Effect of iodine supplementation in pregnant women on child neurodevelopment: a randomised, double-blind, placebo-controlled trial

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Summary

Background Iodine deficiency during pregnancy might be associated with reduced intelligence quotient (IQ) score in offspring. We assessed the effect of iodine supplementation in mildly iodine-deficient pregnant women on neurodevelopment of their offspring in areas where schoolchildren were iodine sufficient.

Methods In this randomised, placebo-controlled trial, pregnant women in Bangalore, India, and Bangkok, Thailand, were randomly assigned (1:1) to receive 200 µg iodine orally once a day or placebo until delivery. Randomisation was done with a computer-generated sequence and stratified by site. Co-primary outcomes were verbal and performance IQ scores on the Wechsler Preschool and Primary Scale of Intelligence Third Edition (WPPSI-III) and the global executive composite score from the Behaviour Rating Inventory of Executive Function-Preschool Version (BRIEF-P) in the children at age 5–6 years. The trial was double-blinded; some unmasking took place at age 2 years for an interim analysis, but participants and nearly all investigators remained masked to group assignment until age 5–6 years. Analysis was by intention to treat using mixed-effects models. This trial is registered with ClinicalTrials.gov, number NCT00791466.

Findings Between Nov 18, 2008, and March 12, 2011, 832 women entered the trial at a mean gestational age of 10·7 weeks (SD 2·7); median urinary iodine concentration was 131 µg/L (IQR 81–213). Mean compliance with supplementation was 87%, assessed by monthly tablet counts. 313 children (iodine group, n=159; placebo group, n=154) were analysed for verbal and performance IQ with WPPSI-III and 315 (iodine group, n=159; placebo group, n=156) for overall executive function with BRIEF-P. Mean WPPSI-III scores for verbal IQ were 89·5 (SD 9·8) in the iodine group and 90·2 (9·8) in the placebo group (difference –0·7, 95% CI –2·9 to 1·5; p=0·77), and for performance IQ were 97·5 (12·5) in the iodine group and 99·1 (13·4) in the placebo group (difference –1·6, –4·5 to 1·3; p=0·44). The mean BRIEF-P global executive composite score was 90·6 (26·2) in the iodine group and 91·5 (27·0) in the placebo group (difference –0·9, –6·8 to 5·0; p=0·74). The frequency of adverse events did not differ between groups during gestation or at delivery: 24 women in the iodine group and 28 in the placebo group reported adverse events (iodine group: abortion, n=20; blighted ovum, and n=2; intrauterine death, n=2; placebo group: abortion, n=22; blighted ovum, n=1; intrauterine death, n=2; early neonatal death, n=1; and neonatal death, n=2).

Interpretation Daily iodine supplementation in mildly iodine-deficient pregnant women had no effect on child neurodevelopment at age 5–6 years.

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Introduction

Iodine is an essential component of thyroid hormones, which are needed for normal fetal growth and development.[1] At week 4 of pregnancy, maternal thyroid hormone is present in utero and promotes neuronal proliferation and migration in the developing brain.[2] Fetal thyroid hormone synthesis begins at about week 20;[2] thereafter, both maternal and fetal thyroid hormones support fetal neurodevelopment.[1,2] To maintain maternal and fetal euthyroidism, iodine requirements during pregnancy increase by about 65%, and WHO recommends an intake of 250 µg per day for pregnant women.[3] In randomised controlled trials in regions of severe endemic goitre, iodine supplementation in pregnancy improved maternal thyroid status and child neurodevelopment.[1]

Although severe iodine deficiency now only rarely occurs in most countries, mild iodine deficiency during pregnancy remains common.[4] WHO recommends measurement of median urinary iodine concentration to assess population-level iodine nutrition during pregnancy; in a population of pregnant women, a median concentration of 150–250 µg/L indicates optimal iodine nutrition whereas 50–150 µg/L suggests mild iodine deficiency.[5] In national studies of pregnant women in Europe, about two-thirds of countries reported mild iodine deficiency based on the median urinary iodine concentration.[4] Pregnant women in the USA are also mildly deficient, with a median urinary iodine concentration of 129 µg/L.[6] Two observational studies

Research in context

Evidence before this study

We searched PubMed with the terms "iodine supplementation" OR "iodine supplements" OR "oral iodine" AND "pregnancy" with no language or date restrictions. The date of our last search was April 24, 2017. Iodine deficiency during pregnancy might be associated with reduced intelligence quotient (IQ) score in offspring. In randomised controlled trials in regions of severe endemic goitre, iodine supplementation in pregnancy improved maternal thyroid status and child neurodevelopment. Two observational studies reported lower IQ and poorer school performance in children born to mildly iodine-deficient mothers than in children of mothers without deficiency, but other studies showed no difference in neurodevelopment between infants of mothers who had mild iodine deficiency and those of mothers who had iodine sufficiency. Controlled trials of iodine supplementation in mildly iodine-deficient pregnant women have shown no clear benefits on maternal or newborn thyroid hormone concentrations. Systematic reviews have concluded that the effects of mild iodine deficiency during pregnancy are uncertain because no placebo-controlled intervention trial has measured child development following maternal iodine supplementation in women with mild iodine deficiency.

Added value of this study

To our knowledge, our study is the first randomised, double-blind, placebo-controlled trial to assess the effects of oral iodine supplementation in mildly iodine-deficient pregnant women on neurodevelopment of their children. We assessed neurocognitive outcomes during infancy and early school age. Although supplementation was safe and increased iodine intake into the sufficient range, we found no significant differences in cognitive developmental scores between children whose mothers were assigned to receive iodine supplementation during pregnancy and children of those assigned to placebo.

Implications of all the available evidence

Our finding that iodine supplementation of mildly iodine-deficient pregnant women had no clear benefits on maternal thyroid function or child neurodevelopment needs to be confirmed in future studies in other populations and other settings. However, our results generally support findings from previous intervention studies suggesting that pregnant women might be able to physiologically adapt to mildly low iodine intakes to maintain fetal euthyroidism, allowing healthy in-utero development. This conclusion is consistent with current WHO recommendations that iodine supplementation is unlikely to harm, but might not be justified in mildly iodine-deficient pregnant women.

reported lower intelligence quotient (IQ) scores and poorer school performance in children born to mildly iodine-deficient mothers than in children of mothers without deficiency;[7,8] another study comparing different doses of iodine supplements in pregnancy showed no effect on neuropsychological development of infants.[9] Controlled trials of iodine supplementation in mildly iodine-deficient pregnant women have shown no clear benefits on maternal or newborn thyroid hormone concentrations.[10] Systematic reviews have concluded that the effects of mild iodine deficiency during pregnancy remain uncertain because no placebo-controlled intervention trial has measured child development.[10,11]

Although they acknowledge the paucity of data regarding benefits, the American Thyroid Association[12] and European Thyroid Association[13] recommend that women take a supplement containing 150 µg iodine daily during pregnancy. By contrast, WHO does not recommend maternal iodine supplements in countries with iodised salt programmes,[14] concluding that if women are iodine sufficient before they enter pregnancy, they can cover their requirements by increasing fractional clearance of plasma iodide and drawing from thyroidal iodine stores. Of concern, observational studies have linked excessive maternal iodine intake with mild maternal hypothyroidism,[15] and maternal iodine supplementation with impaired infant development.[9] Therefore, we aimed to assess the safety and efficacy of iodine supplementation in mildly iodine-deficient pregnant women on child neurodevelopment. Our hypothesis was that iodine supplementation of this group would be safe, but would have no significant benefits on child development.

