The Effects of Iodine Deficiency in Pregnancy and Infancy

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Abstract

Iodine requirements are increased ≥50% during pregnancy. Iodine deficiency during pregnancy can cause maternal and fetal hypothyroidism and impair neurological development of the fetus. The consequences depend upon the timing and severity of the hypothyroidism; the most severe manifestation is cretinism. In moderate-to-severely iodine-deficient areas, controlled studies have demonstrated that iodine supplementation before or during early pregnancy eliminates new cases of cretinism, increases birthweight, reduces rates of perinatal and infant mortality and generally increases developmental scores in young children by 10–20%. Mild maternal iodine deficiency can cause thyroid dysfunction but whether it impairs cognitive and/or neurologic function in the offspring remains uncertain. Two meta-analyses have estimated that iodine-deficient populations experience a mean reduction in IQ of 12–13.5 points. In nearly all regions affected by iodine deficiency, salt iodisation is the most cost-effective way of delivering iodine and improving maternal and infant health.

Keywords: *iodine, deficiency, pregnancy, infancy, thyroid, cognition, intelligence, infant mortality.*

Iodine (atomic weight 126.9) is an essential component of the hormones produced by the thyroid gland. Thyroid hormones, and therefore iodine, are essential for mammalian life. In the early 1920s, Switzerland was the first country to fortify household salt with iodine to control endemic goiter and cretinism. In the 1970s and 1980s, controlled studies showed that iodine supplementation before and during pregnancy not only eliminated new cases of cretinism but also improved cognitive function in the rest of the population.[1] From 1990 to 2007, global population coverage with iodised salt increased from about 20% to 70%.[2] But the International Council for the Control of Iodine Deficiency Disorders (ICCIDD) estimates that nearly two billion individuals in 2011 continue to have insufficient iodine intake worldwide, including 1/3 of all school-age children, and iodine deficiency remains a public health problem in 32 countries.[3] There are insufficient data from nearly all countries to estimate the prevalence of iodine deficiency in pregnant women.

In healthy adults, the absorption of iodide is >90%.[1] The body of a healthy adult contains 15–20 mg of iodine, of which 70–80% is in the thyroid. In chronic iodine deficiency, the iodine content of the thyroid may fall to <20 µg. Iodine is cleared from the circulation mainly by the thyroid and kidney, and while renal iodine clearance is fairly constant, thyroid clearance varies with iodine intake. In conditions of adequate iodine supply, ≤20% of absorbed iodine is taken up by the thyroid. In chronic iodine deficiency, this fraction can exceed 80%. Despite high fractional clearance of iodine by the thyroid, in chronic severe iodine deficiency, thyroid hormone synthesis falls, leading to hypothyroidism and its sequelae.

The iodine requirement during pregnancy is sharply increased because of: (1) an increase in maternal thyroxine (T_4) production to maintain maternal euthyroidism and transfer thyroid hormone to the fetus early in the first trimester, before the fetal thyroid is functioning; (2) iodine transfer to the fetus, particularly in later gestation; and (3) an increase in renal iodine clearance.[4] Iodine requirements from the US Institute of Medicine (IOM)[5] and WHO[2] for pregnancy, lactation and infancy are shown in Table 1. The recommended method to assess iodine nutrition in pregnant women is the urinary iodine concentration (UIC).[2] Because >90% of dietary iodine eventually appears in the urine, UIC is an excellent indicator of recent iodine intake.[1] UIC is usually measured in spot

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Table 1. Recommendations for iodine intake (µg/day) for pregnant and lactating women, and infants

Age or population group[a]	US Institute of Medicine[5]	Age or population group[c]	World Health Organization[2]
Infants 0–12 months[b]	110–130	Children 0–5 years	90
Pregnancy	220	Pregnancy	250
Lactation	290	Lactation	250

[a]Recommended daily allowance.
[b]Adequate intake.
[c]Recommended nutrient intake.

urine specimens from a representative sample of women, and expressed as the median, in µg/L.[2] Recommendations for using the median UIC to classify iodine status of pregnant and lactating women, and infants, are shown in Table 2.[2]

