THERAPY OF ENDOCRINE DISEASE

Impact of iodine supplementation in mild-to-moderate iodine deficiency: systematic review and meta-analysis

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Abstract

Background: Although the detrimental effects of severe iodine deficiency are well recognised, the benefits of correcting mild-to-moderate iodine deficiency are uncertain.
Objectives: We undertook a systematic review of the impact of iodine supplementation in populations with mild-to-moderate iodine deficiency.
Methods: We searched Medline and the Cochrane library for relevant articles published between January 1966 and April 2013, which investigated the effect of iodine supplementation on maternal and newborn thyroid function, infant neurodevelopment and cognitive performance in school-age children. The quality of studies was graded and eligible trials were evaluated in the meta-analysis.
Results: Nine randomised controlled trials (RCTs) and eight observational studies met the inclusion criteria. Controlled trials on infant neurodevelopment were lacking; gestational iodine supplementation reduced maternal thyroid volume and serum thyroglobulin and in some studies prevented a rise in serum thyroid-stimulating hormone. None of the intervention trials recorded an excess frequency of thyroid dysfunction in contrast to observational studies. A pooled analysis of two RCTs which measured cognitive function in school-age children showed modest benefits of iodine supplementation on perceptual reasoning (standardised mean difference (SMD) 0.55; 95% CI 0.05, 1.04; $P=0.03$) and global cognitive index (SMD 0.27; 95% CI 0.10, 0.44; $P=0.002$) with significant heterogeneity between studies.
Conclusion: Iodine supplementation improves some maternal thyroid indices and may benefit aspects of cognitive function in school-age children, even in marginally iodine-deficient areas. Further large prospective controlled studies are urgently required to clarify these findings and quantify the risk/benefits of iodine supplementation in regions previously believed to be iodine sufficient such as the UK.

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Introduction

Iodine is an integral component of thyroid hormones and is essential for normal neurological development (1). The consequences of iodine deficiency are profound, comprising a spectrum of disorders, which includes goitre, hypothyroidism and impaired growth and development in children (2). Furthermore, iodine deficiency increases infant mortality and is the leading preventable cause of mental deficiency in childhood (3). The degree of iodine deficiency in a population is classified according to the median urinary iodine concentration (UIC) as mild (UIC

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50–99 μg/l), moderate (UIC 20–49 μg/l) or severe (UIC < 20 μg/l) (3). Whilst the detrimental effects of severe iodine deficiency are well established, the adverse consequences of mild-to-moderate iodine deficiency are less certain (4) and the benefits of supplementation in this group remain contentious. As early as 1917, Marine & Kimball (5) showed that iodine prophylaxis prevented goitre formation in children. Salt iodisation was subsequently introduced to Europe and the USA and by the 1970s it had become apparent that iodisation reduced cretinism and infant mortality rates (6).

Yet despite decades of advocacy, iodine deficiency remains a global health challenge with an estimated two billion people at risk worldwide (1). In Europe, 44% of school-age children still have insufficient iodine intake and countries such as the UK, Italy and parts of Spain are now moderately iodine deficient (7, 8, 9, 10, 11, 12, 13, 14). Indeed the UK currently ranks among the top ten iodine-deficient countries in the world (1). The health implications of these trends are unclear, especially in children and pregnant women who are most vulnerable to the harmful effects of iodine deficiency. Recently, mild-to-moderate iodine deficiency in the first trimester of pregnancy was associated with increased odds of offspring intelligence quotient (IQ) being in the lowest quartile (OR 1.43, 95% CI 1.04, 1.98, $P=0.03$) with the greatest negative impact observed with verbal IQ (OR 1.66, 95% CI 1.20, 2.31, $P=0.002$) (15). Another study from Tasmania identified that children whose mothers had UIC <150 μg/l during pregnancy had statistically significant reductions in spelling, grammar and English literacy at age 9 even though the children were raised in an iodine sufficient environment (16). In a recent study from The Netherlands, low maternal urinary iodine during pregnancy was associated with impaired executive functioning in children at 4 years of age. In this study, children of mothers with low urinary iodine had worse scores on the problem scales of inhibition $B=0.05$ (95% CI 0.01, 0.10), $P=0.03$ and working memory $B=0.07$ (95% CI 0.02, 0.12), $P=0.003$ (17).

This negative impact of low maternal iodine status during pregnancy is perhaps to be expected, as in pregnancy iodine requirements are increased, due to a combination of renal losses, increased placental delivery and the additional thyroxine production necessary to meet the foetal needs (2, 18). Furthermore, the foetus is largely dependent on maternal thyroxine sources for its optimal neurodevelopment, as its own thyroid gland does not begin to function until 14 weeks' gestation and only attains full maturation after birth (19). Although adequate maternal iodine nutrition is essential in pregnancy, iodised salt is not uniformly available and specific iodisation policies are lacking in some mild-to-moderate iodine-deficient countries such as the UK (20).

It is therefore of substantial public health interest whether iodine supplementation will improve maternal and child health outcomes in areas with mild-to-moderate iodine deficiency. In this systematic review, we evaluate the impact of iodine supplementation in pregnancy and childhood on thyroid function and child neurodevelopment in populations with mild-to-moderate iodine deficiency.

Subjects and methods

Search strategy

We searched Medline and the Cochrane library for relevant articles published in the English language between January 1966 and April 2013. We used various combinations of the following terms: iodine, deficiency, supplementation, mild, moderate, pregnancy, goitre, IQ, childhood, development, neurological, thyroid, TSH, hypothyroidism, thyroiditis, hyperthyroidism, side effects, cost, salt, fortification, maternal and foetus. Additional publications were sourced from references in individual articles. Relevant articles were selected after reading through all titles and abstracts and full texts were obtained if the information contained in the title or abstract was insufficient to exclude the study.

