Report

The effect of iodine supplementation in mildly iodine-deficient pregnant women on child development: a 5-year follow-up of the MITCH Study

Research Protocol

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RESEARCH PROTOCOL

Version 3 (26 juni 2015)
**MITCH Follow up**

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<td>AE</td>
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<td>BRIEF-P</td>
<td>Behavior Rating Inventory of Executive Function</td>
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<td>IC</td>
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<td>ICCIDD</td>
<td>International Council for Control of Iodine Deficiency Disorders</td>
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<td>IQR</td>
<td>Inter Quartile Range</td>
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<td>METC</td>
<td>Medical research ethics committee (MREC); in Dutch: medisch ethische toetsing commissie (METC)</td>
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<tr>
<td>NBAS</td>
<td>Neonatal Behaviour Assessment Scale</td>
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<td>(S)AE</td>
<td>(Serious) Adverse Event</td>
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<td>Sponsor</td>
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<td>Tg</td>
<td>Thyroglobulin</td>
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<td>TPO</td>
<td>Thyroid peroxide</td>
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<td>Thyroid Stimulating Hormone</td>
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<td>TT4</td>
<td>Total Thyroxine</td>
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<td>UIC</td>
<td>Urinary Iodine Concentration</td>
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<tr>
<td>UNICEF</td>
<td>United Nations Children’s Fund</td>
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<td>WHO</td>
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<td>WPSSI</td>
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SUMMARY

Rationale: Severe iodine deficiency during pregnancy increases the risk of adverse pregnancy outcomes (1-5), and impairs motor and cognitive performance in the offspring (6-9). Inadequate thyroid hormone supply to the fetus is the likely cause (10-14). In contrast, the potential adverse effects of mild iodine deficiency during pregnancy are less clear, as controlled trials of iodine supplementation in mildly iodine deficient pregnant women do not increase concentrations of maternal or newborn thyroid hormones (15). Moreover, there are no long-term data from controlled trials in mildly iodine deficient pregnant women that have measured the effect of iodine supplementation on infant or child development.

Objective: The study aim is to determine whether daily oral iodine supplementation in pregnant women with mild iodine deficiency improves cognitive development of their offspring 4 to 5 years postpartum.

Study design: The study is a long-term follow-up of the children of pregnant women who completed a randomized placebo controlled trial of iodine supplementation – the MITCH (Maternal Iodine Supplementation and its Effects on Thyroid function and CHild Development) study – in 2009-2010. The children and their families will be invited to the health clinic where they will answer a socio-demographic questionnaire and complete a dietary assessment of iodine intake. Their height and weight will be measured, and a spot urine sample will be collected for measurement of urinary iodine, and a blood spot from a finger prick will be collected for measurement of thyroid hormones. The children will be tested with the WIPPS and the BRIEF-P to assess cognitive development. Co-primary outcomes are the verbal and performance IQ scores from the WPPSI and the global executive composite score from the BRIEF-P. In addition, because iodine deficiency in utero may be associated with hearing deficits, which in turn may affect cognitive development, we will also assess auditory function by measuring hearing threshold by using otoacoustic emissions.

Study population: Healthy pregnant women, gestational age ≤14 weeks, from two sites (in Bangkok, Thailand and in Bangalore, India) were randomized to receive either a daily supplement of 200 µg oral iodine or placebo from enrollment until delivery. Women were followed through delivery, and then with postnatal follow-up of their infants at 6 weeks, 12 and 24 months. Infant development was assessed using the Neonatal Behavioral Assessment Scale (NBAS) at 6 weeks of age and using the Bayley Scales of Infant Development (BSID III) at 1 and 2 years. At 2 years, the BRIEF (Behavior Rating Inventory of Executive Function)-P was also done in India. There were no significant group differences in the BSID III scores at 1 and 2 years of age at either site, and no significant group differences in the NBAS in Thailand. However, in India, iodine had small but significant benefits on the NBAS at 6 weeks and the BRIEF-P measured at 2 years. The pooled data from the two sites is now being analyzed. The children in the study are now 4 to 5 years old, and developmental tests in children at 4-5 years of age are more robust, reliable and predictive of life-long intelligence than tests given during infancy.

Main study parameters/endpoints: The primary study outcome is the difference in scores on the WIPPS and BRIEF-P between intervention groups, with the verbal and performance IQ scores from the WPPSI and the global executive composite score from the BRIEF-P as co-primary outcomes. Secondary outcomes will be scores on the Strengths and Difficulties questionnaire, as well as auditory function, urinary iodine concentrations (UIC), thyroid function indicators (TSH, TT4), weight and height.
Nature and extent of the burden and risks associated with participation, benefit and group relatedness: The burden and risks associated with participation are negligible. The follow up study will require the children to undergo cognitive and auditory testing (half-day) and their mothers to answer questionnaires related to their children. Children will be asked to hand in a spot urine sample to assess iodine concentration, and a capillary blood spot to assess haemoglobin, thyroid stimulating hormone and free thyroxine concentrations (not obligatory for participation). Parents of children with strongly deviating results (e.g. low intellectual capacity, deafness, anaemia or hypothyroidism) will be informed and referred for treatment, which is a benefit of participation in the follow up study.

Whether it is beneficial to supplement mildly iodine deficient pregnant women with iodine is uncertain. WHO does not recommend supplementation in areas with well-functioning iodized salt programs, while many expert medical groups recommend supplementation in areas of mild iodine deficiency. This is the first randomized controlled trial that will assess the long-term effect on child development of iodine supplementation of mildly iodine deficient pregnant women. It will therefore provide important evidence to inform optimized guidelines on iodine supplementation of this group.
1. INTRODUCTION AND RATIONALE

1.1 Iodine requirements in pregnancy

The iodine requirement during pregnancy is increased due to an increase in maternal T4 production to maintain maternal euthyroidism and transfer thyroid hormone to the fetus, and iodine transfer to the fetus, particularly in later gestation (16-18). There may also be an increase in renal iodine clearance during pregnancy, although this is unclear (19,20). Several methods have been used to estimate iodine requirements in pregnancy. Added to the estimated average requirement (EAR) of 95 µg/day for non-pregnant women, a daily fetal thyroid iodine uptake of ≈75 µg/day would suggest an EAR of 170 µg/day for pregnancy (21). Dworkin et al. (22) reported pregnant women were in iodine balance when consuming ≈160 µg/day. In the U.S., the EAR for iodine has been set at 160 µg/day for pregnant women ≥14 yr, and the RDA, set at 140% of the EAR rounded to the nearest 10 µg, is 220 µg/day (21). WHO/ICCIDD/UNICEF recommended a daily iodine intake of 250 µg for pregnant women (17).

