine during early pregnancy and executive functioning in children at 4 y of age. In addition, we investigated the modification of this association by maternal diet and thyroid function. During pregnancy, we measured urinary iodine and thyroid hormone concentrations in 1156 women. In 692 of their children impairment of executive functioning was assessed by the Behavior Rating Inventory of Executive Function. Five hundred mothers of Dutch national origin completed an FFQ. Analyses were performed by using regression models. The children of mothers with low urinary iodine showed higher scores on the problem scales of inhibition [$\beta$ = 0.05 (95% CI: 0.01, 0.10), $P$ = 0.03] and working memory [$\beta$ = 0.07 (95% CI: 0.02, 0.12), $P$ = 0.003]. Although maternal dietary intake and thyroid hormone concentration did not significantly modify these associations, the associations between urinary iodine and problems of inhibition were attenuated after adjustment for maternal psychological symptoms. In addition, the consumption of bread [$\beta$ = 0.61 (95% CI: 0.27, 0.95), $P$ < 0.001] and eggs ($\beta$ = 1.87 (95% CI: 0.13, 3.62), $P$ = 0.04] was associated with higher urinary iodine. Thus, low maternal urinary iodine during pregnancy is associated with impaired executive functioning in children. Because these symptoms were subclinical and occurred at an early age, future studies are needed to show whether these children are more vulnerable to develop later clinical disorders. J. Nutr. 142: 2167–2174, 2012.

## Introduction

Iodine is required for the synthesis of thyroid hormones, which play an essential role in fetal and early postnatal growth and development of most organs, especially of the brain (1). This micronutrient is mainly obtained by the consumption of foods that contain natural or synthetic iodine. Because during pregnancy the production of thyroxin physiologically increases by 50%, this increased need has to be compensated with a 50% increase in daily iodine requirement.

Despite considerable progress over the past decades in developing countries, the prevalence of inadequate iodine intake is estimated at >20% in industrialized countries previously considered to be iodine sufficient (2,3). Surveys indicate that especially girls and women of reproductive age may have deficient iodine consumption (4,5). This also raises concern about a poor iodine intake during pregnancy in the United States and Europe for which changing dietary habits, especially low fish and milk consumption, are suggested to be responsible.

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[3] Supplemental Tables 1–3 are available from the ''Online Supporting Material'' link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.


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Severe iodine deficiency during pregnancy detrimentally affects maternal thyroid function and child neurobehavioral development (6). The severity of maternal iodine deficiency during pregnancy is related to the degree of impaired functioning in children (7). It is unknown, however, whether the increasing mild-to-moderate iodine deficiencies during pregnancy, especially in industrialized countries, detrimentally affects maternal thyroid function and neurodevelopment in offspring (8,9).

Whereas cognition provides global insight of brain functioning, executive functioning represents different structures and functions of the brain involved in the cognitive regulation of behavior (10). Executive function is defined as a group of processes, e.g., inhibition, working memory, and the ability to plan and organize, that are dependent on and influence more basic cognitive abilities, such as attention, language, and perception (11).

Iodine concentration in urine and excreted by the kidneys is a good marker of the dietary intake of iodine during the previous days. It is the measure of choice for assessment of iodine status because of its noninvasiveness (12). In epidemiologic studies urinary iodine concentrations of spot samples are used to define the iodine status in individuals and in populations (13).

Against this background the aims of our study were to examine in a population-based cohort with available assessments of maternal diet and urinary iodine in early pregnancy the associations between the following: *1*) maternal diet and urinary iodine; *2*) maternal urinary iodine and thyroid function; and *3*) maternal urinary iodine, diet, and executive functioning in children at the age of 4 y.

## Participants and Methods

*Design and study population.* This study was embedded in the Generation R Study, an ongoing population-based birth cohort from fetal life onward. Mothers with a delivery date from April 2002 until January 2006 were enrolled in the study. The Generation R Study was designed to identify early environmental and genetic determinants of growth, development, and health. The data obtained comprised detailed questionnaires, ultrasonography, and biological samples. The study has been previously described in detail (14).

The flow chart of the study population is presented in **Figure 1**. For this study we selected all mother-child pairs ($n$ = 1316) with available measurements of urinary iodine and thyroid hormone concentrations in early pregnancy. The sample for iodine measurements was selected semi-randomly from the total cohort with measurements of thyroid hormones ($n$ = 5831), with oversampling of women who had free thyroxin 4 (FT4)[16] concentrations below the 10th percentile: Of the sample, 21.4% ($n$ = 282) of the women had low FT4 concentrations, whereas 78.6% ($n$ = 1035) of the sample consisted of women with higher FT4 concentrations. To account for this oversampling, cases were weighted on the ratio of the population proportion on the sample proportion.

No instance of fertility treatment was reported in this sample. Twin pregnancies ($n$ = 14) were excluded because thyroid variables in multiple pregnancies are different from those in singleton pregnancies (15). In addition, we excluded mother-child pairs in which mothers received any thyroid-related medication including thyroxin ($n$ = 7) or who were thyroid peroxidase antibody–positive ($n$ = 145), which left 1156 mother-child pairs. A total of 574 mothers were of Dutch national origin; 500 of these completed an FFQ, 431 completed the Behavior Rating Inventory of Executive Function for Preschoolers (BRIEF-P) for the child, and 391 completed both an FFQ and the BRIEF-P. Of women who were not of Dutch national origin ($n$ = 583), 354 completed an FFQ, 261 completed the BRIEF-P, and 185 completed both questionnaires.