Methods

Study design and participants

This randomised, placebo-controlled, double-blind trial was done at Ramathibodi Hospital of Mahidol University in Bangkok, Thailand, and St Martha's Hospital in Bangalore, Karnataka, India. These hospitals were chosen because they had large, well-run antenatal clinics and served mainly middle-income families. We chose only one hospital at each site to simplify logistics and follow-up. Although, in 2017, Thailand and India have effective salt iodisation programmes and women of reproductive age are iodine sufficient at the national level,[16] at the time of our intervention, no data were available for iodine status in women of reproductive age, and household coverage with adequately iodised salt was only about 35% in Karnataka and 60% in Thailand, but school-aged children (aged 6–12 years) were iodine sufficient on the basis of their median urinary iodine concentration.[17,18]

Ethical review boards at both study sites and at Wageningen University, Netherlands, approved the study. Approval was first granted for a study up to 2 years after delivery, but approval was subsequently granted to extend the study up to 5–6 years post partum. Change to the primary outcome was approved at both study sites. An external data safety monitoring board supervised the study.

We recruited pregnant women presenting at their first antenatal visit, and all gave written informed consent. Women aged 18–40 years were eligible if they had a singleton pregnancy less than or equal to 14 weeks of gestation, were not lactating, were generally healthy with no thyroid diseases or major medical illnesses, and were not taking iodine-containing supplements. We excluded women with a thyroid stimulating hormone concentration of more than 6 mIU/L at screening and referred them for treatment.

Randomisation and masking

We randomly assigned (1:1) women to receive either iodine supplementation or placebo by use of simple randomisation stratified by site. We used a computer-generated randomisation sequence. Masking was achieved by use of tablets with identical appearance and taste and coding of participants. An individual at Wageningen University who was not involved in the study coded the iodine and placebo supplements, and sealed envelopes with the code were sent to the data safety monitoring board members. The ethical review board at Wageningen University asked for an interim analysis of data up to 2 years offspring age during review of the application for study extension in June, 2015. One of the authors (AMB) was unmasked to provide the interim analysis, which was not published. Participants, the study team assessing outcomes, and the team analysing the data remained masked to group assignment until analysis of the final data.

Procedures

Women received 200 µg iodine given as potassium iodide tablets (Merck, Darmstadt, Germany) or an identical placebo tablet (Merck) taken once daily until delivery. We gave out tablets, assessed compliance by tablet counting, and assessed side-effects by use of a questionnaire at monthly visits. Serious adverse events were defined as death or hospital admission of either mother or baby for a cause other than delivery. At baseline, we administered a structured multiple-choice questionnaire to collect data on household income, and household use of iodised salt or maternal use of nutritional supplements. At baseline, during the second trimester (20–24 weeks), and during the third trimester (30–33 weeks), we measured maternal weight and height, collected venipuncture blood for measurement of thyroid function, collected a spot urine sample for measurement of urinary iodine concentration; and measured thyroid volume with a portable echocamera (Aloka, Mure, Japan) with a 7·5-MHz linear transducer. We obtained birth outcomes from the hospital record; measured height, weight, and head circumference of the infants at birth; and collected newborn heel prick blood within 72 h after birth.

At 6 weeks after delivery, we administered the Neonatal Behavioural Assessment Scale (NBAS) test to assess newborn development individually for each child.[19] The NBAS contains 28 behavioural items, 18 neurological reflex items, and seven supplementary items that measure infant responsiveness. Scores on the NBAS were reduced to seven clusters: habituation; orientation; motor; range of state; regulation of state; autonomic stability; and reflexes, including supplementary items.

Within 1 week before or after the child's first and second birthdays, we measured their height, weight, and head circumference; obtained a heel prick blood sample and a spot urine sample; and administered the Bayley Scales of Infant Development Third Edition (BSID-III) to obtain scores for each infant's cognitive, language, and motor development.[20] The BSID-III has three main subtests. The cognitive scale includes items such as attention to objects and pretend play. The language scale assesses understanding and expression of language, object recognition, and following directions. The motor scale assesses gross and fine motor skills including grasping, stacking blocks, sitting, and climbing stairs. We did not assess the social-emotional or adaptive behaviour scales, which are done with parent questionnaires. We used raw scores because age-specific norms were not available for the Indian or Thai populations and the assessments at both sites occurred within a narrow age window. The BSID-III raw scores were adjusted for infant's gestational age at birth.

When children were aged between 5 and 6 years, we measured height and weight, obtained a fingerprick blood sample and a spot urine sample, and obtained audiograms using a Grason-Stadler GSI 61 audiometer (Grason-Stadler, Eden Prairie, USA). During the acoustic testing, pure tone was determined as average level of signal response during two ascending processes. Starting signal level was about 10 dB below the level at which the child responded during the familiarisation session. The signal was presented for 2–3 s; if the child failed to respond to the signal, the level was increased by 5 dB until the child responded. The time between presentations was about 5 s. To assess verbal and performance IQ, performance speed quotient, and full scale IQ, we administered the Wechsler Preschool and Primary Scale of Intelligence Third Edition (WPPSI-III) individually for each child.[21] The subtests included block design, information, matrix reasoning, vocabulary, picture concepts, word reasoning, coding, and symbol search. To assess executive function, we used the Behaviour Rating Inventory of Executive Function-Preschool Version (BRIEF-P).[22] BRIEF-P was administered to the mother of each child. It consists of

For the **earlier protocol** see https://www.research-collection.ethz.ch/handle/20.500.11850/187229

For the **final protocol** see https://www.research-collection.ethz.ch/handle/20.500.11850/187239

an 86-item questionnaire in eight clinical scales and two validity scales; the global executive composite score takes into account all of the clinical scales and represents the child's overall executive function. To assess behaviour, we administered the Strengths and Difficulties Questionnaire (SDQ) to the mother of each child.[23] Each of its five scales were scored from 0 to 10, the emotional and peer items were summed for an internalising problems score (range 0–20), the conduct and hyperactivity items summed for an externalising problems score (range 0–20), and four of the scales (emotional, conduct, hyperactivity, and peer problems) were summed to create a total difficulty score (range 0–40). All of the developmental tests have been widely used in Thailand and India and were administered in the local language. However, population-specific norms were not available and because there were several months of variation in the children's age at the time of testing, BRIEF-P and WPPSI-III scaled scores were generated using US norms for both sites, allowing us to pool the data. Testing techniques were carefully standardised between the two study sites and were done by Master's-level clinical psychologists. During the course of the study, the senior psychologist (KS) reviewed the cognitive assessments for correctness of administration and scoring.

Outcomes

The co-primary outcomes in the final protocol (2015) were the verbal and performance IQ scores on WPPSI-III and the global executive composite score from BRIEF-P in children aged between 5 and 6 years. Secondary outcomes were the child's auditory performance, weight and height, urinary iodine concentration, thyroid-stimulating hormone (TSH) concentration, and total thyroxine (T_4) concentration, all measured between 5 and 6 years. In the protocol, we planned to study children at age 4–5 years, but because of administrative delays in locating the children, they were tested at a mean age of 5·4 years. All of the protocol outcomes are reported in this study.