1.2 Defining iodine status in pregnancy and childhood

The median UI is recommended by WHO/ICCIDD/UNICEF (17) for assessing iodine nutrition in populations. A median UI in school children in the range of 100-299 µg/L and in pregnant women in the range of 150-250 µg/L indicates optimal iodine nutrition (17). Daily iodine intake can be extrapolated from UI assuming median 24-hr urine volumes for girls aged 7-15 yr of 0.9 mL/hr/kg (23), and for adult women of ≈1.5 L (24). Assuming a mean iodine bioavailability of 92% and a modest increase in renal iodine clearance during pregnancy (19,20,25), recommended daily iodine intakes for pregnancy of ca. 250 µg (16,17,21) correspond to a median UI of ≥150 µg/L in adult pregnant women. Thus, mild-to-moderate deficiency in pregnancy could be defined as a median UI of 100-150 µg/L. However, the recommendations for iodine intake for pregnancy are not based on functional endpoints but rather were estimated based on a factorial method. Thus, despite their high vulnerability, the precise requirements for optimal iodine intake during pregnancy remain uncertain.

1.3 Cross sectional studies of iodine status and thyroid function in pregnancy

In a cross-sectional study in Denmark, iodine supplement use (150 µg/d) and thyroid function were assessed in pregnant women and their newborns (n=144) (26). At term, the median UI in supplemented mothers was 60 µg/l, compared to 35 µg/l in nonsupplemented mothers. In the supplement group, thyroglobulin (Tg) in both maternal and cord blood was significantly lower, and free T4 significantly higher, compared to the nonsupplemented group. Several studies have reported on changes in thyroid size during pregnancy as a sensitive indicator of iodine status. As reviewed by Berghout and Wiersinga (27), in countries affected by mild or moderate iodine deficiency (Ireland, Germany, Belgium, Italy, Denmark), thyroid volume increases 15-31% during pregnancy, while in iodine-sufficient countries (Finland, USA, the Netherlands), there is little or no increase in thyroid volume during pregnancy (27).

1.4 Randomized controlled trials of iodine supplementation during pregnancy

In Europe, 6 small, randomized, controlled trials of iodine supplementation in pregnancy have been done in women with mild-to-moderate ID (28-33). Romano et al (28) gave 120-180 µg iodine as iodized salt or control daily beginning in the 1st trimester to healthy
pregnant women (n=35; median UI 31-37 µg/l). In the treated group, median UI increased 3-fold and thyroid volume did not change. In the controls, there was no change in UI, but a 16% increase in thyroid volume. Treatment had no effect on maternal TSH. Pedersen et al (29) randomized pregnant women (n=54) to receive either 200 µg iodine/d as potassium iodide (KI) solution or no supplement from 17 wk to term. Median UI increased from 55 µg/l to 90-110 µg/l in treated group. Maternal thyroid volume increased 16% in the treated group vs. 30% in controls. Maternal serum thyroglobulin (Tg) and TSH, and cord Tg were significantly lower in the treated group. No significant differences were found between groups comparing maternal or cord T4, T3, and FT4. In a double-blind, placebo-controlled trial, Glinoer et al. (30) supplemented pregnant women (n=120; median UI 36 µg/l; biochemical criteria of excess thyroid stimulation) with 100 µg iodine/day or control from ~14 wk to term. Treatment had no significant effect on maternal or cord T3, FT4, and T3/T4 ratio. The treated women had significantly higher UI, smaller thyroid volumes, and lower TSH and Tg concentrations, compared to controls. Newborns of the treated group also had significantly higher UI, smaller thyroid volumes and lower Tg concentrations compared to controls.

Liesenkötter et al. (31) reported results from a controlled trial of 230 µg iodine/day from 11 wk to term in pregnant women (n=108; median UI 53 µg/g creatinine (cr); goiter rate 43%). Median UI increased to 104 µg/g cr in the treated group, and median thyroid volume was significantly lower in the newborns of the treated women compared to controls (0.7 ml vs. 1.5 ml, respectively). Treatment had no significant effect on maternal TSH, T3, T4, thyroid volume, or Tg, and had no effect on newborn TSH. In a placebo-controlled, double-blind trial, Nohr et al (32) gave a multinutrient supplement containing 150 µg iodine/day or control to pregnant women positive for anti-thyroid peroxidase antibodies (TPO-Ab) (n=66) from 11 wk to term. Median UI was significantly higher in the treated women at term, but there were no differences in maternal TSH, FT4 or Tg between groups. In a prospective, randomized, open-label trial, Antonangeli et al. (33) supplemented pregnant women (n=67; median UI 74 µg/g cr) with 50 µg or 200 µg iodine/day from 18-26 wk to 29-33 wk. Median UI was significantly higher in the 200 µg group than in the 50 µg group (230 vs. 128 µg/g cr). However, there were no differences in maternal FT4, FT3, TSH, Tg or thyroid volume between groups.

Summarizing the results of these trials (28-33), supplementation significantly increased maternal UI in all studies. But iodine doses varied between 50 and 230 µg/day, and the data indicate no clear dose-response relationship for UI, TSH, Tg, thyroid hormones, or thyroid volume. In 3 of the 5 trials that measured maternal thyroid volume, supplementation was associated with significantly reduced maternal thyroid size, and the data also suggest an increase in newborn thyroid volume and Tg can be prevented or minimized by supplementation. The data are equivocal for an effect on maternal TSH; values are generally lower (within the normal reference range) with iodine supplementation. But importantly, supplementation appeared to have no affect on maternal and newborn total or free thyroid hormone concentrations (15). Moreover, there are no clinical data on the effect of iodine supplementation on birth outcomes, and no data on long-term outcomes, such as maternal goiter, thyroid autoimmunity, or child development (15).

1.5 Maternal thyroid function and child development

Severe ID during pregnancy increases the risk of spontaneous abortion, low birth weight and infant mortality (2-6). In regions of severe endemic goiter, the adverse effects of in
utero iodine deficiency on neuromotor development are well established: randomized controlled trials of iodine supplements given to iodine deficient mothers before pregnancy or during early pregnancy improve motor and cognitive performance of their offspring (7-9). A meta-analysis of cross sectional studies suggested severe iodine deficiency in a population lowers mean IQ scores by 13.5 points (10). However, the potential adverse effects of mild-to-moderate iodine deficiency during pregnancy are unclear. Inadequate thyroid function in the fetus and newborn are the likely cause of brain damage in iodine deficiency. Maternal thyroxine (T4) crosses the placenta to support neural development before onset of fetal thyroid function at 10-12 week (11). Maternal T4 represents up to 20-40% of T4 measured in cord blood at birth (12). Two prospective case-control studies, using different measures of impaired maternal thyroid function, have reported developmental impairment in offspring of affected mothers. In the study by Haddow et al (13), 7-9 yr-old children of mothers with subclinical hypothyroidism during pregnancy (an increased TSH in the 2nd trimester) were compared to children from mothers with normal thyroid function during pregnancy. None of the children had hypothyroidism as newborns. They were given 15 tests relating to intelligence, attention, language, reading ability, school performance, and visual-motor performance. The children in the first group (n=62) performed slightly less well on all 15 tests. Their IQ scores on the Wechsler Intelligence Scale for Children averaged 4 points lower than those of the 124 matched controls (13).

