Systematic review and meta-analysis of the effects of iodine supplementation on thyroid function and child neurodevelopment in mildly-to-moderately iodine-deficient pregnant women

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Short running head: Effects of iodine supplementation in pregnancy

Abbreviations: ADHD, attention-deficit hyperactivity disorder; BSID, Bayley Scales of Infant Development; FT_4, free thyroxine; IQ, intelligence quotient; KI, potassium iodide; MD, mean difference; PPTD, post-partum thyroid disease; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial; T_4, thyroxine; Tg, thyroglobulin; Tg-Ab, thyroglobulin antibody; TPO-Ab, thyroid peroxidase antibody; TSH, thyroid stimulating hormone; TT_4, total thyroxine; UIC, urinary iodine concentration; UK, United Kingdom; WHO, World Health Organisation;

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Abstract

Background: Mild-to-moderate iodine deficiency, particularly in pregnancy, is prevalent; this is of concern as observational studies have shown negative associations with child neurodevelopment. Though neither the benefits nor the safety of iodine supplementation in pregnancy in areas of mild-to-moderate deficiency are well researched, such supplementation is increasingly being recommended by health authorities in a number of countries.

Objective: By reviewing the most recent published data on the effects of iodine supplementation in mildly-to-moderately deficient pregnant women on maternal and infant thyroid function and child cognition, we aimed to determine whether the evidence was sufficient to support such recommendations in these areas.

Design: A systematic review of randomised controlled trials (RCTs), non-RCT interventions and observational studies was conducted. To identify relevant papers we searched the PubMed and Embase databases. We defined mild-to-moderate iodine deficiency as a baseline, median, urinary iodine-concentration (UIC) of 50-149 µg/L. Eligible studies were included in meta-analyses.

Results: In total, 37 publications were included – ten RCTs, four non-RCT interventions and 23 observational studies. Most studies showed no effect of iodine supplementation on maternal or infant thyroid-stimulating hormone and free-thyroxine. Most RCTs found that supplementation reduced maternal thyroglobulin and in three RCTs, it prevented or diminished the increase in maternal thyroid volume during pregnancy. Three RCTs addressed child neurodevelopment; only one was adequately-powered. Meta-analyses of two RCTs showed no effect on child cognitive [mean difference (MD) (95%CI): -0.18 (-1.22, 0.87)], language [MD (95%CI): 1.28 (-0.28, 2.83)] or motor scores [MD (95%CI): 0.28 (-1.10, 1.66)].

Conclusions: There is insufficient good-quality evidence to support current recommendations for iodine supplementation in pregnancy in areas of mild-to-moderate deficiency. Well-designed RCTs with child cognitive outcomes are needed in areas of moderate deficiency (median UIC<100 µg/L). The maternal intra-thyroidal iodine stores should be considered in future trials by including appropriate measures of pre-conceptional iodine intake.

Keywords: iodine, iodine supplementation, pregnancy, mild-to-moderate deficiency, child neurodevelopment, thyroid function, systematic review

Introduction

Although tremendous progress has been made in achieving iodine sufficiency in the general population of many countries (1,2), some population sub-groups, such as pregnant women, still have inadequate iodine intake and are at high risk of deficiency (2,3). As a result of the physiological changes that occur in pregnancy (4,5), pregnant women have higher iodine requirements than the general population (6) that can be more difficult to meet through diet, and therefore supplementation may need to be considered. This is of public-health concern as iodine deficiency in pregnancy can have adverse consequences on child neurodevelopment (7); however the role of iodine supplements in pregnancy is not clear.

Iodine is essential for the production of thyroid hormones that are required for brain development in pregnancy and early life. Severe iodine deficiency is known to have a negative effect on thyroid function (8); when it occurs during pregnancy, it may result in cretinism (9). Nowadays, severe iodine deficiency is relatively rare largely as a result of salt-iodisation programmes (1) but mild-to-moderate iodine deficiency, particularly in pregnant women is prevalent (2). Observational studies are suggestive of a deleterious effect of maternal mild-to-moderate iodine deficiency on child neurodevelopmental outcomes e.g., executive function (10), intelligence quotient (IQ) scores (11), reading ability (11), school performance (12,13), cognitive scores (14) and language skills (15), though not all studies have found significant associations (16–18).

The benefits and safety of iodine supplementation in pregnancy in mild-to-moderate deficiency remain unclear; two previous systematic reviews found inconsistent results on the effects of iodine supplementation of mildly-to-moderately iodine-deficient mothers on maternal and infant thyroid function and few studies have reported on the effects on child development (19,20). Despite the insufficient evidence available and the inconsistency of findings, countries are increasingly introducing recommendations for iodine supplementation

in pregnancy. The National Health and Medical Research Council in Australia and New Zealand (21) and both the European and American Thyroid Associations (22,23) recommend supplements containing 150 µg iodine/day for women who are pregnant or planning a pregnancy. By contrast, the World Health Organisation (WHO) only recommends iodine supplementation in areas with low coverage of iodised salt (24). The United Kingdom (UK) has no official recommendations for iodine supplementation (7).

In an attempt to assess whether the current evidence in mild-to-moderate deficiency is sufficient to support recommendations for iodine supplementation in pregnancy in areas of mild-to-moderate deficiency, we aimed to review systematically the most up-to-date evidence on the effects of maternal iodine supplementation on maternal and infant thyroid function and child cognition. Our review focuses on summarising aspects of study design that might explain inconsistency in results and may need to be considered in future studies (e.g., baseline iodine status and timing of supplementation).

Methods

The reporting of this systematic review follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (25). The review is registered with PROSPERO (registration number: CRD42018100277) and the study protocol is available online (https://www.crd.york.ac.uk/prospero).

Search strategy and eligibility criteria

We searched PubMed (http://www.ncbi.nlm.nih.gov/pubmed/) and Embase (http://www.embase.com/) databases for relevant articles from inception through to January 2020, using a combination of search terms (**Supplementary Methods 1**). Additional studies were identified from the reference lists of retrieved publications and from iodine experts.

We included studies on the basis of: (i) the exposure of interest i.e., any type (e.g., iodine-only supplements or iodine as part of multivitamin/mineral tablets or as iodised salt), dose and regimen of iodine supplementation during pregnancy; (ii) the population of interest i.e., pregnant women with mild-to-moderate iodine deficiency [median urinary iodine concentration (UIC) of 50-149 μg/L (26) at baseline in the total population or in the group of non-users of iodine supplements and/or iodised salt]; (iii) the outcomes of interest, including maternal and infant/child thyroid function [e.g., thyroid-stimulating hormone (TSH), thyroxine (T_4), thyroglobulin (Tg) concentration, thyroid volume, thyroid-peroxidase antibody (TPO-Ab) titre, thyroglobulin antibodies (Tg-Ab), prevalence of hypothyroxinaemia, hypothyroidism, or hyperthyroidism and any other relevant thyroid effects], and child neurodevelopment (e.g., measures of motor and mental development, IQ scores, language, communication, and behaviour-related outcomes); and iv) study design i.e., observational, non-randomised and/or uncontrolled intervention studies and randomised controlled trials (RCTs); we included all types of study design to maximise information on the effect of iodine supplementation in pregnancy.

As the focus of this review was on mild-to-moderate iodine deficiency, studies in iodine-sufficient (UIC ≥ 150 μg/L) (6) or severely iodine-deficient populations (UIC < 50 μg/L; areas of endemic goitre) (26) were excluded. We excluded supplementation studies in infants or in women with known thyroid disease, studies in languages other than English, unpublished or non-peer-reviewed articles (e.g., meeting abstracts or letters), case-reports, narrative reviews/comment articles, and other systematic reviews or meta-analyses.

Study selection and data extraction

Titles and abstracts of all articles were independently screened by three reviewers (MD, HF and SB) using a pre-specified abstract checklist with the study eligibility criteria. If the

abstract did not provide enough information to determine eligibility, the full text was examined; after reviewing all potentially eligible full-texts, articles were either excluded (with documented reasons) or included for data extraction. Disagreement between reviewers was resolved through discussion.

Relevant data were independently extracted by two reviewers (MD and HF) using a predefined and piloted data-extraction form and included: reference details (author(s), year of publication), study details (study design, country), participant details (sample size, baseline iodine status), intervention details (type and dosage of supplement, start and duration of intervention, information about placebo/control treatment), details of supplement use for observational studies (study groups and comparisons, iodine dose and vehicle, start and/or duration of reported supplement use), and outcome details (results on all pre-specified maternal and infant/child thyroid-function outcomes, time-point at measurement, and results on any child-neurodevelopment outcomes, including type of cognitive assessment, assessor, and child age at testing). Where possible, the percentage change in maternal thyroid-function parameters during pregnancy was calculated using the first and last reported values; if only one measurement was available during gestation, term or post-partum values were used.

Meta-analyses

After assessing the comparability (e.g., design and reported data), the quality and the risk of bias of the included studies, we performed meta-analyses of RCTs only. Meta-analyses were performed in R software. For the RCTs that reported outcome data as medians, the meta-analysis was performed using the pool.med function of the metamedian package developed by Sean McGrath *et al.* (27). The RCTs that reported outcome data as means were combined using random effects meta-analysis performed with the metacont function of the meta package.

Risk-of-bias judgment and quality assessment

The Cochrane Risk-of-Bias Tool was used for RCTs and non-randomised and/or uncontrolled intervention studies (28,29). Risk of bias was judged as low, high or unclear for individual elements from six domains of bias (selection, performance, detection, attrition, reporting, and other sources of bias). The quality of cohort- and cross-sectional studies was judged using the Newcastle-Ottawa scale (good, fair or poor) (30) based on three study perspectives (i.e., *selection* of study groups, *comparability* of the groups, and *ascertainment of the outcomes).*

Results

The study selection process and the number of studies at each review stage are illustrated in a PRISMA flow diagram (**Figure 1**). The initial electronic database search yielded a total of 567 records. Seven other potentially relevant articles were identified after consulting experts in the field or the reference lists of articles identified by the search. In total, 144 duplicates were removed and 379 of the remaining records failed to meet the inclusion criteria and were excluded. Following full-text review of the remaining 51 records, 37 publications were included (Figure 1).

Characteristics of included studies

The 37 studies were published between 1981 and 2019; 23 were observational (ten prospective cohort studies and 13 cross-sectional studies) and 14 were interventions (ten RCTs and four non-randomised and/or uncontrolled interventions). Only four studies addressed all three outcomes (maternal and infant thyroid function and child neurodevelopment) (31–34). Studies were mostly based in Europe including Spain (14,16,17,32,33,35–38), Italy (39–44), Norway (15,45–48), Denmark (49–51), France (31,52), Germany (53,54), Poland (55,56), Sweden (57), Latvia (58) and Hungary (59). Four

studies were conducted outside Europe [Russia (60), Chile (61), Australia (62,63), India and Thailand (34)]. The sample-size ranged from 60 to 77, 164 in the observational studies and from 35 to 832 in the intervention studies. The forms of iodine supplementation were iodised salt (three studies) (39,41,42), drops of potassium-iodide (KI) solution (two studies) (50,61), KI tablets (nine studies) (32–34,38,43,44,53,54,62), and iodine-containing multivitamin tablets (16 studies) (15,16,31,40,45–49,51,52,55–59). The exact iodine vehicle was unclear in five studies – it was either a KI or an iodine-containing multivitamin tablet (14,17,35,36,60); in two studies the iodine vehicle was not specified (37,63). In intervention studies, the dose of iodine ranged from 50 (43) to 300 µg/day (32,33,61), mainly as KI tablets. In observational studies, the iodine dose in the supplement-user groups ranged from ≤100 to ≥200 µg/day, mainly in the form of multivitamin tablets. The exact dose of iodine supplement was not reported or was unclear in five studies (36,37,41,47,56). A few observational studies specifically investigated the effect of initiation of iodine-supplement in the pre-conception period as iodized salt (39–41) or iodine-containing multivitamins (47,59).

Risk of bias and quality of included studies

As a result of incomplete reporting, the risk of bias in many of the RCTs and intervention studies was unclear in several domains, particularly those of allocation-concealment and selective-reporting (**Supplementary Figure 1**). Adequate random-allocation sequence was used to generate the study groups in only five RCTs (31,34,44,52,62) and in one intervention study (32). Only three trials were double-blinded and/or placebo-controlled (34,44,51); another study was initiated as double-blind and placebo-controlled but was aborted due to withdrawal of funding support at which time it was unblinded (62). Most trials and intervention studies had effective blinding of outcome assessors for subjective outcomes (e.g., child neurodevelopment) or the outcomes were objective (e.g., laboratory measurements). The

quality of all cohort studies was rated as ‘good’, while cross-sectional studies were mostly of ‘poor’ or ‘fair’ quality (**Supplementary Table 1**).