The first protocol (2008) specified follow-up of children to age 2 years. In the first protocol, the co-primary outcomes were maternal and infant thyroid hormone concentrations (TSH, total T_4, total tri-iodothyronine [T_3], free T_4, free T_3, maternal thyroglobulin, thyroxine-binding globulin, and antithyroid peroxidase antibodies [TPO-Ab]); ultrasound measurement of maternal and infant thyroid gland volumes; newborn development at 6 weeks of age assessed with the NBAS; and infant development at 6 months, 1 year, and 2 years assessed with the BSID-III. Secondary outcomes were maternal pregnancy outcomes; infant birthweight, length, head circumference, and Apgar scores; maternal and infant urinary iodine concentrations; and breastmilk iodine concentrations. All outcomes from this protocol are included in this report apart from infant thyroid gland volume, newborn and infant free T_4, free T_3 and total T_3, maternal thyroxine-binding globulin, Apgar scores, breastmilk iodine concentrations, and BSID-III at 6 months, because these variables were not recorded. Both the earlier 2008 protocol and final 2015 protocol are available online.

The justification for the change in the primary outcomes from the first to the final protocol was that cognitive assessment at early school age assesses a wider array of cognitive functions than does broad domain-wise assessment in infancy. We felt that the tests administered later in childhood would be more predictive of future development and long-term intelligence than tests given during infancy. Serious adverse events were reported to the external data safety monitoring board.

Biochemical analyses

We determined urinary iodine concentration by spectrophotometry at Swiss Federal Institute of Technology (ETH) Zurich, Switzerland, for the Indian samples and at Mahidol University, Bangkok, Thailand, for the Thai samples;[24] laboratory-specific urine controls were used for the calibration at both sites and at certified urinary iodine concentrations of 74, 162, and 282 µg/L, mean measured values were 77, 156, and 271 µg/L, respectively, giving coefficients of variation of about 11%, 9%, and 13%, respectively. In women, thyroid function, thyroglobulin, and TPO-Ab were measured by immunoassay (IMMULITE, Siemens Healthcare Diagnostics, UK) at ETH Zurich for the Thai samples and at St John's Hospital, Bangalore, India, for the Indian samples. With the exception of TSH and total T_4 during pregnancy, we used the manufacturer's reference ranges: 0·4–4·0 mIU/L for TSH, 58–161 nmol/L for total T_4, 0·89–1·76 ng/dL for free T_4, 1·3–2·6 nmol/L for total T_3, 1·8–4·2 pg/mL for free T_3, less than or equal to 55 ng/mL for thyroglobulin, and less than 35 IU/mL for TPO-Ab. For TSH during pregnancy, we used trimester-specific reference ranges: 0·1–2·5 mIU/L for the first trimester, 0·2–3·0 mIU/L for the second trimester, and 0·3–3·0 mIU/L for the third trimester.[25] For total T_4 until gestational week 6, we used the reference range of 58–161 nmol/L; from week 7, we increased the upper reference range by 5% per week until week 15; from week 16 until delivery, we multiplied the non-pregnancy reference range by 1·5 and used the resulting range of 87·0–241·5 nmol/L as a reference.[26] For the thyroglobulin assay, we used standards provided by the manufacturer (IMMULITE, Siemens) to calibrate the assay. In children, a heel prick or fingerprick blood sample was spotted onto filter paper and TSH and T_4 concentrations were measured by fluoroimmunoassay (TSH, DELFIA NeoTSH, PerkinElmer Life Sciences, Turku, Finland; and T_4, Delfia Neonatal T4 kit, PerkinElmer Life Sciences). We applied age-specific reference ranges for TSH and total T_4 as supplied by the manufacturer: for 0–7 days after birth, TSH 0·1–10·5 mIU/L and total T_4 114–245 nmol/L; after 155 days, TSH 0·1–3·7 mIU/L and total T_4 65–165 nmol/L.

Data and statistical analysis

In the first protocol, we calculated that to have 80% power to detect a decrease of 0·8 in the proportion of raised newborn TSH values, from an anticipated incidence of 10% in the control group to 2% in the treatment group, with a significance level of 0·05 (two-sided), we would require a sample size of 250 women per group; anticipating a 30–35% loss to follow-up, we aimed to enrol 800 pregnant women to our study. In the second protocol, we calculated that to have 80% power to detect a 5-point difference on the full scale IQ score of the WPPSI-III between groups at 5–6 years, with SD of 15, and a significance level of 0·05 (two-sided), we would require a sample size of 142 children per group on the

