Effect of iodine supplementation in pregnancy on neurocognitive development on offspring in iodine deficiency areas: a systematic review

ABSTRACT

Objective: To investigate the effect of iodine supplementation during gestation on the neurocognitive development of children in areas where iodine deficiency is common. Materials and methods: Based on the PRISMA methodology, we conducted the search for articles in the PubMed, LILACS and Scopus databases, between March and April 2020, without limitation of dates. We used descriptors in English, Portuguese, and Spanish, without filters. Four clinical trials and four cohort articles were included in the review. Results: The maximum supplementation was 300 μg of potassium iodide per day. The Bayley scale and Children’s Communication Checklist-Short were used to assess neurodevelopment in children. There was no significant improvement in the children’s mental development index and behavioural development index in the supplemented group; however, the psychomotor development index (PDI) showed improvement in the poorer gross motor skills. We found differences in the response time to sound in the supplemented group living in mild deficiency areas. Conclusion: Daily supplementation with iodine can improve poor psychomotor development of children living in mild to moderate iodine deficiency areas. Thus, it is necessary to perform further studies to assess the effect of supplementation on neurodevelopment before, during and after gestation in mild to moderate iodine deficiency areas. Arch Endocrinol Metab. 2021;65(3):352-67

Keywords
Potassium iodide; cognition; child; pregnant woman

INTRODUCTION

Iodine deficiency affects almost 2 billion people worldwide (1). In 2017, 18 countries were identified in which women of reproductive age were iodine-deficient, whereas for pregnant women, this was found in 39 countries (2). At this stage, deficiency induces the occurrence of irreversible brain damage in children (1). In fact, inadequate iodine intake in the foetal period may cause dwarfism, cretinism, mental retardation, deafness, psychomotor defects, or congenital anomalies, and may lead to miscarriage or stillbirth (3). Throughout growth, it negatively affects physical and neurocognitive development, especially hippocampal development and memory functions, and in adult life, causes goiter and hypothyroidism (4).

The recommended daily intake of iodine is 90 μg in the age group 0-59 months, 120 μg in 6-12-year-olds, 150 μg in adolescents and adults, and 250 μg during gestation and lactation (5). To ensure sufficient iodine intake, women who are planning pregnancy, pregnant or lactating should be recommended by the American Thyroid Association and European Thyroid Association to ingest daily oral supplements containing 150 μg of iodine (6,7). The World Health Organization (WHO) affirm that this supplementation should be
undertaken when iodized salt does not reach over 90% of households (5).

Recent findings in mild iodine deficiency areas in Israel and Iceland report the improvement of iodine intake in pregnant women supplemented with iodine compared with those not taking iodine supplements (8,9). Other studies in mild iodine deficiency areas in Brazil showed that supplementation corrects maternal thyroid indices and avoids impairment of the neuropsychological development in the offspring (10).

However, the effectiveness of iodine supplementation in pregnant women at improving children’s cognitive development is poorly explored and uncertain (11-13). Therefore, this review aimed to investigate the effect of iodine supplementation during gestation on children’s neurocognitive development in iodine deficiency areas.

**MATERIALS AND METHODS**

This systematic review sought to answer the following question: “What is the effect of iodine supplementation during gestation on children’s cognitive development?”. The review protocol was registered in PROSPERO (International Prospective Register of Ongoing Systematic Reviews) with the identification number CRD42019116962.

We used the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) (14) methodology to select articles. To identify the articles, we conducted the search in the PubMed, LILACS (Health Sciences in Latin America and the Caribbean) and Scopus databases, from March 1st to April 1st 2020, without limitations of dates. We used the descriptors: “iodine AND supplementation AND child AND development AND cognitive”, provided by DeCS (Health Science Descriptors) (15), in English, Portuguese, and Spanish, without filters (Supplemental Appendix 1).