In nearly all regions affected by iodine deficiency, salt iodisation is the most cost-effective way of delivering iodine and of improving cognition.[1,2] Worldwide, the annual costs of salt iodisation are estimated at US$0.02–0.05 per child covered, and the costs per child death averted are US$1000 and per Disability-adjusted life year (DALY) gained are US$34–36.[6] However, in some regions, iodisation of salt may not be practical for control of iodine deficiency, at least in the short term. In these areas, iodised oil supplementation can be used. Iodised oil can be given orally or by intramuscular injection. Usual doses are 200–400 mg iodine/year[1] and it is often targeted to women of childbearing age and pregnant women. Iodine can also be given as KI or KIO_3 as drops or tablets. In order to ensure adequate iodine supply during pregnancy, women should ideally be provided with ample

Table 2. Epidemiological criteria from the World Health Organization for assessment of iodine nutrition in pregnant and lactating women, and infants based on median or range of urinary iodine concentrations[2]

	Iodine intake
Pregnant women	
<150 µg/L	Insufficient
150–249 µg/L	Adequate
250–499 µg/L	More than adequate
≥500 µg/L	Excessive
Lactating women	
<100 µg/L	Insufficient
≥100 µg/L	Adequate
Children less than 2 years of age	
<100 µg/L	Insufficient
≥100 µg/L	Adequate

iodine intake (at least 250 µg/day) for a long period before conception to ensure plentiful intrathyroidal iodine stores.

Methods

A systematic literature search in PubMed, Current Contents Connect® and ISI Web of Science® for articles in English, French, German, Spanish (search terms included: iodine, urinary iodine, iodine deficiency, iodine status, pregnancy, infancy, children, cretinism, cognition, school performance, mental development, intelligence, growth, perinatal mortality, infant mortality, maternal mortality, preterm birth, prematurity, abortion, stillbirth, miscarriage, birthweight, meta-analysis) was conducted. Study reports were also obtained from book chapters and through correspondence with iodine experts around the world. Approximately 3300 abstracts were reviewed. Of these, approximately 450 full-length papers were reviewed. Of these, 27 original studies and two meta-analyses were included in this review. It was decided not to attempt to perform a meta-analysis of the pregnancy studies because: (i) the number of randomised controlled intervention trials of iodine in pregnancy and/or infancy is small; (ii) in many, blinding is uncertain, drop-outs were high and follow-up was inconsistent; and (iii) the studies vary widely in their designs (oral vs. intramuscular delivery of high doses of iodised oil; daily low dose potassium iodide; iodisation of irrigation water; timing of intervention).

Results

Cretinism, cognition and thyroid function

Iodine deficiency has multiple adverse effects on growth and development in animals and humans. These are collectively termed the iodine deficiency

disorders and are one of the most important and common human diseases.[1] They result from inadequate thyroid hormone production due to lack of sufficient iodine. Iodine deficiency during pregnancy impairs the neurological development of the fetus. In areas of severe chronic iodine deficiency, maternal and fetal hypothyroxinemia can occur from early gestation onwards.[7] Thyroid hormone is required for normal neuronal migration and myelination of the brain during fetal and early postnatal life, and hypothyroxinemia during these critical periods causes irreversible brain damage, with mental retardation and neurological abnormalities.[7] The consequences depend upon the timing and severity of the hypothyroxinemia (Table 3). The most severe manifestation of in utero iodine deficiency is cretinism. Two classic forms of cretinism – neurological and myxedematous – have been described.[1] The three characteristic features of neurological cretinism in its fully developed form are severe mental retardation with squint, deaf mutism and motor spasticity. The typical myxedematous cretin has a less severe degree of mental retardation than the neurological cretin. But myxedematous cretins have all the features of severe hypothyroidism present since early life, including severe growth retardation, incomplete maturation of the facial skeleton, puffy features, thickened and dry skin, dry and rare hair, and delayed sexual maturation. Whether mild-to-moderate maternal iodine deficiency produces more subtle changes in cognitive and/or neurologic function in the offspring remains uncertain. But two prospective case–control studies in iodine-sufficient women have reported even mild thyroid dysfunction during pregnancy may impair cognitive development of the offspring.[8,9]