Pop et al (14) reported a prospective study of pregnant women and their children up to the age of 2 years. Child development was assessed using the Bayley Scales of Infant Development in children with hypothyroxinemia (free T4 below the tenth percentile at 12 weeks' gestation) (cases), and in children of women with free T4 between the 50th and 90th percentiles at 12 weeks’ gestation (controls). Infants from mothers whose maternal hypothyroxinemia did not improve over the course of pregnancy had delayed mental and motor function compared to controls: 10 index points on the mental scale and eight on the motor scale at the age of 1 year, as well as eight index points on the mental, and 10 on the motor scale at the age of 2 years. Despite the potential limitations of their case-control design, these studies suggest even marginal maternal thyroid dysfunction can cause fetal harm. However, in these studies, the maternal thyroid abnormalities were not due to iodine deficiency.

1.6 Observational studies of iodine status in pregnancy and child development

Two recent observational studies from the U.K. and Australia report lower IQ and poorer school performance in children born to iodine-deficient mothers. In the UK study (34), Bath et al. assessed a cohort of pregnant mother–child pairs (n=1040) from western England. They measured urinary iodine concentration (UIC) per gram creatinine (UICcreat) in stored samples from women at the end of the first-trimester, then dichotomized the women to a UICcreat less than 150 μg/g or 150 μg/g or more, based on WHO UIC criteria (17) for classifying iodine status in pregnancy. Children were born in 1991-92 and assessed at 8 to 9 years of age. Those born to deficient women were more likely to have scores in the lowest quartile for verbal IQ (odds ratio 1.58, 95% CI 1.09–2.30), reading accuracy (1.69, 1.15–2.49) and reading comprehension (1.54, 1.06–2.23). Moreover, when the less than 150 μg/g group was subdivided, scores worsened going from 50–150 μg/g to less than 50 μg/g, suggesting more severe iodine deficiency was linked to poorer performance.
Similarly, in the Australian study (35), Hynes et al. examined 9 year-old children born in Tasmania in 2000-01, and compared those born to mothers with UICs less than 150 μg/L during pregnancy to those whose mothers had a UIC of 150 μg/L or more. Mean gestational age at UI collection was 24.6 (SD 9.8) weeks; in 46% of women, UIC was calculated as the mean of 2 or 3 samples during pregnancy. Children from deficient mothers had significantly lower scores on standard tests of spelling, grammar and English-literacy (-10.0% 7.6% and 5.7%, respectively) compared to the children from sufficient mothers. But only the differences in spelling remained significant after adjustment for socioeconomic factors.

In these two studies, confounding by unrecognized or unmeasured factors is a possibility. In the UK study, mothers with better iodine status were also slightly older and had higher educational levels. Also, higher iodine intakes could simply be a proxy for better overall dietary quality, although the UK study included dietary intakes of iron and n-3 fatty acids as covariates. As with any observational data, we should be cautious not to over-interpret the findings; they need confirmation in RCTs, as emphasized by the authors of both studies. RCTs are needed because, if confirmed, these findings have wide implications. In the UK study, the women classified as deficient had a median UIC of 91 μg/L and in the Australian study, the overall median UIC was 81 μg/L. Maternal UICs at this level are common in pregnant women in many countries, including high-income countries such as France, Norway, Spain, and Denmark in the European region, and many others worldwide (36).

1.7 Iodine status and childhood cognition

There have been many cross-sectional studies comparing cognition and/or motor function in children from chronically iodine deficient and iodine sufficient areas, including children from Asian and European backgrounds (37-47). These cross-sectional studies, with few exceptions, report impaired intellectual function and motor skills in children from iodine deficient areas. However, observational studies are often confounded by other factors that affect child development [59]. Also, these studies could not distinguish between the persistent effects of in utero ID and the effects of current iodine status. Several randomized, controlled trials in school aged children have tried to measure the effect of iodized oil on cognition [48-51] but methodological problems limit their interpretation.

Two randomized controlled trials (RCTs) have shown that mild-to-moderate iodine deficiency at primary school age (10-12 years of age) impairs cognition (52,53). In a placebo controlled, double-blind 6 month intervention trial, moderately iodine deficient 10-12 y-old children (n=310) in Albania were randomized to receive either 400 mg of iodine as oral iodized oil or placebo. Treatment with iodine markedly improved iodine and thyroid status: at 24 wk, median UI in the treated group was 172 µg/L and mean circulating T4 increased ≈40%. Compared to placebo, iodine treatment significantly improved information processing, fine motor skills, and visual problem solving [52].

A randomized controlled trial in 10–13 y children (n=184) in New Zealand [53] gave a daily tablet containing 150 µg iodine as KI or placebo for 28 wk. Cognitive performance was assessed through 4 subtests from the Wechsler Intelligence Scale for Children after 28 wk. Thyroid hormone concentrations were in the normal range at baseline for all children. Despite this, iodine improved scores on 2 of the cognitive tests: picture concepts (P = 0.023) and matrix reasoning (P = 0.040). Overall cognitive score of the iodine group was 0.19 SDs higher than that of the placebo group (P = 0.011).
In these two studies (52,53), increasing iodine intakes over several months improved cognition in older children who presumably grew up under conditions of ID. This short-term beneficial effect may have been due to improvements in myelination of central nervous system mediated by an increased supply of thyroid hormone (54). Myelinization continues throughout childhood particularly in the frontal cortex, the brain area responsible for higher-order cognition and fluid intelligence. Alternatively, better thyroid function could improve cognition by effects on neurotransmitters and/or glucose metabolism (55).

1.8 Meta-analyses and systematic reviews of the effects of iodine on cognition

A meta-analysis of the effect of ID on mental development (56) pooled data from 21 observational and experimental studies done in areas of moderate-to-severe ID. The IQs of non-ID groups were on average 13.5 IQ points higher than those of the ID groups. In a second meta-analysis by Qian et al. of Chinese studies (57), there was an increase of ≈12 IQ points for children born more than 3.5 years after iodine prophylaxis was introduced.