Maternal thyroid function

The effects of iodine supplements on maternal thyroid function were addressed in 27 studies (13 intervention and 14 observational; **Table 1**). In all nine RCTs that assessed maternal TSH, there was no difference between the iodine and control groups at various time-points during, or at the end of the intervention (31,34,42,44,50–52,54,61). Additionally, five of those trials also found no difference between groups in the change of TSH over time (31,34,42,52,54). However, four RCTs (baseline median UIC in the range 51-56 µg/L) found a differential effect of iodine supplementation on the trajectory of TSH over the course of pregnancy – two studies in Denmark (50,51) reported no change in TSH in the iodine group and an increase in the control group; one study in Chile showed a decrease in TSH in the iodine group and no change in the controls (61); and a study in Italy showed a significantly greater increase in TSH in the controls than in the iodine group (44).

A meta-analysis of two of the RCTs, which administered 200-225 µg iodine/day from the first trimester (34,44), showed significantly lower median TSH in the iodine *vs.* placebo groups during pregnancy [pooled median difference (95% CI): -0.08 (-0.10, -0.05) mIU/L in the second trimester; -0.34 (-0.47, -0.20) mIU/L in the third trimester] (**Supplementary Table 2**).

Three out of four non-RCTs found no difference in TSH at different doses (32,43) or timing of initiation (38) of KI supplement. Three prospective, cohort studies in Italy found lower TSH in pregnant women who used iodised salt for at least two years prior to conception and continued into pregnancy (long-term users) than in those who started using iodised salt on becoming pregnant (39), or in non-users of iodised salt during pregnancy (41), or in those

who took 150 µg iodine/day from multivitamin/mineral supplements in early pregnancy (40). However, when comparing iodine-supplement users to the non-users of iodised salt, there was no difference in the proportion with elevated TSH. Results from cross-sectional studies comparing maternal TSH between iodine-supplement users *vs.* non-users during pregnancy were mixed – six studies found no difference (36,37,47,56,57,60), two studies found higher (35,59), and one lower TSH (49) in pregnant women who used iodine supplements.

Maternal thyroxine concentration was investigated in eight RCTs; six found no difference in free T_4 (FT_4) (31,44,50–52) or total T_4 (TT_4) (54) between the iodine and control groups, while two found a slightly higher FT_4 (34) and higher TT_4 (61) in the iodine group. Seven RCTs found that FT_4 or TT_4 decreased during pregnancy and there was no differential effect of iodine supplementation on the change during gestation (31,34,44,50–52,54).

A meta-analysis of two of the RCTs (34,44) showed no difference in FT_4 between the iodine and placebo groups in the second trimester [pooled median difference (95% CI): 0.01 (-0.12, 0.13)] but a significantly lower median FT_4 in the iodine group in the third trimester [pooled median difference (95% CI): -0.26 (-0.38, -0.13) pmol/L] (Supplementary Table 2).

Additionally, other intervention studies found either no difference in FT_4 between different doses of iodine supplements (32,43), or higher FT_4 when supplementation was started during pregnancy *vs.* at term (38), or lower FT_4 in the iodine group (33). Higher FT_4 in pregnancy was found in long-term users of iodised salt (i.e., started at least two years prior to pregnancy) than in women who either started using it when pregnant (39) or did not use it at all (41). Another study by the same group in Italy found that women who started taking 150 µg/day (as part of a multivitamin/mineral tablet) had a significantly lower FT_4 during pregnancy than long-term users of iodised salt, though there was no difference compared with non-users of iodine supplements/salt (40). Results from cross-sectional studies were

inconsistent – five studies found no difference in FT_4 (36,37,56,59) or TT_4 (57), two studies found lower (35,47), and one higher FT_4 (49) in iodine-supplement users.

Five of seven RCTs that measured Tg found it to be lower in the iodine group than in controls (31,34,44,50,52), while there was no difference in two trials (51,54). Four trials showed a decrease in Tg over the course of pregnancy in the iodine group, while Tg increased in the controls (31,44,50–52).

A pooled meta-analysis of two of the RCTs (34,44) showed that the median Tg during pregnancy was significantly lower in the iodine group than in the placebo group [pooled median difference (95% CI): -1.1 (-1.5, -0.6) µg/L in the second trimester; -2.5 (-3.7, -1.2) µg/L in the third trimester] (Supplementary Table 2).

In non-RCT intervention studies, one showed no change in Tg during pregnancy in the group taking iodine (33), one showed no difference in Tg or its change over time according to different doses of iodine supplement (300 *vs.* 200 µg/day) (32), while another showed a decrease in Tg in response to a higher dose (200 µg/day) *vs.* an increase with a lower dose (50 µg/day) (43). One cohort study found lower serum Tg in pregnant women who were long-term users of iodised salt than in women who started using it upon becoming pregnant (39). Three cross-sectional studies found lower Tg in women who used iodine supplements than in those who did not (49,57,59), with one reporting lower Tg only in women who started taking iodine supplements pre-pregnancy (59).

Five out of six RCTs found no difference in thyroid volume between the iodine and the control groups during or at the end of the intervention (34,42,44,52,54). However, in three of the six trials, iodine supplementation prevented (42) or diminished the increase in thyroid volume with advancing pregnancy (44,50). No difference in thyroid volume was reported in two intervention studies that used different doses of iodine (32,43), though one of the studies showed a decrease in post-partum thyroid volume only in the group taking the higher dose

(200 *vs.* 50 µg/day) (43). A cross-sectional study found lower thyroid volume in mothers who used iodine supplements than those who did not (60), while two studies found no difference between those groups (53,56).

Iodine supplements did not affect thyroid autoimmunity in any of the RCTs; there was no difference in the frequency of TPO-Ab positivity or TPO-Ab titre (34,51,54), nor in the percentage with detectable Tg-Ab (51). Furthermore, one trial found no difference in the proportion of women that developed post-partum thyroid disease (PPTD), or in its type or severity between the group supplemented with iodine and the controls (51). A later intervention study also reported no enhancement of the occurrence of PPTD or any side effects in the mothers in relation to iodine supplementation (43). None of the eight cross-sectional studies that investigated the effect of iodine-supplement use *vs.* no use on markers of thyroid autoimmunity found a difference in the frequency of Tg-Ab (36,47,49) or TPO-Ab positivity (36,37,47,57,58,60), or their titres (56). Risk of maternal thyroid failure (overt hypothyroidism or isolated hypothyroxinaemia in pregnancy) was reduced with long-term (started pre-pregnancy) but not short-term (started in pregnancy) use of iodised salt, as reported in an observational cohort study (39).

Infant/child thyroid function

Markers of infant/child thyroid function were assessed in 14 studies (nine intervention and five observational; **Table 2**).

Cord-blood markers

The majority of studies showed no effect of maternal iodine supplementation on cord-blood TSH or FT_4. None of the four RCTs that reported cord-blood TSH showed any difference between the iodine and control groups (31,50,61,62). One of two non-RCT intervention

studies also showed no effect of different doses of maternal iodine supplementation on cord-blood TSH (32). Only two studies – one cross-sectional (49) and one inadequately controlled intervention (33) – showed an increase in cord-blood TSH in the iodine-supplemented women. Three of four RCTs that assessed cord-blood FT_4 or TT_4 showed no difference between the iodine and control groups (31,50,62). Only one of the RCTs showed higher cord-blood TT_4 in the iodine group than in the controls (61). Only one cross-sectional study reported on FT_4; it showed higher cord-blood FT_4 in mothers who used iodine than in non-users (49). One RCT reported lower cord-blood Tg in the intervention than in the control group (50), while two reported no difference between groups (31,62). Only one cross-sectional study reported on serum Tg and found lower cord-blood concentration in iodine-users *vs.* non-users (49). The same study also found no difference in the frequency of cord-blood Tg-Ab positivity between iodine-users and non-users (48).

Thyroid function in infant/child

None of the three RCTs that reported TSH in newborns (34,44,62) or in children (34) found a difference between the iodine and control groups. There was also no difference in infant TSH between supplement users and non-users in all four cross-sectional studies (36,53,55,63). Only one of the RTCs reported on FT_4 and TT_4 in newborns and in children; it showed no difference between the iodine and control groups (34). The only RCT that reported on infant thyroid volume found that it was lower in the iodine group than in the control group (54). One uncontrolled intervention study found no difference in infant thyroid volume between two groups of mothers taking different doses of iodine and a group using only iodised salt (32). A cross-sectional study found lower thyroid volume in infants of mothers who were iodine-supplement users than in those of non-users (53). There was no increase in the frequency of TPO-Ab placental transfer in infants of iodine-supplemented mothers in an RCT (54).

Child neurodevelopment

Child neurodevelopmental outcomes were reported in 14 studies (six intervention and eight observational; **Table 3**). Three RCTs (baseline median UIC 117-137 µg/L) that gave doses of 150 or 200 µg/day as KI or iodine-containing multivitamin tablets studied the effect of iodine supplementation in pregnancy on child neurodevelopment (31,34,62), however only one was adequately-powered (34). We performed meta-analyses of the two RCTs that were comparable in study design [e.g., both administered iodine as KI tablets in a similar dose (150 or 200 µg/day) from early pregnancy until delivery, used a placebo tablet as the control treatment, assessed child cognition using the same cognitive tool (Bayley scales) and children were tested at a similar age (at 1.5 or 2 years)] (34,62). We did not include the other RCT because it used iodine as part of multivitamin/mineral tablets (31). The meta-analyses showed that there was no effect of iodine supplementation *vs.* placebo on child cognitive, language or motor scores (**Figure 2**).

Motor development

None of the three trials found either a beneficial or harmful effect of maternal iodine supplementation on child motor development measured at 1 to 2 years. Three non-randomised and/or inadequately controlled intervention studies looked at the effect of iodine supplementation on child neurodevelopment (32,33,38) and in two, there was a beneficial effect of iodine supplementation, given as 200 or 300 µg/day as KI, on motor development at 1.5 years (33,38). Maternal iodine-supplement use in doses ≥150 µg/day *vs.* 0-99 µg/day (taken as iodine-containing multivitamin or KI tablet) was negatively associated with child psychomotor development at 1 year when estimates were pooled from four sub-cohorts of the Spanish INMA prospective multi-centre study (16,17); however the overall estimate was driven by only two of the sub-cohorts (i.e., Valencia and Asturias). In a later study by the

same group, negative effects on motor development were not confirmed at age 4-5 years in any of the sub-cohorts nor when the estimates were pooled (14). Two cohort studies in Norway showed mixed results – one found no association between maternal iodine-supplement use and child fine or gross motor-development at 3 years, nor with the odds of not walking unaided at 17 months (45), while another study showed a negative association with gross motor but not with fine motor-development in infancy and toddlerhood (15).

Mental development

Cognitive development and language at age 1 to 2 years, IQ, processing speed, global executive function, and auditory performance at 5.4 years, did not differ between the iodine and the control groups in the RCTs (31,34,62). In the non-RCT intervention studies, there was no beneficial effect on mental development (32,33), language quotient (38), or total development (32,38). Observational studies also did not find associations between supplement use and overall mental development scores at 1 year (16,17), cognitive and language scores at 6 and 12 months (15), language or communication delay at 3 years (45), cognitive function at 4-5 years (14), or child language, reading and writing skills at 8 years (48). By contrast, a cohort study in Italy reported a beneficial effect of iodine, supplied as iodised salt for at least two years pre-conception (long-term use), on child IQ at 6-12 years (41).

Behavioural development

There was no effect of iodine supplementation in RCTs on child behaviour, including adaptive behaviours at 1.5 years (62), social-emotional behaviours at 1.5 (62) and 2 years (31), and total difficulties at 5.4 years (34). Two non-RCT intervention studies reported a better socialisation quotient (38) and a more favourable behaviour (33) in children of iodine-supplemented mothers than those of mothers who were not supplemented during pregnancy.

In the Norwegian MoBa cohort, children born to women with low habitual iodine intake (<160 µg/day) and who took an iodine-supplement containing up to 200 µg/day, were more likely to have internalising (but not externalising) behavioural problems (45), had an increased risk of attention-deficit hyperactivity disorder (ADHD) diagnosis and a higher ADHD symptom score at 8 years than those of non-supplement users (46).