In a landmark trial in an area of severe iodine deficiency in Papua New Guinea,[10,11] alternate families received saline (control) or iodised oil injection. The primary outcome was the prevalence of cretinism at 4 and 10 years follow-up, with more sensitive diagnostic tests applied at the 10-year follow-up. Iodine supplementation was associated with a significant reduction in the prevalence of endemic cretinism: at 4 years of age, the relative risk [95% CI] was 0.27 [0.12, 0.60] and at 10 years of age, the relative risk [95% CI] was 0.17 [0.05, 0.58]. A long-term follow-up was done on a small sample of non-cretinous children at 11 and 15 years of age,[12] but found no significant differences in motor and cognitive function between the children born to supplemented families and controls.

In a study in Zaire, participants were pregnant women attending antenatal clinics in an area of severe iodine deficiency with a 4% cretinism rate.[13–15] Pregnant women were randomly allocated to two groups: one received iodised oil injection, the other an injection of vitamins. Women were on average 28 weeks pregnant when they were treated. Psychomotor development scores were measured in the offspring at ≈72 months of age, but there was a loss to follow-up of ≈50% in both groups. The psychomotor development scores were significantly higher in the iodine group (mean psychomotor development score, 91 ± 13 vs. 82 ± 14 in the controls); the prevalences of psychomotor scores ≤60 were 0.5% in the iodine group vs. 9.7% in the controls.

In a study in western China, an area of severe iodine deficiency and endemic cretinism, participants were groups of children from birth to 3 years and women at each trimester of pregnancy.[16] Untreated children 1–3 years of age, studied when first seen, served as controls. The intervention was oral iodised oil and treated children and the babies born to the treated women were followed for two years. The main outcomes were neurologic examination, head circumference, and indexes of cognitive and motor development. A small subsample was followed out to ≈7 years of age.[17] The prevalence of moderate or severe neurologic abnormalities among the infants whose mothers received iodine in the first or second trimester was 2%, as compared with 9% among the infants who received iodine during the third trimester (through the treatment of their mothers) or after birth. Treatment in the third trimester of pregnancy or after delivery did not improve neurologic status, but head growth and developmental quotients improved slightly. Treatment at the end of the first trimester did improve neurologic outcome. The prevalence of microcephaly was 27% in the untreated children compared with 11% in the treated children. The mean (±standard deviation) developmental quotient at 2 years of age was higher in the treated than in the untreated children (90 ± 14 vs. 75 ± 18). In the long-term follow-up study, development of children (range 4–7.3 years) whose mothers received iodine during pregnancy, and children who received iodine first in their second year, was examined.[17] A second group of children (range 5.8–6.9 years) whose mothers received iodine while pregnant were examined 2 years later. Head circumference was improved for those who received iodine during pregnancy (compared with

Table 3. Summary of findings and assessment of quality of evidence, by outcome, for RCTs of iodine given before or during pregnancy