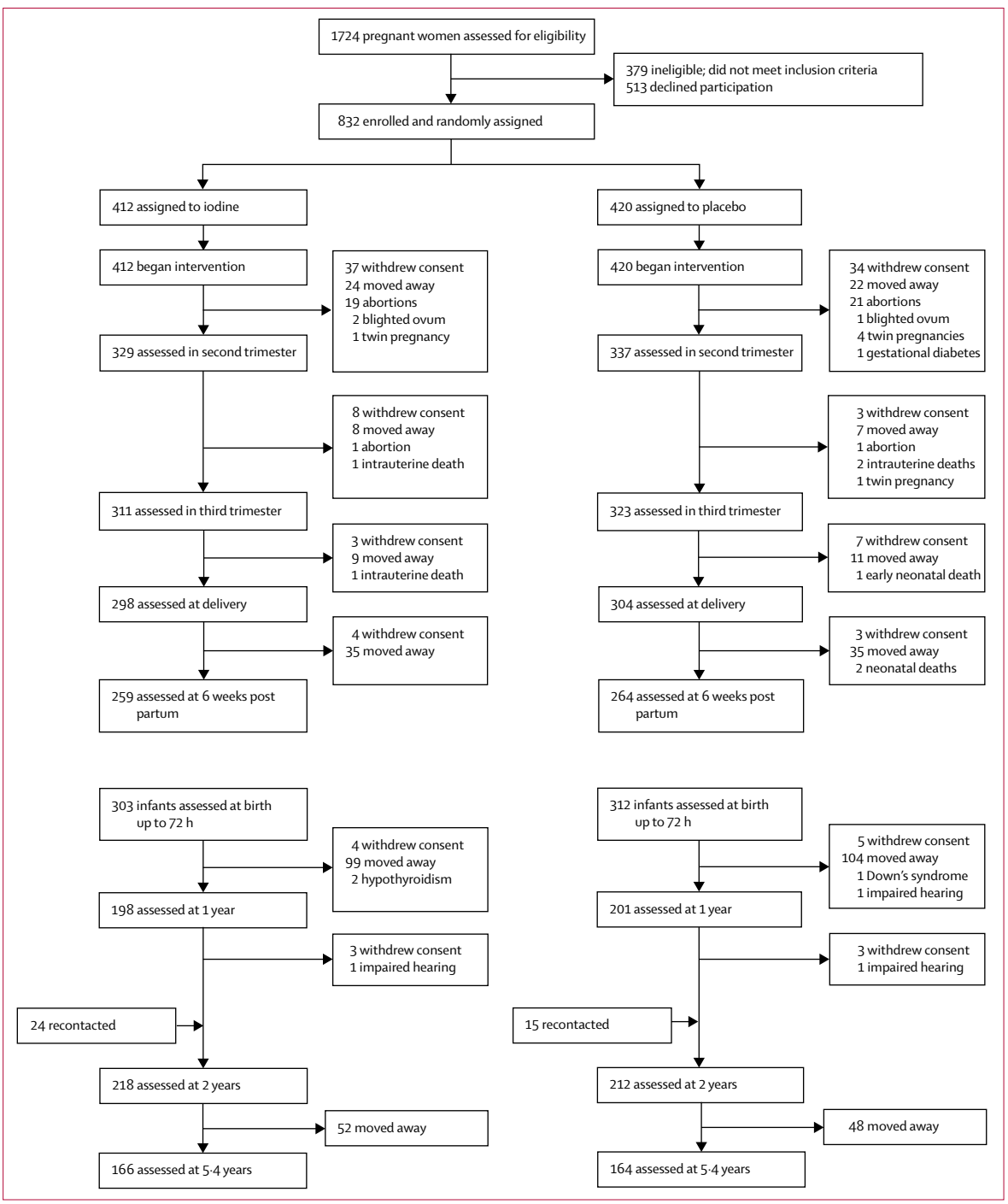

Figure 1: **Trial profile**

	Iodine		Placebo	
	N	Mean (SD), n (%), or median (IQR)	N	Mean (SD), n (%), or median (IQR)
Age (years)	412	28·0 (5·4)	420	27·8 (5·4)
BMI (kg/m²)	410	22·2 (3·9)	417	22·3 (3·9)
Gestational age (weeks)	412	10·8 (2·7)	420	10·7 (2·8)
First pregnancy	403	223 (55%)	415	205 (49%)
Completed secondary education	410	376 (92%)	417	377 (90%)
Using iodised salt at home	376	353 (94%)	381	357 (94%)
Household income tertile				
Lower	401	182 (45%)	407	175 (43%)
Middle	401	93 (23%)	407	106 (26%)
Upper	401	126 (31%)	407	126 (31%)
Urinary iodine concentration (µg/L)	404	134 (80–219)	409	125 (81–210)
Thyroid volume (mL)	411	7·2 (2·4)	420	7·4 (2·5)
Thyroid stimulating hormone (mIU/L)	406	1·0 (0·6–1·7)	415	1·2 (0·7–1·7)
Thyroglobulin (µg/L)	384	8·0 (3·8–14·6)	389	9·0 (4·6–14·6)
Free T_3 (ng/L)	390	3·34 (2·87–3·99)	399	3·44 (2·91–3·89)
Total T_3 (nmol/L)	398	2·0 (1·7–2·4)	409	2·0 (1·6–2·3)
Free T_4 (ng/dL)	396	1·09 (1·00–1·21)	411	1·08 (0·97–1·18)
Total T_4 (nmol/L)	402	128 (107–154)	410	124 (105–149)
TPO-Ab (IU/mL)	408	15·1 (10·0–23·4)	418	14·8 (10·0–24·5)
Raised TPO-Ab (>35 IU/mL)	408	57 (14%)	418	59 (14%)
Isolated hypothyroxinaemia	398	4 (1%)	407	2 (<1%)
Subclinical hypothyroidism	398	37 (9%)	407	45 (11%)
Overt hypothyroidism	398	2 (<1%)	407	0
Subclinical hyperthyroidism	398	11 (3%)	407	12 (3%)
Overt hyperthyroidism	398	6 (2%)	407	2 (<1%)

T_3=tri-iodothyronine. T_4=thyroxine; TPO-Ab=antithyroid peroxidase antibodies.

Table 1: **Baseline maternal characteristics**

basis of studies of mild thyroid deficiency in pregnancy and offspring IQ at school age;[27] anticipating a loss to follow-up of about 25% between 2 years and 5–6 years, our sample size of 218 children in the iodine group and 212 in the placebo group at the time of the second protocol being approved was deemed sufficient.

Gestational age was estimated from maternal report of last menstrual period at the first prenatal visit and confirmed by a dating ultrasound later in pregnancy. BMI was calculated by bodyweight (kg) divided by height (m) squared. We used WHO criteria based on the median urinary iodine concentration to classify adequate iodine intake for pregnant women (≥150 µg/L), postpartum women, infants, and children (≥100 µg/L).[3] Overt hypothyroidism was defined as a high TSH and a low total T_4; subclinical hypothyroidism as a high TSH and a normal total T_4; isolated hypothyroxinaemia (in the pregnant women) was defined as a normal TSH and a low total T_4; overt hyperthyroidism was defined as a low TSH and a high total T_4; subclinical hyperthyroidism as a low TSH and a normal total T_4. Thyroid function tests from the mothers were measured only after delivery. From the thyroid ultrasound measurements, we calculated thyroid volume as previously described.[3] We defined low birthweight as weight at birth of less than 2·5 kg irrespective of gestational age,[28] preterm birth as gestational age at birth of less than 37 completed weeks, and stunting as height-for-age more than two SDs below the WHO Child Growth Standards median.[29] On the WPPSI-III, we defined a score of lower than 85 as abnormally low and a score of lower than 70 as severely abnormally low.[21]

We analysed data using R (version 3.3.1). We ran descriptive statistics for all variables. From crude continuous variables, we identified outliers by visual inspection of box plots stratified by group and timepoint. We assessed normality by testing the distribution of continuous variables against a normal distribution using the Shapiro-Wilk W test. When departing significantly from normality, the variables were transformed using log(x), sqrt(x), or –1/x to correct positive skewness or x^2, x^3, or antilog(x) to correct negative skewness, until achieving W>0·97 before proceeding with further data analysis. Values in the text and tables are presented as mean (SD) for normally distributed data, median (IQR) for non-normal data, and number (%) for prevalence. We assessed the intervention effect by fitting linear mixed effects models to continuous dependent variables and by fitting logistic regression mixed effects models to categorical dependent variables using maximum likelihood procedure for the estimation of variance components. Analysis was intention to treat and missing values were dropped from analysis by list-wise deletion. During gestation, we defined the fixed effects on the variance as treatment, trimester, treatment-by-trimester interaction, household average monthly income, maternal education, and maternal BMI at trial entry; the random structure was defined as study site=~trimester*treatment and individual=~trimester, to control for between-study site and between-individual differences, respectively. At delivery and at 6 weeks after delivery, we defined the fixed effect as treatment, household average monthly income, maternal education, and maternal BMI at trial entry; whereas at 1, 2, and 5–6 years, we defined the fixed effect as treatment, household average monthly income, maternal education, child's birthweight, child's age, and child's sex. At these timepoints, in absence of a time variable, we defined the random structure as tester=~1 for cognitive outcomes and as study site=~1 for all other outcomes. We checked models' normality and homoscedasticity by residuals plot analysis. Statistical significance was set at p<0·05. In the assessment of the co-primary outcomes, to avoid type I error caused by multiple comparisons, a two-tailed p value of <0·01 was considered statistically significant. This trial is registered at ClinicalTrials.gov, number NCT00791466.

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or

writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

We recruited pregnant women between Nov 18, 2008, and March 12, 2011, and completed data collection on July 30, 2016. We assessed 1724 pregnant women for eligibility; 892 declined to participate or did not meet the inclusion criteria (figure 1). 514 pregnant women in Bangkok and 318 in Bangalore (n=832) were enrolled and randomly assigned to the two groups. Mean gestational age at trial entry was 10·7 weeks (SD 2·7) and median urinary iodine concentration was 131 µg/L (IQR 81–213), indicating mild iodine deficiency.[3] Baseline characteristics were similar between groups (table 1). We analysed data from 399 children at age 1 year, 430 children at age 2 years, and 330 children at age 5·4 years; attrition was balanced between groups and the main reason was a move away from the trial area around the time of delivery (figure 1). Baseline characteristics of women who were lost to follow-up did not differ from those of women who completed the study, although women completing the study were enrolled a mean 4·2 gestational days later (appendix p 1). The women in India had a higher median urinary iodine concentration at baseline than did those in Thailand (188 µg/L [IQR 97–338] *vs* 112 [75–170]; appendix p 2), with those in India at the lower end of iodine sufficiency.