Inclusion criteria

We selected studies for review if they were randomised controlled trials (RCTs), quasi-randomised trials, or prospective cohort or case–control studies which investigated: i) the effects of maternal iodine supplementation in pregnancy on a) maternal thyroid function, b) foetal thyroid function and c) child neurodevelopment; and ii) the effects of childhood iodine supplementation on child cognitive performance. Studies were chosen if: i) participants received iodine supplements; ii) an appropriate control group was included which comprised participants who either received no supplements or received a significantly lower dose of supplements; iii) thyroid function, thyroid volume or cognitive performance were determined as outcomes; and iv) the study was limited to populations with mild-to-moderate iodine deficiency as determined from the median population urinary iodine.

Quality of studies

The quality of randomised trials was assessed using the criteria set by Jadad *et al*. (21). Studies were graded as high, moderate and low quality according to specific scores on the randomisation procedure, blinding of participants and investigators, and withdrawal rates from the study. We graded the quality of non-randomised trials using the Newcastle–Ottawa scale (22). This assessed the key domains of study selection, comparability and exposure (case–control studies) or outcome (cohort studies). Points were awarded for each study as follows: maximum of 4 for study selection, 2 for comparability and 4 for exposure or outcome. Based on total scores, studies were graded as high (9–10 points), moderate (7–8 points) or low (<7 points) quality.

Data extraction

Study selection and data extraction were independently conducted by two reviewers (P N Taylor and O E Okosieme) using preset selection criteria. Differences were resolved by consensus or by referral to the other authors (C M Dayan and J H Lazarus). Extracted information included sample size, geographical area, baseline iodine status according to the population median UIC and iodine supplementation (preparation, dose and route of administration). The outcomes examined were thyroid function, thyroid volume, and scales of childhood neurodevelopment and cognition.

Statistical analysis

A meta-analysis of studies of iodine supplementation in pregnancy was not considered feasible due to wide disparities in study selection criteria and lack of controlled trials on newborn cognitive outcomes. We undertook a meta-analysis of RCTs, which addressed iodine supplementation and its effect on cognitive function in school-age children. For each cognitive test we calculated the standardised mean difference (SMD) and S.E.M. as the difference in change from baseline between treated and control participants divided by the pooled S.D. Improved cognitive performance from baseline was reported as a positive effect and scores for tests in which lower scores indicated better performance were multiplied by −1. Cognitive tests were grouped according to domains and combined averages were calculated where more than one test assessed a single cognitive domain. A global cognitive score was derived from the average of all the individual domains. Unadjusted and adjusted effect sizes were derived using a random effects model (23) and inverse variance method and heterogeneity was assessed with the χ^2 test. The analysis was performed with the Review Manager (RevMan) Software, version 5.2 (The Nordic Cochrane Centre, The Cochrane Collaboration, 2012).

Results

Study selection

The study selection flow process is shown in Fig. 1. Nine RCTs (24, 25, 26, 27, 28, 29, 30, 31, 32) and eight observational studies (33, 34, 35, 36, 37, 38, 39, 40) were included in the review. Seven RCTs were reported on the effects of maternal supplementation on maternal thyroid function (26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40). Of these, four RCTs also contained data on neonatal thyroid function (27, 29, 30, 32). One RCT (32) and four observational studies (33, 36, 39, 40) addressed the impact of gestational iodine supplementation on infant neuropsychological function, while two RCTs investigated the impact of iodine supplementation on cognitive performance in school-age children (24, 25).

Maternal iodine supplementation and foeto-maternal thyroid function

All seven RCTs which determined the effects of maternal iodine supplementation on maternal thyroid function

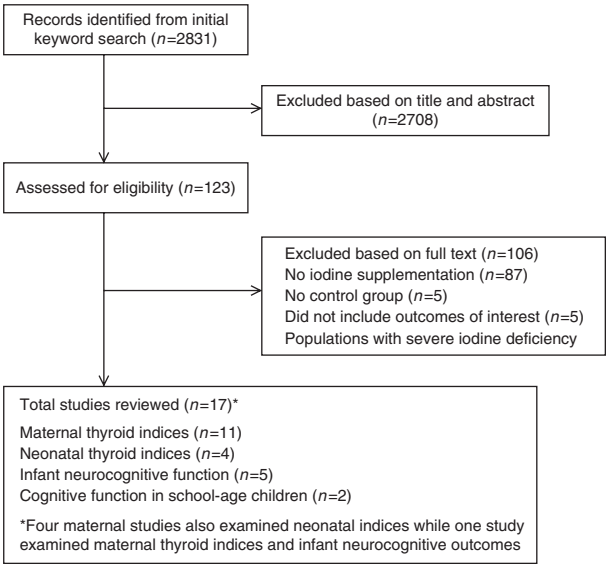

Figure 1
Flow process of study selection.

were conducted in European countries, namely Italy (26, 28), Denmark (27, 31), Belgium (29), Germany (30) and Spain (32). All studies were in the area of mild-to-moderate iodine deficiency with median population urinary iodine excretion (UIE) ranging from 36 to 109 μg/l. Iodine supplementation doses varied from 50 to 300 μg daily of iodide. Three studies were graded as moderate quality while four were low quality. The trials included a total of 641 participants who received various doses of iodine supplementation in pregnancy ($n=370$) or served as controls who either received no treatment ($n=174$), placebo ($n=24$), a lower dose of supplements ($n=35$) or iodised salt alone ($n=38$) (Table 1). The median onset of intervention was earlier than 12 weeks in five of the studies (28, 29, 30, 31, 32) while follow-up continued into the *postpartum* in five studies (26, 27, 30, 31, 32) (Table 1). Iodine was administered in the form of potassium iodide (KI) preparations, iodine-containing vitamin preparations or iodised salt and one trial included an intervention arm which received KI in combination with levothyroxine (L-T_4) (29).