Quality assessment						Summary of findings	
No. of studies and study design	Heterogeneity of results?	Consistent size of effect?	Generalisable to population of interest?	Generalisable to intervention of interest?	Other sources of bias (e.g. major limitations in study design)	No. of participants	Effect estimate
Cretinism: overall quality of evidence grade = high							
5 RCTs	No, all studies showed a positive effect of intervention on reduction in incidence of cretinism.	All differences statistically significant, but size of effects poorly quantified in 4 studies.	Yes, all studies conducted in low-income countries.	All studies supplemented with injections of iodised oil.	High loss to follow-up in most of the studies, questionable blinding in 2 studies.	≈9500	Relative risk [95% CI]: 0.27 [0.12, 0.60].
Cognitive development: overall quality of evidence grade = high							
4 RCTs	Yes, all studies showed a positive effect of an increase in development or intelligence quotient	All differences statistically significant of comparable size.	Yes, all studies conducted in low- income countries.	All studies supplemented with injections of iodised oil.	High loss to follow-up in most of the studies, questionable blinding in 2 studies.	≈1200	Developmental scores 10–20% higher in young children born to mothers treated during early pregnancy or before.
Birthweight (g): overall quality of evidence grade = low							
2 RCT	Difficult to assess; poor description of findings.	Both studies showed an increase in birthweight.	Studies conducted in low-income countries.	Oral iodised oil.	Questionable blinding.	1831	3.8–6.3% higher birthweights with treatment.
Infant mortality rate: overall quality of evidence grade = moderate							
2 RCTs	Yes, both studies showed a reduction.	No, the two studies showed a wide range in reductions.	Yes, studies conducted in low-income countries.	One study used injectable iodised oil, one study used iodine addition to irrigation water.	Questionable blinding in both studies.	≈37 400	Depending on severity of iodine status and baseline infant mortality rate, reductions in mortality were in the range of 25–60%.

those receiving iodine at age 2) and for those supplemented before the end of the second trimester (relative to those supplemented during the third trimester). Iodine before the third trimester predicted higher psychomotor test scores for children relative to those provided iodine later in pregnancy (−5.4%) or at 2 year (−16.1%).[17]

In a randomised Peruvian trial, women of childbearing age from Andean villages in an area of severe iodine deficiency with a 1–3% cretinism rate were studied.[18,19] The treatment group received iodised oil injection either before conception or during pregnancy; the control group did not receive an injection. Cognitive development scores were done in a subsample of their children between 1 and 4 years of age. The initial publication did not find a statistical difference in cognitive outcomes.[18] A subsequent reanalysis reassigned children to two groups, iodine-deficient or iodine-sufficient at time of cognitive testing, based on their UIC and T_4. This analysis found a significant higher IQ score in the iodine-sufficient group compared with the iodine-deficient group (85.6 ± 13.9 vs. 74.4 ± 4.8).[19]

In two villages in Ecuador with severe intellectual disability and a cretinism rate of up to 8%, one village received iodine treatment, and one did not and served as an iodine-deficient control.[20] Participants were all women of child-bearing age, pregnant women and children, and coverage with iodine was estimated to be about 90%. The treatment village received an injection of iodised oil and was then followed at 4-year intervals for ≈20 years, and the effects on the offspring were recorded.[20,21] No more cretins were born in the treated village. Two years after treatment had began, the mean developmental quotient in infancy was not significantly different between villages. However, mean IQ measured in first and second grade children was higher by ≈10 points in the treated village than in the control village. Five years after treatment began, the treated group was divided into three groups: (i) children born after treatment had begun; (ii) children whose mothers had received iodine during pregnancy; and (iii) children whose mothers had received iodine prior to conception. The later group had significantly higher IQ than the first two groups (76.8 vs. 72.3 vs. 65.2, respectively). Studies done several years later in these children also suggested that iodine treatment late in pregnancy or afterward had no benefits of children's IQ at 3–5 years of age, but treatment early in pregnancy or prior to conception improved IQ (83.7 ± 13.4 vs. 72.7 ± 14.0 in treated vs. control villages).[21]

Endemic cretinism is the extreme expression of the abnormalities in physical and intellectual development caused by iodine deficiency, but the cognitive deficits associated with iodine deficiency may not be limited to remote, severely iodine-deficient areas. Many authors have argued that even mild-to-moderate iodine deficiency in pregnancy, still present in many industrialized countries, may affect cognitive function of the offspring. The controlled trials of iodine treatment in mild-to-moderately iodine-deficient pregnant women discussed below did not report data on infant or child development. However, several reported measures that might be surrogate markers of future infant development, including maternal and newborn thyroid function.