For each mother, compliance by tablet counting was assessed monthly and an average monthly compliance was calculated to assess study mean compliance. Groups did not differ (p=0·76, mixed effect model analysis). Mean compliance with supplementation was 87% (SD 13). No significant differences were evident between the iodine and placebo groups in any characteristics of the children who were tested for the primary outcomes at 5·4 years (appendix p 2).

At 5·4 years, no significant differences were evident between groups in children's mean WPPSI-III or BRIEF-P scores, overall (figure 2; table 2) or by site (appendix p 6). These results did not change when testing gestational age at study entry as a covariate (data not shown). The prevalence of abnormal (<85) WPPSI-III composite scores did not differ between groups (verbal IQ: 48 [30%] of 159 in the iodine group *vs* 44 [29%] of 154 in the placebo group; performance IQ: 30 [19%] of 159 *vs* 24 [16%] of 154; processing speed quotient: none of 159 *vs* one [1%] of 154; full scale IQ: 25 [16%] of 159 *vs* 22 [14%] of 154). Only three children had severely abnormal (<70) WPPSI-III composite scores: one in the iodine group and one in the placebo group for verbal IQ, and one in the placebo group for performance IQ. SDQ scores did not differ between groups (table 3). Acoustic testing scores of the right or the left ear did not differ between groups (table 3).

Maternal urinary iodine concentration was significantly higher in the iodine group than in the placebo group during pregnancy (p<0·0001) but not at 6 weeks post partum (p=0·61; table 4). During pregnancy and at 6 weeks post partum, there were no significant differences between groups in maternal thyroid function tests, thyroid volume, TPO-Ab, or thyroid disorders; however, free T_4 and total T_4 were slightly higher in the iodine group during pregnancy (p=0·0005 and p=0·04, respectively). Free T_3 and total T_3 were slightly higher in the placebo group than in the iodine group at 6 weeks post partum (p=0·03, p=0·0003, respectively). Two cases of overt hypothyroidism were evident at baseline (both in the iodine group), but patients became euthyroid in the later trimesters. Although serum thyroglobulin concentration was less than 10 µg/L during pregnancy in both groups,[30] this marker was significantly higher in the placebo group than the iodine group (p=0·0009), suggesting mild thyroidal adjustment to the lower iodine intakes in the placebo group.

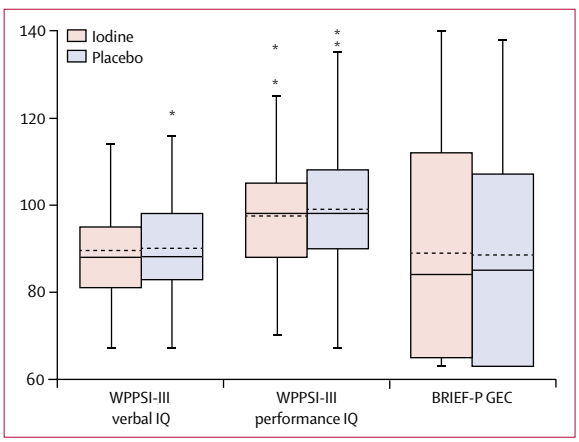

Figure 2: **Developmental outcomes at mean age 5·4 years**
Verbal intelligence quotient (IQ) and performance IQ scores from the Wechsler Preschool and Primary Scale of Intelligence Third Edition (WPPSI-III) and the global executive composite (GEC) score from the Behaviour Rating Inventory of Executive Function Preschool Version (BRIEF-P) assessed at mean age 5·4 years. The box goes from the 25th to the 75th percentile of the data (IQR). The solid line indicates the median; the dashed line indicates the mean. The whiskers extend to the furthest datapoint that is within 1·5 times the IQR. Data were analysed using linear mixed effect models testing treatment effect (iodine *vs* placebo) and controlling for household average monthly income, maternal education, child's birthweight, child's age, and child's sex. There were no significant differences between groups. *Data points that lay outside 1·5 times the IQR.

See Online for appendix

	Iodine (n=159)	Placebo (n=154)	Difference (95% CI)	p value
WPPSI-III, verbal IQ	89·5 (9·8)	90·2 (9·8)	−0·7 (−2·9 to 1·5)	0·77
WPPSI-III, performance IQ	97·5 (12·5)	99·1 (13·4)	−1·6 (−4·5 to 1·3)	0·44
WPPSI-III, processing speed	113·4 (11·6)	115·0 (11·7)	−1·6 (−4·2 to 1·0)	0·15
WPPSI-III, full scale IQ	94·9 (10·4)	96·1 (10·6)	−1·2 (−3·5 to 1·1)	0·44
BRIEF-P, global executive*	90·6 (26·2)	91·5 (27·0)	−0·9 (−6·8 to 5·0)	0·74

Data are mean (SD), unless otherwise stated. Data were analysed using linear mixed effect models testing treatment (iodine *vs* placebo) effect and controlling for household average monthly income, maternal education, child's birthweight, child's age, and child's sex. BRIEF-P=Behaviour Rating Inventory of Executive Function Preschool Version. IQ=intelligence quotient. WPPSI-III=Wechsler Preschool and Primary Scale of Intelligence Third Edition. *Iodine group, n=159; placebo group, n=156.

Table 2: **Primary outcomes in children at mean age 5·4 years**

	Iodine (n=159)	Placebo (n=156)	p value
Sex (male)	74 (47%)	73 (47%)	0·96
Age (years)	5·4 (0·7)	5·5 (0·7)	0·58
Bodyweight (kg)	18·1 (4·2)	19·1 (5·3)	0·34
Height (cm)	109·5 (6·8)	110·9 (6·7)	0·25
Height-for-age *Z* score	−0·5 (1·1)	−0·3 (1·0)	0·25
Stunting*	10 (6%)	4 (3%)	0·19
Urinary iodine concentration (μg/L)†	236 (137–365)	224 (140–314)	0·83
Total T_4 (nmol/L)‡	87·6 (75·9–111·9)	91·8 (75·1–111·2)	0·28
Thyroid stimulating hormone (mIU/L)‡	0·9 (0·7–1·2)	1·0 (0·8–1·3)	0·07
SDQ, externalising problem	5·4 (3·5)	5·3 (3·7)	0·47
SDQ, internalising problem	3·8 (2·9)	3·8 (3·0)	0·26
SDQ, total difficulties	9·3 (5·3)	9·1 (5·6)	0·23
Auditory performance, left ear§	15·0 (11·7–17·5)	13·3 (11·6–16·7)	0·08
Auditory performance, right ear¶	13·3 (11·7–16·6)	13·3 (11·6–15·0)	0·45

Data are median (IQR), mean (SD), or n (%), unless otherwise stated. Continuous data were analysed using linear mixed effect models with non-transformed or transformed dependent variable and frequencies were analysed using mixed effects logistic regression testing treatment (iodine *vs* placebo) effect and controlling for household average monthly income, maternal education, child's birthweight, child's age, and child's sex. SDQ=Strengths and Difficulties Questionnaire. T_4=thyroxine. *Stunting was defined as height for age more than two SDs below the WHO Child Growth Standards median.[30] †Iodine group, n=157; placebo group, n=152. ‡Iodine group, n=154; placebo group, n=148. §Iodine group, n=115; placebo group, n=117. ¶Iodine group, n=116; placebo group, n=118.