After the searches and elimination of duplicates by database and between databases, we registered all articles in a spreadsheet in Microsoft Excel. Then, we recorded data from the articles, detailing the year, authorship, place of origin, type of study, target population, sample size, dose and time of supplementation, tests to assess neurocognitive development, and main results observed.

The inclusion criteria were that the studies should be randomized or non-randomized controlled trials or cohorts that evaluated the effect of iodine supplementation during gestation on the neurocognitive development of children living in moderate to severe, mild to moderate, severe, moderate, or mild iodine deficiency regions. We included all children in this study, without any age limit, provided that the study presented some scale of measurement of their neurodevelopment. Studies on the effect of intake of fortified foods, as well as literature reviews, cross-sectional studies, animal model studies and studies that assessed supplementation in pregnant women with thyroid disease were discarded (Supplemental Table 1).

The PICO was defined, namely: Population – pregnant women; Intervention – iodine supplements (iodine supplement use, iodine supplement coverage, iodine content in supplements); Comparator – other children of mothers without iodine supplement use; and Outcomes – development index (mental, psychomotor and verbal), sound response time, IQ (Intelligence Quotient) score (verbal, performance, and reasoning), skills score (language, reading, and writing), mapping test, reading, mathematics and special education.

The scale used to assess neurodevelopment in children selected from the included articles was the Bayley and Children’s Communication Checklist-Short (CCC-S).

The Bayley scale has three indices: mental, psychomotor, and behavioural development. The mental development index assesses the visual perceptual acuity, discrimination between objects, problem solving skills, language, and memory (16-18). The psychomotor development index (PDI) is assessed through postural control and appendicular motricity (16-18). The behavioural development index (BDI) assesses the follow-up of instructions, attitudes, and energy during the test, among other social behaviors (16-18). The Bayley score includes cognition and psychomotor skills with mental index (MDI), with a mean score of 100 (SD 15, range 55-155). The mean language (BDI) score was 100 (SD 15; range 45-155). Severe to moderate neurodevelopmental issues were defined as a mean MDI < 85 or BDI < 85, or both < 70; mild to moderate issues were defined as 85–100, and adequate function was defined as ≥ 100 (19).

However, the CCC-S is effective as a standardized assessment at identifying children with clinically-significant language impairment (20), containing 13 items that best discriminate typically-developing children from peers with language impairment in the
validation study (21), with a high degree of internal consistency. Each item provides an example of language behaviour in everyday contexts and covers speech, vocabulary, grammar, and discourse. The items are scored as 0 – absent response, or 1 – present response, with final analysis using statistical methods.

The quality of the studies was assessed according to the checklist of Joanna Briggs Institute (JBI) Critical Appraisal Tools of the Faculty of Health and Medical Sciences at the University of Adelaide, South Australia (22,23). The checklist consider each question should be answered through four options: Yes (Y), No (N), Unclear (U) and Not Applicable (NA). The bias risk percentage calculation is done by the amount of “Y” that has been selected in the checklist. When “NA” was selected, this question was not considered in the calculation, according to the guidelines of JBI. This tool classifies the studies in: up to 49% is considered a high risk of bias. From 50% to 70% is moderate and above 70% is low risk of bias.

RESULTS

The search resulted in 136 articles, of which eight were included in the review (Figure 1 and Supplement Appendix 1). The studies dated from the year 2009 (24) to 2019 (28), four of which were performed in Spain (24,26,27,29), two in Norway (25,28), one in India or Thailand (30), and the other in Australia or New Zealand (31). Two studies were performed in mild to moderate iodine deficiency areas (24,31), five in mild iodine deficiency areas (25-29), and one in a severe iodine deficiency area (29).