Discussion

This systematic review has assessed the available evidence on the effects of iodine supplementation in pregnancy in areas of mild-to-moderate iodine deficiency. There was a lack of RCT evidence, and many observational studies were classed as of poor quality. While few studies showed an effect of iodine supplements on maternal or infant TSH or FT_4, most RCTs showed a reduction in maternal Tg and in half of the RCTs, there was a lower increase in maternal thyroid volume with advancing gestation. Only few studies showed lower cord-blood Tg and lower infant thyroid volume with iodine supplementation.

Overall there was a lack of data on child cognitive outcomes with only one adequately-powered RCT (34); that RCT showed no effect on child motor or mental development, or behaviour. Results from cohort studies and non-RCT interventions showed no effect of maternal iodine supplements on mental development (14–17,32,33,38,45,48), but there were inconsistent effects, both harmful (15–17) and beneficial (33,38), respectively, on motor development. Non-RCT interventions showed positive effects on externalising-type behaviour (33,38), while cohort studies reported negative associations with internalising behaviour (45) and ADHD symptoms/diagnosis (46) in those with low iodine intake (though after adjustment for multiple testing and using matched controls, these effects were attenuated).

We suggest that the inconsistencies in the evidence in mild-to-moderate deficiency might be explained by: (i) maternal pre-pregnancy/baseline iodine status; (ii) dose and form of iodine supplement; (iii) timing of supplement; and (iv) the cognitive tests used.

Firstly, maternal intrathyroidal iodine stores accumulated pre-pregnancy (4) may allow the thyroid to adapt to low iodine intake in pregnancy and maintain normal function despite the increased demands of pregnancy. However, adaptation requires enhanced thyroidal stimulation (4) which may put a strain on the maternal thyroid resulting in an elevation of serum Tg and progressively, goitrogenesis. Indeed in most studies, iodine supplementation resulted in a reduction in Tg, though not maternal thyroid volume which may take longer to respond (64). Because the early stages of pregnancy are a critical time for adequate iodine supply (65), supplementation following confirmation of pregnancy might be too late. Indeed, a series of cohort studies (39–41) has shown that mothers who used iodised salt before pregnancy, thus likely optimising their iodine stores, had lower TSH and higher FT_4 during pregnancy than those who either did not use iodised salt, or who started using it in pregnancy. Pre-pregnancy iodine stores might have affected the null outcome in the Gowachirapant *et al.* RCT as it was set in countries that had universal salt iodisation (34).

An abrupt increase in iodine intake during pregnancy might have negative effects, especially in those with low pre-pregnancy iodine intake. Women who started taking iodine supplements (40) or iodised salt (39) on becoming pregnant had higher TSH and lower FT_4 than women who had been using iodised salt pre-pregnancy. Another study showed that the introduction of iodine-containing supplements at 13 weeks was associated with lower FT_4, while longer-term use was not (47). In women with a habitually low iodine-intake (below 160 µg/day), iodine supplements were negatively associated with behaviour, including an increased risk of ADHD diagnosis, higher ADHD symptom-score, and increased odds of a high score for internalising-behaviour problems (45,46).

Differences in maternal baseline iodine status might also partly explain the inconsistent results on thyroid function. For instance, iodine supplements lowered cord-blood Tg only in the studies where baseline median UIC was <100 µg/L (49,50) but not in the studies where median UIC was >100 µg/L (31,62). Similarly, iodine supplements resulted in lower infant thyroid volume in studies with a median UIC <100 µg/L (53,54) but not in one study with a median UIC of 109 µg/L (32). In observational studies where baseline UIC was >100 µg/L (35,37,59), mothers who used iodine supplements during pregnancy had higher TSH and/or a higher percentage with elevated TSH. The RCTs with baseline UIC >100 µg/L found mostly no difference in maternal TSH or FT_4 between the iodine and control groups (31,34,52); by contrast, in a number of RCTs with median UIC <100 µg/L (44,50,51,61) iodine supplementation prevented or reduced the increase in TSH over the course of pregnancy.

Secondly, form and dose of iodine may affect results. In 16 studies iodine was part of a multivitamin/mineral supplement, making it hard to isolate its effect from that of other components. In the observational studies that showed negative effects of iodine supplementation on infant psychomotor development (dose ≥150 µg/day) (15–17) and behaviour (dose up to 200 µg/day) (45,46), iodine was supplied mostly as a multivitamin/mineral preparation. Sometimes it was unclear whether the dose was expressed as µg KI or µg of iodide (from KI); as only 76% of KI is iodide (66), the dose must be clearly specified. None of the studies that looked only at specific KI supplements have reported negative effects on child neurodevelopment. Regardless of supplement type, in observational studies it is important to consider the behaviours associated with supplement taking that could bias results in either direction (e.g., worried/health-seeking behaviour of the mother) (46).

Thirdly, the timing of supplementation is also likely to be important. An intervention study administering iodine supplements at different times during pregnancy found that

supplementation at 4-6 weeks was more effective in improving infant neurodevelopment than supplementation at 12-14 weeks or later (38). In that study, however, women in the group with the earliest administration of supplement were euthyroid at baseline, while the other two groups with later administration were hypothyroxinaemic, thus the effect of timing of iodine supplementation cannot be distinguished from that of maternal baseline FT_4 concentrations (38). Two RCTs (31,34) and one non-RCT intervention study (32) that administered iodine in the first trimester (around 10 weeks) showed no effect on child development, while one non-RCT intervention study (33) reported a beneficial effect. Although all these studies administered iodine early in pregnancy, they showed mixed results which may relate to pre-pregnancy status, or a lag-period before any benefits of iodine supplementation are seen (4).

Finally, the methods for assessing child neurodevelopment may explain null findings. In most studies, global assessments [e.g., Bayley Scales of Infant Development (BSID)] were used which, if conducted in infancy, may have low predictive capacity for childhood intelligence and behaviour (67,68). Indeed, in INMA, the negative effect on motor development (using BSID) at 1 year (16,17), was not confirmed at age 4-5 years (14). Though cognitive tests may be more valid at older ages, there are also more confounders (69,70). Understanding specific brain systems that are vulnerable to deficiency might enable iodine-sensitive cognitive tasks to be used in future trials e.g., visual information-processing (71).

There was some weak evidence, mainly from observational studies, that supplement use was associated with elevated maternal (35,37,59), and newborn TSH (33,49), and some negative effects on child psychomotor development (15–17) and behaviour (45,46). We found no evidence that iodine supplements were associated with markers of maternal or infant thyroid-autoimmunity. Negative effects were not confirmed in an RCT [with 200 µg iodine/day (34)] but further evidence of safety is needed in areas of moderate deficiency.

Our study is limited by the fact that we only included papers in English, and that we used non-validated cut-offs (UIC of 50-149 µg/L) to identify mild-to-moderate deficiency in pregnancy (26) thus study misclassification may have occurred.

In summary, there is insufficient, good-quality evidence to support current recommendations for iodine supplementation during pregnancy in areas of mild-to-moderate iodine deficiency. There is a need for well-designed randomised trials with child-cognitive outcomes in areas of moderate deficiency (i.e., UIC < 100 µg/L). Considering the potential importance of iodine stores, future trials should include appropriate measures (e.g., dietary questionnaire) of pre-pregnancy iodine intake as part of the study design. However, ethical and feasibility considerations are likely to limit the potential for future iodine RCTs.

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Table 1: Summary of findings from 27 studies for the effect of iodine supplements during pregnancy on maternal thyroid function

Study design				Maternal thyroid outcomes				
First author, year (ref.), country	**Iodine status[1]**	**Iodine exposure: dose[2], study group (start of supplement) (n)**	**Iodine vehicle/s**	**TSH**	**FT_4**	**Serum Tg**	**Thyroid volume**	**Other**
RCTs (n=9)								
Silva, 1981 (61), Chile	54 µg/g	A: 300 µg/d, iodine (9-32 wks.) (n=36) B: no iodine (n=10)	KI solution at 785 µg/ml (10 drops)	A: ↓46% B: ↓13% (NS) (wks. 9-32 vs 15-40) Decreased in iodine grp; no change in no-iodine grp; no difference between grps at delivery	Total T_4 was assessed: A: ↑44% B: ↓1% (NS) (wks. 9-32 vs 15-40) Increased in iodine grp; no change in no-iodine grp; higher in iodine grp at delivery	N/A	N/A	N/A
Romano, 1991 (42), Italy	31 µg/24h	A: 120-180 µg/d, IS (≤13 wks.) (n=17) B: no IS (n=18)	IS at 20 mg iodide per kg	No change in either grp (1st - 3rd trim); no difference between grps at any time-point between 1st and 3rd trim	N/A	N/A	A: ↑ 4% (NS) B: ↑16% (1st - 3rd trim) Increased in B vs no change in A; no difference at 3rd trim between A vs B (10.2 vs 11.7 ml, NS)[3]	N/A
Pedersen, 1993 (50), Denmark	51 µg/L	A: 200 µg/d, iodine (17-18 wks.) (n=28) B: no iodine (n=26)	KI solution (10 drops)	A: ↑5% (NS)[4] B: ↑21% (wks. 17 vs 37) Increased in B vs no change in A; no difference between grps at any time-point	A: ↓13% [4] B: ↓20% [4] (wks. 17 vs 37) Decreased in both grps with no difference in variation over time or at any time-point between grps	A: ↓18% [4] B: ↑60% [4] (wks.17 vs 37) Decreased in A; increased in B; lower in A at all time-points	A: ↑16% B: ↑31% (wks. 17 vs 37) Increased in both grps with higher increase in no-iodine grp	N/A
Liesenkötter, 1996 (54), Germany	64 µg/L (53 µg/g)	A: 230 µg/d, iodine (11.2 wks.) (n=38) B: no iodine (n=70)	KI tablet (300 µg)	A: ↓32% (NS) B: ↑29% (NS) (wks. 10-12 vs PP) No difference between grps at end of intervention PP	Total T_4 was assessed: A: ↓22% (NS) B: ↓40% (NS) (wks. 10-12 vs PP) No difference between grps at end of intervention PP	A:↓50% (NS) B:↓19% (NS) (wks. 10-12 vs PP) No difference between grp PP	A: ↑27% (NS) B: ↑19% (NS) (wks. 10-12 vs PP) No difference between grps PP	No change in frequency of TPO-Ab positivity in either grp

(continued)

Table 1: Summary of findings from 27 studies for the effect of iodine supplements during pregnancy on maternal thyroid function *(continued)*

Study design				Maternal thyroid outcomes				
First author, year (ref.), country	**Iodine status[1]**	**Iodine exposure: dose[2], study group (start of supplement) (n)**	**Iodine vehicle/s**	**TSH**	**FT_4**	**Serum Tg**	**Thyroid volume**	**Other**
RCTs *(continued)*								
Nøhr, 2000 (51), Denmark[5]	51 µg/L	A: 150 µg/d, MV + iodine (P+PP) (11 wks.) (n=22) B: 150 µg/d, MV + iodine (P) (11 wks.) (n=20) C: MV - iodine (n=24)	MV tablet (+ 50 µg Se)	A&B: ↑4 % (NS) C: ↑25% (wks. 11 vs 35) Increased in the no-iodine grp only; difference in the change over time between grps; no difference between grps at 35 wks.	A: ↓5% B: ↓16% C: ↓20% (wks. 11 vs 35) Decreased in all grps; no difference in change over time or at 35wks. between grps	A: ↓37% B: ↑5% (NS) C: ↑13% (wks. 11 vs 35) Decreased in MV+iodine & increased in MV-iodine; no difference between grps at 35 wks.	N/A	No difference PPTD between grps (59 vs 60 vs 46 %, NS); no difference in TPO-Ab titres between grps; no difference in % with Tg-Ab between grps at 35 wks.
Brucker-Davis, 2013 (52), France	103 µg/L	A: 150 µg/d, MV + iodine (<12 wks.) (n=32) B: MV - iodine (n=54)	MV tablet	A: ↓6% (NS) B: ↑16% (NS) (wks. 12 vs 33) No change in both grps; no difference between grps at any time-point	A: ↓18% B: ↓21% (wks. 12 vs 33) Decreased in both grps similarly; no difference between grps at any time-point	A: ↓29% B: ↑28% (NS) (wks. 12 vs 22) Decreased only in iodine grp at 2nd trim only; lower in iodine grp in 2nd trim	A: ↓3% (NS) B: ↑8% (NS) (wks. 12 vs 33) No change in both grps; no difference between grps at any time-point	N/A
Brucker-Davis, 2015 (31), France	117 µg/L	A: 150 µg/d, MV + iodine (<10 wks.) (n=19) B: MV - iodine (n=25)	MV tablet	A: ↓3% (NS) B: ↑14% (NS) (wks. 12 vs 33) No difference between grps at any time-point	A: ↓18% B: ↓17% (wks. 12 vs 33) No difference between grps at any time-point	A: ↓17% B: ↑61% (wks. 12 vs 33) Lower in iodine grp (2nd & 3rd trim)	N/A	N/A
Gowachirapant 2017 (34), Thailand & India	131 µg/L	A: 200 µg/d, iodine (10.8 wks.) (n=412) B: placebo (n=420)	KI tablet	A: ↑18% B: ↑25% (wks. 10-11 vs 30-33) No difference between grps during pregnancy	A: ↓24% B: ↓22% (wks. 10-11 vs 30-33) Marginally higher in iodine grp during pregnancy	A: ↑5% B: ↑7% (wks. 10-11 vs 30-33) Lower in iodine grp during pregnancy	A: ↑7% B: ↓1% (wks. 10-11 vs 30-33) No difference between grps in pregnancy	No difference in TPO-Ab titres or % with raised TPO-Ab (>35 IU/ml) during pregnancy