Two recent systematic reviews (10, 58) have confirmed the benefits of correcting iodine deficiency. The first systematic review looked at 89 studies that provided iodised salt to populations and recorded a significant 72–76% reduction in risk for low intelligence (defined as IQ <70) and an 8:2–10:5 point overall increase in IQ (10). The second systematic review similarly concluded that iodine-sufficient children have a 6:9–10:2 point higher IQ than iodine-deficient children (58). The International Child Development Steering Group identified iodine deficiency as a key global risk factor for impaired child development (59).

1.9 The advantages of developmental testing in older children compared to testing in infancy

Developmental assessments are important as they offer information on any aspect in the development of a child that needs special attention, in terms of a deficiency, or strength. Developmental assessments in infancy are usually carried out to understand developmental delays. However, it is known that infants do not develop uniformly. Development occurs in spurts, and it is hypothesized that higher cognitive functions (executive functions: working memory, response inhibition, shifting), integrated attention (60) and theory of mind (61) start developing during the preschool age (3-5 years), due to development of the prefrontal area (62). Metacognitive executive functions (such as planning and verbal fluency) develop around the age of 3. Metacognitive executive functions (but not emotional executive functions) are correlated with the child's general intellectual level (intelligence) (63). Due to this, cognitive assessment at pre-school age allows to evaluate a wide array of cognitive functions, as opposed to broad domain-wise assessment (motor, language, cognitive and adaptive) in infancy. Another advantage in testing older children is that testing at this age involves direct assessment, which is more objective, as opposed to reports from parents, which could have subjective elements to it. Some scales for infants require familiar surrounding and familiar persons to be present during assessment, whereas older children would be more comfortable in a testing situation, as they would be exposed to such situations in preschool. Moreover, infants tend to be affected more by constitutional variables such as fatigue, hunger or illness which may affect the performance. For all of these reasons, it is generally accepted that
developmental tests in children at 4-5 years of age are more predictive of future development and long-term intelligence than tests given during infancy.

1.10 Iodine deficiency and auditory function

In a comprehensive review we have recently highlighted the lack of data regarding iodine deficiency, thyroid function and auditory outcomes (64). In utero induction of hypothyroidism has been shown to induce a delay in maturity and a degeneration of the sensitive epithelium of the inner ear, a distortion of the tectorial membrane, and the presence of acidophilic precipitates in the ductus (65-69). Thyroid hormones may also be necessary for the maturation not only of the cochlear organ but also of the central auditory areas (70). Animal studies have revealed that α and β thyroid hormone receptors are not homogeneously distributed throughout the auditory system. During critical developmental stages, shortage of T3 might therefore fail to adequately stimulate hormone-receptor interaction in the corresponding auditory structures (71). In fact, both congenital and acquired hypothyroidism are known to produce conduction deafness, which may be reversible after treatment with T4, (65, 72-74), and that neural sensitivity defects as a cause of hearing loss, are also found in persons with congenital hypothyroidism (73-75).

Several observational studies have shown that iodine deficiency is associated with increased hearing thresholds. A study in 381 Chinese children showed that iodine contents in hairs of children with perceptive nerve deafness (PND) were much lower than those of healthy children (P<0.01) (76). A study among 150 Spanish school children showed an inverse relation between the auditory threshold at all frequencies and UI in those with palpable goiter. Moreover, those with thyroglobulin values >10 ng/mL had higher auditory thresholds at all frequencies, and children with a thyroid size >95th percentile had an odds ratio of 3.86 (95% CI, 2.59-5.10) of having a threshold >20 dB (77). In a study among 642 preschool children in France, high hearing thresholds were more commonly found in children with lower urinary iodine excretion (78,79).

In a study in Guizhou Province, China, auditory function of children living in an endemic iodine deficient area was shown to be impaired when compared to children living in a non-endemic control area. Three years after introduction of iodized salt prophylaxis, hearing thresholds significantly improved and were nearly similar in both groups (80). In an intervention trial in 197 Beninese children, those with higher serum thyroglobulin concentrations had significantly higher hearing thresholds in the higher frequency range (>2000 Hz) than children with lower serum thyroglobulin concentration. Moreover children with lower hearing thresholds performed significantly better on the mental tests used (81). To date, auditory function has never been reported as an outcome of studies on iodine supplementation during pregnancy.

1.11 The MITCH study

The MITCH study (Maternal Iodine Supplementation and its Effects on Thyroid function and CHild Development) is a multicenter randomized controlled trial of 200 μg iodine/d or placebo given to mildly iodine-deficient pregnant women in Thailand and India from the first trimester to delivery.

The Thai portion of the MITCH study was conducted in pregnant women who registered at Ramathibodi Hospital of Mahidol University in Bangkok. The Indian portion was conducted at St Martha’s Hospital in Bangalore. All study and analytic procedures were
standardized to allow pooling of the data from the two sites. The study was approved by the ethical review boards at Ramathibodi Hospital in Bangkok, Thailand, at St. John’s National Academy of Health Sciences, St Martha’s Hospital, in Bangalore, and by Wageningen University in the Netherlands. It was supervised by an external data safety and monitoring board and registered at http://www.clinicaltrials.gov/ with its identifier: NCT00791466. All women gave signed informed consent. Women for the study were recruited between 2008 and 2011. Inclusion criteria included: 1) singleton pregnancy; 2) age 18 to 40 y; 3) gestational age ≤14 weeks; 4) generally healthy. Women who had an elevated thyroid stimulating hormone (TSH) concentration at screening were excluded from the study.

In Bangkok, 511 pregnant women were enrolled; in Bangalore 318 pregnant women were enrolled (total n=829). They were randomized to receive either 200 µg iodine (as potassium iodide tablets, Merck, Darmstadt, Germany) or an identical placebo tablet (Merck, Darmstadt, Germany) taken daily until delivery. Compliance with supplement use was assessed by direct questioning and tablet counting. Maternal thyroid function, urinary iodine concentration (UIC) and thyroid volume (by using ultrasound) were measured at baseline, at the beginning of the 2nd and 3rd trimester, and at delivery. Birth outcomes were recorded. Maternal and infant thyroid function and UIC were measured postpartum at 6 weeks, 6 months postpartum, 1 and 2 years.