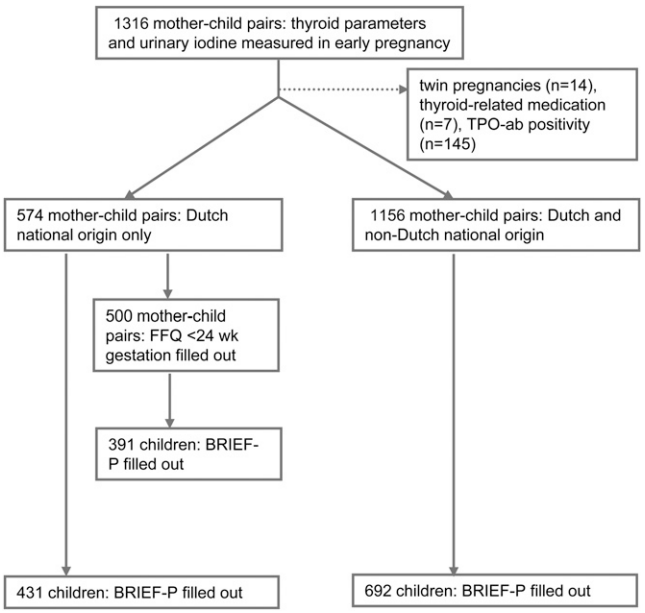


**FIGURE 1** Selected characteristics of mothers and children by iodine intake. Thirty-seven mothers with ≥2 children participated. BRIEF-P, Behavior Rating Inventory of Executive Function for Preschoolers; TPO-ab, thyroid peroxidase antibody.

The study was approved by the Medical Ethics Committee of the Erasmus MC, University Medical Centre, Rotterdam, The Netherlands. Written informed consent was obtained from all individuals before participation.

*Maternal dietary intake.* In early pregnancy (median: 13.2 wk; 95% range: 10.2–17.6) the nutritional intake of the previous 3 mo was assessed by using a modified version of a validated semiquantitative FFQ (16). The FFQ consists of 293 food items and is structured according to meal patterns. Questions on the FFQ include consumption frequency, portion size, preparation method, and additions of the foods. Portion sizes were estimated by using household measures and photographs (17). To calculate average daily nutritional values, the Dutch food composition table 2006 was used (18).

The 293 food items were reduced to 19 food groups, according to the European Prospective Investigation into Cancer and Nutrition classification, on the basis of origin, culinary usage, and nutrient profiles (19).

To extract dietary patterns from food consumption data in the selected study population, we used principal components analysis (PCA) as previously described by Hu (20) and applied in a number of recent studies of dietary patterns and fetal and child development (21,22). PCA was performed in the total Generation R cohort of women of Dutch national origin ($n$ = 3463). Because of the larger number of cases this gives a more accurate estimate.

Each woman was given a score for each of the factor or dietary patterns, calculated as the product of the food group value and its factor loadings summed across foods. For convenience we termed this score "adherence to dietary pattern." The 3 most prevalent dietary patterns were selected for further analysis.

Spearman correlation coefficients were used to correlate the dietary patterns after the PCA with the original food groups.

*Maternal urinary iodine and thyroid function.* At the same time of the assessment of nutritional intake, maternal single voided 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

[16] Abbreviations used: ADHD, attention-deficit hyperactivity disorder; BRIEF-P, Behavior Rating Inventory of Executive Function for Preschoolers; FT4, free thyroxin 4; PCA, principal components analysis; TSH, thyroid-stimulating hormone.

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 iodine to creatinine ratio. Spot urine sampling is considered to be a reliable and practical laboratory technique available to quantify iodine excretion in individuals (23). Because >90% of iodine intake is excreted in the urine, urinary iodine excretion is considered the most appropriate indicator of iodine intake of the previous days as well as of iodine status (12). We defined low urinary iodine as an iodine:creatinine ratio below the 10th percentile of the study sample [0.04–0.12 mmol/mol creatinine (48.6–136.1 μg/g creatinine)].

To assess maternal thyroid function, at the same time of urine sampling venous blood samples were collected in plain tubes. Serum was transported to the regional laboratory for storage at −80°C within 3 h after sampling (24). Thyroid-stimulating hormone (TSH) and FT4 from the stored samples were assayed in batches of 50–150 over a 6-mo period by using a chemiluminescence assay on the Vitros ECI Immunodiagnostic System (Ortho Clinical Diagnostics). The interassay CV for TSH and FT4 were <4.1 and <5.4%, respectively, and the intraassay CV for TSH and FT4 were <1.2 and <2.7%, respectively.

Thyroid peroxidase antibodies were measured by using ImmunoCAP 250 assays (Phadia AB) and regarded as positive when >0.06 IU/L.

*Assessment of executive functioning.* We measured impairment of executive functioning in children at 4 y of age by using the BRIEF-P (25). The BRIEF-P is a standardized rating scale developed to provide a window into behaviors associated with specific domains of executive functioning in children aged 2 to 5 y.

The BRIEF-P consists of a single rating form, completed by parents or other caregivers, with 63 items in 5 scales: inhibition (to stop own behavior), shifting (to make a transition and change focus from one mindset to another), emotional control (to modulate emotional responses), working memory (to hold information in mind for the purpose of completing a task), and planning/organization (to manage current and future-oriented task demands within the situational context). The scales can be combined into the global executive composite. Raw scale scores are transformed to age- and gender-normed T-scores [50 ± 10 (mean ± SD)] to make scores comparable. Higher scores indicate more problems with executive functioning. In the present study, the parents were asked to rate how often a particular behavior of the child was problematic in the preceding month.

Other researchers have shown the content validity of the BRIEF-P (26). The subscales of BRIEF-P show adequate to high test-retest reliability, indicating suitability for research purposes.

*Covariates.* Information was obtained by questionnaires during pregnancy on maternal age, national origin, education, parity, prenatal tobacco and alcohol use, and the use of folic acid supplements or (iodine- and non-iodine-containing) multivitamin supplements. The season of completing the FFQ was registered. National origin of the mother was based on the country of birth of her parents. The educational level of the mother was assessed by the highest completed grade and reclassified into 3 categories: primary school, secondary school, and higher education (e.g., higher vocational education or higher).