(continued)

Table 1: Summary of findings from 27 studies for the effect of iodine supplements during pregnancy on maternal thyroid function *(continued)*

Study design				Maternal thyroid outcomes				
First author, year (ref.), country	**Iodine status[1]**	**Iodine exposure: dose[2], study group (start of supplement) (n)**	**Iodine vehicle/s**	**TSH**	**FT_4**	**Serum Tg**	**Thyroid volume**	**Other**
RCTs *(continued)*								
Censi, 2019 (44), Italy	56 µg/L (53 µg/g)	A: 225 µg/d, iodine (11 wks.) (n=52) B: placebo (10 wks.) (n=38)	KI tablet (294 µg)	A: ↑32% B: ↑60% (wks. <12 vs 29-38) Increased in both grps but the increase was significantly greater in B vs A; no diff. between grps during pregnancy; lower TSH in A vs B only at 8 wks. PP	A: ↓15% B: ↓14% (wks. <12 vs 29-38) Decreased in both grps; no difference between grps at any time-point	A: ↓27% B: ↑17% (wks. <12 vs 29-38) Decreased in A; increased in B; lower in A vs B in 3rd trim only	A: ↑7% B: ↑11% (wks. <12 vs 29-38) Increased in both grps with greater increase in B; no difference between grps at any time-point	N/A
Intervention studies (n=4)								
Antonangeli, 2002 (43), Italy	74 µg/g	A: 200 µg/d, iodine (10-16 wks.) (n=32) B: 50 µg/d, iodine (10-16 wks.) (n=35)	KI tablet (262/131 µg)	A: ↑9% (NS)[6] B: ↑9% (NS)[6] (wks. 10-16 vs 29-33) No change in either grp; no difference between grps at any time-point	A: ↓13% [6] B: ↓13% [6] (wks. 10-16 vs 29-33) Decreased in both grps similarly; no difference between grps at any time point	A:↓36% (NS)[6] B: ↑25% (NS)[6] (wks. 10-16 vs 29-33); NS change in either grp; no diff. between grps at any time-point	A: ↑3% (NS) B: ↑10% (NS) (wks. 10-16 vs 29-33); Small increase in B; no diff. between grps at any time-point in pregnancy; decreased PP in A	No difference in the occurrence of PPTD; no side effects
Berbel, 2009 (38), Spain[7]	75 µg/L[8]	A: 153 µg/d, iodine (4-6 wks) (n=92) B: 153 µg/d, iodine (12-14 wks) (n=102) C: 153 µg/d, iodine (term) (n=151)	KI tablet (200 µg)	No difference between grps at term A vs B vs C (2.10 vs 2.28 vs 2.13 mU/L, NS)	Higher in grps A & B (when iodine was started in pregnancy) vs C (at term) (13.3 vs 13.1 vs 9.9 pmol/L); no difference for A vs B	N/A	N/A	N/A
Velasco, 2009 (33), Spain	69 µg/L[9]	A: 300 µg/d, iodine (≤13 wks.) (n=133) B: no iodine (n=61)	KI tablet (300 µg)	A: ↑8% (NS) B: N/A (1s - 3rd trim) No change in iodine grp; lower in iodine grp in 3rd trim (1.99 vs 2.47 mU/L)	A: ↓26% B: N/A (1s - 3rd trim) Decreased in iodine grp; lower in iodine grp in 3rd trim (7.77 vs 8.98 pmol/L)	A: ↓27% (NS) B: N/A (1s - 3rd trim) Decreased in iodine grp but NS	N/A	N/A

(continued)

Table 1: Summary of findings from 27 studies for the effect of iodine supplements during pregnancy on maternal thyroid function *(continued)*

Study design				Maternal thyroid outcomes				
First author, year (ref.), country	**Iodine status[1]**	**Iodine exposure: dose[2], study group (start of supplement) (n)**	**Iodine vehicle/s**	**TSH**	**FT_4**	**Serum Tg**	**Thyroid volume**	**Other**
Intervention studies *(continued)*								
Santiago, 2013 (32), Spain[10]	109 µg/L	A: 300 µg/d, iodine (<10 wks.) (n=38) B: 200 µg/d, iodine (<10 wks.) (n=55) C: dose n/r, IS (<10 wks.) (n=38)	KI tablet (300/200 µg) & IS	A: ↑43% (NS) B: ↑20% (NS) C: ↑30% (NS) (wks. <10 vs 36) No difference in the change over time or at any time-point between grps	A: ↓25% B: ↓27% C: ↓28% (wks. <10 vs 36) No difference in change over time or at any time-point between grps	A:↑7% (NS) B:↓2% (NS) C:↑0% (NS) (wks. <10 vs 36) No change in all grps; no diff between grps	A: ↑7% B: ↑28% C: ↑3% (wks. <10 vs 36) No difference in change over time or any time-point	N/A
Prospective cohort studies (n=3)								
Moleti, 2008 (39), Italy	63 µg/L	A: 190 µg/d, long-term IS-user (min 24 months pre-conception) (n=62); B: 105 µg/d, short-term IS-user (pregnant) (n=38)	IS at 30 ppm KIO_3	A:↑ 28%(1^{st} - 3^{rd} trim) B:↑ 37% Lower in long-term IS-users at all time-points	A: ↓ 19% (1^{st} - 3^{rd} trim) B: ↓ 19% Decreased in both grps; higher in long-term IS-users at all time-points	Lower in long-term IS-users: (10.2 vs 24.1 µg/L)	N/A	82.5% RR reduction of thyroid failure[11] in long vs short-term IS-users
Moleti, 2011 (40), Italy	52 µg/L	A: 150 µg/d, iodine-user (+IS) (9 wks. median) (n=168) B: dose n/r, long-term IS-user (min 24 months pre-conception) (n=105) C: non-user (n=160)	MV tablet & IS	A: ↑ 3% (NS) B: ↑ 12% (NS) C: ↑ 7% (NS) (wks. 6-9 vs 33-term) Higher in iodine-users vs long-term IS-users at all time-points and vs non-users in late pregnancy; higher % with elevated TSH in A vs B and no difference vs C	A: ↓ 21% B: ↓ 21% C: ↓ 21% (wks. 6-9 vs 33-term) Decreased in all grps; lower in iodine-users vs long-term IS-users & no difference vs non-users; higher % with low FT_4 in non-users vs iodine-users and long-term IS-users	N/A	N/A	N/A
Moleti, 2016 (41), Italy	48 µg/L	A: dose n/r, IS-user (min 24 months pre-conception) (n=15) B: no IS-user (n=15) C: dose n/r, IS-user (+LT4) (n=15) D: dose n/r, no IS-user (+LT4) (pre-conception) (n=15)	IS & LT4	A: ↑ 57% B: ↑ 77% C: ↓ 34% (NS) D: ↓ 54% (wks. ≤12 vs 31-term) Lower in IS-users vs no IS-users from 13-18 wks. onwards	A: ↓ 23% B: ↓ 17% C: ↓ 13% D: ↓ 7% (wks. ≤12 vs 31-term) Higher in IS-users vs no IS-users at all time-points; no difference between C & D	N/A	N/A	N/A

(continued)

Table 1: Summary of findings from 27 studies for the effect of iodine supplements during pregnancy on maternal thyroid function *(continued)*

Study design				Maternal thyroid outcomes				
First author, year (ref.), country	**Iodine status[1]**	**Iodine exposure: dose[2], study group (start of supplement) (n)**	**Iodine vehicle/s**	**TSH**	**FT_4**	**Serum Tg**	**Thyroid volume**	**Other**
Cross-sectional studies (n=11)								
Klett, 1999 (53), Germany	48 µg/L[8]	A: 135 µg/d, iodine-user (n=32) B: non-user (n=57)	KI tablet (175 µg)	N/A	N/A	N/A	No difference between A vs B at delivery (16.7 vs 19.5 ml, NS)	N/A
Nøhr, 2000 (49), Denmark	35 µg/L[8] (39 µg/g)	A: 150 µg/d, iodine-user (n=49) B: non-user (n=95)	MV tablet	Lower in iodine-users at term (2.06 vs 2.23 mU/L)	Higher in iodine-users at term (8.4 vs 7.9 pmol/L)	Lower A at term (14.7 vs 25.8 µg/L)	N/A	No difference in frequency of Tg-Ab positivity
Fadeyev, 2003 (60), Russia	44-87 µg/L[12]	A: 150-200 µg/d, iodine-user (n=90) B: non-user (n=125)	KI or MV tablet	No difference between A vs B in any trimester (3rd trim: 0.93 vs. 1.26 mU/L, NS)	N/A	N/A	Lower A in 3rd trim (12.9 vs. 16.8 ml)	No difference in TPO-Ab +ve
Marco, 2010 (36), Spain	164 µg/L (135 µg/L in C)	A: dose n/r, iodine-user (n=381) B: dose n/r, IS-user (n=75) C: non-user (n=69)	KI or MV tablet & IS	No difference between A vs B vs C at 26 wks. (1.73 vs 1.67 vs 2.51 mU/L, NS); no difference in % with TSH > 4 mU/L	No difference between A vs B vs C at 26 wks. (11.6 vs 11.6 vs 11.6 pmol/L, NS); no difference in % with FT_4 < 5.1 pmol/L	N/A	N/A	No difference in Tg-Ab and TPO-Ab +ve and % with hypoT4
Rebagliato, 2010 (35), Spain	137 µg/L	A: ≥200 µg/d, iodine-user (3 mo pre-conception up to < 24 wks.) (n=601) B: 100-199 µg/d, iodine-user (3 mo pre-conception up to < 24 wks.) (n=298) C: <100 µg/d, iodine-user/non-user (3 mo pre-conception up to < 24 wks.) (n=945)	KI or MV tablet	Higher % with TSH > 3 mU/L in ≥200 µg/d iodine-users (7.5 vs 6.7 vs 4.9 %); being in ≥200 µg/d iodine-user grp vs <100 µg/d associated with higher TSH and increased risk of TSH > 3 mU/L (OR=2.5)	Lower in A (≥200 µg/d iodine-users) vs B & C (10.1 vs 10.9 vs 10.7 pmol/L)	N/A	N/A	N/A
Menéndez-Torre, 2014 (37), Spain	197 µg/L (138 µg/L in B)	A: dose n/r, iodine-user (n=88) B: non-user (n=85)	N/A	No difference between A vs B (2.30 vs 1.94 mU/L, NS); higher % with TSH > 2.5 mU/L (42.5 vs 26.5 %)	No difference between A vs B (15.2 vs 14.9 pmol/L, NS)	N/A	N/A	No diff in % TPO-Ab positive (9.4 vs 9.1 %, NS)

(continued)

Table 1: Summary of findings from 27 studies for the effect of iodine supplements during pregnancy on maternal thyroid function *(continued)*

