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Suboptimal Maternal Iodine Intake Is Associated with Impaired Child Neurodevelopment at 3 Years of Age in the Norwegian Mother and Child Cohort Study

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Abstract

Background: Severe iodine deficiency in pregnancy has major effects on child neurodevelopment, but less is known about the potential consequences of mild-to-moderate deficiency and iodine supplement use.

Objective: We explored the associations between maternal iodine intake and child neurodevelopment at 3 y of age and the potential impact of maternal intake of iodine from supplements on the same outcomes.

Methods: This population-based prospective observational study included 48,297 mother-child pairs recruited during pregnancy from 2002 to 2008. Maternal iodine intake was calculated based on a validated food-frequency questionnaire answered during midpregnancy that covered mean intake since the beginning of pregnancy. Associations between iodine intake and maternal-reported child language and motor development and behavior problems were explored by multivariable regression analyses.

Results: In 33,047 mother-child pairs, excluding iodine supplement users, maternal iodine intake was associated with child language delay ($P = 0.024$), externalizing and internalizing behavior problems (both $P < 0.001$), and fine motor skills ($P = 0.002$) but not gross motor skills or the risk of not walking unaided at 17 mo of age. In 74% of the participants who had an iodine intake <160 μg/d (Estimated Average Requirement), suboptimal iodine intake was estimated to account for ~5% (95% CI: −5%, 14%) of the cases of language delay, 16% (95% CI: 0%, 21%) of the cases of externalizing behavior problems >1.5 SD, and 16% (95% CI: 10%, 21%) of the cases of internalizing behavior problems >1.5 SD. In 48,297 mother-child pairs, including iodine supplement users, we found no protective effects of supplemental iodine during pregnancy on neurodevelopment.

Conclusions: Maternal iodine intake below the Estimated Average Requirement during pregnancy was associated with symptoms of child language delay, behavior problems, and reduced fine motor skills at 3 y of age. The results showed no evidence of a protective effect of iodine supplementation during pregnancy. *J Nutr* doi: 10.3945/jn.117.250456

Keywords: iodine, dietary supplements, pregnancy, neurodevelopment, Norwegian Mother and Child Cohort Study, MoBa

Introduction

Iodine deficiency (ID) is one of the most common micronutrient deficiencies worldwide (1). Iodine is required for the production of thyroid hormones, which in turn are essential for brain development in fetal and postnatal life. ID is recognized globally as the main cause of potentially preventable brain damage (1). A recent systematic review estimated that introducing salt iodization in areas of chronic ID may increase mean intelligence quotients (IQs) by 8–10 points (2). Although the consequences of severe ID have been thoroughly investigated, less is known about the potential effects of mild-to-moderate ID during pregnancy (3). Results from 2 observational studies indicate that it might affect cognitive development negatively (4, 5).

Iodine requirements are higher during pregnancy because of the increased production of maternal thyroid hormones, transfer of iodine to the fetus, and increased renal clearance of iodine (6). In 2001, the Institute of Medicine established an Estimated

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Average Requirement (EAR) for pregnant women of 160 μg/d (7), a value also recommended as a cutoff for estimating the prevalence of inadequate iodine intake (8).

In countries in which the population is at risk of ID, the WHO recommends iodine supplementation to secure adequate iodine intake in pregnancy (9). There is, however, a lack of evidence to support the recommendation for iodine supplements during pregnancy in areas with mild-to-moderate ID, and some studies have even indicated that supplemental iodine is associated with adverse effects on child neurodevelopment (10, 11).

The Norwegian population has been considered iodine-replete since iodine was added to cow fodder in the early 1950s, but trends in food consumption over the last decades, characterized by decreases in milk and fish intake, have led to the reappearance of insufficient iodine intakes (12, 13). In Norway, the contribution of iodine from iodized salt for home use (0–5 μg I/g NaCl) and drinking water (~2 μg/L) are negligible (14); thus, iodine intake depends on individual food choices. In Norway, there is no official recommendation for iodine supplement use. Estimated iodine intake based on a validated FFQ in 61,904 pregnant women in the Norwegian Mother and Child Cohort Study (MoBA) revealed a large variation in iodine intake and high prevalence of inadequate intakes (median: 166 μg/d; interdecile range: 71, 369 μg/d) (13). Thirty-two percent of the women reported taking supplements containing iodine. MoBa is one of the world's largest pregnancy cohorts, and it is also the largest study to our knowledge to include data on iodine intake during pregnancy. It thus provides a unique opportunity for studying the impact of inadequate maternal iodine intake and prenatal supplement use on developmental outcomes in children.

The primary aim of this study was to explore associations between iodine intake from food during pregnancy and measures of child neurodevelopment (language, communication, motor development, and behavior problems) at 3 y of age. A second aim was to explore the potential impact of prenatal iodine supplement use, both the dosage and timing of introduction, on the same outcome measures.

Methods

Subjects and design

This study was based on data from MoBa, a prospective population-based pregnancy cohort study conducted by the Norwegian Institute of Public Health (15). Participants were recruited from all over Norway from 1999 to 2008 and were asked to answer questionnaires (in Norwegian) at regular intervals during pregnancy and after birth. In total, >99% of the participants were Caucasian. Pregnancy and birth records from the Medical Birth Registry of Norway are linked to the MoBa database (16). The women consented to participation in 41% of the pregnancies. The cohort now includes 114,500 children, 95,200 mothers, and 75,200 fathers. This study was based on version 8 of the quality-assured data files released for research in 2015 and restricted to participants recruited from 2002 to 2008 because the FFQ was included in the study from March 2002.

A total of 48,297 mother-child pairs were included in this study (60,318 for first steps unaided) (**Figure 1**). For the main analysis, which was restricted to participants who did not report the use of supplements containing iodine during pregnancy, 33,047 mother-child pairs were included (41,245 for first steps unaided). To be eligible for inclusion, participants had to have responded to *1*) a general questionnaire around gestational week 17, *2*) an FFQ around gestational week 22, and *3*) a questionnaire when the child was 3 y of age (or alternatively, for the first steps unaided outcome, a questionnaire at 18 mo of age). Only singleton pregnancies were included. Mothers who reported the use of thyroid medication at any time during pregnancy were excluded from the study. Only participants with information in all covariates were included in the analysis because of the large sample size and low rates of missing values. FFQs with >3 blank pages or with calculated energy intakes <4.5 or >20 MJ/d were excluded (17).

Exposure variables: iodine intake from food and supplements

The FFQ was specifically designed for MoBa (18) and was introduced in March 2002. It is a semiquantitative questionnaire designed to capture dietary habits and the use of dietary supplements during the first half of pregnancy and included questions about the intake of 255 food items or dishes (17). The intake of specific foods and nutrients were calculated based on standard Norwegian portion sizes, the Norwegian food composition table, an analysis of Norwegian milk and food samples (14, 19), and data on the content of >1000 food supplements collected from suppliers (20).