Table 3: **Secondary outcomes in children at mean age 5·4 years**

No significant differences were evident between groups in sex, age, anthropometric variables, TSH, total T_4, or urinary iodine concentration in children at birth, 1 year, 2 years, or 5·4 years post partum (table 3, appendix pp 3–5). Children in both groups were iodine sufficient on the basis of their median urinary iodine concentration.[3] No significant differences were evident between groups in frequency of preterm birth (21 [7%] of 300 in the iodine group *vs* 28 [9%] of 309 in the placebo group; p=0·56), low birthweight (34 [12%] of 286 *vs* 32 [11%] of 296; p=0·74), or raised (>5 mIU/L) newborn TSH (two [1%] of 207 *vs* four [2%] of 212; p=0·41). NBAS scores at 6 weeks after birth did not differ between groups (appendix pp 3–5). At 1 and 2 years of age, BSID-III scores did not differ between groups, apart from the score for expressive language at 1 year, which was lower in the iodine group than in the placebo group (14·8 [SD 3·1] in the iodine group *vsw* 15·2 [3·3] in the placebo group; p=0·009; appendix pp 3–5).

All adverse events during gestation and delivery were recorded; the frequency of adverse events did not differ between groups: 24 women in the iodine group and 28 in the placebo group reported adverse events (table 5).

Discussion

To our knowledge, this study is the first randomised, placebo-controlled trial to assess the effect of iodine supplementation in mildly iodine-deficient pregnant women on child development. Although we found higher scores on one subtest of the BSID-III at 1 year (favouring placebo), there were no significant differences between groups in all other tests, including the co-primary outcomes (WPPSI-III verbal and performance IQ scores and BRIEF-P global executive composite score at mean age 5·4 years). Thus, iodine supplementation of pregnant women who were mildly iodine deficient at baseline did not affect overall child neurodevelopment. In cohort studies in the UK and Australia, more severe maternal iodine deficiency than in our study (maternal median urinary iodine concentration of 91 μg/L and 81 μg/L, respectively) was associated with lower IQ[7] and reduced educational outcomes[8] at school age. However, findings from other cohort studies showed no difference in neurodevelopment in infants of mothers who had mild iodine deficiency or iodine sufficiency.[9] It is likely that any potential benefits of maternal iodine supplementation on offspring development would be caused by correction of mild maternal or fetal hypothyroidism; however, two controlled trials[31,32] have reported that correction of subclinical hypothyroidism or isolated hypothyroxinaemia with levothyroxine did not improve offspring development; one of these trials was in an iodine-deficient population.[32] We tested children at age 5–6 years because investigation at this age allows assessment of a wider array of cognitive functions, as opposed to broad domain-wise assessment (motor, cognitive) in infancy. Scores on the BSID-III at 1 and 2 years show only modest association with adult IQ, and developmental tests in children at 5 years or older are better predictors of adult intelligence than tests given during infancy.[33]

The pregnant women in our study had a median urinary iodine concentration of 131 μg/L at baseline; this degree of mild maternal iodine deficiency is common worldwide: the national median concentration in pregnant women is 100–150 μg/L in many high-income and low-income countries, despite adequate median urinary iodine concentrations in school-aged children.[4,6,16] By site, the median urinary iodine concentration of the women in Thailand was in the deficient range while in India it was at the lower end of iodine sufficiency. Despite this difference, there were no site-specific differences in the effects of iodine supplementation on the primary outcomes (appendix p 6). We chose a daily dose of 200 μg because expert recommendations vary: the American Thyroid Association[12] and the European Thyroid Association[13] recommend 150 μg per day whereas WHO recommends 250 μg per day.[3] The 200 μg dose of iodine was effective: in the iodine group, median urinary iodine concentration increased to 231–247 μg/L in the second and third trimesters, at the upper end of the reference range for pregnancy of 150–249 μg/L.[3] Iodine supplementation had minimal effects on maternal thyroid function; there were no differences in thyroid disorders between the iodine and placebo groups, and nearly all women were euthyroid. The marginally higher TSH and thyroglobulin concentrations in the placebo group might represent physiological adaptation of the maternal thyroid to low iodine intake through increased turnover of thyroidal iodine stores. However, these small differences in thyroid function (as well as the slight

	Baseline		Second trimester		Third trimester		p value	6 weeks post partum		p value
	N	Median (IQR), mean (SD), or n (%)	N	Median (IQR), mean (SD), or n (%)	N	Median (IQR), mean (SD), or n (%)		N	Median (IQR), mean (SD), or n (%)	
Urinary iodine concentration (µg/L)										
Iodine	404	135 (80–219)	291	231 (131–365)	280	247 (140–349)	<0·0001	217	119 (73, 186)	0·61
Placebo	409	125 (81–210)	274	174 (92–284)	299	159 (105–252)	..	218	112 (63, 194)	..
Thyroid volume (mL)										
Iodine	411	7·24 (2·38)	294	7·36 (2·27)	286	7·29 (2·20)	0·52	230	6·87 (2·36)	0·90
Placebo	420	7·39 (2·53)	286	7·30 (2·52)	303	7·33 (2·14)	..	228	6·89 (2·41)	..
Thyroid stimulating hormone (mIU/L)										
Iodine	406	1·0 (0·6–1·7)	286	1·3 (0·9–1·9)	261	1·3 (0·9–1·8)	0·10	212	1·2 (0·9–1·8)	0·79
Placebo	415	1·2 (0·7–1·8)	284	1·4 (0·9–2·0)	280	1·5 (1·0–1·9)	..	203	1·3 (0·9–1·8)	..
Thyroglobulin (µg/L)										
Iodine	384	7·99 (3·80–14·58)	280	7·50 (4·15–13·33)	254	8·39 (4·62–14·35)	0·0009	205	7·81 (4·51–13·60)	0·19
Placebo	389	8·95 (4·59–14·60)	270	9·00 (4·60–13·98)	276	9·59 (5·07–16·93)	..	199	8·65 (4·76–14·60)	..
Free T_3 (ng/L)										
Iodine	390	3·34 (2·87–3·99)	276	3·62 (3·08–4·14)	251	3·57 (3·09–4·13)	0·84	202	2·85 (2·43–3·20)	0·03
Placebo	399	3·44 (2·91–3·89)	268	3·53 (3·04–4·23)	276	3·54 (3·02–4·24)	..	191	2·90 (2·57–3·34)	..
Total T_3 (nmol/L)										
Iodine	398	1·97 (1·66–2·40)	293	2·51 (2·14–2·93)	262	2·57 (2·22–2·95)	0·13	205	1·54 (1·35–1·75)	0·0003
Placebo	409	1·97 (1·63–2·29)	281	2·55 (2·10–2·93)	284	2·61 (2·19–3·03)	..	194	1·63 (1·44–1·89)	..
Free T_4 (ng/dL)										
Iodine	396	1·09 (1·00–1·21)	289	0·86 (0·76–0·94)	265	0·83 (0·73–0·93)	0·0005	206	1·03 (0·94–1·13)	0·42
Placebo	411	1·08 (0·97–1·18)	281	0·85 (0·78–0·95)	288	0·84 (0·75–0·94)	..	195	1·03 (0·93–1·15)	..
Total T_4 (nmol/L)										
Iodine	402	128·0 (107·0–153·8)	289	128·0 (108·0–155·7)	265	128·0 (107·6–153·0)	0·04	209	90·4 (74·0–105·0)	0·19
Placebo	410	124·0 (105·0–149·0)	286	128·6 (109·0–157·0)	285	127·3 (107·0–153·2)	..	203	91·5 (77·7–106·1)	..
TPO-Ab (IU/mL)										
Iodine	408	15·1 (10·0–23·4)	299	11·9 (10·0–19·4)	276	11·2 (10·0–18·8)	0·64	212	24·3 (11·1–41·8)	0·95
Placebo	418	14·8 (10·0– 24·5)	291	12·1 (10·0–20·4)	295	10·7 (9·7–18·4)	..	205	24·9 (11·9–41·0)	..
Raised TPO-Ab (>35 IU/mL)										
Iodine	408	57 (14%)	299	35 (12%)	276	25 (9%)	0·14	212	69 (33%)	0·99
Placebo	418	59 (14%)	291	25 (9%)	295	23 (8%)	..	205	70 (34%)	..
Isolated hypothyroxinaemia										
Iodine	398	4 (1%)	283	20 (7%)	259	16 (6%)	0·71	209	9 (4%)	0·64
Placebo	407	2 (<1%)	283	12 (4%)	279	16 (6%)	..	203	8 (4%)	..
Subclinical hypothyroidism										
Iodine	398	37 (9%)	283	17 (6%)	259	11 (4%)	0·63	209	0	0·14
Placebo	407	45 (11%)	283	14 (5%)	279	14 (5%)	..	203	2 (1%)	..
Overt hypothyroidism										
Iodine	398	2 (<1%)	283	3 (1%)	259	1 (<1%)	0·95	209	1 (<1%)	0·31
Placebo	407	0	283	1 (<1%)	279	0	..	203	0	..
Subclinical hyperthyroidism										
Iodine	398	11 (3%)	283	4 (1%)	259	7 (3%)	0·48	209	8 (4%)	0·15
Placebo	407	12 (3%)	283	5 (2%)	279	4 (1%)	..	203	14 (7%)	..
Overt hyperthyroidism										
Iodine	398	6 (2%)	283	0	259	0	0·14	209	5 (2%)	0·52
Placebo	407	2 (<1%)	283	0	279	0	..	203	3 (1%)	..