Study design				Maternal thyroid outcomes				
First author, year (ref.), country	**Iodine status[1]**	**Iodine exposure: dose[2], study group (start of supplement) (n)**	**Iodine vehicle/s**	**TSH**	**FT_4**	**Serum Tg**	**Thyroid volume**	**Other**
Cross-sectional studies *(continued)*								
Konrade, 2015 (58), Latvia	69 µg/L (81 µg/g)	A: ≥150 µg/d, iodine-user (n=48) B: 100-149 µg/d, iodine-user (n=70) C: <100 µg/d, iodine-user/non-user (n=570)	MV tablet	N/A	Only baseline levels in total sample were reported	N/A	N/A	No diff in % with TPO-Ab > 60 U/ml between grps (12.8 vs 8.9 vs 13.7 %) and no diff in odds of elevated TPO-Ab in A vs C
Zygmunt, 2015 (56), Poland	80 µg/L	A: dose n/r, iodine-user (n=52) B: non-user (n=63)	MV tablets	No difference between A vs B (1.76 vs 1.76 mU/L, NS)	No difference in A vs B (13.0 vs 13.3 pmol/L, NS)	N/A	No difference between A vs B (12.2 vs 11.8 ml, NS)	No difference in TPO-Ab between A vs B (27.9 vs 30.6 IU/ml, NS) or Tg-Ab (20.4 vs 40.2 IU/ml, NS)
Katko, 2017 (59), Hungary	162 µg/L (130 µg/L or 113 µg/g in C)	A: ≥150 µg/d, iodine-user (min 4wks. preconception) (n=27) B: ≥150 µg/d, iodine-user (pregnancy ≤16 wks.) (n=51) C: non-user (n=74)	MV tablets	Higher in iodine-user (P) vs non-user (1.97 vs 1.62 mU/L); no difference in iodine-user (pre-P) vs non-user (1.72 vs 1.62 mU/L, NS)	No difference between A vs B vs C (13.9 vs 13.2 vs 13.3 pmol/L, NS)	Lower in A vs C (9.1 vs 14.6 µg/L); no difference between B vs. C (14.5 vs 14.6 µg/L, NS)	N/A	N/A
Abel, 2018 (47), Norway	68 µg/L (91 µg/g)	A: dose n/r, iodine-user (1-26 wks. preconception) (n=347) B: dose n/r, iodine-user (pregnancy 0-12 wks.) (n=323) C: dose n/r, iodine-user (pregnancy 13-20 wks.) (n=194) D: non-user (n=1738)	MV tablet mainly	No difference between grps A vs B vs C vs D at 18.5 wks. (1.2 vs 1.2 vs 1.3 vs 1.2 mU/L, NS) [13]	Lower in C vs D at 18.5 wks. (12.4 vs 12.6 pmol/L, *P*=0.027); No difference in grps A & B vs D (12.7 & 12.6 vs 12.6 pmol/L, NS) [13]	N/A	N/A	No diff in % TPO-Ab or Tg-Ab +ve between grps A vs B vs C vs D (TPO-Ab: 8.1 vs 9.5 vs 7.5 vs 8.5 %, NS; Tg-Ab: 8.1 vs 11 vs 7 vs 7.9 %, NS) [13]

(continued)

Table 1: Summary of findings from 27 studies for the effect of iodine supplements during pregnancy on maternal thyroid function *(continued)*

Study design				Maternal thyroid outcomes				
First author, year (ref.), country	**Iodine status[1]**	**Iodine exposure: dose[2], study group (start of supplement) (n)**	**Iodine vehicle/s**	**TSH**	**FT_4**	**Serum Tg**	**Thyroid volume**	**Other**
Cross-sectional studies *(continued)*								
Manousou, 2019 (57), Sweden	101 µg/L (110 µg/g)	A: ≥150 µg/d, iodine-user (n=253) B: <150 µg/d, iodine-user/non-user (n=440)	MV tablet	No difference between grps at median 23 wks. (median values per grp not reported, *P*=0.63; overall median measured from DBS 0.7 mU/L)	Total T4 was assessed: No difference between grps at median 23 wks. (median values per grp not reported, *P*=0.33; overall median measured from DBS 124 nmol/L)	Lower in A vs B at 23 wks. (19.1 vs 24.4 µg/L)	N/A	No difference in % TPO-Ab +ve and % with hypothyroidism, hypo- and hyper-thyroxinaemia

[1]Baseline iodine status was expressed as median urinary iodine concentration (UIC, µg/L), median urinary iodine-to-creatinine ratio (UI/Creat, µg/g) or median urinary iodine excretion (UIE, µg/24h) of the total sample. If baseline iodine status values were not available for the total sample, values for the control group/group who did not use iodine-containing supplements and/or iodised salt were used. [2]In some cases where the authors only provided the KI dose used but not the actual iodine content of the tablets, the dose was converted to µg of iodide to facilitate comparisons between studies. [3]Thyroid volume values were estimated from a bar-chart in the original paper in Romano, 1991 (42). [4]Values for these parameters were estimated from graphs in the original paper in Pedersen, 1993 (50). [5]Women in this study were a selected group positive for TPO-Ab in Nøhr, 2002 (51). [6]The calculated % values are based on values for these parameters estimated from graphs in the original paper in Antonangeli, 2002 (43). [7]Women in this study were a very selected group (i.e., A=euthryoid vs B&C=hypothyroxinaemic in 1st trim or at term, respectively) in Berbel, 2009 (38). [8]Median UIC values at baseline were not reported and values measured at delivery/term were used for these studies - Berbel, 2009; Klett, 1999; Nøhr & Laurberg, 2002 (38,49,53). [9]Baseline iodine status value was based on a sub-group of women from the area who had miscarriage and were not included in this study in Velasco, 2009 (33). [10]Women in this study were also split by IS-use for at least 1 year before pregnancy; IS-users had significantly lower thyroid volume in 3rd trim vs no IS-users (no differences in TSH, FT_4 or Tg were observed), regardless of iodine-supplement use and group allocation in Santiago, 2013 (32). [11]Maternal thyroid failure was defined as overt hypothyroidism or isolated hypothyroxinaemia during pregnancy in Moleti, 2008 (39). [12]Baseline iodine status value was based on the median UIC in parts of the study area, as the median of exact sample was not reported in this study in Fadeyev, 2003 (60). [13]These values were estimated from a figure in the original paper in Abel 2018 (47).

Abbreviations: DBS, dried blood spot; Diff., difference; FT_4, free thyroxine; Grp/s, group/s; IS, iodised salt; KI, potassium iodide; LT4, levothyroxine; mo., months; MV, multivitamin supplement; N/A, data not available/reported; n/r, not reported; NS, not statistically significant; OR, odds ratio; P, pregnancy; PP, post-partum; PPTD, post-partum thyroid disease; Pre-P, pre-pregnancy; RCTs, randomised controlled trials; Ref., reference; RR, relative risk; Se, selenium; T_4, thyroxine; Tg, thyroglobulin; Tg-Ab, thyroglobulin antibody; TPO-Ab, thyroid peroxidase antibody; Trim, trimester; TSH, thyroid stimulating hormone; Wks., weeks;

Table 2: Summary of findings from 14 studies for the effect of iodine supplements during pregnancy on neonatal/child thyroid function

Study design				Neonatal/child thyroid outcomes				
First author, year (ref.), country	**Iodine status[1]**	**Iodine exposure: dose[2], study group (start of supplement) (n)**	**Iodine vehicle/s**	**TSH**	**FT_4**	**Serum Tg**	**Thyroid volume**	**Other**
RCTs (n=7)								
Silva, 1981 (61), Chile	54 µg/g	A: 300 µg/d, iodine (9-32 wks.) (n=36) B: no iodine (n=10)	KI solution at 785 µg/ml (10 drops)	No difference between grps A vs B in cord-blood (5.7 vs 8.3 mU/L, NS)	Higher total T_4 in iodine group (145.4 vs 119.7 nmol/L)	N/A	N/A	N/A
Pedersen, 1993 (50), Denmark	51 µg/L	A: 200 µg/d, iodine (17-18 wks.) (n=28) B: no iodine (n=26)	KI solution (10 drops)	No difference between grps A vs B in cord-blood (6.8 vs 7.8 mU/L, NS)	No difference between grps A vs B (13.6 vs 13.6 pmol/L, NS)	Lower in iodine group (38 vs 67 µg/L)	N/A	N/A
Liesenkötter, 1996 (54), Germany	64 µg/L (53 µg/g)	A: 230 µg/d, iodine (11.2 wks.) (n=38) B: no iodine (n=70)	KI tablet (300 µg)	Measured in new-born but not reported	N/A	N/A	Lower in iodine group (0.7 vs 1.5 ml)	No difference in frequency of TPO-Ab placental transfer between grps
Brucker-Davis, 2015 (31), France	117 µg/L	A: 150 µg/d, MV + iodine (<10 wks.) (n=19) B: MV - iodine (n=25)	MV tablet	No difference between grps A vs B in cord-blood (8.0 vs 6.2 mU/L, NS)	No difference between grps A vs B (13.4 vs 12.8 pmol/L, NS)	No difference between grps A vs B (66.8 vs 96.1 µg/L, NS)	N/A	N/A
Zhou, 2015 (62), Australia	137 µg/L	A: 150 µg/d, iodine (15.2 wks.) (n=29)[3] B: placebo (n=30)[3]	KI tablet	No difference between grps A vs B in cord-blood (8.2 vs 6.6 mU/L, NS) or in new-born (2.1 vs. 2.2 mU/L, NS)	No difference between grps A vs B (14.4 vs 13.8 pmol/L, NS)	No difference between grps A vs B (73 vs 64 µg/L, NS)	N/A	N/A
Gowachirapant, 2017 (34), Thailand & India	131 µg/L	A: 200 µg/d, iodine (10.8 wks.) (n=412)[4] B: placebo (n=420)[4]	KI tablet	No difference between grps at birth, 1 year, 2 or 5 years	No difference between grps in total T_4 at birth, 1 year, 2 or 5 years; FT_4 measured in newborns and at 2 years but not reported	N/A	Measured at 2 years but not reported	N/A
Censi, 2019 (44), Italy	56 µg/L (53 µg/g)	A: 225 µg/d, iodine (11 wks.) (n=52) B: placebo (10 wks.) (n=38)	KI tablet (294 µg)	No difference between grps A vs B in new-born (2.7 vs 3.6 mU/L, NS)	N/A	N/A	N/A	N/A

(continued)

Table 2: Summary of findings from 14 studies for the effect of iodine supplements during pregnancy on neonatal/child thyroid function *(continued)*

Study design				Neonatal/child thyroid outcomes				
First author, year (ref.), country	**Iodine status[1]**	**Iodine exposure: dose[2], study group (start of supplement) (n)**	**Iodine vehicle/s**	**TSH**	**FT_4**	**Serum Tg**	**Thyroid volume**	**Others**
Intervention studies (n=2)								
Velasco, 2009 (33), Spain	69 µg/L[5]	A: 300 µg/d, iodine (≤13 wks.) (n=133) B: no iodine (n=61)	KI tablet (300 µg)	Higher in iodine group in cord-blood (7.93 vs 3.77 mU/L)	N/A	N/A	N/A	N/A
Santiago, 2013 (32), Spain	109 µg/L	A: 300 µg/d, iodine (<10 wks.) (n=38) B: 200 µg/d, iodine (<10 wks.) (n=55) C: dose n/r, IS (<10 wks.) (n=38)	KI tablet (300/200 µg) & IS	No difference between grps A vs B vs C in cord-blood (3.22 vs 2.49 vs 2.98 mU/L, NS)	N/A	N/A	No difference between grps A vs B vs C (0.42 vs 0.42 vs 0.49 ml, NS)	N/A
Cross-sectional studies (n=5)								
Klett, 1999 (53), Germany	48 µg/L[6]	A: 135 µg/d, iodine-user (n=32) B: non-user (n=57)	KI tablet (175 µg)	No difference between grps in new-born (exact values not reported by group)	N/A	N/A	Lower in iodine group (1.0 vs 1.2 ml)	N/A
Nøhr, 2000 (49), Denmark	35 µg/L[6] (39 µg/g)	A: 150 µg/d, iodine-user (n=49) B: non-user (n=95)	MV tablet	Higher in iodine group in cord-blood (9.00 vs 7.07 mU/L)	Higher in iodine group (12.5 vs 11.7 pmol/L)	Lower in iodine group (34.3 vs 56.7 µg/L)	N/A	No difference in frequency of Tg-Ab positivity between grps
Gietka-Czernel, 2010 (55), Poland	113 µg/L	A: 150 µg/d, iodine-user (n=35) B: non-user (n=65)[7]	MV tablet	No difference between grps A vs B in new-born (1.57 vs 1.33 mU/L, NS)[8]	N/A	N/A	N/A	N/A
Marco, 2010 (36), Spain	164 µg/L (135 µg/L in C)	A: dose n/r, iodine-user (n=381) B: dose n/r, IS-user (n=75) C: non-user (n=69)	KI or MV tablet & IS	No difference between grps in new-born (exact values not reported by group)	N/A	N/A	N/A	N/A
Mitchell, 2018 (63), Australia	96 µg/L [9]	A: 200-300 µg/d, iodine-user (n=43) B: 150 µg/d, iodine-user (n=21) C: 0-75 µg/d, iodine-user/non-user (n=47)	N/A	No difference between grps A vs B vs C in new-born (2.0 vs 2.2 vs 2.0 mU/L, NS)[10]	N/A	N/A	N/A	N/A

[1]Baseline iodine status was expressed as median urinary iodine concentration (UIC, µg/L), median urinary iodine-to-creatinine ratio (UI/Creat, µg/g) or median urinary iodine excretion (UIE, µg/24h) of the total sample. If baseline iodine status values were not available for the total sample, values for the control group/group who did not use iodine-containing supplements and/or iodised

salt were used. [2]In some cases where the authors only provided the KI dose used but not the actual iodine content of the tablets, the dose was converted to µg of iodide to facilitate comparisons between studies. [3]Numbers for the cord-blood tests were smaller 19 and 22 for group A and B, respectively in Zhou, 2015 (62). [4]Numbers for child blood tests were smaller (e.g., at 5 years there were 159 in each group) in Gowachirapant, 2017 (34). [5]Baseline iodine status value was based on a sub-group of women from the area who had miscarriage and were not included in this study in Velasco, 2009 (33). [6]Median UIC values at baseline were not reported and values measured at delivery were used for these studies - Klett, 1999; Nøhr & Laurberg, 2002 (49,53). [7]Some of the women in group B (n=35) also took MV tablets (without iodine) in Gietka-Czernel, 2010 (55). [8]TSH measurements were performed for a total of 68 newborns, numbers per group were not reported in Gietka-Czernel, 2010 (55). [9]Baseline iodine status value was based on the median UIC in a previous study of pregnant women from the region (Rahman et al. 2011) (72), as the baseline iodine status of the exact sample was not reported in this study in Mitchell, 2018 (63). [10]TSH values for groups A and C were estimated from a bar-chart in the original paper in Mitchell, 2018 (63).