Maternal smoking and alcohol use were classified as "no use," "use until pregnancy was confirmed," and "continued use during pregnancy." Women were asked about the use of any multivitamin supplement or folic acid supplement during the past 6 mo.

Height and weight were measured without shoes or heavy clothing; BMI was calculated from height and weight (kg/m$^2$). At 20 wk pregnancy, we measured maternal psychological problems by using the Brief Symptom Inventory (27).

Child gender, birth weight, Apgar score 1 min after birth, and the mode of delivery were derived from the medical records completed by gynecologists and midwives. To define gestational age at birth, we used the last menstrual period of the mother and the ultrasound examination at the first prenatal visit. In case these methods disagreed, pregnancy was dated on the ultrasound data.

The following covariates were considered as potential confounders: maternal age, national origin, education, BMI, parity, prenatal psychological problem score, smoking, alcohol use, energy intake, use of any multivitamin, folic acid supplement use, season of completing FFQ, and child's gender, gestational age at birth, birth weight, Apgar score 1 min after birth, and the mode of delivery.

*Statistical analysis.* Because the FFQ used is only validated in Dutch populations, all analyses with food intake were primarily restricted to mothers of Dutch national origin ($n$ = 500).

First, associations between separate food groups as independent variables and urinary iodine as an outcome variable were analyzed by using multivariable regression analyses. Second, Pearson's correlation coefficients between urinary iodine and maternal TSH and FT4 were calculated. Prior to analyses, TSH concentrations were transformed by the natural logarithm to achieve normal distribution. Third, associations between urinary iodine as a categorical determinant (below or above the 10th percentile) and BRIEF-P problem scores were calculated with multivariate regression analyses. Because BRIEF-P scores were non-normally distributed, scores were transformed by the natural logarithm. Associations between urinary iodine and BRIEF-P problem scores were further explored by adding FT4 in the model. Maternal psychological problems were added separately in the model to assess the change in estimate due to psychological problems. In addition, we stratified the analysis on executive functioning for gender, and tested interactions between gender and low urinary iodine. For any observed association between urinary iodine and executive functioning the model was further explored by adjustment for maternal intake of food groups. To reduce the number of comparisons, we tested only food groups that were associated with urinary iodine as mediators. To test whether the estimates were influenced by maternal national origin, all analyses were repeated among children of pooled Dutch and non-Dutch mothers ($n$ = 692). Finally, to test whether results depended on the choice of the 10th percentile cutoff for urinary iodine, all analyses were repeated using a 5th- and 15th-percentile threshold.

All analyses were adjusted for gestational age at blood and urine sampling and estimated protein intake. A covariate was selected as a confounding variable if the effect estimates changed by ≥5% in the exploratory regression analyses. By using this criterion, maternal age, national origin, education, prenatal smoking, and child's birth weight and gestational age at blood sampling were included as confounders in the final multivariable analyses.

Differences between characteristics of mothers and children were tested by using Student's $t$ test or Mann-Whitney $U$ test for continuous variables and Pearson's chi-square test for categorical variables.

Missing data of covariables were completed by using the Markov chain Monte Carlo multiple imputation technique, creating 5 data sets. Subsequently, multivariable regression analyses were performed separately on each completed data set and thereafter combined to one pooled estimate (28). For all analyses, results including imputed missing data are presented. All analyses were performed by using SPSS software, version 17.0 (SPSS, Inc.).

## Results

Characteristics of mothers and children categorized by urinary iodine are presented in **Table 1**. In comparison to mothers with urinary iodine above the 10th percentile, mothers with low urinary iodine (mothers of Dutch national origin only, $n$ = 56; all mothers, $n$ = 117) were younger, had a higher BMI, and less often experienced an instrumental delivery. They presented more often with psychological symptoms and showed lower TSH concentrations.

Associations between the separate food groups and urinary iodine were analyzed by using multivariable regression analyses. In mothers of Dutch national origin, cereal products [$\beta$ = 0.61 (95% CI: 0.27, 0.95), $P$ < 0.001] and eggs [$\beta$ = 1.87 (95% CI: 0.13, 3.62), $P$ = 0.04] were significantly associated with higher urinary iodine (**Supplemental Table 1**).

**TABLE 1** Selected characteristics of mothers and children by maternal urinary iodine excretion[1]

| | Low urinary iodine, <10th percentile ($n$ = 117) | Urinary iodine ≥10th percentile ($n$ = 1039) | P value |
|---|---|---|---|
| Mothers | | | |
| Age, *y* | 27.4 ± 5.4 | 30.2 ± 5.0 | <0.001 |
| Gestational age at enrollment, *wk* | 13.2 (9.2, 17.7) | 13.2 (10.2, 17.6) | 0.55 |
| National origin, *%* | | | 0.19 |
| Dutch | 48.2 | 50.7 | |
| Western, other | 8.9 | 14.0 | |
| Non-Western | 42.9 | 35.3 | |
| Parity, *% primiparous* | 61.1 | 62.8 | 0.95 |
| BMI, *kg/m²* | 25.4 ± 5.6 | 24.4 ± 4.3 | 0.05 |
| Educational level, *%* | | | 0.18 |
| Primary school | 31.3 | 23.9 | |
| Secondary school | 48.2 | 52.5 | |
| High education | 20.5 | 23.6 | |
| Psychological symptoms | 0.2 (0.0, 1.6) | 0.2 (0.0, 1.3) | 0.003 |
| Smoking during pregnancy, *%* | | | 0.30 |
| Never | 67.6 | 74.9 | |
| Until pregnancy was confirmed | 12.0 | 9.9 | |
| Continued | 20.4 | 15.2 | |
| Multivitamin use, *% yes* | 27.1 | 30.8 | 0.50 |
| TSH, *mU/L* | 1.3 ± 0.8 | 1.5 ± 1.0 | 0.001 |
| FT4, *pmol/L* | 15.0 ± 3.3 | 14.6 ± 3.4 | 0.14 |
| Children | | | |
| Gender, *% male* | 47.0 | 50.8 | 0.33 |
| Birth weight, *kg* | 3.4 ± 0.5 | 3.5 ± 0.5 | 0.31 |
| Gestational age, *wk* | 40.1 ± 1.6 | 40.1 ± 1.6 | 1.00 |
| Apgar score 1 min after birth | 8.5 ± 1.1 | 8.6 ± 1.1 | 0.44 |
| Mode of delivery, *%* | | | 0.04 |
| Spontaneous vaginal | 87.2 | 77.4 | |
| Instrumental vaginal | 9.2 | 14.9 | |
| Cesarean section | 3.7 | 7.7 | |