Five observational studies also assessed the impact of iodine supplementation on maternal thyroid function (33, 34, 35, 37, 38). Of these, three were of moderate quality while two were low quality. The interpretation and comparative analysis of the studies was compounded by their divergent study designs. In some studies estimation of iodine intake was partly dependent on patient recall of iodine intake (37, 38) or derived from semi-quantitative food questionnaires (34). Iodine supplements were taken in the form of tablets or iodised salt and two studies compared long-term pre-gestation iodised salt intake with post-conception supplementation (37, 38).

Maternal UIE ▸ A significant increase in maternal UIE was consistently seen with iodine treatment in all studies (Table 1). The magnitude of this increase ranged from 43 to 170%. UIE in untreated women either fell or remained stable except in one study by Romano *et al.* (28), which showed an increase in UIE in the untreated group that was still significantly lower than in the treated group. Most trials reported higher third trimester UIC in treated women than in untreated controls (26, 27, 29, 30, 31). Similar findings were reported in observational studies and, in addition, long-term consumption of iodised salt was associated with higher UIC than recent consumption (33, 37, 38).

Maternal thyroglobulin ▸ Four RCTs compared maternal serum thyroglobulin levels in treated women with those of untreated controls (27, 29, 30, 31). Three of these showed a rise in thyroglobulin levels in untreated controls, while thyroglobulin levels fell in women who received supplements (27, 29, 31) (Table 1). Only one study by Liesenkotter *et al.* (30) failed to show a difference in thyroglobulin levels between controls and women who received iodine.

Maternal thyroid-stimulating hormone ▸ Five RCTs compared thyroid-stimulating hormone (TSH) in treated women with TSH in controls (27, 28, 29, 30, 31) (Table 1). Three of these showed a rise in TSH levels within the normal pregnancy-related reference range during pregnancy in untreated controls, an effect which was not observed in women receiving iodine supplements (27, 29, 31). In the other two RCTs, by Romano *et al.* (28) and Liesenkotter *et al.* (30), TSH was not increased either in controls or in treated women. Antonangeli *et al.* (26) compared maternal TSH in women who received two different daily doses of iodine (50 vs 200 μg) and found no change in TSH levels with either doses. Santiago *et al.* (32) reported no difference in TSH between women who took iodised salt only and those who took 200 or 300 μg of iodine daily.

An observational study by Moleti *et al.* (37) showed that consumption of iodised salt for more than 2 years before pregnancy was associated with lower TSH and lower rates of gestational hypothyroidism than supplementation commenced in pregnancy. A second study by the same group reported higher TSH concentrations in women who took iodine supplements from early gestation compared with women who consumed iodised salt alone from 2 years before conception or those who took no supplements at all (38). In a third study by Rebagliato *et al.* (34), TSH was higher in women with self-reported supplementary iodine intake in excess of 200 μg daily compared with those with estimated intake <200 μg daily.

Maternal FT_4 ▸ Two RCTs showed a fall in FT_4 concentration in both treated and control groups but with no differences observed between the groups (27, 31) (Table 1). In two other RCTs, FT_4 was unchanged in both groups (26, 30). Glinoer *et al.* (29) showed a reduction in FT_4 in the control group as well as in a group treated with 100 μg of KI, while an increase in FT_4 was observed in women who received L-T_4 in addition to KI. A long-term prophylaxis with iodised salt was associated with higher FT_4 levels than prophylaxis initiated in pregnancy in the

Table 1 Randomised controlled trials on the impact of iodine supplementation on maternal thyroid function.

		Maternal outcomes[a]				
References	**Intervention**	TSH	T_4	UIC	Serum Tg	Thyroid volume
(28), Italy	120–180 μg iodine/day from 1st trimester ($n=17$); control ($n=18$)	No change in either group	Not assessed	Increased by 170% in iodine group and by 64% in controls	Not assessed	Increased by 16% in controls only
(27), Denmark	200 μg KI/day from 17 to 18 weeks ($n=28$); control ($n=26$)	Increased by 21% in controls; no change in KI group	Decreased in both groups	Increased by 90% in KI group; decreased by 20% in controls[b]	Increased by 50%[b] in controls; reduced in KI group	Increased by 31% in controls and 16% in KI group
(29), Belgium	100 μg/day KI ($n=60$); 100 μg KI + 100 μg L-T_4/day ($n=60$); placebo ($n=60$)	Increased by 120% in controls and 67% in KI; decreased by 40% in KI + L-T_4	Decreased by 10% in controls and KI, increased by 17–23% in KI + L-T_4 group	Increased by 120% in KI and KI + L-T_4 groups; decreased by 30% in controls[b]	Increased by 50% in controls; decreased by 30% in KI and by 50% in KI + L-T_4[b]	Increased by 30% in controls, by 15% in KI, and 8% in KI + L-T_4
(30), Germany	300 μg/day KI from 1st trimester ($n=38$); control ($n=70$)	No change in either group	No change in either group	Increased by 113% in KI group; no change in controls	No difference between groups	No difference between groups
(31), Denmark	150 μg/day iodine from 1st trimester ($n=42$); placebo ($n=24$)	Increased by 29% in controls and by 4% in iodine group	Decreased in both groups	Increased by 110% in iodine group; no change in controls	Increased in controls; decreased in iodine group	Not assessed
(26), Italy	200 μg/day ($n=32$); 50 μg/day iodide ($n=35$) from 10 to 16 weeks, gestation	No change in either group	No change in either group	Increased by 153% in 200-group and 95% in 50-group	No change in either group	Increased by 3% in 200-group and 10% in 50-group
(32), Spain	IS only ($n=38$); 200 μg/day KI ($n=55$); 300 μg/day KI ($n=38$) from 1st trimester	No change in all three groups	No difference between groups	Increased by 43% in 200-group and 55% in 300-group	No difference between groups	No difference between groups

UIC, urinary iodine concentration; KI, potassium iodide; L-T_4, levothyroxine; TPOAb, thyroid peroxidase antibody; PPTD, *postpartum* thyroid dysfunction; TV, thyroid volume; IS, iodised salt; NA, not assessed.