Regarding the design, four studies were randomized clinical trials (RTC) (24,26,30,31) and four were cohorts (25,27,28,29). Seven of eight authors used the Bayley scales to assess development of children under 36 months old (24-27,29-31), Gowachirapan and cols. also assessed the IQ of children above 60 months old (30), whereas Abel and cols. used the Children’s Communication Checklist-Short for children between 36 and 96 months old (28) (Table 1).


| Author/Year                  | Children by type of mother’s supplementation | Study design | Skills assessed | Main results                                                                                                                                 |
|------------------------------|----------------------------------------------|--------------|----------------|---------------------------------------------------------------------------------------------------------------------------------------------|
| Murcia et al., 2011 (27)     | Spain                                        | Study: Cohort | Bayley Scales 1st ed. (16) | Mild iodine deficiency areas  
|                              | <100 µg/day of KI (n = 169)  
100-149 µg/day (n = 298)  
≥150 µg/day (n = 222)  
Maternal MUIC: NA  
Maternal UIC in both group:  
102 (71-169) µg/L | CA: 11-16 months  
GA: < 12th weeks  
NA | Mental development  
Psychomotor development | ↑ in the KI group (≥150 µg), compared to the KI group (<100 and between 100-149 µg)  
↑ in the KI group (≥150 µg), compared to the KI group (<100 and between 100-149 µg)  
↑ 5.2 scores and ↑ 1.8 odds of a PDI < 85 in the KI group (≥150 µg/day).* |
| Rebagliato et al., 2013 (29)| Spain                                        | Study: Cohort | Bayley Scales 1st ed. (16) | Mild iodine deficiency areas  
|                              | <100 µg/day of KI  
100–149 µg/day  
≥150 µg/day  
Maternal UIC in both group:  
102 (71-169) µg/L | CA: 12-30 months  
GA: NA | Mental development  
Psychomotor development | ↑ odds in the KI group (≥150 µg), compared to KI groups (<100 and 100-149 µg)  
↓ score in KI group (≥150 µg).  
↓ odds in the KI group (≥150 µg), compared to KI groups (<100 and 100-149 µg)  
↓ score in KI group (≥150 µg). |
| Markhus et al., 2018 (25)   | Norway                                       | Study: Cohort | Bayley Scales 3rd ed. (18) | Mild iodine deficiency areas  
|                              | 175 µg/day of KI (n = 155)  
Placebo (n = 658)  
851 pregnant women  
Maternal UIC: 92 (56-200) µg/L in supplemented group, 77 (50-120) µg/L in control. | CA: 6 and 18 months  
CA: 16-26th week | Mental development  
Psychomotor Development  
Behavior  
Verbal IQ (WPPSI – III) | ↑ In the treated group compared to the placebo group  
↑ in the treated group compared to the placebo group  
↑ in the treated group compared to the placebo group  
↑ in the treated group compared to the placebo group |
| Abel et al., 2019 (28)      | Oslo, Norway                                 | Study: Cohort | CCC-S and CCC-2 (20,21) | Mild iodine deficiency areas  
|                              | 175 µg/day of KI (n = 14,665)  
Placebo (n = 24,806)  
39,471 pregnant women  
Maternal UIC: 83 (43-138) µg/L in supplemented group, 59 (32-101) µg/L in control. | CA: 36 and 96 months  
CA: 1-22th week | Language skills  
Reading skills  
Writing skills  
Mapping test Reading  
Mapping test mathematics  
Special education | ↑ In the treated group compared to the placebo group  
↓ in the treated group compared to the placebo group  
↓ in the treated group compared to the placebo group  
↓ in the treated group compared to the placebo group  
↓ in the treated group compared to the placebo group |
| Velasco et al., 2009 (24)   | Spain                                        | Study: Non-randomized controlled trial | Bayley Scales 2nd ed. (17) | Mild to Moderate iodine deficiency areas  
|                              | 300 µg/day of KI (n = 133)  
Placebo (n = 61)  
Maternal MUC: 263.0 ± 120.8 µg/L in supplementation, in control: 87.6 ± 62.1 µg/L | CA: 3-18 months  
GA: 8º to 12th week until lactation | Mental development  
Psychomotor Development  
Behavior | ↑ In the treated group, compared to the control group.  
↑ in the treated group, compared to the control group.*  
↑ in the treated group, compared to the control group.* |
| Santiago et al., 2013 (26)  | Spain                                        | Study: Randomized controlled trial | Bayley Scales 3rd ed. (18) | Mild iodine deficiency areas  
|                              | Iodized salt (n = 38)  
200 µg of KI (n = 55)  
300 µg (n = 38)  
Maternal MUC: NA  
Maternal MUIC: 23.4 ± 110.8 µg/L in supplementation, in control: 86.7 ± 62.1 µg/L | CA: 6-18 months  
GA: 10th week | Mental development  
Psychomotor Development | ↑ In the control group, compared to the KI group (200 µg), compared to 300  
↑ in the control group, compared to the KI group (200 µg), compared to 300 |
| Zhou et al, 2015 (31)       | New Zealand and Australia  
150 µg/day KI (n = 27)  
Placebo (n = 26)  
Maternal MUC: 200 µg/L in supplementation and 150 µg/L in control | Study: Randomized controlled trial | Bayley Scales 3rd ed. (18) | Mild to Moderate iodine deficiency areas  
|                              | Mental development  
Psychomotor Development  
Behavior | CA: 18 months  
GA: 20th week | ↑ in the placebo group, compared to the treated group.  
↑ in the placebo group, compared to the treated group.  
↑ in the placebo group, compared to the treated group. |
| Gowachirapant et al., 2017 (30) | Thailand and India  
200 µg/day of KI (n = 303)  
Placebo (n = 312)  
832 pregnant women (T0)  
Maternal MUC: NA  
Maternal MUIC: 200 µg/L in supplementation and 150 µg/L in control | Study: Randomized controlled trial | Bayley Scales 3rd ed. (18) | Mild iodine deficiency areas  
|                              | Mental development  
Psychomotor Development  
Behavior  
Sound response time (T)  
Verbal IQ (WPPSI – III)  
IQ performance (WPPSI – III)  
IQ reasoning (WPPSI – III) | CA: 12 and 24 months  
GA: 14th week  
CA: 60 and 72 months  
GA: 14th week | ↑ in the placebo group, compared to the treated group*  
↓ between groups  
↓ between groups  
↑ in the treated group compared to the placebo group*  
↑ in the treated group compared to the placebo group |