Infant development testing - At 6 weeks postpartum, the Neonatal Behavioral Assessment Scales (NBAS) test was done to assess newborn development. The NBAS has been used to examine the effects of pre- and perinatal risk factors on infant development (82,83). Results of a study among low birth weight and/or premature Japanese infants confirmed the usefulness of the NBAS for predicting the risk of later developmental disabilities (84). The NBAS contains 28 behavioral items, 18 neurologic reflex items, and 7 supplementary items that measure the quality of responsiveness and the amount of input that the infant needs from the examiner to show their best performance. Scores on the NBAS were reduced to the following 7 clusters: 1) habituation; 2) orientation; 3) motor; 4) range of state; 5) regulation of state; 6) autonomic stability; and 7) reflexes, including supplementary items.

At 1 and 2 years postpartum, the Bayley Scales of Infant Development (BSID III) was administered to obtain standard scores for cognitive and motor (gross and fine subtests) scales (85). BSID III uses standardized administration and scoring procedures to provide the infant and toddler with situations and tasks that capture his or her interest and that provide an observable set of behavioral responses. The cognitive scale assesses play skills, information processing, information processing speed, problem solving, and number concepts. The motor subtests assess quality of movement, sensory and perceptual motor integration, and basic locomotion milestones. In addition, at 2 years of age, in India only, executive functioning in children was assessed by using the BRIEF (Behavior Rating Inventory of Executive Function)-P (86). More details on this test are described in the study design section of this application.

Thailand interim results - Of the original women, 369 completed the supplementation trial to delivery. The 27% drop out rate was equal between groups and was due mainly to: a) women moving out of the study area; b) women declining further participation; and c) miscarriages, but the frequency of these did not differ between the two groups. An intention-to-treat analysis was done. There were no differences in median UIC between
the two groups at baseline, and median UIC increased significantly from baseline in both groups (from 110.1 µg/L to 154.6 µg/L in the placebo group and from 112.0 µg/L to 233.3 µg/L in the iodine group) (p<0.001). At 30 weeks, only 2% of the women in the placebo group and 7% in the iodine group reported a median UIC > 500 µg/L, suggesting possible excess iodine intakes. There were no significant differences between groups in maternal thyroid function tests or thyroid volume during gestation. Within both groups, there was no significant change in TSH but a significant decrease in fT4 from baseline to 30 weeks; median Tg concentration increased significantly in the placebo group during the intervention (p<0.05). At baseline, 4.7% of women had subclinical hyperthyroidism and 8.6% of women had subclinical hypothyroidism, but the prevalence of all subtypes of thyroid dysfunction, or anti-TPO antibodies, did not differ significantly during the study.

The percentage of low birth weight and preterm birth were higher in the placebo group (8.8% and 10.6%, respectively) than in the iodine group (5.4% and 5.4%, respectively), but these differences were not statistically significant. There were no significant differences between newborn groups in thyroid function, thyroid volume, birth characteristics or UIC (p>0.05). At 6-week postpartum (n=311), the prevalence of postpartum thyroiditis (hyperthyroidism) was significantly lower in the iodine group (3%) as compared to the placebo group (9%) (OR: 95%CI, 0.17: 0.04-0.70). There were no significant differences between newborn groups in NBAS score. However, the NBAS cluster scores of state regulation and supplementary items were significantly lower in low birth weight infants compared to normal weight infants. In the BSID III assessed in children at 1 and 2 years of age, there were no significant group differences.

India interim results - Of the original women who were enrolled (n=318), 221 remained in the study at delivery (31% drop out rate) and 192 remained in the study at 2 years. The gestational age at recruitment was 10.3±2.4. The median UIC of all the women in first trimester was 187 µg/L and in the intervention group, UIC increased by 18.8% and 35.5% in the second and third trimester of pregnancy while in the placebo group, there was no significant change in UIC. The median UIC at the third trimester was significantly higher in the intervention group (279 vs. 180 µg/L; p=0.0032). There were no significant differences between groups in maternal thyroid function tests or thyroid volume during gestation. The prevalence of all subtypes of thyroid dysfunction, or anti-TPO antibodies, did not differ significantly during gestation. Postpartum, there were no significant differences between the maternal and infant groups in thyroid function, birth outcomes or UIC.

In the NBAS at 6 weeks, infants in the intervention group scored significantly higher in the orientation cluster (8.1 vs 7.1) (p=0.018). In the BSID III assessed in children at 1 and 2 years of age, there were no group differences in the unadjusted sub scales of cognitive, receptive and expressive communication, fine and gross motor development at 2 years. At 1 year, unadjusted expressive communication was statistically significantly different between the two groups but this might be a transient effect because it did not sustain at 2 years of age. However, in the BRIEF-P in children at 2 years, the children of mothers in the placebo group showed higher problem scores of inhibition (median (IQR): 21.0 (19.0, 24.0) compared to children from the intervention group (median (IQR): 20.0 (18.0, 21.0) (p=0.028). There were no significant group differences in auditory performance at 2 years at any of the frequencies tested.

Summary - The pooled analysis of the data is currently underway. The median UICs of the pooled sample of pregnant women, by trimester, are shown in the table below. The
preliminary findings of the study suggest that supplementation with 200 µg iodine/day in mildly iodine-deficient pregnant is effective in increasing iodine intakes into the adequate range, and was safe. However, other than a modest but significant reduction in the risk of maternal postpartum thyroid dysfunction in Thailand, it appears to have had no clear benefit on maternal or infant thyroid function. It also had no clear effect on birth outcomes, although there was a trend toward a lower percentage of low birth weight and preterm birth in the Thai study in the intervention group. In the BSID III at 1 and 2 years of age, there were no significant group differences at either site, and no significant group differences in the NBAS at 6 weeks in Thailand. In India, iodine had small but significant benefits on the NBAS at 6 weeks and the BRIEF-P measured at 2 years. This proposed study offers a unique opportunity to follow up this important group of children at 4 to 5 years, when developmental testing is more robust, reliable and predictive of future intelligence.

The following table shows the baseline UIC and the changes in UIC during pregnancy in the pooled data set (as median (25, 75th percentiles) of UIC (in µg/L).

<table>
<thead>
<tr>
<th></th>
<th>A=placebo</th>
<th>B=iodine</th>
</tr>
</thead>
<tbody>
<tr>
<td>baseline</td>
<td>129 (80, 213)</td>
<td></td>
</tr>
<tr>
<td>2nd trimester</td>
<td>174 (92, 284)</td>
<td>231 (131, 365)*</td>
</tr>
<tr>
<td>3rd trimester</td>
<td>159 (105, 251)</td>
<td>247 (140, 349)*</td>
</tr>
</tbody>
</table>

*p<0.02 between groups.
2. OBJECTIVES

The study aim is to determine whether iodine supplementation in mildly iodine-deficient pregnant women improves cognitive development of their offspring at 4 to 5 years of age.