Romano *et al*. gave 120–180 μg iodine as iodised salt or control daily beginning in the first trimester to healthy pregnant Italian women ($n = 35$; median UIC 31–37 μg/L).[22] In the treated group, median UIC increased threefold and thyroid volume did not change. In the controls, there was no change in UIC, but a 16% increase in thyroid volume. Treatment had no effect on maternal thyroid-stimulating hormone (TSH). Pedersen *et al*. randomised pregnant Danish women ($n = 54$) to receive either 200 μg iodine/day as KI solution or no supplement from 17 weeks to term.[23] Median UIC 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 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 T_4, triiodothyronine (T_3) and free (F)T_4. In a double-blind, placebo-controlled trial, Glinoer *et al*. supplemented pregnant Belgian women ($n = 120$; median UIC 36 μg/L; biochemical criteria of excess thyroid stimulation) with 100 μg iodine/day or control from ~14 weeks to term.[24] Treatment had no significant effect on maternal or cord T_3, FT_4 and T_3/T_4 ratio. The treated women had significantly higher UIC, smaller thyroid volumes, and lower TSH and Tg concentrations, compared with controls. Newborns of the treated group also had significantly higher UIC, smaller thyroid volumes and lower Tg concentrations compared with controls.

Liesenkötter *et al*. reported results from a quasi-random, controlled trial of 230 μg iodine/day from 11 weeks to term in pregnant German women ($n = 108$;

median UIC 53 µg/g creatinine; goiter rate 42.5%).[25] Median UIC increased to 104 µg/g creatinine in treated group, and median thyroid volume was significantly lower in the newborns of the treated women compared with controls (0.7 vs. 1.5 mL, respectively). Treatment had no significant effect on maternal TSH, T_3, T_4, thyroid volume or Tg, and had no effect on newborn TSH. In a placebo-controlled, double-blind trial, Nohr *et al.* gave a multinutrient supplement containing 150 µg iodine/day or control to pregnant Danish women positive for anti-thyroid peroxidase antibodies (TPO-Ab) ($n = 66$) from 11 weeks to term.[26] Median UIC was significantly higher in the treated women at term, but there were no differences in maternal TSH, FT_4 or Tg between groups. Finally, in a prospective, randomised, open-label trial, Antonangeli *et al.* supplemented pregnant Italian women ($n = 67$; median UIC 74 µg/g creatinine) with 50 µg or 200 µg iodine/day from 18–26 weeks to 29–33 weeks of gestation.[27] Median UIC was significantly higher in the 200 µg group than in the 50 µg group (230 vs. 128 µg/g creatinine). However, there were no differences in maternal FT_4, FT_3, TSH, Tg or thyroid volume between groups.

Maternal goiter

In areas of mild-to-moderate iodine deficiency, pregnancy has often been suggested as an environmental factor contributing to a higher prevalence of goiter and thyroid disorders in women, compared with men. But the data to support this are scarce. In European studies, an uncontrolled prospective study in 10 women,[28] a retrospective study[29] and a cross-sectional study in smoking women[30] suggest goiters formed during pregnancy may only partially regress after parturition.

Birthweight and infant growth

In a severely iodine-deficient area of western China, iodine repletion of pregnant women ($n = 295$) improved head circumference and reduced the prevalence of microcephaly from 27% to 11% ($P = 0.006$).[16] In Zaire, treatment with iodised oil during pregnancy resulted in 3.7% higher birthweights compared with offspring of untreated mothers.[15] In a region of endemic goiter area in Algeria, treatment of pregnant women ($n = 1536$) with oral iodised oil just before conception or during the first trimester significantly increased birthweights (6.25%) compared with non-treated women.[31] Household use of iodised salt correlated with increased weight-for-age and mid-upper-arm circumference during infancy in a large Asian study.[32]

Infant mortality

Infant survival is improved in infants born to women whose iodine deficiency is corrected before or during pregnancy. Delong *et al.* added potassium iodate to irrigation water over a 2- to 4-week period in three area of severe iodine deficiency in China and found a large reduction in both neonatal and infant mortality in the following 2–3 years compared with areas that did not receive iodine.[33] The median UI increased in women of child-bearing age from <10 to 55 µg/L, while the infant mortality rate (IMR) decreased in the three treated areas from a mean of 58.2 to 28.7/1000 births, from 47.4 to 19.1/1000, and from 106.2 to 57.3/1000. Similar results were also observed for neonatal mortality; the odds of neonatal death were reduced by about 65% in the population who had iodine treatment. Iodised oil given intramuscularly to iodine-deficient pregnant women in Zaire at ≈28 weeks of gestation decreased infant mortality.[15] In severely iodine-deficient women, the IMR in infants of treated and untreated mothers was 113/1000 and 243/1000 births, respectively, and in women with mild or moderate iodine deficiency, the IMR with and without treatment was 146/1000 and 204/1000 births.