[a]Maternal outcomes are presented as percentage change in thyroid indices at the end of pregnancy relative to baseline.

[b]Values are approximate estimates from figure in original paper. Baseline median UICs were as follows: Romano *et al*. (28), 31 μg/24 h in controls and 37 μg/24 h in intervention group; Pedersen *et al*. (27), 51 μg/l in controls and 55 μg/l in intervention; Glinoer *et al*. (29), 36 μg/l; Liesenkotter *et al*. (30), 64 μg/l; Nohr *et al*. (31), 50–52 μg/l in intervention and control groups; Antonangeli *et al*. (26), 74 μg/g creatinine and Santiago *et al*. (32), 109 μg/l.

observational study by Moleti *et al.* (37). In contrast, a second observational study by Velasco *et al.* (33) reported higher FT_4 concentrations in control subjects, although this was associated with higher TSH levels in these subjects.

Maternal thyroid volume ▸ Three RCTs showed an increase in thyroid volume through the course of pregnancy in untreated women, with a mean increase from baseline ranging from 16 to 30% (27, 28, 29) (Table 1). A lesser magnitude of increase was seen in women who took iodine supplements, with a mean increase of 3–16% (27, 28, 29). Only one study by Liesenkotter *et al.* (30) showed no difference in thyroid volume between the treated and untreated groups. Also, no difference in thyroid volume was observed between groups of women who took iodised salt only vs 200 or 300 μg KI daily (32) or between those who received 50 vs 300 μg of iodine daily (26).

Thyroid peroxidase antibodies ▸ Four RCTs contained data on thyroid peroxidase antibody (TPOAb) in pregnancy and the *postpartum* (26, 27, 30, 31). Nohr *et al.* (31) randomised TPOAb-positive women to receive either placebo or iodine and found an overall rate of *postpartum* thyroid dysfunction (PPTD) of 55% with no statistically significant differences between the iodine-treated and untreated groups. Three RCTs determined the prevalence of TPOAb in early pregnancy in unselected women and monitored their subsequent progression rates to PPTD. In the study by Liesenkotter *et al.* (30), the prevalence of TPOAb was 6% and none of the women in their cohort developed thyroid dysfunction. Pedersen *et al.* (27) detected antibodies in four women out of 54 (7%) with thyroid dysfunction developing in two of these; one woman developed hyperthyroidism while the other had subclinical hypothyroidism. In a third study by Antonangeli *et al.* (26), thyroid antibodies were positive in ten women out of 67 (15%) of which five developed PPTD. The overall prevalence of TPOAb in early pregnancy in these studies therefore ranged from 6 to 15% and except for the study by Liesenkotter *et al.* (30), which did not observe thyroid dysfunction in any of the women, the PPTD rates in antibody-positive women was between 50 and 55% whereas no antibody-negative women developed PPTD. No difference in PPTD rates was seen between treated and untreated women and no excess cases of TPOAb positivity developed in relation to iodine supplementation.

Neonatal thyroid function ▸ Four RCTs reported on thyroid function in the newborns of women receiving iodine supplements in pregnancy (27, 29, 30, 32) (Table 2). Three studies demonstrated higher thyroglobulin levels or larger thyroid volumes in neonates of women who did not receive supplements (22, 24, 25). Only two controlled studies assessed neonatal thyroid function in the offspring of treated and untreated women and these showed no difference in TSH or FT_4 between the groups (22, 24). A more recent study by Santiago *et al.* (32) has reported no difference in serum thyroglobulin levels, thyroid volume or serum TSH concentration in the neonates of mothers who either took supplements or iodised salt alone in pregnancy. An observational study reported higher serum TSH in the newborns of women who received iodine supplements (300 μg KI) compared with the children of untreated mothers (33).

Maternal iodine supplementation and neurodevelopmental function in the child

One RCT (32) and four observational studies (33, 36, 39, 40) examined the impact of maternal iodine supplementation on child neurodevelopment, evaluated between 6 and 18 months of age. These studies were of low to moderate quality and differed in design. Santiago *et al.* (32) compared different doses of supplementary iodide with iodised salt consumption alone while Berbel *et al.* (36) compared early with delayed or no iodine supplementation at all in mildly hypothyroxinaemic women. Two of the observational studies estimated supplementary iodine intake from a semi-quantitative food frequency questionnaire which relied on participant recollection of dietary and supplementary iodine intake (34, 35).

The outcomes of these studies in terms of mental development scales (MDS), psychomotor development scales (PDS) and developmental quotients (DQs) are presented in Fig. 2. No differences were observed in MDS in any of the studies and the differences which attained significance were seen with PDS (Fig. 2a and b). Velasco *et al.* (33) observed that the children of treated women had better behavioural performance and psychomotor performance than those of untreated mothers (Fig. 2b). In a second study from Spain by Berbel *et al.* (36), the DQ was found to be higher in children of women who started taking supplementation from early pregnancy (4–6 gestational weeks) and in addition had a FT_4 above the 20th percentile compared with infants of mothers who commenced supplements in the second or third trimesters

Table 2 Randomised controlled trials on the impact of iodine supplementation on neonatal thyroid function.