A validation study of 119 women in MoBa recruited 24 ± 12 d (mean ± SD) after the completion of the MoBa FFQ showed that, relative to a dietary reference method (4-d weighed food diary) and several biological markers, the MoBa FFQ produces a realistic estimate of habitual intake and is a valid tool for ranking pregnant women according to high and low intakes of energy, nutrients, and foods (21). The relative validity of total iodine intake from food and supplements and the intake of specific food groups such as dairy products and seafood were evaluated separately (22). The total iodine intake calculated from the FFQ correlated well with the iodine intake reported from the 4-d food diaries at midpregnancy (r = 0.48; 95% CI: 0.33, 0.61) and with 24-h urinary iodine excretion data (r = 0.42; 95% CI: 0.26, 0.56). The triangular validity coefficient for total iodine intake by the FFQ was (r = 0.62; 95% CI: 0.46, 0.77). However, the methods covered somewhat different time periods and the reported supplement use varied between the periods, and large day-to-day within-person variation in iodine intake (reflected in urinary iodine excretion) could be expected. In fact, the FFQ correlation coefficients for the calculated iodine intake and major iodine food sources were higher than for most other foods and nutrients, indicating a regular consumption pattern of food items containing iodine (21). In nonusers of iodine supplements, the estimated median iodine intake from food was 122 μg/d from the FFQ, 120 μg/d from the 4-d food diary, and 122 μg/d based on 24-h urinary iodine excretion data (assuming that 90% is excreted in the urine) (22, 23).

We divided iodine contributed from supplements into 3 categories (0, 1–200, and >200 μg/d). Supplemental iodine >200 μg/d (reported by 2.4% of the women) was defined as a separate category because higher intakes might increase the risk of iodine excess. The timing of the first reported use of supplements containing iodine up to gestational week 22 was reported in the general questionnaires at weeks 17 and (if available) 30 and was coded in 4 categories (never, 0–26 wk before pregnancy, gestational weeks 0–12, and gestational week ≥13).

Neurodevelopmental outcomes

Mothers' reports on child development and behavior provided the basis for the outcome variables. The assessment tools in MoBa are based on standardized and validated scales constructed to identify difficulties within each developmental domain (24–27). Included items were selected from full scales and represented key developmental domains (**Supplemental Methods**). Data on all outcomes were coded as missing when the age of the child at the time of the report was ≥3.5 y, except for the motor milestone.

Language delay. The child's typical level of sentence completeness at 3 y of age was reported by the mothers on a scale developed by Dale et al. (24). The mother classified her child's language competence according to 6 different categories: *1*) not yet talking, *2*) talking but incomprehensibly, *3*) talking in one-word utterances, *4*) talking in 2- to 3-word phrases, *5*) talking in fairly complete sentences, and *6*) talking in long and complicated sentences. The validity of the language and grammar scale has been evaluated by Roth et al. (28). We defined options 5 and 6 as normal language development, options 1–4 as language delay (including severe language delay), and options 1–3 as severe language delay.

Communication skills. Six items from the validated Norwegian version of the Ages and Stages Questionnaire (ASQ) on communication skills

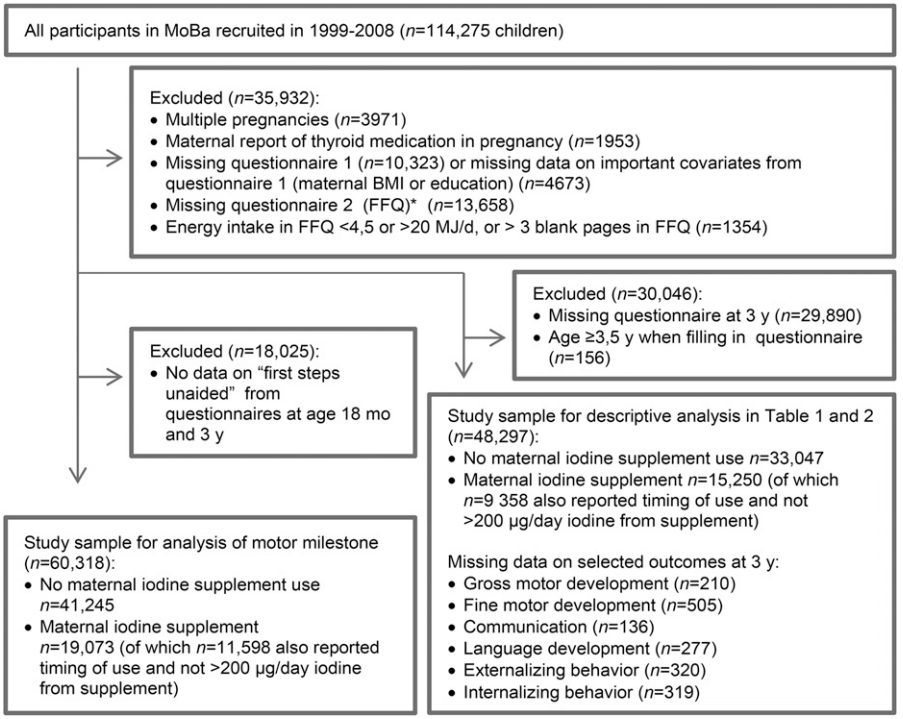

FIGURE 1 Flowchart of inclusion. The general questionnaire was answered around gestational week 17, and the FFQ was answered around gestational week 22. The FFQ was included in the MoBa from 2002. MoBa, the Norwegian Mother and Child Cohort Study.

were included in the questionnaire at 3 y of age (29). Mean scores were calculated and standardized. Good reliability of the scale in MoBa was previously demonstrated with the use of a 2-parameter item response theory analysis (mean factor loading: 0.82) (30).

Motor milestone. The age when the child started walking unaided was reported by the mother when the child was aged 18 mo and/or 3 y. The report on this motor milestone has been shown to be highly reliable (31). Still not walking at 17 mo, corresponding to the 95th percentile, was used as a cutoff for delay.

Motor skills at age 3 y of age. Four items from the ASQ provided the basis for a previously validated score on motor skills—2 on gross motor development and 2 on fine motor development (32). Mean scores were calculated and standardized.

Behavior problems. Externalizing and internalizing behaviors were measured with the use of the child behavior checklist (33). The selected 20 items represented subscales of the internalizing domain (emotionally reactive, anxious and/or depressed, and somatic complaints) and subscales of the externalizing domain (attention problems and aggressive behavior). Mean scores were calculated and standardized. Previous studies reported adequate reliability for the externalizing and internalizing behavior scales (30). The subset of items used in MoBa has been found to be representative (34). A cutoff for child behavior checklist domain scores ≥1.5 SD was chosen to recognize children with high levels of behavior problems.