[1] Values are means ± SD, medians (95% range), or percentages; total $n$ = 1156. FT4, free thyroxin 4; TSH, thyroid-stimulating hormone.

Three factors were derived from the PCA as the most prominent dietary patterns used in the study group of women of Dutch national origin. The first factor was labeled the Mediterranean dietary pattern and explained 8.1% of the variance of dietary intake of the total study group. It comprised high intakes of vegetables, fruit, cereal products, vegetable oil, and fish and shellfish. The second factor, which explained 6.9% of the total variance, was labeled a traditionally Dutch dietary pattern because it was characterized by high intakes of potatoes, fresh and processed meat, and margarine and a low intake of fruit. The third pattern, a confectionary dietary pattern, explained 6.1% of the variance and was characterized by a high intake of cakes, sugar and confectionary, and tea (all $r \geq 0.20$ and $P- < 0.05$) (**Supplemental Table 2**). No significant association was established between adherence to the dietary patterns and urinary iodine (**Supplemental Table 3**).

Urinary iodine showed no correlation with FT4 and a borderline correlation with TSH [Pearson's rank correlation coefficients: −0.04 ($P$ = 0.17) and 0.06 ($P$ = 0.05), respectively].

For children from mothers of Dutch national origin with the lowest decile of urinary iodine, the problem scores on inhibition [$\beta$ = 0.08 (95% CI: 0.02, 0.14), $P$ = 0.008], working memory [$\beta$ = 0.07 (95% CI: 0.01, 0.12), $P$ = 0.03], and global executive composite [$\beta$ = 0.06 (95% CI: 0.00, 0.12), $P$ = 0.04] were significantly higher than those from mothers with urinary iodine at or above the 10th percentile p10 (**Table 2**). After adjustment for maternal psychological problems in pregnancy, associations between urinary iodine and problems of child executive functioning became smaller [inhibition $\beta$ = 0.06 (95% CI: 0.00, 0.12), $P$ = 0.046; working memory $\beta$ = 0.05 (95% CI: −0.01, 0.11), $P$ = 0.11; and global executive composite $\beta$ = 0.04 (95% CI: −0.02, 0.10), $P$ = 0.19]. As expected, adjustment of the association between urinary iodine and executive functioning for maternal FT4 did not change the effect estimates (data not shown).

When analyses were stratified by gender, the association between urinary iodine on inhibition did not reach significance in these smaller subpopulations. The effect on working memory and global executive composite was, if anything, more prominent in girls [$\beta$ = 0.12 (95% CI: 0.05, 0.20), $P$ = 0.002, and $\beta$ = 0.09 (95% CI: 0.009, 0.17), $P$ = 0.03, respectively] and was not significant in boys. However, an interaction effect of gender was not found (data not shown).

Because of the association between urinary iodine and cereals, bread, and eggs, we tested whether maternal intake of these separate food groups modified the association between urinary iodine and executive functioning. The addition of these food groups did not significantly change the effect estimates (data not shown).

Finally, after pooling of mothers of Dutch and non-Dutch national origin ($n$ = 692) we showed associations between

**TABLE 2** Associations between low maternal urinary iodine and children's score on the BRIEF-P stratified by maternal national origin[1]

| | Dutch women ($n$ = 431) | | | | All women ($n$ = 692) | | | |
|---|---|---|---|---|---|---|---|---|
| | Adjusted[2] | | Additionally adjusted[2,3] | | Adjusted[2,4] | | Additionally adjusted[2–4] | |
| BRIEF-P problem scale | $\beta$ (95% CI) | $P$ value | $\beta$ (95% CI) | $P$ value | $\beta$ (95% CI) | $P$ value | $\beta$ (95% CI) | $P$ value |
| Inhibition | 0.08 (0.02, 0.14) | 0.008 | 0.06 (0.00, 0.01) | 0.05 | 0.05 (0.01, 0.10) | 0.03 | 0.04 (−0.00, 0.09) | 0.07 |
| Shifting | −0.01 (−0.06, 0.04) | 0.76 | −0.02 (−0.07, 0.03) | 0.51 | −0.01 (−0.05, 0.03) | 0.64 | −0.02 (−0.06, 0.02) | 0.41 |
| Emotional control | 0.02 (−0.05, 0.08) | 0.59 | 0.00 (−0.07, 0.07) | 0.99 | 0.01 (−0.04, 0.06) | 0.63 | 0.00 (−0.05, 0.05) | 0.94 |
| Working memory | 0.07 (0.01, 0.12) | 0.03 | 0.05 (−0.01, 0.11) | 0.11 | 0.07 (0.03, 0.12) | 0.003 | 0.06 (0.01, 0.10) | 0.01 |
| Planning/ organization | 0.05 (−0.01, 0.11) | 0.11 | 0.03 (−0.03, 0.10) | 0.28 | 0.03 (−0.02, 0.08) | 0.19 | 0.02 (−0.03, 0.07) | 0.43 |
| Global executive composite | 0.06 (0.00, 0.12) | 0.04 | 0.04 (−0.02, 0.10) | 0.19 | 0.05 (0.00, 0.10) | 0.05 | 0.03 (−0.01, 0.08) | 0.16 |