MUC: median urinary iodine concentration; NA: not available; GA: gestational age at the beginning of supplementation; Ed.: edition; KI: potassium iodide; n: sample number; T0: initial time; PDI: Psychomotor Development Index; T.: test; WPPSI-III: 3rd ed Primary Intelligence Scale; IQ: intelligence quotient; CA: Child’s age in the test application; NA: not applicable; a. standardized beta; b. odds ratio. * Results with statistical significance. ↑ - increased; ↓ - reduced; ↔ - no difference.
The maximum supplementation was 300 μg of potassium iodide (KI) per day (24,26) and one study did not specify supplementation dosages (28). Among the reviewed studies, five started supplementation in the first trimester (24,26,27,29), one in the 14th week (30), another between the 16th and 26th week (25), and one used four different start time categories (28). Only one study continued the supplementation in the lactation period (24); the others finished at the child’s birth (Table 1). Most studies used KI (24,26,30,31); however, some studies did not specify the source of the supplementation (Table 1 and Supplemental Table 2).

The results found an association between supplementation with 150 μg of KI/day and poorer gross motor skills of the PDI standardized beta 0.18 (95% CI: -0.33, - 0.03, p = 0.02) in one study (25), but in another four studies (24,26,27,29) supplementation with ≥ 150 μg of KI/day was associated with a 5.2-point decrease in PDI (95% confidence interval: -8.1, -2.2), decrease in PDI with < 85, odds ratio: 1.7 (95% confidence interval: 1.1, 2.6). The supplementation with 200 or 300 μg of KI/day was related to lower PDI than the iodized salt group. However, another outcome of our study showed that intake of 300 μg of KI/day in breastfeeding was associated with a mean 6.1 ± 0.9 -point increase in PDI compared to the control. Three other studies (28,30,31) did not find an association between iodine supplementation and neurodevelopment in children (Table 1 and Supplemental Table 3).