Covariates

Maternal age was obtained from the Medical Birth Registry of Norway. Prepregnancy BMI, educational status, parity, and parental bilingualism were obtained from the first general questionnaire. Furthermore, because of previous reports of associations between folic acid supplement use and developmental outcomes in MoBa (28, 35), we included a variable that reflected the use of folic acid supplements within the interval from 4 wk before to 8 wk after conception. Maternal energy intake, fiber intake (as a marker of a healthy dietary pattern), and total EPA and DHA intake (from food and dietary supplements) were calculated from the MoBa FFQ. Smoking during pregnancy was collected from questionnaires at gestational weeks 17 and (if available) 30 and when the child was aged 6 mo. Smoking during pregnancy was coded in 3 categories: no reported smoking during pregnancy, reported occasional smoking or stopped smoking before gestational week 12, and reported daily smoking (at any time during pregnancy and had not stopped smoking before gestational week 12).

Other potential covariates or effect modifiers that were explored but not included in the final analysis because they did not change the effect estimates were maternal intake of alcohol and fish, child's sex, year of birth, marital status, paternal educational status, parents' income, maternal chronic illness, and child's age at assessment. Total intake of the n–3 FAs EPA and DHA was only included as a covariate in the analysis of supplemental iodine because it did not change the effect estimates of iodine from food.

Ethics

MoBa was conducted according to Declaration of Helsinki guidelines, and written informed consent was obtained from all participants. This study was approved by the Regional Committee for Medical Research Ethics (Oslo, Norway).

Statistics

We estimated the associations between exposures and neurodevelopmental outcomes with multivariable regression models. Dichotomous outcomes were analyzed with the use of logistic regression, and continuous outcomes were analyzed with the use of generalized linear models with the distribution family that provided the best fit (γ or Gaussian) and identity link. Because some mothers participated in MoBa with >1 pregnancy, all models were adjusted for random effects of sibling clusters.

Analyses of associations between iodine intake from food and neurodevelopmental outcomes were restricted to nonusers of iodine supplements to isolate the effect of long-term iodine intake (as a proxy of iodine status). Iodine intake was modeled with the use of restricted cubic splines with 4 knots at the 5th, 35th, 65th, and 95th percentiles that corresponded to estimated iodine intakes of 54, 102, 142 and 243 μg/d, respectively. All regression models (including crude models) were adjusted for energy intake to control for measurement error. We used 2 different methods to control for energy intake: *1*) the residual method with an energy adjustment of the exposure variable and *2*) the addition of energy intake as a separate covariate. We compared the results to models based on a subsample with a highly restricted energy filter (8–11 MJ/d). The residual method introduced errors at the high and

low levels of exposure, so the second strategy was chosen. Energy intake was modeled with the use of piecewise linear splines (knots at 8.5 and 11 MJ/d) in models in which energy intake was not linearly related to the outcomes when adjusting for all other covariates. Adjusted models also included the following baseline characteristics: maternal age, educational status, parity, prepregnancy BMI, fiber intake, and smoking during pregnancy. For language and communication outcomes, parental bilingualism and folic acid supplement use within the interval from 4 wk before to 8 wk after conception were also included in the adjusted models. Possible interaction effects were explored for BMI, age, educational status, smoking during pregnancy, child's sex, and parity.

The reference value of iodine intake was set at 160 μg/d, which corresponds to the EAR for iodine during pregnancy established by the Institute of Medicine (7). Results are reported as ORs or standardized β coefficients with 95% CIs, and *P* values are reported for overall associations between exposure and outcome and for evidence of nonlinearity in the associations. The tests for overall associations were performed by testing the coefficients of all 3 spline transformations of iodine intake equal to zero and for nonlinearity by testing the coefficients of the second and third spline transformation equal to zero. Tabular results were calculated based on the spline models. Associations were also explored with iodine intakes categorized in 6 categories, and the results were in agreement with results from the flexible spline models (data not shown).

Attributable risk fractions were estimated for *1*) all participants with iodine intakes <160 μg/d (corresponding to the EAR) and *2*) restricted to iodine intakes <100 μg/d. The estimated risks attributed to low iodine intake were calculated based on the models described previously by comparing an ideal situation of women having an iodine intake of 160 μg/d (scenario 1) to the actual situation of reported intakes (scenario 0).

The impact of the amount of iodine from supplements was explored with the use of multivariable regression, including interaction terms between supplemental iodine (no supplement, 1–200, and >200 μg/d) and iodine from food (<160 and ≥160 μg/d). Crude models and adjusted models were adjusted with the use of the same covariates described previously, including maternal folic acid supplement within the interval from 4 wk before to 8 wk after conception and total EPA/DHA intake in the adjusted models.

TABLE 1 Maternal and child characteristics by maternal iodine intake from food (in micrograms per day) during the first half of pregnancy (Norwegian Mother and Child Cohort Study)[1]

		Iodine intake from food[2]					
	All	<50	50–99.9	100–149.9	150–199.9	200–250	>250
Mother-child pairs, *n* (%)	48,297 (100)	1779 (3.7)	14,127 (29.3)	17,698 (36.6)	9133 (18.9)	3465 (7.2)	2095 (4.3)
Maternal age at delivery, y	30.4 ± 4.4[3]	29.8 ± 4.5	30.4 ± 4.4	30.6 ± 4.3	30.4 ± 4.4	30.2 ± 4.5	29.7 ± 4.7
<25	8.9	12.8	8.8	7.7	9.2	9.9	13.8
25–34	73.3	71.3	73.9	73.8	72.9	72.6	71.0
≥35	17.7	16.0	17.3	18.5	17.9	17.5	15.2
Parity							
0	49.6	54.2	52.5	48.5	47.2	47.4	50.3
1	34.4	33.4	33.4	35.3	35.4	34.3	31.3
≥2	15.9	12.4	14.1	16.3	17.3	18.3	18.5
Maternal education, y							
≤12	26.7	36.1	25.9	24.5	26.5	30.5	36.3
13–16	44.9	43.5	44.2	45.2	46.0	45.3	42.7
>16	28.5	20.5	29.9	30.3	27.4	24.3	21.0
Married/cohabitant	96.8	95.8	96.8	97.1	96.9	96.5	95.0
Prepregnancy BMI, kg/m^2	23.9 ± 4.1	24.8 ± 4.7	24.0 ± 4.2	23.8 ± 4.1	23.8 ± 4.1	23.9 ± 4.1	24.3 ± 4.5
<18.5	2.9	3.4	2.8	2.8	2.9	3.1	2.7
18.5–24.9	66.9	55.4	66.7	68.3	68.2	65.9	62.8
25–30	21.4	27.7	21.5	20.7	20.7	22.7	23.8
>30	8.8	13.5	9.1	8.2	8.3	8.3	10.7
Smoking during pregnancy							
No	80.9	76.1	80.6	82.0	81.5	79.8	77.9
Occasionally or quit before GW 12[4]	14.1	15.8	14.8	13.5	13.6	14.1	15.7
Daily	4.9	8.1	4.6	4.5	4.9	6.1	6.3
Alcohol during pregnancy (first half)							
No	89.1	90.9	88.4	88.4	89.9	90.1	92.6
Yes	10.9	9.1	11.6	11.6	10.1	9.9	7.4
Chronic illness	10.0	13.7	11.0	9.4	8.9	9.3	10.0
Parents' income							
Low	25.0	28.3	23.4	23.8	26.4	28.6	30.9
Medium	41.3	41.7	40.2	40.9	42.4	43.6	43.0
High	31.5	27.3	34.4	33.2	29.1	25.0	23.0
Missing	2.2	2.8	2.0	2.1	2.1	2.8	3.2
Child's sex							
Male	51.0	48.9	51.3	50.9	51.1	50.4	51.8
Female	49.0	51.1	48.7	49.1	48.9	49.6	48.2
Bilingual parent(s)	9.7	10.1	10.3	10.1	8.8	8.1	9.1

[1] All values are percentages unless otherwise indicated. GW, gestational week.
[2] Excludes iodine from supplements.
[3] Mean ± SD (all such values).
[4] Mothers who reported daily smoking early during pregnancy but no smoking after GW 11.