2.1 Primary Objective

The co-primary outcomes will be: a) the verbal and performance IQ scores of the child using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI); and b) the global executive composite (GEC) score from the Behavior Rating Inventory of Executive Function (BRIEF-P).

2.2 Secondary Objective(s)

Secondary outcomes will be the child’s auditory performance, weight, height, UIC, TSH, and TT4.

3. STUDY DESIGN

This follow-up study to the MITCH study will be registered in an international trial database. Ethical approval for the study will be obtained from the review committees of Wageningen University and the ethical review boards in Bangkok and Bangalore. The families will be contacted, and written informed consent will be obtained from the mother, father or legal guardian. The families will then come to the clinic for all measurements and cognitive testing.

In Thailand, data collection for the majority of the mother-children pairs will be done at the Department of Pediatrics, Ramathibodi Hospital of Mahidol University in Bangkok. Women-children who live outside of Bangkok will be contacted to travel to the hospital. Travel and related expenses and compensation will be provided to all participants. In India, this will be at the Nutrition OPD Clinic, St John’s Research Institute, Bangalore. Most of the women and their children will be assessed at the clinic; for those who are unable to come top the clinic, the study team will make a home visit. Two psychologists will perform the auditory assessment, executive function using Brief P, verbal and performance IQ scores using WPPSI; parental intelligence using IQ tests, maternal depression during pregnancy, home environment in which the child is being brought up. A research assistant will administer the structured questionnaire, perform the dietary assessment, and anthropometric measurements; and a trained nurse or lab technician will collect the biological samples and a household salt sample.

The MITCH study has been conducted double blinded, and mothers have not yet been informed about the treatment they received during pregnancy. Although treatment code was broken in February 2015 for the research team, research staff that will conduct the data collection during the follow up will remain blinded to the treatment code.
4. STUDY POPULATION

4.1 Population (base)

The study groups will be the 4 to 5 year old children born to the MITCH study pregnant women who were randomized to receive either a daily supplement of 200 µg iodine (as potassium iodide) or a placebo tablet until delivery.

4.2 Inclusion/ exclusion criteria

We will include all possible children from mothers who participated in the MITCH study and who completed the supplementation protocol until delivery, and who can be contacted and agree to participate in the study.

4.3 Sample size calculation

In Bangkok, 211 families have agreed to participate: 123 girls and 88 boys, 109 from the iodine group and 102 from the placebo group. The ages of the children (on June 1, 2015): 4 years = 94; 5 years = 108; 6 years = 9. In Bangalore, 159 families have agreed to participate: 83 boys and 76 girls, 81 from the iodine group and 78 from the placebo group. The ages of the children are 3 yr6m-4 yr: 25, 4yr1m-5 yr:72, 5yr1m-6yr:62.

Assuming a 5 point difference on the WPPSI between groups to be of clinical relevance, with a standard deviation of 15, α of 0.05 (two-sided) and 80% power, we will need 142 children in each group. The total number of children involved will be 370 (as above), 190 from the iodine group and 180 from the placebo group. This will allow us to estimate a 4.4 point difference between groups with α of 0.05 (two-sided) and 90% power.

5. METHODS

5.1 Study parameters/endpoints

5.1.1 Main study parameter/endpoint

The co-primary outcomes will be: a) the verbal and performance IQ scores of the child using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI); and b) the global executive composite (GEC) score from the Behavior Rating Inventory of Executive Function (BRIEF-P).

5.1.2 Secondary study parameters/endpoints (if applicable)

Secondary outcomes will be the child’s auditory performance, scores on the Strengths and Weaknesses Questionnaire, weight, height, UIC, TSH, and TT4.

5.1.3 Other study parameters (if applicable)

Additional parameters will be the consumption of iodine rich foods, iodine content of household salt, parental IQ, maternal depression during pregnancy and the home environment of the child.

5.2 Study procedures

Developmental testing
We will assess the verbal and performance IQ scores of the children using the Wechsler Preschool and Primary Scale of Intelligence (WPPSI). The WPPSI is an intelligence test designed for children ages 2 to 7 years and consists of 14 subtests:

1. **Block Design** - while viewing a constructed model or a picture in a stimulus book, the child uses color blocks to re-create the design within a specified time limit.
2. **Information** - for picture items, the child responds to a question by choosing a picture from four response options. For verbal items, the child answers questions that address a broad range of general knowledge topics.
3. **Matrix Reasoning** - the child looks at an incomplete matrix and selects the missing portion from 4 or 5 response options.
4. **Vocabulary** - for picture items, the child names pictures that are displayed in a stimulus book. For verbal items, the child gives definitions for words that the examiner reads aloud.
5. **Picture Concepts** - the child is presented with two or three rows of pictures and chooses one picture from each row to form a group with a common characteristic.
6. **Symbol Search** - the child scans a search group and indicates whether a target symbol matches any of the symbols in the search group.
7. **Word Reasoning** - the child is asked to identify the common concept being described in a series of increasingly specific clues.
8. **Coding** - the child copies symbols that are paired with simple geometric shapes. Using a key, the child draws each symbol in its corresponding shape.
9. **Comprehension** - the child answers questions based on his or her understanding of general principles and social situations.
10. **Picture Completion** - the child views a picture and then points to or names the important missing part.
11. **Similarities** - the child is read an incomplete sentence containing two concepts that share a common characteristic. The child is asked to complete the sentence by providing a response that reflects the shared characteristic.
12. **Receptive Vocabulary** - the child looks at a group of four pictures and points to the one the examiner names aloud.
13. **Object Assembly** - the child is presented with the pieces of a puzzle in a standard arrangement and fits the pieces together to form a meaningful whole within 90 seconds.
14. **Picture Naming** - the child names pictures that are displayed in a stimulus book.

The WPPSI–III provides verbal and performance IQ scores as well as a full-scale IQ score. In addition, the Processing Speed Quotient can be derived for children aged 4 – 7 years, and a General Language Composite can be determined for children 4 to 7 years. Quotient and Composite scores have a mean of 100 and a standard deviation of 15. Subtest scaled scores have a mean of 10 and a standard deviation of 3. The WPPSI–III has been translated and adapted for use in Thailand and India. At both sites, the U.S. age-standardized norms will be used.