Regarding the quality analysis of the studies, the authors observed some limitations in reporting the methods of all trials, leaving some uncertainty in the assessment of several bias criteria, because in two points assessed in RCT studies were high risk of bias (<50%) but, as the studies in many points were moderate or above low risk bias and evidenced a clear delineation of the intervention, as well as were published in good journals we assumed to use all studies include in our review (Figures 2 and 3).

**DISCUSSION**

The findings showed an association between iodine supplementation and poor psychomotor development of children aged between 3 and 18 months, living in mild to moderate iodine deficiency areas.

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**Figure 2.** Methodological assessment quality of included studies using Joanna Briggs Institute’s standardized critical appraisal instrument for cohort studies.
Although not significant, other studies have shown positive results, in which children of supplemented mothers presented higher values of the psychomotor development index (25,27,29,31), behavioural (25,27,29), mental (24,25,30) and communication skills (28), when compared to those who were not supplemented. On the other hand, supplementation of mothers with between 150 and 200 μg of KI per day had no positive effect on the neurocognitive development of their children, as much as in those living in mild as well as moderate iodine deficiency areas, and in some studies the scores were low PDI point and your chance assessed were worse in the treated group (Supplemental Table 2).

None of the RCTs show an association between supplementation and child neurodevelopment, except for a negative association between iodine supplementation and expressive language (BSID) at 1 year in a single trial. The non-RCT studies show mixed results: with a positive association in one case and a negative association in the second. Children in the treatment group were associated with a lower PDI score than in the control group, with a better speaker skills score, poorer skills in the languages domain, lower mapping test results in reading in school, and suboptimal or low scores in mathematics.

Recent evidence has demonstrated these outcomes presented above, showing that 18-month-old children of mothers supplemented with 220-390 μg of KI per day had lower cognitive, language and motor scores (32).

In addition, Gowachirapan and cols. (2017) identified all development scale in primary results with placebo group had higher scores than the treatment group (30) in children aged 12 to 24 months in mild iodine deficiency areas.

Our findings mostly covered children under 24 months old, and the poor psychomotor effect on the children of supplemented mothers was demonstrated in this age group. In our results, the mothers supplemented from the 14th gestational week showed our findings seem to be
late to start supplementation, since the development of the nervous system occurs mainly between the 5-6th gestational weeks and birth, and between birth and 2 years, for infants and children (33,34).

Most of the mothers were supplemented from the 1st trimester of gestation, and in one study, the treatment continued during lactation. Through the results of this study, it was possible to verify that the psychomotor and behavioral development differed significantly among children of mothers supplemented with 300 μg of KI per day, living in areas with mild to moderate iodine deficiency (24). Recommendations from the American Thyroid Association and European Thyroid Association indicate that supplementation started in the pre-gestational period is more effective (6,7).

Supplementation with ≥ 150 μg of KI per day in pregnancy can be improve poor psychomotor development in children. This outcome is observable in lactation if supplementation dose is doubled (300 μg of KI per day).

In another study, children of mothers living in mild iodine deficiency areas and supplemented with 200 μg of KI per day during gestation showed a better response time to sound at 60 to 72 months than their is not supplemented group, but there was no difference between the groups (Supplemental Table 2) (30). This was the only study that used other methods to assess child development beyond the Bayley scale (30), and was the only one that assessed children over two years old, showing that this may be a more interesting time to assess the children’s development. However, use of the Children’s Communication Checklist-Short showed to be better for the assessment of skills and knowledge, including the domains of writing, speaking, reading, mathematical calculations and all languages in older children (>3 years old). This method uses the mental and behavioural skills applicable to the Bayley scale (mental and behaviour development index), and we did not find an association between iodine supplementation and this score in our results (28). These findings were reported for other authors that used the CCC-S to assess older children and used the Bayley score to assess the infant group; they did not find clear differences between these groups (35).