Infant survival may also be improved by iodine supplementation in the newborn period. A randomised, placebo-controlled trial of oral iodised oil (100 mg iodine) was conducted in an area of presumed iodine deficiency in Indonesia to evaluate the effect on mortality.[34] The iodine or placebo was given in conjunction with oral poliovirus vaccine; infants ($n = 617$) were treated at ≈6 weeks of age and were followed to 6 months of age. There was a significant 72% decrease in risk of infant death during the first 2 months of follow-up. In a large cross-sectional study in Indonesia, use of adequately iodised salt was associated with a significantly lower prevalence of child malnutrition and mortality in neonates, infants and children aged <5 years.[35]

Meta-analyses

A meta-analysis was done of 21 observational and experimental studies including a control group of the

effect of iodine deficiency on mental development (Table 4).[36] Of these, 16 studies were in children, 4 included adults, and 2 included infants; the age range was 2–45 years. The final meta-analysis included 2214 participants (mainly children) and IQ was used as the main outcome measure. The studies were all done in areas of moderate-to-severe iodine deficiency. The IQs of non-ID groups were on average 13.5 IQ points higher than those of the iodine-deficient groups. In the second meta-analysis by Qian *et al.*,[37] inclusion criteria were all studies conducted in China, comparing children (<16 years old) living in naturally iodine-sufficient areas with those: (i) in severely iodine-deficient areas; (ii) children in iodine-deficient areas born before the introduction of iodine prophylaxis; and (iii) children in iodine-deficient areas born after the introduction of iodine prophylaxis. IQ was measured using the Binet or Raven's Scales. The effect size was an increase of 12.45, 12.3, 4.8 IQ points, respectively, for the iodine-sufficient group and the later two groups, compared with those in iodine-deficient areas. Compared with severely iodine-deficient children, there was an increase of ≈12 IQ points for children born more than 3.5 years after iodine prophylaxis was introduced.

Comments

The five early intervention trials, in severely iodine-deficient populations,[10–21] were ground breaking studies done under difficult conditions in remote areas. The Papua New Guinea study had the strongest design and clearly demonstrates that iodine treatment in a population with high levels of endemic cretinism sharply reduces or eliminates incidence of the condition.[10,11] The Zaire and China trials report developmental scores were 10–20% higher in young children born to mothers treated during pregnancy or before.[13–16] The studies in Peru and Ecuador were less well controlled but also suggest modest cognitive benefits for infants and children of maternal iodine treatment.[18–21] Although the data from the Zaire trial indicate correction of ID even at mid-to-late pregnancy improves infant cognitive development,[13–15] data from the other trials suggest the full picture of neurological cretinism can only be prevented when iodine is given before or early in pregnancy.

The six controlled studies of iodine supplementation in pregnant women in Europe[22–27] suggest that in areas of mild-to-moderate iodine deficiency, the maternal thyroid is able to adapt to meet the increased thyroid hormone requirements of pregnancy. Although supplementation was generally effective in minimising an increase in thyroid size during pregnancy, only two of the six studies reported maternal TSH was lower (within the normal reference range) with supplementation, and in none of the studies showed a clear impact of supplementation on maternal and newborn total or free thyroid hormone concentrations. Thyroid hormone concentrations may be the best surrogate biochemical marker for healthy fetal development. Thus, the results of these trials are reassuring. However, because none of the trials measured long-term clinical outcomes such as maternal goiter or infant development, the potential adverse effects of mild-to-moderate iodine deficiency during pregnancy remain unclear.