The impact of the timing of the first reported use of supplements containing iodine (0–26 wk before pregnancy, gestational weeks 0–12, or gestational week ≥13) was explored in participants who reported an intake of 1–200 μg supplemental iodine/d in the FFQ and who also had provided information on the timing of use in the general questionnaires. Timing was explored in the same way as dosage, including an interaction term with iodine from food (>160 or <160 μg/d), and adjusted for the same covariates. *P* values for tests of associations between iodine supplement use and the outcomes were reported separately in participants with a low (<160 μg/d) and high (≥160 μg/d) intake of iodine from food.

Iodine intake from food and the reported use of supplements containing iodine were explored in participants and eligible nonparticipants with missing data on outcomes and/or covariates. A paired-sample *t* test was conducted to compare iodine intake from food (log-transformed), and a chi-square test was used to determine whether the use of supplements was different in the 2 groups.

Statistical analyses were performed with the use of Stata version 14.0 (StataCorp), including a package for calculating tabular estimates based on the models (package xblc) (36) and another for estimating attributable risk fraction (package punaf) (37). $P < 0.05$ was regarded as statistically significant to avoid unduly reducing the power (38). We also report the significance after Bonferroni correction for multiple comparisons ($P < 0.002$).

Results

Background characteristics. The estimated iodine intake from food (not supplements) during the first half of pregnancy ranged from 9 to 678 μg/d (median: 122 μg/d; IQR: 89, 175 μg/d), and 74% had an estimated intake from food lower than the EAR during pregnancy (160 μg/d). Maternal and child characteristics by iodine intake from food (not including iodine from supplements) are shown in **Table 1**. There were only minor differences in background characteristics by dietary iodine intake level.

Maternal dietary characteristics during pregnancy are shown in **Table 2**. The iodine intake from food was positively correlated with the consumption of known iodine sources (milk and yogurt, fish, eggs) and with total energy and nutrient intakes. The Pearson's correlation coefficient (*r*) between energy and iodine intake was 0.57 ($P < 0.001$). Iodine from supplements did not correlate with iodine intake from food ($r = 0.01$).

Participants compared with nonparticipants. The estimated maternal iodine intake from diet did not differ between our study population (n = 48,297) and participants with dietary information who were excluded because of missing data on outcomes and/or covariates (n = 34,355) (mean difference: 0.9 μg/d; $P = 0.87$). Reported iodine supplement use in the FFQ was slightly higher in participants than in nonparticipants (31.6% compared with 29.6%; $P < 0.001$).

Iodine from food and neurodevelopment. Associations between maternal iodine intake from food and neurodevelopmental

TABLE 2 Maternal dietary characteristics and supplement use by maternal iodine intake from food (in micrograms per day) during the first half of pregnancy (Norwegian Mother and Child Cohort Study)[1]

		Iodine intake from food[2]					
	All	<50	50–99.9	100–149.9	150–199.9	200–250	>250
Mother-child pairs, *n* (%)	48,297 (100)	1779 (3.7)	14,127 (29.3)	17,698 (36.6)	9133 (18.9)	3465 (7.2)	2095 (4.3)
Reported energy intake, MJ/d	9.6 ± 2.5[3]	7.1 ± 1.7	8.4 ± 1.9	9.5 ± 2.0	10.8 ± 2.2	11.8 ± 2.4	13.4 ± 2.6
Food intake, g/d							
Milk/yogurt	445 ± 355	54 ± 60	175 ± 122	392 ± 159	637 ± 206	918 ± 232	1426 ± 422
Lean fish	21 ± 13	8 ± 8	17 ± 11	21 ± 12	25 ± 14	27 ± 15	28 ± 18
Fatty fish	12 ± 14	5 ± 6	9 ± 9	12 ± 12	15 ± 16	17 ± 19	19 ± 23
Eggs	11 ± 12	6 ± 6	9 ± 9	11 ± 12	13 ± 14	13 ± 14	14 ± 17
Fruits and vegetables	441 ± 245	297 ± 181	398 ± 214	443 ± 236	482 ± 254	505 ± 287	549 ± 328
Nutrient intake, g/d							
Protein	87 ± 21	60 ± 12	73 ± 13	85 ± 13	98 ± 15	111 ± 15	131 ± 20
Sugar	61 ± 37	52 ± 42	54 ± 34	59 ± 34	66 ± 37	71 ± 41	82 ± 47
Fiber	31 ± 10	22 ± 8	27 ± 8	31 ± 9	34 ± 10	36 ± 11	39 ± 13
Alcohol	0.1 ± 0.7	0.1 ± 0.4	0.1 ± 0.7	0.1 ± 0.8	0.1 ± 0.5	0.1 ± 0.3	0.1 ± 0.8
Iodine source, μg/d							
Milk/yogurt	61 ± 51	6 ± 6	22 ± 16	54 ± 22	89 ± 29	131 ± 33	205 ± 61
Fish	23 ± 16	8 ± 7	17 ± 11	23 ± 14	28 ± 17	32 ± 20	35 ± 26
Eggs	5 ± 5	3 ± 3	4 ± 4	5 ± 5	6 ± 6	6 ± 6	6 ± 7
Supplements	36 ± 72	33 ± 65	35 ± 71	36 ± 73	35 ± 70	36 ± 74	36 ± 73
Supplements (users only)	113 ± 88	105 ± 76	111 ± 88	114 ± 89	113 ± 84	114 ± 91	117 ± 87
Iodine supplement							
No	68.4	68.6	68.3	68.2	68.9	68.2	69.1
1–99 μg/d	15.7	16.4	16.2	15.7	14.8	16.2	14.8
100–199 μg/d	13.5	12.7	13.0	13.8	14.0	13.0	13.5
≥200 μg/d	2.4	2.4	2.5	2.3	2.2	2.6	2.6
n–3 FA supplement	70.1	58.4	68.8	71.1	72.0	72.0	69.3
Folic acid supplement[4]	75.2	72.3	76.8	76.0	74.1	72.1	69.0
Any supplement (in FFQ)	87.3	81.0	86.7	88.1	88.2	87.8	85.9

[1] Values are percentages unless otherwise indicated.
[2] Excludes iodine from supplements.
[3] Mean ± SD (all such values).
[4] Any reported use of folic acid supplements from 4 wk before to 8 wk after conception reported in the general questionnaire (not in the FFQ).