Although the findings showed poor psychomotor development in the children of the supplemented mothers, it seems that this effect is more pronounced in younger children compared to older children using the Bayley scale. However, we observed a high score of the sound response time in children from 60 months, open in this age the children are keen senses.

The use of developmental scales requires caution, since they depend on the evaluator’s observation (36). Despite this, the use of these scales seems to have good results for those living in areas with mild to moderate iodine deficiency. However other factors that may interfere in test results are family income, mother’s education, inadequate urinary iodine concentration (UIC) of the mother, and the presence of siblings, since they directly influence the family stimulus that the child receives (7,11,30,36).

The lack of similarity between initial time, duration, dosage of supplementation, and the time of application of neurocognitive development tests were limiting factors. In addition, three of the seven studies did not assess behavioural development.

The authors observed that supplementation during lactation brings interesting results, which may be the starting point for future research. In areas with mild to moderate iodine deficiency, changes are more likely to develop in children’s psychomotor, behavioural, and mental capabilities. The authors questioned whether the duration of supplementation may have a greater influence than the dose administered, since we did not find any studies with a longer time of supplementation with a lower dose of iodine content, nor did we obtain further assessments of lactation.

The best neurodevelopmental can be good in children with mother living in iodine adequate areas. However, in these results, the mothers in the control group had below adequate UIC, showing iodine deficiency for maternal group in region, which can affect the outcomes in their offspring. Additionally, according to Mao and cols. (2018), the supplementation of pregnant women living in areas of mild iodine deficiency did not have any effect on their children’s neurocognitive development (35).

Improving some factors, such as the start and end times of supplementation, iodine sufficiency of the mothers and the iodine deficiency in the areas where the mothers live, as well as the age of the children and the type of scale used in the tests, can contribute to better results. Therefore, iodine supplementation, if well implemented, can reduce risks to the population and, consequently, reduce public health expenditure.

Final remarks: In general, in this study we did not find an association between iodine supplementation in pregnant women and the neurodevelopment of their children in mild to
moderate iodine deficiency areas. Despite this, supplementation in pregnancy and lactation can be improve poor psychomotor development in children. However, in older children, it seems to have a greater effect on the sound response time. Supplementation in pregnant women also improved urinary iodine concentration of the mother and her children, as well as leading to a high PDI score in young children. Thus, it is necessary to perform further studies using the Bayley scale or another scale alongside the Children’s Communication Checklist-Short (CCC-S) or CCC-2 to assess the effect of iodine supplementation in pregnant women in iodine deficiency areas on the neurodevelopment of children before, during and after pregnancy.

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**Supplement Appendix 1**

The full list of search terms used in the literature search

In March 1st to April first week of 2020 The PubMed, LILACS and Scopus databases were searched for relevant articles. For PubMed (01 RCT and 02 cohort article), LILACS (01 cohort articles) and Scopus database (03 RCT and 01 cohort articles) the following search terms were used; “iodine AND supplementation AND child AND development AND cognition”.

For PubMed (03 articles), the following search terms were used: (iodine[MeSH Terms] OR “iodine”[All Fields] OR “iodides”[MeSH Terms] OR “iodides”[All Fields]) AND Supplementation[All Fields]) AND (“child”[MeSH Terms] OR “child”[All Fields]) AND (“growth and development”[Subheading] OR “growth”[All Fields] AND “development”[All Fields] OR “growth and development”[All Fields] OR “development”[All Fields]) AND (“Cogn Int Conf Adv Cogn Technol Appl”[Journal] OR “cognitive”[All Fields])

For LILACS (01 article), the following search terms were used: “iodine AND supplementation AND child AND development AND cognition”.