[1] Results are from multivariable regression analyses. The 5 scales of executive function were analyzed by using log-transformed standardized scores (T-scores) to achieve normal distribution. BRIEF-P, Behavior Rating Inventory of Executive Function for Preschoolers.
[2] Adjusted for gestational age at blood and urine sampling, maternal age, education, BMI, smoking, alcohol use, protein intake, and child's birth weight.
[3] Additionally adjusted for maternal psychological symptoms.
[4] Additionally adjusted for maternal national origin.

urinary iodine and higher problem scores of inhibition [$\beta$ = 0.05 (95% CI: 0.005, 0.10), $P$ = 0.03], working memory [$\beta$ = 0.07 (95% CI: 0.02, 0.12), $P$ = 0.003], and global executive composite [$\beta$ = 0.05 (95% CI: 0.00, 0.10), $P$ = 0.05] in children (Table 2). These results changed slightly after adjustment for maternal psychological symptoms [inhibition $\beta$ = 0.04 (95% CI: −0.004, 0.09), $P$ = 0.07; working memory $\beta$ = 0.06 (95% CI: 0.01, 0.10), $P$ = 0.02; and global executive composite $\beta$ = 0.03 (95% CI: −0.01, 0.08), $P$ = 0.16].

All analyses were repeated using 5th and 15th percentile cutoffs instead of the 10th percentile cutoff as an indicator of low urinary iodine excretion. Results were essentially the same (data not shown).

## Discussion

This study showed that children of mothers with low urinary iodine, a marker of low iodine status, and independent of maternal thyroid concentrations in early pregnancy have higher scores of impaired executive functioning at 4 y of age. Although maternal urinary iodine was positively associated with maternal intake of specific food groups, these intakes could not explain the association between urinary iodine and impaired executive functioning in children.

Food groups for which intake was associated with higher urinary iodine in early pregnancy were cereals, bread, and eggs. In The Netherlands, consumption of bread, meat, vegetables, potatoes, and eggs is relatively high (19). Our results suggest therefore that in the Dutch population the major sources of iodine are bread and bread replacements, which are voluntarily fortified with iodized salt, and eggs. This is in line with other Western countries in which dairy products, bread, seafood, eggs, meat, and poultry are the main sources of iodine (9).

The issue of iodine deficiency during pregnancy is also related to the advisability of iodine supplementation of women as relates to the need for fortification of the food supply. Worldwide, the use of iodized salt is the most important method for preventing iodine deficiencies. Before 2008 the most important source of iodine in The Netherlands was bread, which provides 50% of average iodine intake (29). After 2008 the number of foods containing iodized salt was increased because of the decreasing consumption of bread, especially among teenagers and adolescents. At the same time, however, the iodine content in iodized salt was reduced to avoid overintake, the use of salt in processed foods was reduced to prevent hypertension, and food producers limited the use of iodized salt. This resulted in a 25% decrease in iodine intake as compared with before 2008 (30). Because our data sampling was performed between 2001 and 2006, iodine deficiency might currently be even more prevalent in this population.

In contrast to studies performed in other Western countries (31, 32), dairy foods were not associated with urinary iodine, which might be due to the Dutch legislation on the limitation of iodine in these foods. The content of iodine in milk, poultry, and meat depends on the iodine supplementation of animal foods. In addition, the use of iodophor disinfectants in milking equipment contributes to the iodine concentration of dairy products (33, 34). In The Netherlands only small regional differences in the iodine content of milk were observed that were explained by the type of soil (35). This might explain that, in a study in children aged 6–18 y no differences in urinary iodine were observed (36). Fish, fruit, and vegetables are other iodine-rich sources due to the iodine content of soil and fertilizers and irrigation practices (37). The intake of these foods, however, is low (38). Because urinary iodine reflects short-term iodine status, foods with a low frequency of intake are less reflected by urinary iodine. In addition, we did not establish effect modification by iodine-rich food groups of the association between maternal iodine status and executive functioning in children. This may also be explained by the low frequency of intake of iodine-rich foods.

The amount of variance (21.1%) explained by dietary patterns is suggested to be rather small, but the estimates are comparable with previous dietary studies in pregnant women (39, 40). Moreover, the explained variance of dietary patterns by definition is dependent on the number of included food groups for the factor analyses (20). We used 19 predefined food groups, which allowed more variance in the model, but at the same time reduced the explained variance of the identified dietary patterns.

Because iodine is released from the body through the urine, the measurement of the amounts of iodine in urine samples is a reliable method to determine iodine deficiency across a large population. The median urinary iodine concentration in our population was 203 $\mu$g/L (1.6 mmol/L), which meets the WHO recommendations for pregnant women of 150–249$\mu$g/L (1.2–2.0 mmol/L) (41). However, our estimated range of 9.3–1743.5 $\mu$g/L (0.07–13.7 mmol/L) for iodine was very large, which supports its high variability (42).

In the same population-based cohort, we previously reported an association between mothers' hypothyroxinemia in early pregnancy and cognitive delay in their children at age 3 y (43). In the current analysis, the association between low maternal urinary iodine and impairment of executive function in offspring

could not be explained by derangements of the biomarkers of hypothyroxinemia; FT4 and TSH were both low. There may be other explanations to understand this finding. The current analysis was performed in a study population of the same cohort who had a very low expected frequency of impaired in thyroid function, because women using thyroid medication were excluded for analysis. This implies that we examined associations in mothers with a relatively mild iodine deficiency, as one would expect in an iodine-sufficient area. Our findings are supported by others, which show no relationship between urinary iodine and TSH (44) and FT4 (45, 46). A shortage of maternal iodine intake may result in iodine deficiency in the mother and fetus, but both respond differently, with the mother preserving euthyroidism and the fetus becoming hypothyroid (7). This may explain why the fetus is more affected by iodine deficiency during pregnancy than the mother, resulting in impaired executive functioning of the child and normal maternal biomarkers of thyroid function.