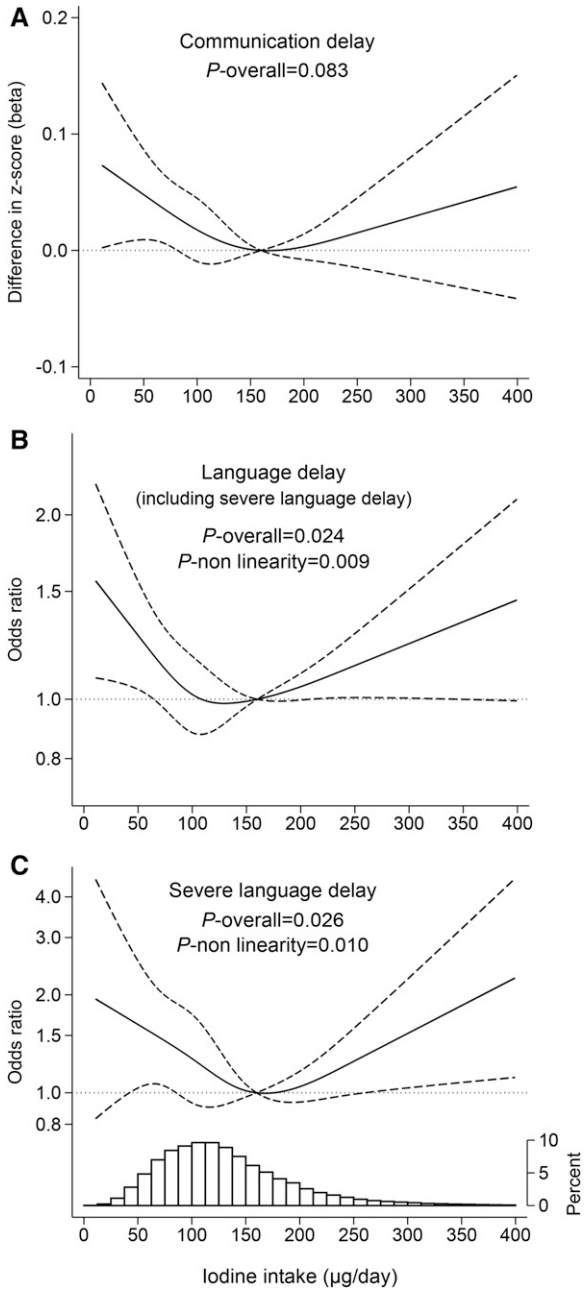

FIGURE 2 Associations between maternal iodine intake from food in pregnancy and child communication (A) and language (B, C) delay at the age of 3 y in the Norwegian Mother and Child Cohort Study. Results are from multivariable regression analyses and restricted to nonusers of iodine supplements during the first half of pregnancy (n = ~33,000 mother-child pairs). Iodine intake was modeled with the use of restricted cubic splines (4 knots), and the reference level was set at 160 µg/d. Dashed lines represent 95% CIs. The histogram in panel C illustrates the distribution of iodine intake. The models were adjusted for maternal age, parity, educational status, BMI, smoking during pregnancy, parent bilingualism, folic acid supplement within the interval from 4 wk before to 8 wk after conception, energy intake, fiber intake, and random effects of sibling clusters. The vertical axes for panels B and C are on a log scale.

outcomes are illustrated in **Figures 2–4.** Low iodine intake was associated with an increased risk of language delay (P-overall = 0.024) and with language delay when restricted to severe delay (P-overall = 0.026). A similar trend was indicated for an association with communication skills (P-overall = 0.083) (Figure 2). The curve shapes for these language outcomes were nonlinear and U-shaped, and the lowest risk of delay was indicated at intakes of ~150–200 µg/d. The group of children characterized with language delay overlapped to a large degree with children who scored low on communication skills [43% of children with language delay and 93% of children with severe language delay also scored low (+2 SD) on communication skills].

Low maternal iodine intake was also associated with more externalizing and internalizing behavior problems (P-overall <0.001) that also remained significant after Bonferroni adjustment for multiple comparisons (Figure 3). The curves displayed similar shapes for continuous outcomes (standardized problem score) and dichotomous outcomes (odds of scoring above the cutoff of +1.5 SD). Maternal iodine intake below ~200 µg/d was associated with an increased risk of both types of behavior problems. For internalizing behavior the curve plateaued when iodine intake reached ~200 µg/d, whereas for externalizing behavior no plateau was observed. Correlations between the 2 behavior scores were r = 0.45. Low maternal iodine intake was also associated with lower fine motor skills (P-overall = 0.002) but not gross motor skills at the age of 3 y or no steps unaided at the age of 17 mo (Figure 4).

Tabular results from unadjusted and adjusted analyses are provided in **Supplemental Tables 1** and **2**.

Significant interaction effects were not detected for iodine with BMI, educational status, parity, smoking during pregnancy, and child's sex. The associations between maternal iodine intake from food and neurodevelopmental outcomes by child's sex are presented in **Supplemental Figures 1–3**. We also explored associations between total iodine intake (including iodine from supplements) and the outcomes, and the associations were attenuated, indicating a differential impact of iodine from food and supplements (data not shown). Venn diagrams illustrating the overlap between the different neurodevelopmental outcomes are presented in **Supplemental Figures 4–8**.

Attributable risk fraction. Attributable risk fraction was calculated for all significant associations between iodine intake from food and dichotomous neurodevelopment outcomes based on the adjusted models described previously, and the reference level was set at 160 µg/d (corresponding to the EAR). In the 74% of participants who had an iodine intake <160 µg/d (median: 105 µg/d; IQR: 80, 129 µg/d) in this sample of nonusers of iodine supplements, the low iodine intake was estimated to account for ~5% (95% CI: −5%, 14%) of cases of language delay (including severe language delay); 21% (95% CI: 0%, 37%) of cases of severe language delay; 16% (95% CI: 10%, 21%) of cases of externalizing behavior problems >1.5 SD; and 16% (95% CI: 10%, 21%) of cases of internalizing behavior problems >1.5 SD.

In the 33% of participants who had an estimated iodine intake from diet of <100 µg/d (median: 77 µg/d; IQR: 62, 89 µg/d) within this subsample, inadequate iodine intake was estimated to account for ~12% (95% CI: −2%, 23%) of cases of language delay; 31% (95% CI: 5%, 50%) of cases of severe language delay; 24% (95% CI: 17%, 31%) of cases of externalizing behavior problems >1.5 SD; and 24% (95% CI: 17%, 31%) of cases of internalizing behavior problems >1.5 SD.