Although there are too few studies to draw firm conclusions, the available data suggest iodine prophylaxis in severely iodine-deficient populations, or iodine supplementation of severely deficient pregnant women or infants, may reduce the IMR by ≥50%.[15,33–35]

The two meta-analyses of the effects of iodine status on IQ include data mainly from comparative cross-sectional community-based studies. It is therefore impossible to distinguish the relative contribution of differences in iodine status during pregnancy vs. differences in iodine status in later life, on IQ. The studies included in the analysis of Bleichrodt and Born[36] were of varying quality; much of the data came from observational studies and only six of the papers cited were published in peer-reviewed journals. In the meta-analysis of Qian *et al.*,[37] although it is stated that the iodine-sufficient control groups were comparable socially, economically and educationally, it is difficult to judge the overall quality of the studies reported in Chinese included in this meta-analysis. However, despite the clear limitations of the mainly cross-sectional data included in these two meta-analyses,[36,37] their overall conclusions are similar. They estimate that populations, and particularly children, in areas of chronic iodine deficiency experience a mean reduction in IQ of 12–13.5 points.

Priorities for future research should include: (i) development of new biomarkers of individual iodine status; and (ii) controlled trials in mild-to-moderate iodine-deficient pregnant women, with the primary outcomes being long-term clinical outcomes such as maternal goiter, post-partum thyroid dysfunction and/or infant development. Considering the poten-

Table 4. Summary of findings and overall assessment of quality of evidence from meta-analyses of observational studies comparing cognition in iodine-deficient to iodine-sufficient populations

Quality assessment					Summary of findings		
No. of studies	Design	Limitations	Consistency	Generalisability to population of interest	No. of subjects	Effect estimate	Reference

Intelligence quotient: overall quality of evidence: moderate

No. of studies	Design	Limitations	Consistency	Generalisability to population of interest	No. of subjects	Effect estimate	Reference
21, but 3 were omitted because of heterogeneity, so final number was 18	Mainly cross-sectional studies, some intervention trials. IQ measured by varying methods.	Varying quality; only 6 of the papers cited were published in peer-reviewed journals; many studies not fully reported; most studies not adjusted for potential confounders.	In all 18 studies, the iodine-deficient had lower mean scores than the iodine-sufficient; for 14 studies the correlation coefficients were significant at the 1% level	Studies conducted in low and middle income countries. All in areas of moderate-to-severe iodine deficiency. 16 studies were in children, 4 included adults, and 2 included infants; the age range was 2–45 years. Most subjects were <15 years of age.	2214	Weighted population effect size (weighted mean r) was 0.40, with a [95% CI] of [0.36, 0.43] ($P < 0.0001$). The mean standardised difference was 0.90. Thus, IQs of iodine-sufficient groups were on average 13.5 IQ points higher than those of the iodine-deficient groups	Bleichrodt and Born[36]
37	Cross-sectional studies of children from mothers supplemented during pregnancy or before, compared with after. IQ measured in all studies using the Binet or Raven's Scales.	Difficult to judge; most of the original studies reported only in Chinese	In all 37 studies, the groups iodine-deficient during pregnancy had lower mean scores than the iodine-sufficient group.	Studies conducted in low to middle income regions of China. All in areas of moderate-to-severe iodine deficiency. All in children, age range was 4.5–15 years. Intervention was iodised salt or, in a few studies, iodised oil.	12 291	The effect size was an increase of 0.83, 0.82 and 0.32 SD IQ points respectively, for the children living in IS communities compared with those living in iodine deficient areas with no iodine supplementation, with inadequate iodine supplementation, or children who had received iodine during their mothers' pregnancy and after birth (equal to 12.45, 12.3, 4.8 IQ points, respectively).	Qian et al.[37]

IQ, intelligence quotient; SD, standard deviation.

tially irreversible adverse impact of iodine deficiency during early life on neurodevelopment, regional and national public health programs should focus on effective and sustained iodine prophylaxis of pregnant women and infants.

Conflicts of interest

The author has no conflicts of interest to declare.

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