		Neonatal thyroid indices			
References	**Intervention**	TSH (mU/l)[a]	FT_4 (pmol/l)[a]	TV (ml)	Serum Tg (μg/l)
(27), Denmark	200 μg KI/day from 17 to 18 weeks; control ($n=54$)	No difference between: controls and KI; median TSH 6.8 vs 7.8; $P=$NS	No difference between controls and KI: median FT_4 13.6 vs 13.6; $P=$NS	Not assessed	Higher in controls than KI: median Tg 67 vs 38; $P=0.005$
(29), Belgium	100 μg KI/day ($n=60$); 100 μg KI + 100 μg L-T_4/day ($n=60$); placebo ($n=60$)	No difference between groups: median TSH 7.0 (control) vs 8.0 (KI) vs 8.0 (KI + L-T_4); $P=$NS	No difference between groups: mean T_4 14.0 (control) vs 14.6 (KI) vs 14.3 (KI + L-T_4); $P=$NS	Larger in controls: mean TV 1.05 (control) vs 0.76 (KI) vs 0.75 (KI + L-T_4); $P=0.0001$	Higher in controls: median Tg 113 (control) vs 65 (KI) vs 56 (KI + L-T_4); $P=0.0001$
(30), Germany	Intake of 300 μg KI/day from 1st trimester ($n=38$); control ($n=70$)	Not assessed	Not assessed	Larger in controls than KI: median TV 0.7 vs 1.5; $P<0.004$	Not assessed
(32), Spain	IS ($n=38$); 200 μg/day KI ($n=55$); 300 μg/day KI ($n=38$) from 1st trimester	No difference between groups: mean TSH 2.98 (IS) vs 2.49 (200 μg) vs 3.22[b] (300 μg); $P=0.4$	Not assessed	No difference between groups: mean TV 0.49 (IS) vs 0.42 (200 μg) vs 0.42 (300 μg); $P=0.5$	Not assessed

UIC, urinary iodine concentration; TV, thyroid volume; Tg, thyroglobulin; KI, potassium iodide; L-T_4, levothyroxine, IS, iodised salt.
[a]Thyroid hormones were measured in cord blood.
[b]TSH is in mU/ml for this study. Baseline median UICs were as follows: Pedersen *et al*. (27), 51 μg/l in controls and 55 μg/l in intervention; Glinoer *et al*. (29), 36 μg/l; Liesenkotter *et al*. (30), 64 μg/l and Santiago *et al*. (32), 109 μg/l.

with free T_4 between 0 and 10th percentiles (Fig. 2c). Delayed neurobehavioural performance was observed in none of the infants of mothers who received supplements from early gestation compared with 25 and 37% of children of mothers who started supplements from second or third trimesters respectively (36).

A third study by Murcia *et al*. (40) showed that infants of mothers who self-reported a supplementary iodine intake of >150 μg/day scored lower on the psychomotor development index (PDI) than infants born to mothers with intake of <100 μg/day (Fig. 2b) from supplements only. This study also reported a higher risk of having a PDI <85 in children of women with iodine intake >150 μg/day (OR 1.8, CI 1.0, 3.3). A more recent study by the same group has demonstrated a significantly lower PDS in association with supplementary iodine intake >150 μg/day in three additional areas of Spain (Fig. 2b) (39). In the RCT by Santiago *et al*. (32), no differences in MDS or PDS were demonstrable between the infants of women who were randomised in the first trimester to receive either iodised salt only, or 200 or 300 μg daily of KI (Fig. 2a and b).

Iodine supplementation in childhood and cognitive function ▸ A number of studies have examined the relationship between cognitive function in children and iodine nutrition status, but the majority of such studies were observational or conducted in severely iodine-deficient areas and were excluded from further analysis (Fig. 1). Excellent reviews of these studies have been published elsewhere (2, 4, 41, 42). We excluded one randomised trial in which iodised salt was introduced into the area during the course of the study thus compelling the authors to undertake a *post hoc* analysis based on final urine iodine concentrations (43). In the analysis they showed that children with improved UICs scored better on a combination of mental development tests than those with no improvement (43).

Only two RCTs which determined cognitive performance in children living in areas with mild-to-moderate iodine deficiency were suitable for meta-analysis. In a double blind trial, Zimmermann *et al*. (25) measured cognitive and motor performance in 310 Albanian children aged 10–12 years (median UIC 44 μg/l), who were randomly assigned to receive 400 mg of intramuscular iodine or placebo (25). Compared with placebo, the iodine-treated group showed improvements in four out of seven tests of cognition and motor performance, namely, rapid target marking, symbol search, rapid object naming and