Iodine from supplements and neurodevelopment. The use of supplements containing iodine during the first half of pregnancy was reported by 32% of the mothers in the FFQ. The median contribution of iodine from supplements in this group was 107 µg/d (IQR: 64, 150 µg/d). Only 2.4% of the

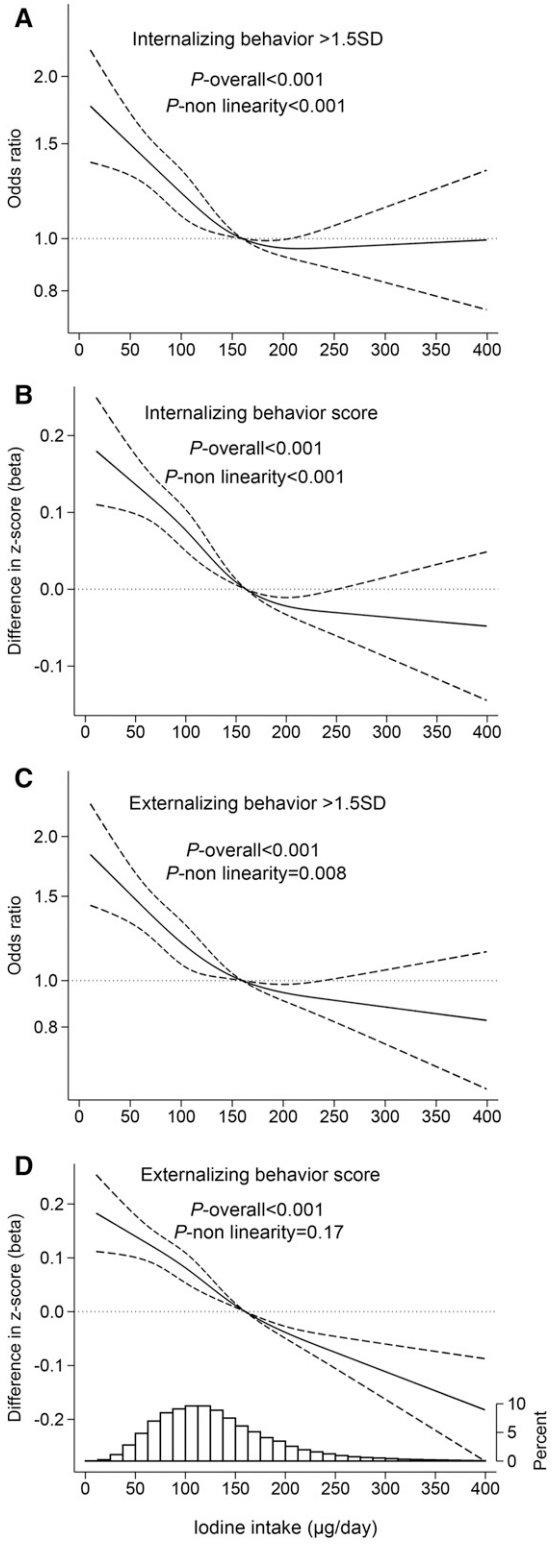

FIGURE 3 Associations between maternal iodine intake from food in pregnancy and internalizing (A, B) and externalizing (C, D) child behavior problems at the age of 3 y in the Norwegian Mother and Child Cohort Study. Results are from multivariable regression analyses and restricted to nonusers of iodine supplements during the first half of pregnancy (n = ~33,000 mother-child pairs). Iodine intake was modeled with the use of restricted cubic splines (4 knots), and the reference level was set at 160 µg/d. Dashed lines represent 95% CIs. The histogram in panel D illustrates the distribution of iodine intake. The models were adjusted for maternal age, parity, educational status, BMI, smoking during pregnancy, energy intake, fiber intake, and random effects of sibling clusters. The vertical axes for panels A and C are on a log scale.

mothers reported taking >200 µg/d. Nine women took single iodine supplements, whereas the remaining women (n = 15,241) reported taking multisupplements containing iodine.

Of the mothers who reported the use of supplements containing iodine in the FFQ, 66% also provided information on the timing of use in the general questionnaires. Among these women, 40% used it before pregnancy (0–6 mo before conception), 29% reported first use in gestational weeks 0–12, and 31% reported first use in gestational week ≥13.

The potential impact of iodine from supplements was explored in 2 groups defined by maternal iodine intake from food (<160 or >160 µg I/d from food), and the results from the multivariable regression analysis are shown in **Table 3**. We found no evidence of beneficial effects on the outcomes for supplemental iodine during pregnancy. Most of the estimates pointed toward small negative effects of supplemental iodine when iodine intake from food was <160 µg/d, but the association was statistically significant only for internalizing behavior problems (P < 0.001), which also remained significant with the Bonferroni correction. Results from crude models are shown in **Supplemental Table 3**.

The impact of the timing of the first report of iodine supplement use was explored in women reporting the use of supplemental iodine (maximum of 200 µg/d) in the FFQ (n = 9358) and compared with the reference group of nonsupplement users (n = 33,047) (**Supplemental Tables 4** and **5**). In women with iodine intake from food >160 µg/d, iodine supplement use was not significantly associated with the outcomes regardless of timing. In women with an intake from food <160 µg/d who reported taking supplements containing iodine before pregnancy (dosage before pregnancy unknown), supplement use was not significantly related to any of the outcomes. However, in those reporting first use in gestational weeks 0–12, supplement use was associated with an increased risk of externalizing behavior problems (adjusted OR of scoring >1.5 SD: 1.28; 95% CI: 1.09, 1.49), and the introduction of supplements in gestational week ≥13 was associated with an increased risk of internalizing behavior problems (adjusted OR of scoring >1.5 SD: 1.27; 95% CI: 1.10, 1.46). These results did not remain statistically significant after adjusting for multiple comparisons.

Discussion

The main finding from this study was that an iodine intake below the EAR value of 160 µg/d was associated with an increased risk of language delay, behavior problems, and fine motor development in children aged 3 y but not with measures of gross motor development (Figures 2–4). We found no evidence of a beneficial effect of supplemental iodine in pregnancy, and there were some indications of negative effects of supplements on behavior outcomes in children of mothers with a low iodine intake from food (<160 µg/d). To our knowledge, this is the most extensive study to date on the potential consequences of maternal iodine intake on child neurodevelopment.