Abbreviations: FT_4, free thyroxine; Grp/s, group/s; IS, iodised salt; KI, potassium iodide; MV, multivitamin supplement; N/A, data not available/reported; n/r, not reported; NS, not statistically significant; RCTs, randomised controlled trials; Ref., reference; T_4, thyroxine; Tg, thyroglobulin; Tg-Ab, thyroglobulin antibody; TPO-Ab, thyroid peroxidase antibody; TSH, thyroid stimulating hormone; Wks., weeks;

Table 3: Summary of findings from 14 studies for the effect of iodine supplements during pregnancy on child neurodevelopment

Study design				Cognitive assessment			Child neurodevelopment outcomes
First author, year (ref.), country	**Iodine status[1]**	**Iodine exposure: dose[2], study group (start of supp) (n)**	**Iodine vehicle/s**	**Cognitive test (scales)**	**Child age (years) at assessment**	**Assessor**	
RCTs (n=3)							
Brucker-Davis, 2015 (31), France	117 µg/L	A: 150 µg/d, MV + iodine (<10 wks.) (n=19) B: MV - iodine (n=25)	MV tablet	Bayley Scales of Infant and Toddler Development – 3rd ed.	2 years	Blinded investigator & parent-reported (social-emotional behaviour scale)	No differences in composite scores or percentile ranks between grps for any of the outcomes: **Cognitive development:** 110 vs 110, NS; **Language:** 104.5 vs 100, NS; **Motor development:** 110 vs 110, NS; **Social-emotional behaviours score:** 100 vs 90, NS
Zhou, 2015 (62), Australia	137 µg/L	A: 150 µg/d, iodine (15.2 wks.) (n=29) B: placebo (n=30)	KI tablet	Bayley Scales of Infant and Toddler Development – 3rd ed.	1.5 years	Blinded investigator & parent-reported (behaviour scales only)	No differences continuously or as % with delayed score (score < 85/70) between grps for any of the outcomes: **Cognitive development:** 99.4 vs 101.7, NS; **Language:** 97.2 vs 97.9, NS; **Motor development:** 93.9 vs 92.4, NS; **Social-emotional behaviour:** 105.8 vs 105.4, NS; **Adaptive behaviours score:** 105.2 vs 103.5, NS
Gowachirapant 2017 (34), Thailand & India	131 µg/L	A: 200 µg/d, iodine (10.8 wks.) (n=412)[3] B: placebo (n=420)[3]	KI tablet	WPPSI - 3rd ed. BRIEF-P (executive function); SDQ (behaviour); Acoustic testing; NBAS (newborn development); BSID – 3rd ed.	5.4 years (WPPSI, BRIEF-P, SDQ, Acoustic) 6 wks. (NBAS) 1 & 2 years (BSID)	Clinical psychologist administered to the child (WPPSI, NBAS, & BSID) and to the mother of each child (BRIEF-P & SDQ)	No differences continuously or as % with delayed score (score < 85) between grps for verbal, performance, full-scale IQ, processing speed and global executive function: **Verbal IQ:** 89.5 vs 90.2, NS; **Performance IQ:** 97.5 vs 99.1, NS; **Processing speed:** 113.4 vs 115.0, NS; **Full-scale IQ:** 94.9 vs 96.1, NS; **Global execute function:** 90.6 vs 91.5, NS; **Total difficulties:** 9.3 vs 9.1, NS; **Auditory performance:** left (15.0 vs 13.3, NS) or right ear (13.3 vs 13.3, NS); **New-born neurodevelopment**: No difference overall; **Infant cognitive development**: No difference; **Infant language:** lower expressive language at 1 year in A vs B (14.8 vs 15.2); **Infant motor development:** No difference
Intervention studies (n=3)							
Berbel, 2009 (38), Spain[4]	75 µg/L[5]	A: 153 µg/d, iodine (4-6 wks.) (n=92)[6] B: 153 µg/d, iodine (12-14 wks.) (n=102)[6] C: 153 µg/d, iodine (term) (n=151)[6]	KI tablet (200 µg)	Brunet-Lézine scale, revised 1997 (gross & fine motor coordination, language skills, socialisation)	1.5 years	Two blinded specialists	**Total development quotient:** Higher in A vs B & C (101.8 vs 92.2 vs 87.5); no difference between B vs C (NS); % with delayed performance (< 85) observed only in B & C (25% & 36.8%); **Gross motor coordination quotient:** Higher in A vs B & C (108 vs 91 vs 92)[7]; no difference between B vs C (NS) **Fine motor coordination quotient:** Higher in A vs B & C (110 vs 95 vs 90)[7]; no difference between B vs C (NS)**; Language quotient:** No difference between grps A vs B vs C (96 vs 92 vs 90)[7]**; Socialisation quotient:** Higher in A vs C only (102 vs 87)[7]; no diff. between A or C vs B (95, NS)[7]

(continued)

Table 3: Summary of findings from 14 studies for the effect of iodine supplements during pregnancy on child neurodevelopment *(continued)*

Study design				Cognitive assessment			Child neurodevelopment outcomes
First author, year (ref.), country	**Iodine status[1]**	**Iodine exposure: dose[2], study group (start of supp) (n)**	**Iodine vehicle/s**	**Cognitive test (scales)**	**Child age (years) at assessment**	**Assessor**	
Intervention studies *(continued)*							
Velasco, 2009 (33), Spain	69 µg/L[8]	A: 300 µg/d, iodine (≤13 wks.) (n=133) B: no iodine (n=61)	KI tablet (300 µg)	Bayley Scales of Infant Development (mental, motor and behaviour scales)	0 - 1.5 years (mean per group A vs B: 5.5 vs 12.4 months)	Independent researcher blind to the design sequence of the study	**Mental development:** No difference between grps A vs B (109.2 vs 108.9, NS); **Psychomotor development:** Higher in A vs B (108.7 vs 102.7); highest values seen only in breast-fed children; **Behaviour rating:** Higher odds of a more similar or a higher mode than the mode for the age group in A vs B for reaction to persons (OR=6.93), reaction to the mother (OR=2.68), cooperation (OR=22.45), activity (OR=9.67), arousal (OR=5.87), and producing sounds (OR=10.24)
Santiago, 2013 (32), Spain	109 µg/L	A: 300 µg/d, iodine (<10 wks.) (n=38)[9] B: 200 µg/d, iodine (<10 wks.) (n=55)[9] C: dose n/r, IS (<10 wks.) (n=38)[9]	KI tablet (300/ 200 µg) & IS	Bayley Scales of Infant Development (mental and motor scales)	1 year (mean 12.8 months)	Independent investigator blind to the type of study design	**Mental development:** No difference between grps A vs B vs C (104.5 vs 101.3 vs 105.6, NS); **Psychomotor development:** No difference between grps A vs B vs C (98.6 vs 94.2 vs 100.9, NS); **Total development**: No difference between grps A vs B vs C (203.5 vs 195.5 vs 206.9, NS) No difference in any of the outcomes when split by long-term IS-use (for at least 1 year pre-pregnancy)
Prospective cohort studies (n=8)							
Murcia, 2011 (16), Spain	132 µg/L[10]	A: ≥150 µg/d, iodine-user (≤13 or >13 wks.) (n=222) B: 100-149 µg/d, iodine-user (≤13 or >13 wks.) (n=298) C: <100 µg/d, iodine-user/non-user (≤13 or >13 wks.) (n=169)	MV tablet	Bayley Scales of Infant Development	1 year (mean 12.3 months)	Trained psychologist	**Mental development:** No difference between grps A vs B vs C (99.6 vs 99.8 vs 100.7, NS); no association in adjusted analyses A vs C (+0.7 points, NS); no difference in odds of MDI < 85 A vs C (OR=1.1, NS); **Psychomotor development:** Lower in A and B vs C (97.1 vs 100.6 vs 102.6); negative association in adjusted analyses A vs C (-5.2 points); higher odds of PDI < 85 in A vs C (OR=1.8) with stronger association in girls vs boys (OR=4.0 vs 1.1)
Rebagliato, 2013 (17), Spain	125 µg/L	A: ≥150 µg/d, iodine-user (≤13 or >13 wks.) (n=598) B: 100-149 µg/d, iodine-user (≤13 or >13 wks.) (n=228) C: <100 µg/d, iodine-user/non-user (≤13 or >13 wks.) (n=675)	KI or MV tablet	Bayley Scales of Infant Development (mental & motor scales)	1 year (mean 16 months)	Trained psychologist	**Mental development:** No difference between grps A vs B vs C in all sub-cohorts (Asturias: 96.8 vs 97.9 vs 98.6, NS; Gipuzkoa: 98.3 vs 101.3 vs 106.7, NS; Sabadell: 99.3 vs. 103.7 vs 98.3, NS); no association in adjusted pooled analyses A vs C (-1.8 points, NS); no difference in risk of MDI < 85 in adjusted pooled analyses in A vs C (OR=1.7, NS); **Psychomotor development:** No difference between grps A vs B vs C in Gipuzkoa and Sabadell (Gipuzkoa: 98.9 vs 98.9 vs 99.4, NS; Sabadell: 101.4 vs 97.4 vs 99.4, NS); lower in A vs B & C in Asturias (Asturias: 93.3 vs 100.5 vs 98.2); no association in adjusted pooled analyses A vs C (-0.9 points, NS); no difference in risk of PDI < 85 in adjusted pooled analyses in A vs C (OR=1.5, NS)

(continued)

Table 3: Summary of findings from 14 studies for the effect of iodine supplements during pregnancy on child neurodevelopment *(continued)*