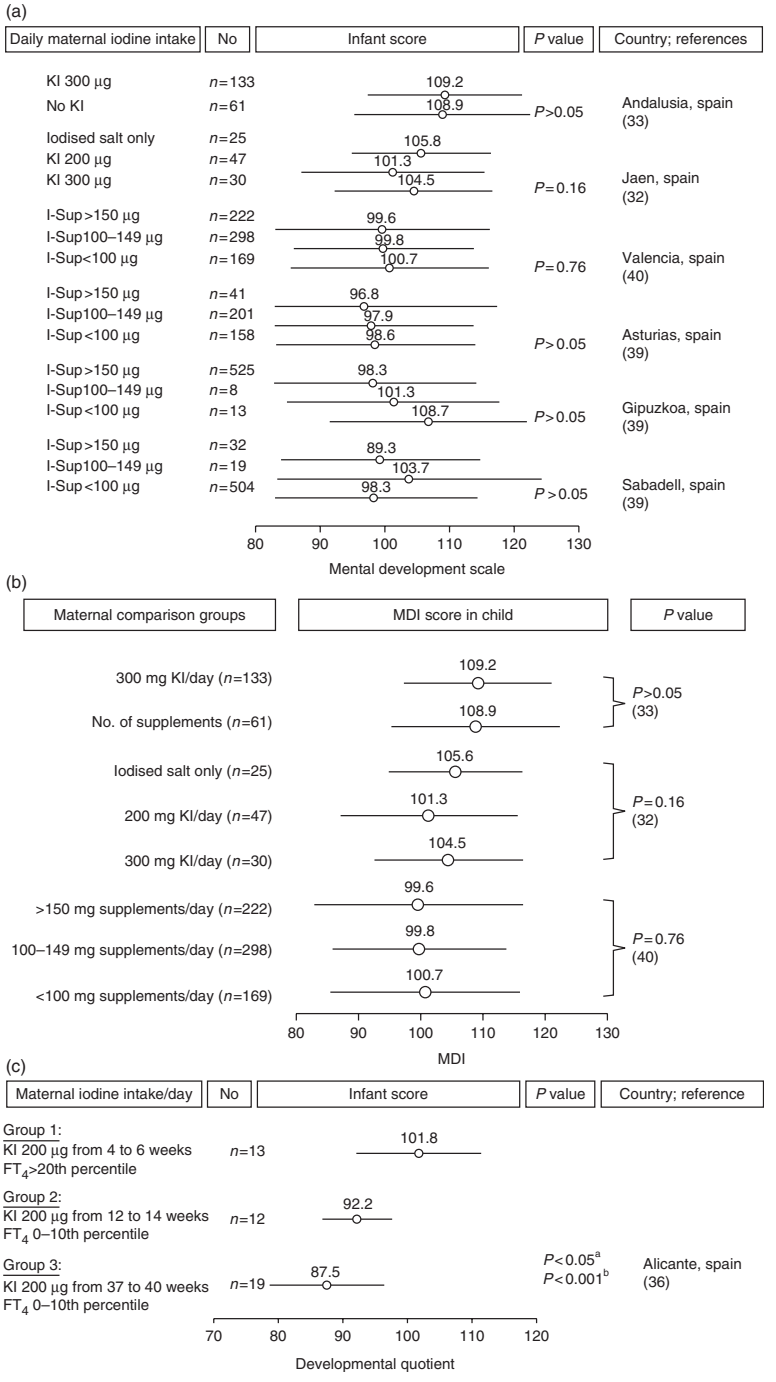

Figure 2

Studies investigating the effect of maternal iodine supplementation on neurodevelopmental indices in the child. Mental development scales (MDS; a), psychomotor development scales (PDS; b) and developmental quotient (DQ; c) were determined in children of mothers who received iodine supplements or no supplements during pregnancy. Children were tested between 6 and 18 months. The MDS and PDS presented are adjusted for age of child at the time of testing and psychologist administering the test and were typified to a mean of 100 with S.D. of 15 points. The mean score for each index is denoted as white circles with black lines on either side of the circles representing the S.D. KI, potassium iodide; I-salt iodised salt, I-Sup Iodine supplements. For (c) $^{a}P<0.05$ group 1 vs 2 and $^{b}P<0.001$ group 1 vs 3.

Raven's Coloured Progressive Matrices ($P<0.0001$) (25). Gordon *et al*. (24) in a marginally iodine-deficient New Zealand population randomly assigned 166 children aged 10–13 years (median UIC 63 μg/l) to receive a daily tablet of 150 μg of iodine or placebo for 28 weeks (24). Children who received iodine supplementation had improved iodine status and in addition scored higher on two out of four subtests for cognitive performance, namely, picture concepts ($P=0.023$) and matrix reasoning ($P=0.040$) (24).

For the meta-analysis cognitive tests were categorised into the following domains: i) perceptual reasoning; ii) processing speed; iii) working memory; and iv) global cognitive index. The global cognitive index was derived from the average of the scores in each of the domains. Unadjusted SMDs of the change in cognitive scores from baseline were computed from the raw scores reported by the authors, while adjusted SMDs were derived from the reported mean-adjusted treatment effects. S.E.M.-adjusted treatment effects were calculated using the recommended formula in the Cochrane handbook (44). The results of the analysis for individual domains are presented in Table 3, while Fig. 3 shows the forest plots for the global cognitive index. Beneficial effects of iodine supplementation were seen for both adjusted and unadjusted global indices with mild heterogeneity observed between the studies. For individual unadjusted domain scores, benefits were seen for processing speed but not for perceptual reasoning or working memory, while for the adjusted domains iodine was beneficial for perceptual reasoning although this was associated with significant heterogeneity.

Discussion

Main findings of the review

Correction of mild-to-moderate iodine deficiency prevented increases in maternal and newborn thyroid volume and serum thyroglobulin. The effect of iodine on maternal thyroid function was less consistent, but three out of five RCTs which included an untreated control group showed that iodisation prevented the rise in serum TSH seen in untreated women while the other two RCTs showed no effect of iodine on TSH. Iodine supplementation at dose ranges of 200–300 μg daily was equally effective as iodised salt in optimising gestational thyroid indices. In a limited number of studies, long-term iodisation before pregnancy had more favourable effects on thyroid indices than recent iodisation and early institution of iodine supplements was more effective than initiation of treatment in late pregnancy. None of the controlled iodine intervention trials reported an excess frequency of overt thyroid dysfunction. In school-age children, iodine supplementation was associated with modest benefits on aspects of cognitive performance, including perceptual reasoning and global cognitive index. However, the impact of maternal iodine supplementation on newborn neurodevelopment remains uncertain due to a lack of appropriate controlled intervention trials.

Comparison to previous reviews

Early studies in severely iodine-deficient areas showed that iodine supplementation reduced the occurrence

Table 3 Results of meta-analysis[a] on the impact of iodine supplementation on childhood cognitive performance.

Cognitive domains	SMD [b]	95% CI	*P* value	I^2 [c]
Unadjusted analysis[d]				
Perceptual reasoning	0.68	−0.10, 1.46	0.09	94% ($P<0.0001$)
Processing speed index	0.31	0.13, 0.49	0.0007	0% ($P=0.95$)
Working memory	0.05	−0.13, 0.23	0.55	0% ($P=0.41$)
Global cognitive index	0.41	0.13, 0.70	0.005	56% ($P=0.13$)
Adjusted analysis[e]				
Perceptual reasoning	0.55	0.05, 1.04	0.03	90% ($P=0.001$)
Processing speed index	0.21	−0.02, 0.44	0.08	59% ($P=0.12$)
Working memory	0.08	−0.07, 0.24	0.30	0% ($P=0.91$)
Global cognitive index	0.27	0.10, 0.44	0.002	26% ($P=0.24$)

[a]Studies included in the meta-analysis (random effects analysis with inverse variance method): i) Gordon *et al*. (24) (iodine group=84, control group=82, baseline median urinary iodine concentration (UIC) 63 μg/l (24)). ii) Zimmermann *et al*. (25) (iodine group=159, control=151, baseline median UIC 44 μg/l (25)). *P* value for significance in SMD between iodine supplemented and control participants.
[b]SMD, standardised mean difference between iodine supplemented and control participants.
[c]Test of heterogeneity; corresponding *P* value in brackets.
[d]Unadjusted SMD of the mean difference from baseline scores.
[e]Cognitive scores adjusted for baseline scores, sex, method of recruitment, cohort, ethnicity and household income (24) and adjusted for sex, school and baseline scores (25).