Iodine from food and neurodevelopment. To isolate the effect of long-term iodine intake, we restricted these analyses to participants who did not report the use of supplements containing iodine in the FFQ. Previous studies have indicated that long-term iodine intake might be more important for thyroid function during pregnancy than recent supplement use (39). Indeed, we also found that the associations between iodine

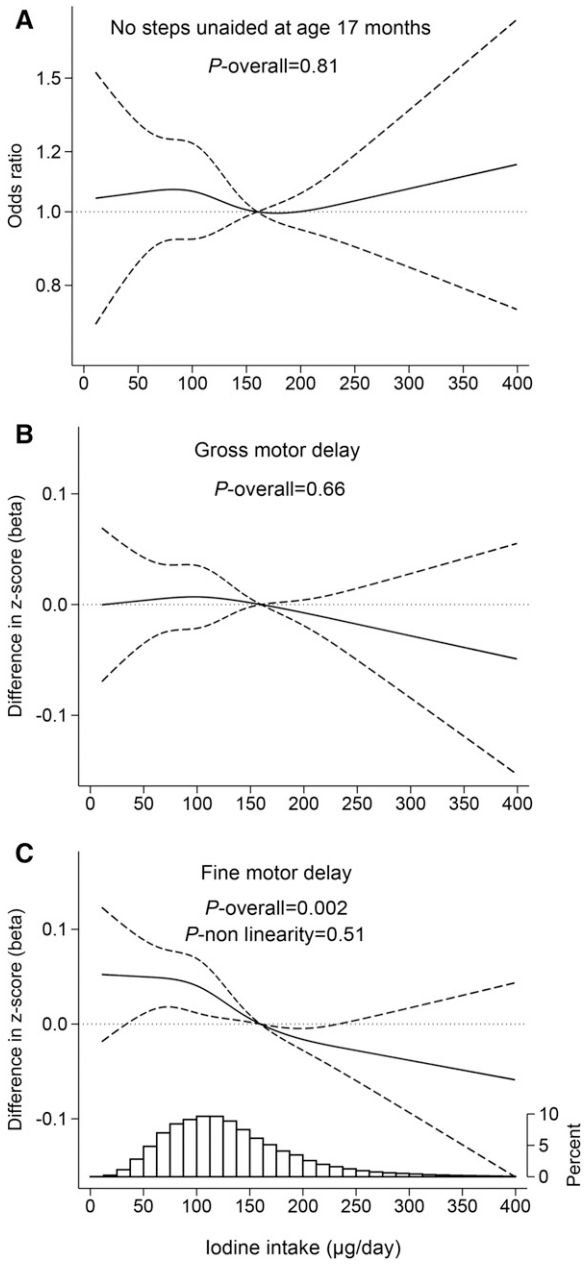

FIGURE 4 Associations between maternal iodine intake from food in pregnancy and child motor development by the age of 3 y in the Norwegian Mother and Child Cohort Study. Results are from multivariable regression analyses and restricted to nonusers of iodine supplements during the first half of pregnancy [n = 41,245 mother-child pairs for first steps (A) and n = ~33,000 for motor scores (B, C)]. Iodine intake was modeled with the use of restricted cubic splines (4 knots), and the reference level was set at 160 µg/d. Dashed lines represent 95% CIs. The histogram in panel C illustrates the distribution of iodine intake. The models were adjusted for maternal age, parity, educational status, BMI, smoking during pregnancy, energy intake, fiber intake, and random effects of sibling clusters. The vertical axis for panel A is on a log scale.

intake and outcomes were attenuated when we included iodine supplement users and modeled the estimated total iodine intake and outcomes.

Results from several studies suggest that maternal general thyroid dysfunction may start to develop when urinary iodine concentration (UIC) in pregnancy is below ~50 µg/L (corresponding to an estimated iodine intake of ~83 µg/d assuming 90% recovery in the urine and a mean urine volume of 1.5 L/d) (40). Shi et al. (41) described a U-shaped relation between urinary iodine excretion and the prevalence of thyroid disorders in a study that included 7190 pregnant women in China, and the risks were lowest in the group of women with a UIC of 150–249 µg/L. This corresponds to a regular iodine intake of ~250–415 µg/d. In our study, the shapes of the association curves indicate that an intake <160 µg/d from food was associated with an increased risk of negative outcomes, in line with the findings of Shi et al. (41). For intakes ≥200 µg/d, our results were not consistent. We found an increased risk of language delay, a reduced risk of behavior problems, and no change in fine motor skills. At 200 µg/d, the intake is still below the recommended intake by the WHO (250 µg/d) (9) and Institute of Medicine (220 µg/d) (7) and well below the upper intake level of 500 µg/d generally regarded as safe (9). Therefore, our study does not consistently indicate an optimal intake level. Caution must be made when interpreting the results for iodine intakes from food >250 µg/d in our study because only 4.3% of the women had such high intakes.

Language development plays a fundamental role in cognition, social development, and learning. Early language deficits may impair long-term social adaptation, cognitive development, and academic achievement and are associated with psychiatric disorders in young adults (42–44). Impairments in cognitive development associated with maternal mild-to-moderate ID have previously been reported in 2 observational studies (4, 5). In a study in the United Kingdom that included 1040 mother-child pairs, Bath et al. (4) found an increased risk of scoring within the lowest quartile on an IQ measure at the age of 8 y (OR: 1.58; 95% CI: 1.09, 2.30) and on reading accuracy (OR: 1.69; 95% CI: 1.15, 2.49) and comprehension (OR: 1.54; 95% CI: 1.06, 2.23) at the age of 9 y in children of mothers with spot urinary iodine below a cutoff of 150 µg creatinine/g during pregnancy (gestational week ≤13; median: 10 wk), indicating mild-to-moderate ID in pregnancy. They also observed a dose-response relation on IQ and reading comprehension when subdividing into 3 categories of exposure (<50, 50–150, >150 µg creatinine/g). Hynes et al. (5) reported lower educational assessment scores (spelling, grammar, and English literacy performance) in Australian children aged 9 y (n = 228) of mothers who had a UIC <150 µg/L during pregnancy (indicating mild-to-moderate ID) than those who had a UIC ≥150 µg/L.

We observed a dose-response relation between maternal iodine intake and externalizing and internalizing behavior problems (Figure 3). The questions on externalizing behavior problems included in our study partly overlapped with screening questions for attention-deficit hyperactivity disorder (ADHD). Mild-to-moderate ID has previously been linked to ADHD in a non-randomized controlled trial in Italy (n = 27 mother-child pairs), in which Vermiglio et al. (45) observed an increased risk of ADHD in children born to mothers from an area with moderate ID (69% fulfilled the diagnostic criteria of ADHD) compared with an area of marginal ID (no cases of ADHD). An increased risk of ADHD has also been reported with generalized resistance to thyroid hormones, indicating the important role thyroid hormone concentrations might play in a possible causal mechanism (46).

Mild-to-moderate ID may affect neurodevelopment by increasing the risk of thyroid disorders, as indicated by Shi et al. (41). Another mechanism could be that ID causes maternal and/or fetal thyroids to be more vulnerable to environmental goitrogens, abundant in certain foods and in cigarettes, causing transient deficits in thyroid hormones during critical periods in neurodevelopment. Román (47) hypothesized that this mechanism is an important cause of autism.