Continuous data were analysed using linear mixed effect models with non-transformed or transformed dependent variable, and frequencies were analysed using mixed effects logistic regression. During gestation: testing the interaction effect of time (first to third trimester) by treatment (iodine *vs* placebo) and controlling for household average monthly income, maternal education, and maternal BMI at trial entry. At 6 weeks post partum: testing treatment (iodine *vs* placebo) effect and controlling for household average monthly income, maternal education, and maternal BMI at trial entry. T_3=tri-iodothyronine. T_4=thyroxine. TPO-Ab=antithyroid peroxidase antibodies.

Table 4: **Maternal measurements during pregnancy and at 6 weeks post partum**

	Iodine	Placebo
First trimester	21 (abortion, n=19; blighted ovum, n=2)	22 (abortion, n=21; blighted ovum, n=1)
Second trimester	2 (abortion, n=1; intrauterine death, n=1)	3 (abortion, n=1; intrauterine death, n=2)
Third trimester	1 (intrauterine death)	1 (early neonatal death)
At delivery	0	2 (neonatal death, n=2)

Data are number of events (type of event).

Table 5: **Adverse events during pregnancy and delivery**

maternal differences in T_3 post partum) are unlikely to be of clinical significance. Our findings are similar to previous studies of iodine supplementation in mild-to-moderately iodine-deficient pregnant women,[5] in which iodine did not improve concentrations of maternal or newborn thyroid hormones, which are likely to be the best biomarker for healthy fetal development.

Although iodine supplementation is generally thought to be safe in healthy pregnant women,[3,12,13] observational studies have suggested that it might not be without risk.[9,15] A large cohort study (>1500 mother-infant pairs) in iodine-sufficient areas of Spain reported maternal intake of a multivitamin-mineral supplement containing at least 150 µg of iodine per day, compared with intake of a supplement containing less than 100 µg iodine per day, increased risk of a BSID-III motor score of less than 85 in 1-year-old children.[9] In a cross-sectional study of 7190 pregnant women at 4–8 weeks' gestation in an iodine-sufficient region of China, spot urinary iodine concentrations of 250–499 µg/L and 500 µg/L or more were associated with 1·7 times and 2·2 times increased risk of subclinical hypothyroidism, respectively, compared with concentrations of 150–250 µg/L.[15] Additionally, urinary iodine concentrations of 500 µg/L or more were associated with a 2·9 times increased risk of isolated hypothyroxinaemia and higher TPO-Ab positivity in pregnant women.[15] By contrast, our data suggest no detrimental effect of iodine supplementation, consistent with previous supplementation studies in pregnant women.[5]

Our study has several strengths. It was randomised and placebo-controlled, compliance was high, and the baseline median urinary iodine concentration was representative of mild iodine deficiency reported in many national studies of pregnant women. We assessed thyroid function at multiple prenatal and postnatal timepoints, and comprehensively assessed neurocognitive outcomes including IQ and executive functions and behaviour at early school age to increase validity.[33] Asking mothers to rate their own child using SDQ and the BRIEF-P might have introduced bias, although this would probably have been similar between groups. The women began iodine supplementation at a mean gestational age of 10·7 weeks. Beginning supplementation earlier might have resulted in different findings, because the fetal brain rapidly develops in the first trimester.[1,2] However, we did not find an effect of gestational age at entry on any of the developmental outcomes in a secondary analysis of the iodine group. We confirmed iodine sufficiency in offspring using repeated measurements of urinary iodine concentration; the only significant difference in median urinary iodine concentrations were due to increased maternal iodine intakes caused by supplementation during gestation.

Our study also has limitations. We used the median urinary iodine concentration from spot samples to classify population iodine status in pregnant women according to recommendations from WHO,[3] but urinary iodine concentration is a poor marker of individual status.[34] Thus, whether all women included in this study were iodine deficient is uncertain and exposure misclassification might have biased our results. We did not collect 24 h urine samples or measure urinary creatinine because these often do not reduce within-individual variability compared with a spot urinary iodine concentration.[34] The median urinary iodine concentration in the placebo group remained within the recommended range (although at the lower end) in the second and third trimesters;[3] this finding might have been caused by a physiological increase in renal iodine clearance[5] or by being enrolled into the study and being told about the importance of iodine nutrition during pregnancy, prompting the women to consume more iodine-rich foods, which might have biased our trial towards a null effect. The dropout rate was high around delivery because many women returned to their hometowns to deliver or care for their babies; thereafter, attrition was low and most children remained in the study. Attrition was balanced between groups, the study was randomised, and there were no significant differences in baseline characteristics between those who completed the study and those lost to follow-up by delivery, suggesting no strong attrition bias that would compromise generalisability. The final sample size at 5·4 years (n=313) was well above the estimated sample size (n=284) needed to discriminate a 5-point difference in WPPSI-III score between groups, suggesting that attrition did not result in a type I error in the primary outcomes.

In conclusion, supplementation with 200 µg iodine in mildly iodine-deficient pregnant women was safe and increased iodine intakes into the sufficient range. However, iodine supplementation had no clear benefits on maternal thyroid function or child neurodevelopment. Our findings suggest that pregnant women might be able to physiologically adapt to mildly low iodine intakes during pregnancy, draw from intrathyroidal iodine stores, and maintain fetal euthyroidism allowing for normal in-utero development.[5] This conclusion is consistent with current WHO recommendations[14] that iodine supplementation is unlikely to be of harm, but might not be justified in mildly iodine-deficient pregnant women residing in countries with effective iodised salt programmes where other population groups have sufficient iodine intakes. Future intervention trials in pregnant women with more severe iodine deficiency (eg, with a median urinary iodine

concentration <100 µg/L) and in settings where women of reproductive age are clearly iodine deficient would be valuable.