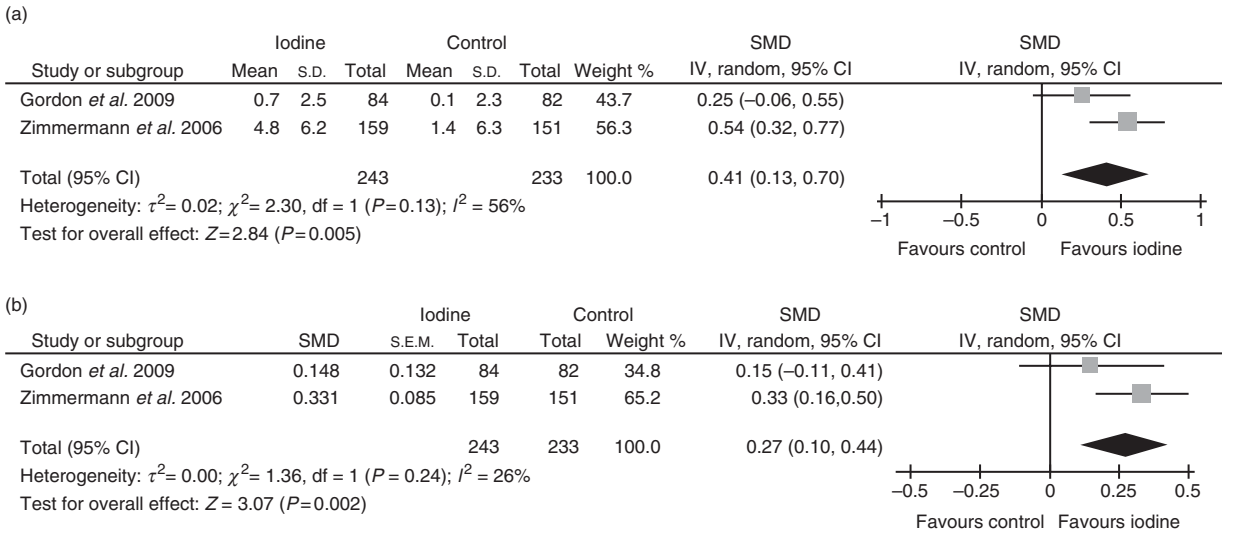

Figure 3

Forest plots showing effect of iodine supplementation on cognitive function (global cognitive index) in school-age children in mild-to-moderate iodine deficiency: (a) unadjusted SMD of the change from baseline. (b) Adjusted SMD of final cognitive scores adjusted for baseline scores, sex, method of recruitment, cohort, ethnicity and household income (24) and adjusted for sex, school and baseline scores (25). SMD, standardised mean difference.

of endemic cretinism (2, 6). A meta-analysis by Bleichrodt & Born (45), comprising 21 observational or quasi-randomised studies, reported a 13.5 deficit in IQ in individuals with moderate to severe iodine deficiency. A more recent Cochrane review comprising 26 prospective trials has observed a trend towards goiter reduction in iodine-supplemented children but found mixed results for cognitive and psychomotor functions (41). In a second Cochrane review of six prospective controlled trials in the general population, favourable effects of iodine supplementation were observed on goiter reduction rates (42). While these reviews have addressed iodine deficiency across a spectrum of severity, only a limited number of reviews focused on iodine supplementation in marginal iodine deficiency states (4, 46). A previous review by Zimmermann (4) addressed the adverse effects of mild-to-moderate iodine deficiency in pregnancy and childhood and highlighted the benefits of maternal iodine supplementation on maternal thyroid indices and the need for further data on infant neurodevelopmental outcomes. The findings from the present systematic review corroborate the conclusions from these previous reviews and in addition provide an updated analysis including recent key trials (24, 25, 32).

Clinical significance of the findings

Pending further studies therefore it is unclear whether the available data on maternal thyroid indices from controlled intervention trials can serve as a surrogate for future child intellectual development. Iodine is required for the syntheses of thyroid hormones which in turn are crucial for normal neuronal myelination, migration and glial differentiation (47). Observational studies show that children born to women with untreated hypothyroidism have a 7–10 points deficit in IQ compared with those of euthyroid mothers (48). Although a recent controlled antenatal trial, the CATS study, failed to show any benefits of treating maternal hypothyroidism on child IQ at 3 years of age, the women in this study had milder degrees of hypothyroidism than in earlier studies and in addition L-T_4 treatment in the CATS study was initiated relatively late in gestation (49). A further consideration is that maternal hypothyroidism carries an increased risk of miscarriages and pre-term deliveries, complications largely preventable by L-T_4 therapy (50, 51, 52). Thus, taken together it is plausible that optimisation of maternal thyroid status through iodine supplementation in marginally iodine-deficient areas will have benefits on newborn cognitive function amongst other outcomes. To explore

this, further RCTs or cluster randomised control trials of iodine supplementation in pre-pregnancy or early in the first trimester are needed with analysis of subsequent offspring IQ.

The benefits of iodine supplementation observed in school-aged children will be relevant to health policy makers. Reduced school performance adversely affects a region's productivity and economic potential. In Germany, analysis from 1981 to 2001 indicated that endemic iodine-deficiency goiter was responsible for costs of approximately one billion Euros per year (53). A comprehensive cost–benefit analysis from the USA showed that the projected benefit of screening and treatment for congenital iodine deficiency including savings in long-term care and productivity losses were thrice the costs incurred from treatment (54). An analysis of universal salt iodisation in the developing world suggests approximate gains of 35 billion USA dollars with a cost:benefit ratio of 1:70 (55). The advantages of correcting mild iodine deficiency will no doubt be less dramatic than for severe deficiency, but substantial returns in productivity and reduced health care costs will still be made.