A more complete picture of general function in children achieved when the WPPSI–III is combined with a test like the BRIEF (Behavior Rating Inventory of Executive Function)–P (86). Whereas cognition provides global insight of brain functioning, executive functioning represents different structures and functions of the brain involved in the cognitive regulation of behavior (88). Executive function is defined as a group of processes, e.g., inhibition, working memory, and the ability to plan and organize, that are dependent on and influence
more basic cognitive abilities, such as attention, language, and perception (89). The BRIEF-P is a standardized rating scale developed to provide a window into behaviours associated with specific domains of executive functioning in children aged 2 to 5 y. The BRIEF-P consists of a single rating form, completed by parents or other caregivers, with 63 items in 5 scales: inhibition (to stop own behaviour), shifting (to make a transition and change focus from one mindset to another), emotional control (to modulate emotional responses), working memory (to hold information in mind for the purpose of completing a task), and planning/organization (to manage current and future-oriented task demands within the situational context). Higher scores indicate more problems with executive functioning, and the scales can be combined into the global executive composite (GEC).

The Strengths and Difficulty Questionnaire (SDQ) is a brief mental health questionnaire for children and adolescents ages 2 through 17 years old (http://sdqinfo.org). The test is available in the local languages for the two study sites (http://sdqinfo.org/py/sdqinfo/b0.py). The SDQ asks about 25 attributes, some positive and others negative; these 25 items are divided between 5 scales: emotional symptoms (5 items); conduct problems (5 items); hyperactivity/inattention (5 items); peer relationship problems (5 items); and prosocial behaviour (5 items). Each of these five scales are scored from 0-10, and one can add up four of these (emotional, conduct, hyperactivity and peer problems) to create a total difficulty score (range 0-40). One can also add the emotional and peer items together to get an internalizing problems score (range 0-20) and add the conduct and hyperactivity questions together to get an externalizing score (range 0-20). The total difficulty score of the SDQ (range 0-40) is a fully dimensional measure, with each one-point increase in the total difficulty score corresponding to an increase in the risk of mental health disorder (67). The SDQ in Thai is available at http://sdqinfo.org/py/sdqinfo/b0.py.

Auditory testing

Auditory function will be measured by Pure Tone Audiometry (PTA). PTA is the key hearing test used to identify hearing threshold levels of an individual, enabling determination of the degree, type and configuration of a hearing loss. The test will be conducted at both study sites in a soundproof room. The test comprises the presentation of sounds of different loudness and frequency to the child by means of an earphone. The child will be asked to indicate whenever he/she hears a sound, as well as on which side. The test will take approximately 15-20 minutes. To our knowledge, this will be the first time that auditory function will be assessed in relation to iodine deficiency during pregnancy.

Questionnaire and assessment of dietary iodine intake

We will use a structured multiple-choice questionnaire to obtain socio-demographic information on household composition, living situation, siblings, education, occupation and income, parity, history of thyroid disease.

Dietary assessment will include a questionnaire on:

- household use of iodized or noniodized salt, iodized or noniodized fish sauce (in Thailand)
- iodine supplement use, multi-micronutrient powders containing iodine
- frequency of seafood, milk and milk products, egg consumption
Anthropometric and biochemical measurements

The following measurements will be done at the clinic visit only after the developmental testing is completed. The child’s height and weight will be measured using standard anthropometric techniques. A spot non-fasting urine sample will be collected, transported on ice, divided into aliquots and stored at -20°C until analysis. UIC will be determined by using the Pino modification of the Sandell-Kolthoff reaction (90) at the Indian Coalition for the Control of Iodine Deficiency Disorders, All India Institute of Medical Sciences, New Delhi, India, for the Indian samples and at Mahidol University for the Bangkok samples. These laboratories participate in the CDC EQUIP external control procedures for UIC.

A finger prick whole blood sample will be collected from the children using sterile technique and will be spotted onto filter paper cards, dried at room temperature, placed into airtight plastic ziplock bags and stored at -80°C until analysis. Collection of the blood spots will be entirely voluntary, the families will be given the option to opt out of this while completing the rest of the protocol. For the Bangkok samples, TSH and T4 concentrations will be measured using an automated time-resolved fluoroimmunoassay (TSH [DELFIA NeoTSH, PerkinElmer Life Sciences, Turku, Finland] and T4 [Delfia Neonatal T4 kit, PerkinElmer Life Sciences) at the ETH Zurich (91). For the Indian samples, the DBS will be analyzed for TSH and T4 using immunoassay in Bangalore, and cross-standardized with the Zurich assays. In addition, a blood spot will be analyzed for hemoglobin using a Hemocue analyzer and the Hb value given immediately to the family.

5.3 Withdrawal of individual subjects

Subjects may discontinue the trial at any moment without the obligation to state the reason for discontinuation. Subjects may be withdrawn from the study by the principal investigator if they do not comply with the rules and regulations of the study. Subjects may be withdrawn from the study by the medical supervisor in case of reported serious adverse events or in case of other medical/social/psychological events as evaluated by the medical investigator and discussed with the principal investigator. Withdrawn subjects will not be followed up or replaced.
6. SAFETY REPORTING

The investigator will inform the subjects and the reviewing accredited ERB if anything occurs, on the basis of which it appears that the disadvantages of participation may be significantly greater than was foreseen in the research proposal. The study will be suspended pending further review by the accredited ERB, except insofar as suspension would jeopardise the subjects’ health. The investigator will take care that all subjects are kept informed.

6.1 AEs, SAEs and SUSARs

6.1.1 Adverse events (AEs)

Adverse events are defined as any undesirable experience occurring to a subject during the study. All adverse events reported spontaneously by the subject or observed by the investigator or his staff will be recorded. For example, an adverse event can also be related to a diagnostic procedure or to an already existing condition. Adverse events will be reported to the reviewing ERB.

6.1.2 Serious adverse events (SAEs)

A serious adverse event is any untoward medical occurrence or effect that:

- results in death;
- is life threatening (at the time of the event);
- requires hospitalisation or prolongation of existing inpatients’ hospitalisation;
- results in persistent or significant disability or incapacity;
- is a congenital anomaly or birth defect;
- Any other important medical event that may not result in death, be life threatening, or require hospitalization, may be considered a serious adverse experience when, based upon appropriate medical judgement, the event may jeopardize the subject or may require an intervention to prevent one of the outcomes listed above.

SAEs will be reported to the accredited ERB at each of the research sites following the local procedures. Coordinating researchers at each of the research sites will report SAEs to the Principle Investigators within 15 days after first knowledge of the event. For SAEs that result in death or are life threatening the expedited reporting will occur not later than 7 days after the responsible investigator has first knowledge of the adverse event.