Contributors

SG, NJ, AM-B, IM, PW, KS, and MBZ designed the study. SG, NJ, ST, PW, and KS did the field work. SG, NJ, and SS did the laboratory analyses. SG, NJ, AM-B, VG, and TT did the statistical analysis. SG, NJ, AM-B, VG, and MBZ wrote the first draft of the report and all authors edited and approved the final text.

Declaration of interests

We declare no competing interests.

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References

1 Zimmermann MB. The effects of iodine deficiency in pregnancy and infancy. *Paediatr Perinat Epidemiol* 2012; **26** (suppl 1)**:** 108–17.

2 Zoeller RT, Rovet J. Timing of thyroid hormone action in the developing brain: clinical observations and experimental findings. *J Neuroendocrinol* 2004; **16:** 809–18.

3 WHO, UNICEF, International Council for Control of Iodine Deficiency Disorders. Assessment of iodine deficiency disorders and monitoring their elimination. A guide for programme managers. Geneva: World Health Organization, 2007. http://www.who.int/nutrition/publications/micronutrients/iodine_deficiency/9789241595827/en/ (accessed Aug 21, 2017).

4 Zimmermann MB, Gizak M, Abbott K, Andersson M, Lazarus JH. Iodine deficiency in pregnant women in Europe. *Lancet Diabetes Endocrinol* 2015; **3**: 672–74.

5 Zimmermann MB. The adverse effects of mild-to-moderate iodine deficiency during pregnancy and childhood: a review. *Thyroid* 2007; **17:** 829–35.

6 Caldwell KL, Pan Y, Mortensen ME, Makhmudov A, Merrill L, Moye J. Iodine status in pregnant women in the National Children's Study and in U.S. women (15-44 years), National Health and Nutrition Examination Survey 2005-2010. *Thyroid* 2013; **23:** 927–37.

7 Bath SC, Steer CD, Golding J, Emmett P, Rayman MP. Effect of inadequate iodine status in UK pregnant women on cognitive outcomes in their children: results from the Avon Longitudinal Study of Parents and Children (ALSPAC). *Lancet* 2013; **382:** 331–37.

8 Hynes KL, Otahal P, Hay I, Burgess JR. Mild iodine deficiency during pregnancy is associated with reduced educational outcomes in the offspring: 9-year follow-up of the gestational iodine cohort. *J Clin Endocrinol Metab* 2013; **98:** 1954–62.

9 Rebagliato M, Murcia M, Alvarez-Pedrerol M, et al. Iodine supplementation during pregnancy and infant neuropsychological development: INMA Mother and Child Cohort Study. *Am J Epidemiol* 2013; **177:** 944–53.

10 Taylor PN, Okosieme OE, Dayan CM, Lazarus JH. Therapy of endocrine disease: impact of iodine supplementation in mild-to-moderate iodine deficiency: systematic review and meta-analysis. *Eur J Endocrinol* 2013; **170:** R1–R15.

11 Zhou SJ, Anderson AJ, Gibson RA, Makrides M. Effect of iodine supplementation in pregnancy on child development and other clinical outcomes: a systematic review of randomized controlled trials. *Am J Clin Nutr* 2013; **98:** 1241–54.

12 Alexander EK, Pearce EN, Brent GA, et al. 2017 guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and the postpartum. *Thyroid* 2017; **27:** 315–89.

13 Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R, Vaidya B. 2014 European Thyroid Association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. *Eur Thyroid J* 2014; **3:** 76–94.

14 WHO Secretariat on behalf of the participants to the Consultation, Andersson M, de Benoist B, et al. Prevention and control of iodine deficiency in pregnant and lactating women and in children less than 2-years-old: conclusions and recommendations of the Technical Consultation. *Public Health Nutr* 2007; **10:** 1606–11.

15 Shi X, Han C, Li C, et al. Optimal and safe upper limits of iodine intake for early pregnancy in iodine-sufficient regions: a cross-sectional study of 7190 pregnant women in China. *J Clin Endocrinol Metab* 2015; **100:** 1630–38.

16 Iodine Global Network. Global iodine scorecard and map. Zurich: Iodine Global Network, 2016. http://www.ign.org/scorecard.htm (accessed March 2, 2017).

17 Rah JH, Anas AM, Chakrabarty A, Sankar R, Pandav CS, Aguayo VM. Towards universal salt iodisation in India: achievements, challenges and future actions. *Matern Child Nutr* 2015; **11**: 483–96.

18 Sinawat S. Iodine deficiency disorders in Thailand. In: Preedy VR, Burrow GN, Watson R, eds. Comprehensive handbook of iodine: nutritional, biochemical, pathological, and therapeutic aspects. Amsterdam: Elsevier Science BV, 2009: 1221–26.

19 Brazelton T, Nugent K. Neonatal Behavioral Assessment Scale. London, UK: Mac Keith Press, 1995.

20 Bayley N. Bayley Scales of Infant and Toddler Development. 3rd edn. San Antonio, TX: Pearson Education, 2006.

21 Ottem E. Confirmatory factor analysis of the WPPSI, WPPSI-R, and the WISC-R: Evaluation of a model based on knowledge-dependent and processing-dependent subtests. *J Psychoeduc Assess* 2003; **21:** 3–15.

22 Sherman EMS, Brooks BL. Behavior Rating Inventory of Executive Function - Preschool Version (BRIEF-P): test review and clinical guidelines for use. *Child Neuropsychol* 2010; **16:** 1–17.

23 Vostanis, P. Strengths and Difficulties Questionnaire: research and clinical applications. *Curr Opin Psychiatry* 2006; **19:** 367–72.

24 Pino S, Fang SL, Braverman LE. Ammonium persulfate: a safe alternative oxidizing reagent for measuring urinary iodine. *Clin Chem* 1996; **42:** 239–43.

25 Stagnaro-Green A, Abalovich M, Alexander E, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid* 2011; **21:** 1081–25.

26 Mandel SJ, Spencer CA, Hollowell JG. Are detection and treatment of thyroid insufficiency in pregnancy feasible? *Thyroid* 2005; **15:** 44–53.

27 Hales C, Channon S, Taylor PN, Draman MS, et al. The second wave of the Controlled Antenatal Thyroid Screening (CATS II) study: the cognitive assessment protocol. *BMC Endocr Disord* 2014; **14**: 95.

28 Wardlaw TM, Blanc A, Zupan J, Ahman E, WHO, UNICEF. Low birthweight: country, regional and global estimates. Geneva, New York: WHO, UNICEF, 2004. https://www.unicef.org/publications/files/low_birthweight_from_EY.pdf (accessed Aug 21, 2017).

29 WHO. The WHO Child Growth Standards. Geneva: World Health Organization. http://www.who.int/childgrowth/standards/height_for_age/en/ (accessed March 2, 2017).

30 Stinca S, Andersson M, Weibel S, et al. Dried blood spot thyroglobulin as a biomarker of iodine status in pregnant women. *J Clin Endocrinol Metab* 2017; **102:** 23–32.

31 Casey BM, Thom EA, Peaceman AM, et al. Treatment of subclinical hypothyroidism or hypothyroxinemia in pregnancy. *N Engl J Med* 2017; **376:** 815–25.

32 Lazarus JH, Bestwick JP, Channon S, et al. Antenatal thyroid screening and childhood cognitive function. *N Engl J Med* 2012; **366:** 493–501.

33 Ardila A. Development of metacognitive and emotional executive functions in children. *Appl Neuropsychol Child* 2013; **2:** 82–87.

34 Zimmermann MB, Andersson M. Assessment of iodine nutrition in populations: past, present, and future. *Nutr Rev* 2012; **70:** 553–70.