In our study low maternal urinary iodine was associated with problems of inhibition, working memory, and global executive composite in children at 4 y of age. Impairments of executive functioning are consistently associated with attention-deficit hyperactivity disorder (ADHD) (45). Children with ADHD are rated higher than controls on all scales of executive functioning, with the largest effect sizes on inhibition and working memory (46). However, deficits in inhibition are not uniquely associated with ADHD but also with oppositional defiant disorder and conduct disorder (45). The children in our study population, however, are too young to be diagnosed with ADHD. Although hyperactive and impulsive symptoms typically are observed by the time the child is 4 y of age, they peak in severity at school age (47). Therefore, future follow-up of executive functioning in these children may show interesting associations.

A relationship between maternal iodine deficiency and poor mental and psychomotor development in the offspring has been described repeatedly (48). This association is suggested among others to be due to the induced derangement in maternal thyroid function. This is supported by the associations between maternal iodine deficiency, congenital hypothyroidism, and ADHD (49, 50). This is further substantiated by the reported higher incidence (70%) of ADHD in individuals with generalized resistance to thyroid hormones (51, 52). However, in these studies maternal thyroid dysfunction was not due to iodine deficiency, because they were conducted in iodine-sufficient populations (53). Because the full causal chain that links iodine and thyroid hormone to risk of developmental problems has not been established, the indirect evidence has to be considered carefully.

Part of the effect of low urinary iodine on executive functioning in our study was explained by maternal psychological symptoms. Maternal psychological distress during and after pregnancy is known to be a strong determinant of behavioral and cognitive functioning of the child (54). After adjustment for this important confounder only the association between urinary iodine and working memory remained. The correlation between diet and mental health is possibly bidirectional. Depression and stress may promote unhealthy dietary preferences (55), whereas an unhealthy diet, in turn, may affect the mental health of the mother (56).

Human studies showed that iodine supplementation trials in iodine-deficient areas were associated with more prominent cognitive improvement among girls (57, 58). Recently Murcia et al. (59) reported potentially deleterious effects of maternal iodine supplement use during pregnancy on psychomotor achievement, especially in girls. This is in line with our data showing a more prominent effect of low urinary iodine on executive functioning in girls as compared with boys. However, because no interaction effect was found, these findings should be interpreted with caution.

A strength of our study is that we examined the relationship between mild iodine deficiency during early pregnancy and executive functioning in children at 4 y of age, thereby including maternal nutrition and thyroid function as determinants of the same pathway. In addition, the large population-based prospective cohort enabled us to control for important confounding factors, including lifestyle factors, socioeconomic factors, and known determinants of fetal and infant development. However, this does not completely exclude residual confounding. Because data were more complete in more highly educated mothers, we cannot rule out that selective nonresponse influenced our findings.

The effect sizes in our study were rather small because executive functions were measured instead of clinical diagnosis of behavioral problems. Nevertheless, the continuous traits of executive functioning provide better statistical power because exposure and outcome are rare. More importantly, the BRIEF-P scale converges with a variety of clinical groups including traumatic brain injury, autism spectrum disorders (60), ADHD, and Tourette syndrome (61).

In conclusion, low maternal urinary iodine status during early pregnancy is associated with impairment of executive functioning in children at 4 y of age. This finding could not be explained by low nutritional iodine intake during pregnancy or maternal thyroid function and should be confirmed by others.

The observed impairments in executive function at an early age are considered to be subclinical symptoms. Only future studies may show whether these children have an increased vulnerability for developing clinical disorders later in life.


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## Literature Cited


1. Kester MH, Martinez de Mena R, Obregon MJ, Marinkovic D, Howatson A, Visser TJ, Hume R, Morreale de Escobar G. Iodothyronine levels in the human developing brain: major regulatory roles of iodothyronine deiodinases in different areas. J Clin Endocrinol Metab. 2004;89:3117–28.
2. Zimmermann MB. Iodine deficiency in industrialized countries. Clin Endocrinol (Oxf). 2011;75:287–8.
3. Viñas BR, Ribas Barba L, Ngo J, Gurinovic M, Novakovic R, Cavelaars A, de Groot LC, Van't Veer P, Matthys C, Serra Majem L. Projected prevalence of inadequate nutrient intakes in Eeurope. Ann Nutr Metab. 2011;59:84–95.