Study design				Cognitive assessment			Child neurodevelopment outcomes
First author, year (ref.), country	**Iodine status[1]**	**Iodine exposure: dose[2], study group (start of supp) (n)**	**Iodine vehicle/s**	**Cognitive test (scales)**	**Child age (years) at assessment**	**Assessor**	
Prospective cohort studies *(continued)*							
Moleti, 2016 (41), Italy	48 µg/L	A: dose n/r, IS-user (min 24 months pre-conception) (n=15) B: no IS-user (n=15) C: dose n/r, IS-user (+LT4) (n=15) D: dose n/r, no IS-user (+LT4) (pre-conception) (n=15)	IS & LT4	Wechsler Intelligence Scale for Children - 3rd ed. (full-scale, verbal and performance IQ)	6-12 years (mean 9.4-9.8 years)	Trained psychologist (blind)	**Full-scale IQ:** Higher in IS-users (A&C) vs non-users (B&D): A vs B (93.1 vs 81.7) & C vs D (96.1 vs 81.3); higher by 13 points in IS-users (A+C) vs non-users (B+D), regardless of LT4 treatment (94.5 vs 81.5); 3-fold higher % with defective cognitive function in no IS vs IS-users (76.9 vs 23.1 %, OR=7.7); **Verbal IQ:** Higher in IS-users (A&C) vs non-users (B&D): A vs B (90.1 vs 80.3) & C vs D (97.2 vs 79.6); higher by 14 points in IS-users (A+C) vs non-users (B+D), regardless of LT4 treatment (93.5 vs 79.6); **Performance IQ:** Higher in IS-users (A&C) vs non-users (B&D): A vs B (98.2 vs 87.3) & C vs D (97.4 vs 87.5); higher by 10 points in IS-users (A+C) vs non-users (B+D), regardless of LT4 treatment (97.4 vs 87.4)
Murcia, 2017 (14), Spain	123 µg/L	A: ≥150 µg/d, iodine-user (≤13 or >13 wks.) (n=610) B: 100-149 µg/d, iodine-user (≤13 or >13 wks.) (n=457) C: <100 µg/d, iodine-user/non-user (≤13 or >13 wks.) (n=719)	KI or MV tablet	McCarthy Scales of Children's Abilities (cognitive and motor scales)	4-5 years (mean 4.8 years)	Trained psychologist	**Cognitive function:** No association with total scale or the subscales in adjusted pooled analyses A vs C (+0.3 points, NS) (mean scores per group not reported); no association of timing or dose of supplement; **Motor function:** No association with total scale or the subscales in adjusted pooled analyses A vs C (+1.2 points, NS) (mean scores per group not reported); no association of timing or dose of supplement;
Abel, 2017 (45), Norway	122 µg/24h[11]	A: >200 µg/d, iodine-user (0-26 wks. pre-conception up to 22 wks.) (n=1159) B: 1-200 µg/d, iodine-user (0-26 wks. pre-conception up to 22 wks.) (n=14091) C: non-user (n=33047)	MV tablet mainly	Language delay scale by Dale et al., 2003; Ages and Stages Questionnaire (comm.& motor skills); Motor milestone (walking unaided); Child behaviour checklist	3 years	Mother-reported	In women with habitual iodine intake ≥160 µg/d – NS associations with all outcomes; results for women with habitual intake <160 µg/d reported: **Language delay:** No association A & B vs C (OR=1.02 & 1.06, NS); **Communication delay z score:** No association A & B vs C (Beta=0.04 & 0.00, NS); **Internalising behaviour problems:** Higher odds in B vs C (OR=1.14) & no difference for A vs C (OR=1.01, NS); **Externalising behaviour problems:** No association A & B vs C (OR=1.21 & 1.07, NS); **Not walking at 17 months:** No association in adjusted analyses A & B vs C (OR=1.15 & 1.05, NS); **Fine motor delay z score:** No association A & B vs C (Beta=0.00 & 0.00, NS); **Gross motor delay z score:** No association A & B vs C (Beta=0.02 & 0.0, NS)

(continued)

Table 3: Summary of findings from 14 studies for the effect of iodine supplements during pregnancy on child neurodevelopment *(continued)*

Study design				Cognitive assessment			Child neurodevelopment outcomes
First author, year (ref.), country	**Iodine status[1]**	**Iodine exposure: dose[2], study group (start of supp) (n)**	**Iodine vehicle/s**	**Cognitive test (scales)**	**Child age (years) at assessment**	**Assessor**	
Prospective cohort studies *(continued)*							
Abel, 2017 (46), Norway	61 µg/L[12]	A: >200 µg/d, (0-26 wks. pre-conception up to 22 wks.) (n=1864) B: 1-200 µg/d (0-26 wks. pre-conception up to 22 wks.) (n=21940) C: non-user (n=53360)	MV tablet manly	ADHD diagnosis; ADHD Rating Scale (ADHD symptom score)	8 years	Patient registry (diagnosis) & mother-reported (symptoms)	**ADHD diagnosis:** no difference in risk between A & B vs C; increased risk in B vs C only when supplement started 0-12 wks. in women with low habitual iodine intake <160 µg/d (HR=1.29); **ADHD symptom score:** higher in B vs C in some adjusted analyses (Beta=0.05) and in fully-adjusted analyses only when supplement start 0-12 wks. (Beta=0.06) in women with iodine intake <160 µg/d
Abel, 2018 (48), Norway	67 µg/L[13] (91 µg/g)	A: dose n/r, iodine-user (0-26 wks. pre-conception up to 22 wks.) (n=14665) B: non-user (n=24806)	MV tablet manly	The Children's communication checklist-Short (CCC-S) (language skills); Vineland Adaptive Behaviour Scale-II: (selected 3 questions on reading & 2 on writing skills); mapping tests (reading & maths); special education in school	8 years	Mother-reported (language, reading & writing skills; results on reading and maths mapping tests; granted special education services)	**Language skills:** no significant association in adjusted analyses (Beta=0.00); **Reading skills:** no significant association in adjusted analyses (Beta= -0.01); **Writing skills:** no significant association in adjusted analyses (Beta= -0.01); **Reading mapping test:** no difference in the odds of attaining poor test results (OR= 0.98); **Maths mapping test:** no difference in the odds of attaining poor test results (OR= 0.99); **Special education:** no difference in the likelihood of receiving special education services (OR=0.96); NS associations with the outcomes when the analyses were done using timing of supplementation as the exposure variable (non-users, start pre-pregnancy, start 0-12 wks. or start >12wks.)
Markhus, 2018 (15), Norway	78 µg/L (82 µg/g)	A: 150-250 µg/d, iodine-user (≤ mean 23.7 wks) (n=155) B: non-user (n=658)	MV	Bayley Scales of Infant and Toddler Development – 3rd ed. (cognitive, language and motor scales)	mean 6.1 and 12.2 months (screening version); mean 18.4 months (full-scale version)	Trained health-care nurses	**Cognitive score:** no significant association in adjusted analyses (Beta=0.02); **Receptive language:** no significant association in adjusted analyses (Beta= -0.02); **Expressive language:** no significant association in adjusted analyses (Beta=0.05); **Fine motor skills**: no significant association in adjusted analyses (Beta= -0.10); **Gross motor skills**: significantly lower in A vs B in adjusted analyses (Beta= -0.18);

[1]Baseline iodine status was expressed as median urinary iodine concentration (UIC, µg/L), median urinary iodine-to-creatinine ratio (UI/Creat, µg/g) or median urinary iodine excretion (UIE, µg/24h) of the total sample. If baseline iodine status values were not available for the total sample, values for the control group/group who did not use iodine-containing supplements and/or iodised salt were used. [2]In some cases where the authors only provided the KI dose used but not the actual iodine content of the tablets, the dose was converted to µg of iodide to facilitate comparisons between studies. [3]Number of children with cognitive tests were smaller (e.g., for WPPSI A=159 vs B=154 and for BRIEF-P A=159 vs B=156) in Gowachirapant, 2017 (34). [4]Women in this study were a very selected group (i.e., A=euthryoid vs B&C=hypothyroxinaemic in 1st trimester or at term, respectively) in Berbel, 2009 (38). [5]Median UIC values at baseline were not reported and values measured at delivery/term were used for this study in Berbel, 2009 (38). [6]Number of children with cognitive tests were smaller (e.g., A=13 vs B=12 vs C=19) in Berbel, 2009 (38). [7]Values

were estimated from bar-charts from the original manuscript in Berbel, 2009 (38). [8]Baseline iodine status value was based on a sub-group of women from the area who had miscarriage and were not included in this study in Velasco, 2009 (33). [9]Number of children with cognitive tests were smaller (e.g., A=30 vs B=47 vs C=25) in Santiago, 2013 (32). [10]Baseline iodine status value was extracted from Rebagliato, 2010 (35), as the median UIC of the exact sample was not reported in this study in Murcia, 2011 (16). [11]Baseline iodine status value for this study was based on 24-hour UIE and iodine intake estimated from a food frequency questionnaire in Abel, 2017 (45). [12]Baseline iodine status was measured only in a sub-set of 1950 women for this study and the presented total value is based only on women who did not use iodine-containing supplements in Abel, 2017 (46). [13]Baseline iodine status was measured only in a sub-set of 2001 women at mean 18.5 weeks in Abel, 2018 (48).

Abbreviations: ADHD, attention-deficit hyperactivity disorder; BRIEF-P, Behaviour Rating Inventory of Executive Function – Preschool Version; BSID, Bayley Scales of Infant Development; Ed., edition; Grp/s, group/s; HR, hazard ratio; IQ, intelligence quotient; IS, iodised salt; KI, potassium iodide; LT4, levothyroxine; MDI, Mental Development Index; MV, multivitamin supplement; N/A, data not available/reported; NBAS, Neonatal Behavioural Assessment Scale; n/r, not reported; NS, not statistically significant; OR, odds ratio; PDI, Psychomotor Development Index; RCTs, randomised controlled trials; Ref., reference; SDQ, Strengths and Difficulties Questionnaire; Supp, supplement; Wks., weeks; WPPSI, Wechsler Preschool and Primary Scale of Intelligence;

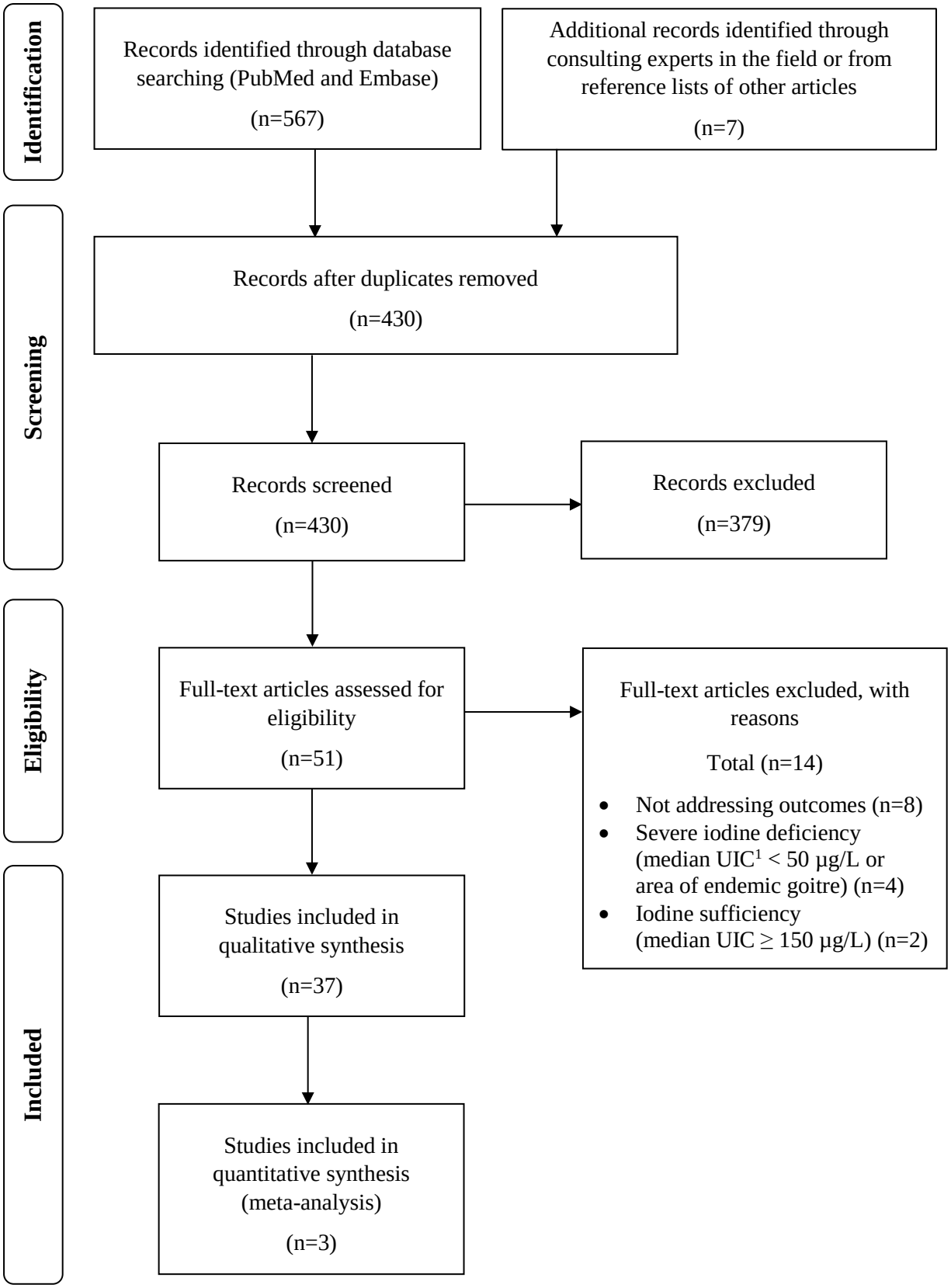


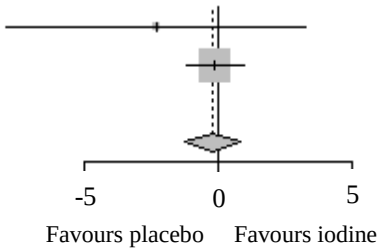
Figure 1: PRISMA flow diagram of the search results and study selection process