A major concern with iodine supplementation has been the risk of iodine-induced thyroid dysfunction. We found no evidence of an excess of thyroid dysfunction in the controlled iodine intervention trials in pregnancy. Furthermore, the incidence of PPTD observed in these trials was not higher than published rates in the general population (50). Epidemiological studies, however, show that sharp increases in iodine intake in severely iodine-deficient populations may precipitate hyperthyroidism especially in elderly individuals with longstanding thyroid autonomy (56). Less striking manifestations are reported in marginally iodine-deficient areas or where iodine prophylaxis has been gradually introduced (56, 57, 58). In Denmark and Switzerland transient increases in the incidence of hyperthyroidism were recorded in the aftermath of iodisation but with reversal to baseline rates occurring within years of iodisation (59, 60). Surveys from Denmark (58), Greece (61), Sri Lanka (62), China (63) and parts of Africa (64) have all documented increases in the occurrence of thyroid dysfunction or autoimmunity in the wake of iodisation. In addition, the prevalence of both TPO-Ab and Tg-Ab (albeit low titre) was higher 4–5 years after cautious iodine fortification of salt was introduced in Denmark, particularly in young women (65). These population-level increases in the adult incidence of autoimmune thyroiditis thus seem an inevitable by-product of iodisation but should not deter future efforts at iodisation as the potential adverse effects of iodine deficiency on child development far outweighs the risk of correctable hypothyroidism in adults.

The mechanism of iodine fortification in mild-to-moderately deficient areas will merit careful consideration. Salt iodisation has proven cost effective in many countries and more than 70% of households worldwide now have access to iodised salt (14, 66, 67). However, salt may not suffice as the sole vehicle of iodisation in some countries. Retail outlet surveys conducted in the UK for example showed that most commercial salt brands lacked adequate iodine and iodised salt was unlikely to contribute substantially to overall iodine nutrition (10, 20). In addition, recent successful public health campaigns aimed at preventing cardiovascular disease through reduced salt consumption may have instigated further reductions in population iodine intake (68). However, a recent WHO forum has indicated that strategies to reduce salt intake and increase iodine fortification should not necessarily be contradictory and such strategies could support each other (69). Alternative strategies such as iodisation of bread as used in Australia and New Zealand (70, 71, 72) have been largely unexplored in the UK. However, supplementary iodine intake may still be indicated in addition to food fortification in vulnerable sub-populations such as pregnant women and children (71, 72). Routine prenatal iodine supplementation is recommended by professional bodies in North America (73) and Europe (74) but it is unlikely that this is systematically adhered to in many European countries where gestational iodine status remains inadequate (75, 76, 77). The method of iodisation notwithstanding, strategies for systematic surveillance should constitute a necessary component of future iodisation programmes.

Overall, the evidence base suggests that iodine supplementation in countries with mild-to-moderate iodine deficiency is beneficial, although data from RCTs remain lacking for maternal iodine supplementation and offspring cognitive development. However, recent studies (15, 16) have indicated that maternal iodine deficiency during pregnancy increased the odds of children having low IQ scores. We therefore agree that whilst awaiting results from current trials of iodine supplementation in pregnancy, pregnant and breastfeeding women should be offered iodine supplementation (78). Results from these ongoing trials and monitored interventions of iodine supplementation in children should ultimately provide a sufficient evidence base to identify if iodine fortification

in countries with mild-to-moderate iodine deficiency would have sufficient benefit to justify implementation.

Strengths and limitations of the review

Ours is the first systematic review to focus exclusively on the benefits of correcting mild-to-moderate iodine deficiency. We have applied stringent selection criteria thereby confining our review to RCTs or observational studies with comparable control groups. The significance of our findings is however limited by the small number of high quality controlled trials especially in relation to maternal iodisation and newborn cognitive function. A key constraint in iodine intervention trials has been in justifying a control group of untreated pregnant women given the established knowledge on the devastating effects of iodine deficiency on foetal well-being. Perhaps reflecting disparities in study designs, the available data from uncontrolled observational studies has been conflicting. For instance, some authors suggest that self-reported supplement intake in excess of 150 μg daily is associated with impaired foetal neurodevelopment (39, 40). This is a concern given that the adaptive mechanisms to counteract the thyroid inhibitory actions of an acute iodide load, or Wolff–Chaikoff effect, do not fully develop in the foetus until late gestation (79). Furthermore, iodine content of food and water (80) is highly variable and some individuals in marginally iodine-deficient countries will inevitably be exposed to higher iodine intake than the WHO-recommended daily upper limit of 500 μg (3). Further studies will thus be necessary to define optimal thresholds of iodisation in marginally iodine-deficient populations.

Conclusion

Correction of mild-to-moderate iodine deficiency improves cognitive performance in school-age children, but there is insufficient data on the developmental outcomes in early life. Large scale controlled trials are now needed to clarify whether gestational supplementation will benefit infant neurodevelopment in countries with marginal iodine deficiency. One such trial is currently in progress in India and Thailand and aims to recruit 800 women randomised to receive 200 μg of KI or placebo in early pregnancy (81). Outcomes will include infant neuropsychiatric function assessed at 12–18 months amongst other indices of thyroid and developmental function. Another randomised control trial is ongoing in Australia, the Pregnancy Iodine and Neurodevelopment in Kids (PINK) (82), which is recruiting women before the 20th week of pregnancy comparing 150 μg iodine with placebo; however, studies from European countries remain desirable. The findings of these studies and this report should substantially add to the evidence base for an iodisation policy in countries with mild-to-moderate iodine deficiency.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the review reported.

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