4. Vanderpump MP, Lazarus JH, Smyth PP, Laurberg P, Holder RL, Boelaert K, Franklyn JA; British Thyroid Association UKISG. Iodine status of UK schoolgirls: a cross-sectional survey. Lancet. 2011;377: 2007–12.
5. Hollowell JG, Haddow JE. The prevalence of iodine deficiency in women of reproductive age in the United States of America. Public Health Nutr. 2007;10:12A:1532–9; discussion 40–1.
6. Zimmermann MB. Iodine deficiency in pregnancy and the effects of maternal iodine supplementation on the offspring: a review. Am J Clin Nutr. 2009;89:668S–72S.
7. de Escobar GM, Obregon MJ, del Rey FE. Iodine deficiency and brain development in the first half of pregnancy. Public Health Nutr. 2007;10:12A:1554–70.
8. Zimmermann MB. The role of iodine in human growth and development. Semin Cell Dev Biol. 2011;22:645–52.
9. Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, Nixon A, Pearce EN, Soldin OP, Sullivan S, et al.; The American Thyroid Association Taskforce on Thyroid Disease During Pregnancy, Postpartum. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. Thyroid. 2011;21:1081–125.
10. Alvarez JA, Emory E. Executive function and the frontal lobes: a meta-analytic review. Neuropsychol Rev. 2006;16:17–42.
11. Gioia GA, Isquith PK, Guy SC, Kenworthy L. Behavior rating inventory of executive function. Child Neuropsychol. 2000;6:235–8.
12. Pardede LV, Hardjowasito W, Gross R, Dillon DH, Totoprajogo OS, Yosoprawoto M, Waskito L, Untoro J. Urinary iodine excretion is the most appropriate outcome indicator for iodine deficiency at field conditions at district level. J Nutr. 1998;128:1122–6.
13. World Health Organization, UNICEF, ICCIDD. Assessment of iodine deficiency disorders and monitoring their elimination: a guide for programme managers. 3rd ed, Geneva: WHO; 2007.
14. Jaddoe VW, van Duijn CM, van der Heijden AJ, Mackenbach JP, Moll HA, Steegers EA, Tiemeier H, Uitterlinden AG, Verhulst FC, Hofman A. The Generation R Study: design and cohort update. Eur J Epidemiol. 2010;25:823–41.
15. Dashe JS, Casey BM, Wells CE, McIntire DD, Byrd EW, Leveno KJ, Cunningham FG. Thyroid-stimulating hormone in singleton and twin pregnancy: importance of gestational age-specific reference ranges. Obstet Gynecol. 2005;106:753–7.
16. Klipstein-Grobusch K, den Breeijen JH, Goldbohm RA, Geleijnse JM, Hofman A, Grobbee DE, Witteman JC. Dietary assessment in the elderly: validation of a semiquantitative food frequency questionnaire. Eur J Clin Nutr. 1998;52:588–96.
17. Donders-Engelen M, van der Heijden L, Hulshof KF. Maten, gewichten en codenummers. Wageningen (Netherlands): Human Nutrition of TNO and Wageningen University; 2003.
18. Netherlands Nutrition Centre. Nevo: Dutch food composition database 2006. The Hague (Netherlands): Netherlands Nutrition Centre; 2006.
19. Slimani N, Fahey M, Welch AA, Wirfalt E, Stripp C, Bergstrom E, Linseisen J, Schulze MB, Bamia C, Chloptsios Y, et al. Diversity of dietary patterns observed in the European Prospective Investigation into Cancer and Nutrition (EPIC) project. Public Health Nutr. 2002; 5:6B:1311–28.
20. Hu FB. Dietary pattern analysis: a new direction in nutritional epidemiology. Curr Opin Lipidol. 2002;13:3–9.
21. Thompson JM, Wall C, Becroft DM, Robinson E, Wild CJ, Mitchell EA. Maternal dietary patterns in pregnancy and the association with small-for-gestational-age infants. Br J Nutr. 2010;103:1665–73.
22. Vujkovic M, Steegers EA, Looman CW, Ocke MC, van der Spek PJ, Steegers-Theunissen RP. The maternal Mediterranean dietary pattern is associated with a reduced risk of spina bifida in the offspring. BJOG. 2009;116:408–15.
23. Kim HK, Lee SY, Lee JI, Jang HW, Kim SK, Chung HS, Tan AH, Hur KY, Kim JH, Chung JH, et al. Usefulness of iodine/creatinine ratio from spot-urine samples to evaluate the effectiveness of low-iodine diet preparation for radioiodine therapy. Clin Endocrinol (Oxf). 2010; 73:114–8.
24. Jaddoe VW, Bakker R, van Duijn CM, van der Heijden AJ, Lindemans J, Mackenbach JP, Moll HA, Steegers EA, Tiemeier H, Uitterlinden AG, et al. The Generation R Study biobank: a resource for epidemiological studies in children and their parents. Eur J Epidemiol. 2007;22:917–23.
25. Gioia GA, Espy KA, Isquith PK. The Behavior Rating Inventory of Executive Function-Preschool version (BRIEF-P). Odessa (FL): Psychological Assessment Resources; 2003.
26. Sherman EMS, Brooks BL. BRIEF-P: test review and clinical guidelines for use. Child Neuropsychology; 2010:1–17.
27. de Beurs E. Brief symptom inventory. Handleiding. Leiden (Netherlands): Pits Publishers; 2004.
28. Rubin DB, Schenker N. Multiple imputation in health-care databases: an overview and some applications. Stat Med. 1991;10:585–98.
29. Brussaard JH, Brants HA, Hulshof KF, Kistemaker C, Lowik MR. Iodine intake and urinary excretion among adults in the Netherlands. Eur J Clin Nutr. 1997;51 Suppl 3:S59–62.
30. Ministry of Health, Welfare and Sports. Inzicht in de jodiuminname van kinderen en volwassenen in Nederland: resultaten uit de voedselconsumptiepeiling 2007–2010. Bilthoven: Rijksinstituut voor Volksgezondheid en Milieu; 2012.
31. Dahl L, Opsahl JA, Meltzer HM, Julshamn K. Iodine concentration in Norwegian milk and dairy products. Br J Nutr. 2003;90:679–85.
32. Pearce EN, Pino S, He X, Bazrafshan HR, Lee SL, Braverman LE. Sources of dietary iodine: bread, cows' milk, and infant formula in the Boston area. J Clin Endocrinol Metab. 2004;89:3421–4.
33. United Kingdom Ministry of Agriculture FaF. Food surveillance sheet 198: iodine in milk. London: United Kingdom Ministry of. Agriculture, Fisheries and Food. 2000.
34. Conrad LM III, Hemken RW. Milk iodine as influenced by an iodophor teat dip. J Dairy Sci. 1978;61:776–80.
35. Verstappen-Boerekamp JAM. Variatie in het jodiumgehalte van Nederlandse melk. Praktijkonderzoek Rundvee, Schapen en Paarden, Intern Rapport 322. 1997.
36. Wiersinga WM, Podoba J, Srbecky M, van Vessem M, van Beeren HC, Platvoet-Ter Schiphorst MC. A survey of iodine intake and thyroid volume in Dutch schoolchildren: reference values in an iodine-sufficient area and the effect of puberty. Eur J Endocrinol. 2001;144: 595–603.
37. van Rossum CTM, Fransen HP, Verkaik-Kloosterman J, Buurma-Rethans EJM, Ocke MC. National Institute for Public Health and the Environment Bilthoven. Dutch National Food Consumption Survey 2007–2010.
38. Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for vitamin A, vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. Washington: National Academy Press; 2001.
39. Northstone K, Emmett PM, Rogers I. Dietary patterns in pregnancy and associations with nutrient intakes. Br J Nutr. 2008;99:406–15.
40. Crozier SR, Robinson SM, Godfrey KM, Cooper C, Inskip HM. Women's dietary patterns change little from before to during pregnancy. J Nutr. 2009;139:1956–63.
41. WHO. Iodine status worldwide: WHO global database on iodine deficiency. Geneva: WHO; 2004.
42. Andersen S, Karmisholt J, Pedersen KM, Laurberg P. Reliability of studies of iodine intake and recommendations for number of samples in groups and in individuals. Br J Nutr. 2008;99:813–8.
43. Henrichs J, Bongers-Schokking JJ, Schenk JJ, Ghassabian A, Schmidt HG, Visser TJ, Hooijkaas H, de Muinck Keizer-Schrama SM, Hofman A, Jaddoe VV, et al. Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the Generation R Study. J Clin Endocrinol Metab. 2010;95:4227–34.
44. Hollowell JG, Staehling NW, Flanders WD, Hannon WH, Gunter EW, Spencer CA, Braverman LE. Serum TSH, T(4), and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). J Clin Endocrinol Metab. 2002;87:489–99.
45. Willcutt EG, Doyle AE, Nigg JT, Faraone SV, Pennington BF. Validity of the executive function theory of attention-deficit/hyperactivity disorder: a meta-analytic review. Biol Psychiatry. 2005;57:1336–46.
46. Mahone EM, Hoffman J. Behavior ratings of executive function among preschoolers with ADHD. Clin Neuropsychol. 2007;21:569–86.
47. Byrne JM, Bawden HN, Beattie TL, DeWolfe NA. Preschoolers classified as having attention-deficit hyperactivity disorder (ADHD): DSM-IV symptom endorsement pattern. J Child Neurol. 2000;15:533–8.
48. Fernald LC. Iodine deficiency and mental development in children. In: Grantham-McGregor SM, ed. Nutrition, health, and child development: research advances and policy recommendations. Washington: Pan