[1] UIC, urinary iodine concentration

A Cognitive scores

Study (ref.)	Iodine Total n	Iodine Mean	Iodine SD	Placebo Total n	Placebo Mean	Placebo SD	Weight	MD (95% CI)
Zhou 2015 (62)	27	99.4	12.2	26	101.7	8.2	3.5%	-2.30 (-7.88, 3.28)
Gowachirapant 2017 (34)	208	63.0	5.3	202	63.1	5.7	96.5%	-0.10 (-1.17, 0.97)
Random effects model	**235**			**228**			**100%**	**-0.18 (-1.22, 0.87)**

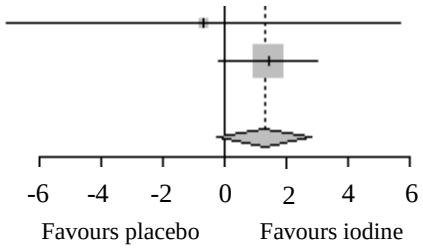
Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P=0.45$



B Language scores

Study (ref.)	Iodine Total n	Iodine Mean	Iodine SD	Placebo Total n	Placebo Mean	Placebo SD	Weight	MD (95% CI)
Zhou 2015 (62)	27	97.2	12.2	26	97.9	11.5	5.9%	-0.70 (-7.08, 5.68)
Gowachirapant 2017 (34)	203	54.8	7.9	196	53.4	8.4	94.1%	1.40 (-0.20, 3.00)
Random effects model	**230**			**222**			**100%**	**1.28 (-0.28, 2.83)**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P=0.53$



C Motor scores

Study (ref.)	Iodine Total n	Iodine Mean	Iodine SD	Placebo Total n	Placebo Mean	Placebo SD	Weight	MD (95% CI)
Zhou 2015 (62)	27	93.9	10.8	26	92.4	9.7	6.2%	1.50 (-4.02, 7.02)
Gowachirapant 2017 (34)	202	96.0	7.7	199	95.8	6.8	93.8%	0.20 (-1.22, 1.62)
Random effects model	**229**			**225**			**100%**	**0.28 (-1.10, 1.66)**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P=0.66$

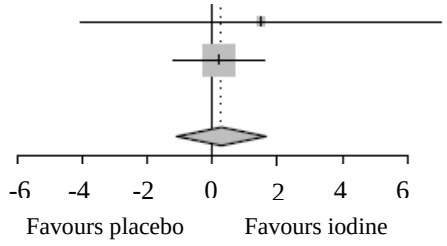


Figure 2: Forest plots of the effect of maternal iodine supplementation *vs.* placebo on child cognitive (**A**), language (**B**) and motor (**C**) scores

Data were analysed using random effects meta-analysis. **Abbreviations:** 95% CI, confidence interval; MD, mean difference; ref., reference; SD, standard deviation

On-line Supplementary Material:

Systematic review and meta-analysis of the effects of iodine supplementation on thyroid function and child neurodevelopment in mildly-to-moderately iodine-deficient pregnant women

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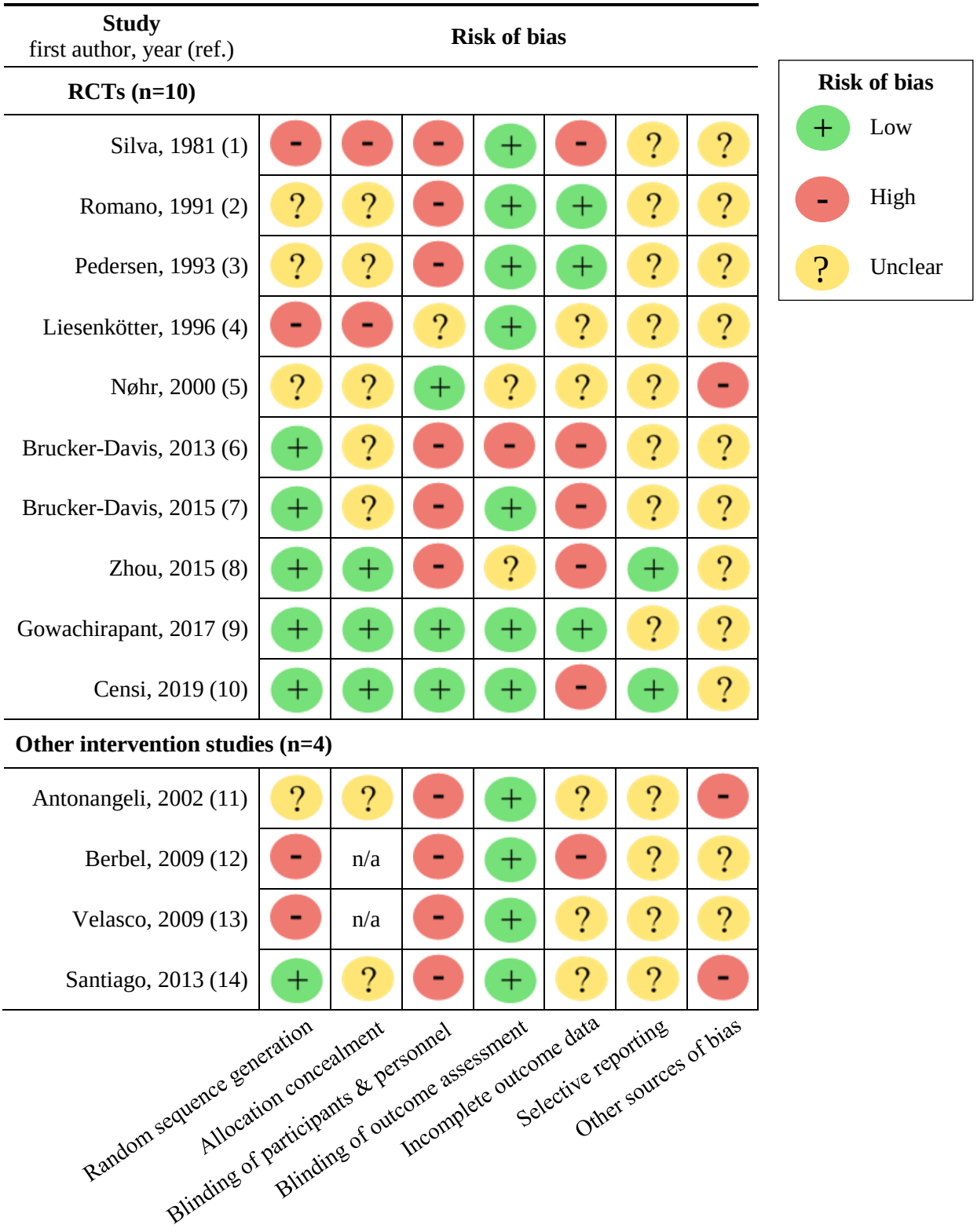
Supplementary Methods 1: Search terms for PubMed and Embase

PubMed search code:

((((((((((((iodine OR iodide OR iodate OR iodis* OR iodiz*))) AND ((supplement* OR prophylaxis OR treat*)))) AND ((pregnant OR pregnancy)))) AND ((neurodevelop* OR cognit* OR develop* OR thyroid OR behaviour OR education* OR ADHD OR hearing OR brain)))) AND ((deficient OR deficiency)))) AND ((thyroid OR thyroid function OR thyroid hormone OR thyroid size)))) AND Humans[Mesh] AND English[lang])

Embase search code:

('iodine'/exp OR iodine OR 'iodide'/exp OR iodide OR 'iodate'/exp OR iodate OR iodis* OR iodiz*) AND (supplement* OR 'prophylaxis'/exp OR prophylaxis OR treat*) AND (pregnant OR 'pregnancy'/exp OR pregnancy) AND (neurodevelop* OR cognit* OR develop* OR 'thyroid'/exp OR thyroid OR 'behaviour'/exp OR behaviour OR education* OR 'adhd'/exp OR adhd OR 'hearing'/exp OR hearing OR 'brain'/exp OR brain) AND (deficient OR 'deficiency'/exp OR deficiency) AND ('thyroid'/exp OR thyroid OR 'thyroid function'/exp OR 'thyroid function' OR (('thyroid'/exp OR thyroid) AND ('function'/exp OR function)) OR 'thyroid hormone'/exp OR 'thyroid hormone' OR (('thyroid'/exp OR thyroid) AND ('hormone'/exp OR hormone)) OR 'thyroid size'/exp OR 'thyroid size' OR (('thyroid'/exp OR thyroid) AND ('size'/exp OR size))) AND [english]/lim AND [article]/lim AND [humans]/lim



Supplementary Figure 2: Risk of bias assessment summary of included randomised controlled trials (RCTs) and other intervention studies using the Cochrane Risk of Bias Tool

Abbreviations: N/A, not applicable (for non-randomised studies); RCT, randomised controlled trial; Ref., reference;

Supplementary Table 1: Quality assessment of included prospective cohort studies and cross-sectional studies using the Newcastle-Ottawa scale

Study first author, year (ref.)	**Selection (max 4 stars)**	**Comparability (max 2 stars)**	**Outcome assessment (max 3 stars)**	**Quality judgement[1]**
Prospective cohort studies (n=10)				
Moleti, 2008 (15)	★★★	★	★★	Good
Moleti, 2011 (16)	★★★	★	★★	Good
Murcia, 2011 (17)	★★★	★★	★★★	Good
Rebagliato, 2013 (18)	★★★	★★	★★★	Good
Moleti, 2016 (19)	★★★	★★	★★★	Good
Murcia, 2017 (20)	★★★	★★	★★	Good
Abel, 2017 (21)	★★★	★★	★★	Good
Abel, 2017 (22)	★★★	★★	★★½	Good
Abel, 2018 (23)	★★★	★★	★★	Good
Markhus, 2018 (24)	★★★	★★	★★★	Good
Cross-sectional studies (n=13)				
Klett, 1999 (25)	★		★★	Poor
Nøhr, 2000 (26)	★★★	★	★★★	Good
Fadeyev, 2003 (27)	★★		★★★	Poor
Gietka-Czernel, 2010 (28)	★		★★	Poor
Marco, 2010 (29)	★		★★	Poor
Rebagliato, 2010 (30)	★★★	★★	★★★	Good
Menéndez Torre, 2014 (31)	★★	★	★★	Fair
Konrade, 2015 (32)	★★	★	★★★	Fair
Zygmunt, 2015 (33)	★		★★	Poor
Katko, 2017 (34)	★★	★	★★★	Fair
Abel, 2018 (35)	★½	★★	★★★	Fair
Mitchell, 2018 (36)	★★★		★★	Poor
Manousou, 2019 (37)	★★		★★★	Poor

[1] Quality Grading: **Good =** 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; **Fair =** 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; **Poor =** 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain;

Abbreviations: Ref., reference;

Supplementary Table 2: Results of meta-analyses on the effect of maternal iodine supplementation *vs.* placebo on maternal TSH, FT_4 and thyroglobulin during pregnancy

Thyroid function parameters [1]	Pregnancy		Post-partum
	Time-point 1	Time-point 2	Time-point 3
	Pooled effect[2] (95% CI)	Pooled effect[2] (95% CI)	Pooled effect[2] (95% CI)
Thyroid-stimulating hormone (TSH), mIU/L	-0.08 (-0.10, -0.05)	-0.34 (-0.47, -0.20)	-0.38 (-0.66, -0.10)
Free thyroxine (FT_4), pmol/L	0.01 (-0.12, 0.13)	-0.26 (-0.38, -0.13)	-0.19 (-0.37, 0.00)
Thyroglobulin (Tg), µg/L	-1.05 (-1.50, -0.60)	-2.47 (-3.73, -1.20)	-0.48 (-0.84, 0.12)

[1] Studies included in the meta-analyses [pooled medians method developed by McGrath *et al.* (38); see 'Methods']: Gowachirapant *et al.* 2017 (9) and Censi *et al.* 2019 (10). [2] Pooled effects represent pooled median differences between the iodine and the placebo groups at each time point (Gowachirapant *et al.* 2017: time-point 1=20-24 weeks, time-point 2=30-33 weeks and time-point 3=6 weeks post-partum; Censi *et al.* 2019: time-point 1=17-25 weeks, time-point 2=29-38 weeks and time-point 3=8 weeks post-partum).

Abbreviations: 95% CI, confidence interval; FT_4, free thyroxine; Tg, thyroglobulin; TSH, thyroid-stimulating hormone

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