6.2 Follow-up of adverse events

All AEs will be followed until they have abated, or until a stable situation has been reached. Depending on the event, follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

SAEs need to be reported till end of study within the Netherlands, as defined in the protocol. The follow-up of AE’s will also be reported in the annual progress report.
7. STATISTICAL ANALYSIS

All study forms will be checked for inconsistencies and data will be double entered; discrepancies or mismatches in the data entry will be corrected by a data entry supervisor. Statistical analyses will be carried out with SPSS (version18, SPSS, Chicago, IL, USA). Normal distribution of the data will be checked using Q-Q plots and Kolmogrov-Smirnov test. Normally distributed data will be reported as arithmetic means ± SD, non-normally distributed data as medians (quartiles) and categorical data as numbers (%). Statistical significance will be set at $p < 0.05$ for all analyses.

7.1 Primary study parameter(s)

The co-primary outcome measures (WSPPI and BRIEF-P scores) will be compared between treatment groups, initially using t-test for normally distributed data and Mann-Whitney U test for non-normally distributed data. Primary data analysis will be based on intention to treat. Linear regression will be used to compare outcomes between study groups including additional covariates, such as study centre, sex, BMI, and parental education. Possible confounders will be identified in separate bivariate analyses.

7.2 Secondary study parameter(s)

Per protocol analysis will be performed for the primary study outcomes as described above, as a secondary analysis. Further, weight, height, UIC, TSH, and TT4 will be compared between treatment groups using t-test and linear regression for normally distributed data and Mann-Whitney U test for non-normally distributed data.

7.3 Other study parameters

Other parameters that will be evaluated in the various models as potential confounders or effect modifiers include socio-demographics, household composition, living situation, siblings, education, occupation and income, parity, history of thyroid disease, and consumption of iodized foods.

7.4 Interim analysis (if applicable)

Not applicable
8. ETHICAL CONSIDERATIONS

8.1 Regulation statement

The study will be conducted according to the principles of the Declaration of Helsinki, adopted by the 18th WMA General Assembly in 1964 up till the most recent amended by the 64th WMA General Assembly held in Fortaleza, Brazil, in 2013.

8.2 Recruitment and consent

Mothers and children that participated in the MITCH study have been contacted by phone to inquire if they would be willing to participate in the follow up study. Those who indicated their willingness will be invited for an information session during which the full study procedures will be explained and they can ask questions. They can then sign the informed consent directly after the session, or in case they need more time to consider their decision can sign at the first appointment before the tests. After participants have signed, researchers will also sign the form in the presence of the participant. Participants will receive a copy of the informed consent form directly after the signing.

All information collected about the participants, their households and the children will be treated as confidential (will not be given, disclosed to or discussed with anybody) and only the research team will have access to the stored data and all relevant documents. Paper files will be stored in safe-locked cabinets. Biological specimen will be stored with a code that cannot directly be linked to the subject (i.e. codes will not contain names, initials or birth dates). The key to the code will be kept safe by the field supervisor in a password protected data file. The data shall be accessible to supervisors, PhD student and only in exceptional cases to other persons after written permission from the project leader. All data files will be safeguarded by an access password.

8.3 Objection by minors or incapacitated subjects (if applicable)

Children will be gently encouraged to cooperate with the help of their mothers, but children who are clearly unwilling to cooperate, either through verbal or non-verbal expression will not be coerced.

8.4 Benefits and risks assessment, group relatedness

This research theme has high public health nutrition relevance. Iodine deficiency is a major cause of preventable mental retardation worldwide, and up to a third of the global population remains mildly iodine deficient. South and Southeast Asia (where the two study sites are located) is the region with the largest number of newborns born ‘unprotected’ from the damage of iodine deficiency: over million per year.

Subjects will not directly benefit from participation in the trial. The burden and risks associated with participation are negligible. The follow up study will require the children to undergo cognitive and auditory testing (half-day) and their mothers to answer questionnaires related to their children. Children will be asked to hand in a spot urine sample to assess iodine concentration, and a capillary blood spot to assess haemoglobin, thyroid stimulating hormone and free thyroxine concentrations (not obligatory for participation).

In terms of impact, the findings of this ambitious study could become the standard reference for developing, monitoring and delivering iodine nutrition in pregnancy and infancy. It will provide the first long-term, functional data on the effect of iodine supplementation in mild-to-moderate iodine deficiency on child development. This has relevance not only in developing
countries, but also in many transition and industrialized countries, where mild iodine deficiency is widespread.

Overall, the study will provide important new data to help design optimal iodine supplementation strategies to improve child development in malnourished populations. This may be particularly valuable in developing and transition countries, where it could contribute to economic development and poverty alleviation.

8.5 Compensation for injury
Liability insurance for staff affiliated to Wageningen University is covered by the University's liability insurance. Insurance for participants in the trial is arranged according to local guidelines.

8.6 Incentives (if applicable)
Participants will receive a small in-kind attention after completing the study procedures. Travel costs will be reimbursed.
9. ADMINISTRATIVE ASPECTS, MONITORING AND PUBLICATION

9.1 Handling and storage of data and documents
Data will be handled confidentially and coded. When it is necessary to trace data of an individual subject, a subject identification code list will be used to link the data to the subject. The code will not be based on the patient initials and birth-date.

9.2 Monitoring and Quality Assurance (if applicable)
Quality of the data will be assured by standardizing the methodology through training sessions involving assessors from both centres. Inter-observer variation will be assessed in case more than one assessor is involved in the measurements.

9.3 Amendments
Amendments are changes made to the research after a favourable opinion by the accredited ERB has been given, and will be notified to the ERB that gave a favourable opinion.

The documentation included in the submission will cover the following information:

1) Covering letter, including the reasons for the amendment in one or two sentences, a brief description of the changes that are included in the amendment and the name of the documents that are modified;

2) An extract of the modified documents, where applicable, showing both the previous and new wording, where applicable.

3) The new version of the modified documents, where applicable, identified with updated number of version and date.

Non-substantial changes (such as typing errors, administrative changes like changes in names, telephone numbers and other contact details of involved persons mentioned in the submitted study documentation) will not be notified to the reviewing ERB.

9.4 Annual progress report
Not applicable, since the study duration is less than a year.

9.5 End of study report
The investigator will notify the accredited ERB of the end of the study within a period of 8 weeks. The end of the study is defined as the last subject’s last visit. In case the study is ended prematurely, the investigator will notify the accredited ERB within 15 days, including the reasons for the premature termination. Within one year after the end of the study, the investigator/sponsor will submit a final study report with the results of the study, including any publications/abstracts of the study, to the accredited ERB.

9.6 Public disclosure and publication policy
Results will be reported in peer-reviewed international journals according to established guidelines about authorship (International Committee Of Medical Journal Editors 1997; Davidoff et al. 2001). All publications and presentations relating to the study will be authorised by the Principal Investigator. The follow up study will be registered at the Clinical Trials register (www.ClinicalTrials.gov).
10. REFERENCES