TABLE 3 Adjusted models of associations between iodine from supplements during the first half of pregnancy and child development by different levels of iodine intake from food during pregnancy (Norwegian Mother and Child Cohort Study)[1]

	Percentage	Language delay[2]	Communication delay *z* score[2]	Internalizing behavior problems		Externalizing behavior problems		Not walking at age 17 mo	Fine motor delay *z* score	Gross motor delay *z* score
				+1.5 SD	*z* score	+1.5 SD	*z* score			
Sample size		48,020	48,161	47,978	47,978	47,977	47,977	60,318	47,792	48,087
Cases, *n* (%)		1947 (4.1)		4389 (9.2)		3848 (8.0)		1800 (3.0)		
Iodine from food <160 μg/d										
No supplement	50.9	1	0	1	0	1	0	1	0	0
1–200 μg/d	21.9	1.06 (0.94, 1.19)	0.00 (−0.02, 0.02)	1.14 (1.06, 1.24)	0.04 (0.02, 0.07)	1.07 (0.98, 1.16)	0.02 (−0.00, 0.04)	1.05 (0.93, 1.19)	0.00 (−0.02, 0.03)	0.00 (−0.02, 0.03)
>200 μg/d	1.8	1.02 (0.71, 1.47)	0.04 (−0.02, 0.11)	1.01 (0.80, 1.28)	0.01 (−0.06, 0.07)	1.21 (0.96, 1.54)	0.05 (−0.02, 0.12)	1.15 (0.82, 1.61)	0.00 (−0.07, 0.06)	0.02 (−0.05, 0.09)
P-overall		0.68	0.44	0.004	<0.001	0.11	0.079	0.56	0.91	0.89
Iodine from food ≥160 μg/d										
No supplement	17.5	1	0	1	0	1	0	1	0	0
1–200 μg/d	7.3	1.09 (0.89, 1.32)	0.03 (−0.01, 0.06)	1.05 (0.91, 1.20)	0.02 (−0.02, 0.06)	1.07 (0.92, 1.24)	0.02 (−0.02, 0.06)	1.02 (0.83, 1.26)	−0.03 (−0.07, 0.01)	−0.03 (−0.07, 0.01)
>200 μg/d	0.6	0.92 (0.49, 1.72)	0.09 (−0.05, 0.24)	0.76 (0.48, 1.21)	0.02 (−0.09, 0.12)	1.02 (0.65, 1.60)	0.05 (−0.06, 0.17)	1.04 (0.58, 1.87)	0.00 (−0.12, 0.12)	−0.07 (−0.17, 0.03)
P-overall		0.67	0.19	0.38	0.55	0.70	0.42	0.97	0.42	0.18

[1] Values are adjusted ORs (95% CIs) for associations with dichotomous outcomes and adjusted standardized β coefficients (95% CIs) for continuous outcomes unless otherwise indicated. Results are from multivariable analyses, including interaction terms between iodine from diet and iodine from supplements, and the models were adjusted for maternal age, BMI, parity, educational status, smoking during pregnancy, energy intake, fiber intake, folic acid supplement within the interval from 4 wk before to 8 wk after conception, total EPA/DHA intake, and random effects of sibling clusters. Reported *P* values reflect the potential effect of iodine from supplements on outcomes in participants with a low (<160 μg/d) or high (≥160 μg/d) intake of iodine from foods during pregnancy.

[2] Additionally adjusted for parental bilingualism.

Iodine from supplements and neurodevelopment. Previous studies on iodine supplement use in pregnancy and child neurodevelopmental outcomes in areas with mild-to-moderate ID have shown inconsistent results (3, 39, 48), and to our knowledge there are no randomized controlled trials published to date. In this study we examined the associations in women with iodine intake from food below and above the EAR (160 μg/d) separately because the effect of supplemental iodine might depend on previous iodine status. Our findings of no beneficial effects and some indications of negative effects are supported by findings from the Environment and Childhood cohort in Spain in which an increased risk of low psychomotor (10, 11) and mental scores (11) in children of women who reported intake of iodine from supplements ≥150 μg/d compared with <100 μg/d was observed. On the other hand, Velasco et al. (49) reported a positive impact on psychomotor scores in children of mothers who received 300 μg I from supplements from the first trimester compared with controls in a nonrandomized intervention study. The negative effects of iodine supplement use observed in our study were seen when mothers had iodine intake from food <160 μg/d and initiated iodine supplement use after conception.

There could be several reasons why no beneficial effects of iodine from supplements were observed. Initiating supplement use during pregnancy might be too late and may also provide less iodine than needed to compensate for the effects of a depleted iodine store on thyroid function. A sudden increase in iodine intake, although modest and within the recommendations, might also lead to a "stunning effect," with transient inhibition of maternal or fetal thyroid hormone production (50). In addition, because the iodine supplements reported by the women in MoBa were almost exclusively multisupplements, we cannot eliminate the possibility of other substances in the supplements acting as confounders or effect modifiers.

Iodine intake as a measure of iodine status. To our knowledge, there are no valid biomarkers for assessing iodine status at an individual level (51). UIC is useful as an indicator of ID at the population level but not at the individual level because of large day-to-day variation. In our study, we used estimated iodine intake from an extensive and validated FFQ that most likely reflects long-term iodine intake and thus iodine status. To our knowledge, iodine intake from food has not previously been used as a measure of individual iodine status in studies that have explored associations with health outcomes. In most countries, iodized salt contributes substantially to iodine intake, making FFQs less suited for estimating iodine intake. In Norway this is not the case, and indeed the MoBa FFQ has proven to be a valid tool for assessing iodine intake, as described previously. The use of calculated iodine intake as opposed to UIC allows for distinguishing between iodine from food and from supplements when exploring exposure-outcome associations.

Strengths and limitations. Potential effects of mild-to-moderate ID are most likely small and only detectable in large studies. Strengths of MoBa include the large sample size, prospective design, and extensive collection of data. The iodine situation among pregnant women in Norway, with a high frequency of low intakes and a large variation in exposure, makes MoBa ideal for studying suboptimal iodine intakes. In Norway, the weaning diet of most children includes iodine-fortified baby foods, and children have a higher intake of dairy products than adults relative to their energy intake. Unless dairy products are excluded from the child's diet, Norwegian infants and toddlers most likely get adequate amounts of iodine (52).

Weaknesses include the observational design, which implies that we cannot rule out the possibility of residual confounding. Self-administered questionnaires introduce the risk of measurement errors and misclassifications, but the biases introduced would most likely tend to weaken associations (53). The participation rate of 41% in MoBa introduces the risk of selection bias. However, a previous study of MoBa found that although the prevalence of exposures and outcomes might be biased, exposure-outcome associations did not differ between MoBa and a nationally representative sample (54).

Clinical relevance and implications. ID is easily preventable at a low cost. The results of this study emphasize the urgent need for preventing inadequate iodine intake in women of childbearing age to secure optimal brain development in children. Securing an adequate long-term iodine intake before pregnancy is important because supplementation during pregnancy might not compensate and could even be harmful in mild-to-moderate ID. The estimated attributable risk fractions of having a lower iodine intake than the EAR indicate that mild-to-moderate ID may be an important risk factor for behavior problems and language delay, especially if maternal long-term iodine intake is <100 μg/d.

Future studies with the use of UIC as the exposure variable should exclude iodine supplement users or at least control for iodine supplement use because short-term iodine intake from supplements seems to have a differential impact than long-term intake. Our results show that maternal iodine intake below the EAR during pregnancy is associated with symptoms of impaired child neurodevelopment. Our study does not support recommending iodine supplementation to pregnant women in areas with suboptimal iodine intakes.

Acknowledgments

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