American Health Organization, The World Bank, and Tropical Metabolism Research Unit, University of the West Indies; 1998. p. 234–55. Scientific Publication No. 566.
49. Weiss RE, Stein MA, Trommer B, Refetoff S. Attention-deficit hyperactivity disorder and thyroid function. J Pediatr. 1993;123:539–45.
50. Vermiglio F, Lo Presti VP, Moleti M, Sidoti M, Tortorella G, Scaffidi G, Castagna MG, Mattina F, Violi MA, Crisa A, et al. Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iodine deficiency: a possible novel iodine deficiency disorder in developed countries. J Clin Endocrinol Metab. 2004;89:6054–60.
51. Hauser P, Zametkin AJ, Martinez P, Vitiello B, Matochik JA, Mixson AJ, Weintraub BD. Attention deficit-hyperactivity disorder in people with generalized resistance to thyroid hormone. N Engl J Med. 1993;328:997–1001.
52. Stein MA, Weiss RE, Refetoff S. Neurocognitive characteristics of individuals with resistance to thyroid hormone: comparisons with individuals with attention-deficit hyperactivity disorder. J Dev Behav Pediatr. 1995;16:406–11.
53. Zoeller RT, Rovet J. Timing of thyroid hormone action in the developing brain: clinical observations and experimental findings. J Neuroendocrinol. 2004;16:809–18.
54. Kingston D, Tough S, Whitfield H. Prenatal and postpartum maternal psychological distress and infant development: a systematic review. Child Psychiatry Hum Dev. 2012;43:683–714.
55. van Gool CH, Kempen GI, Penninx BW, Deeg DJ, Beekman AT, van Eijk JT. Relationship between changes in depressive symptoms and unhealthy lifestyles in late middle aged and older persons: results from the Longitudinal Aging Study Amsterdam. Age Ageing. 2003;32:81–7.
56. Sánchez-Villegas A, Delgado-Rodriguez M, Alonso A, Schlatter J, Lahortiga F, Serra Majem L, Martinez-Gonzalez MA. Association of the Mediterranean dietary pattern with the incidence of depression: the Seguimiento Universidad de Navarra/University of Navarra follow-up (SUN) cohort. Arch Gen Psychiatry. 2009;66:1090–8.
57. Field EM, Robles O, Torrero ORM. The cognitive link between geography and development: iodine deficiency and schooling attainment in Tanzania. National Bureau of Economic Research; 2008. Working Paper No. 13838 [cited 2012 May]. Available from: http://nber.org/papers/w13838.
58. Bautista A, Barker PA, Dunn JT, Sanchez M, Kaiser DL. The effects of oral iodized oil on intelligence, thyroid status, and somatic growth in school-age children from an area of endemic goiter. Am J Clin Nutr. 1982;35:127–34.
59. Murcia M, Rebagliato M, Iniguez C, Lopez-Espinosa MJ, Estarlich M, Plaza B, Barona-Vilar C, Espada M, Vioque J, Ballester F. Effect of iodine supplementation during pregnancy on infant neurodevelopment at 1 year of age. Am J Epidemiol. 2011;173:804–12.
60. Gilotty L, Kenworthy L, Sirian L, Black DO, Wagner AE. Adaptive skills and executive function in autism spectrum disorders. Child Neuropsychol. 2002;8:241–8.
61. Mahone EM, Cirino PT, Cutting LE, Cerrone PM, Hagelthorn KM, Hiemenz JR, Singer HS, Denckla MB. Validity of the behavior rating inventory of executive function in children with ADHD and/or Tourette syndrome. Arch Clin Neuropsychol. 2002;17:643–62.