For Scopus database (04 articles), the following search terms were used: “iodine AND supplementation AND child AND development AND cognition”

Total: 08 articles included
LILACS: 01.
Scopus: 03.
PubMed: 04.

**Supplemental Table 1. Excluded studies and reasons for exclusion**

| Reference                                                                 | Reason for exclusion |
|---------------------------------------------------------------------------|----------------------|
| A review of the iodine status of UK pregnant women and its implications for the offspring | Is revision          |
| Assessing infant cognitive development after prenatal iodine supplementation | Is revision          |
| Benefit-Cost Analysis in Disease Control Priorities, Third Edition.       | Not iodine           |
| Can multi-micronutrient food fortification improve the micronutrient status, growth, health, and cognition of schoolchildren? A systematic review | Is revision          |
| Consequences of iodine deficiency and excess in pregnant women: an overview of current knowns and unknowns | Not iodine           |
| Dietary micronutrients are associated with higher cognitive function gains among primary school children in rural Kenya | Not iodine           |
| Does prenatal micronutrient supplementation improve children’s mental development? A systematic review | Is revision          |
| Driving Policy Change to Improve Micronutrient Status in Women of Reproductive Age and Children in Southeast Asia: The SMILING Project. | Is revision          |
| Effect of iron-, iodine-, and β-carotene-fortified biscuits on the micronutrient status of primary school children: A randomized controlled trial | Not pregnant         |
| Effect of micronutrient supplement on health and nutritional status of schoolchildren: Study design | Not pregnant         |
| Effects of iodine supplementation during pregnancy on child growth and development at school age | Supplementation in child |
| Effects of maternal iodine nutrition and thyroid status on cognitive development in offspring: A pilot study | Not supplementation |
| Effects of nutrients (in food) on the structure and function of the nervous system: Update on dietary requirements for brain. Part 1: Micronutrients | Not iodine           |
| Effects of nutritional interventions during pregnancy on infant and child cognitive outcomes: A systematic review and meta-analysis | Is revision          |
| Feeding the brain – The effects of micronutrient interventions on cognitive performance among school-aged children: A systematic review of randomized controlled trials | Is revision          |
| Food ingredients and cognitive performance | Not iodine           |
| Growth, development and differentiation: A functional food science approach | Not iodine           |
| Hypothyroxinemia and pregnancy | Not child neurodevelopment |
| Impact of iodine supplementation in mild-to-moderate iodine deficiency: Systematic review and meta-analysis | Is revision          |
| Iodine as essential nutrient during the first 1000 days of life | Not pregnant         |
| Iodine deficiency and iodine prophylaxis in pregnancy | Is revision          |
| Reference                                                                 | Reason for exclusion |
|--------------------------------------------------------------------------|----------------------|
| Iodine deficiency in pregnancy and the effects of maternal iodine supplementation on the offspring: a review, | Is revision          |
| Iodine deficiency in pregnancy, infancy and childhood and its consequences for brain development, | Is revision          |
| Iodine fortification of foods and condiments, other than salt, for preventing iodine deficiency disorders. | Not supplementation |
| Iodine intake from supplements and diet during pregnancy and child cognitive and motor development: The INMA Mother and Child Cohort Study. | Not intervention    |
| Iodine Nutrition During Pregnancy: Past, Present, and Future. | Is revision          |
| Iodine nutrition in pregnancy and lactation. | Is revision          |
| Iodine plus n-3 fatty acid supplementation augments rescue of postnatal neuronal abnormalities in iodine-deficient rat cerebellum, | Not human            |
| Iodine supplementation improves cognition in iodine-deficient schoolchildren in Albania: A randomized, controlled, double-blind study | Supplementation in child |
| Iodine supplementation improves cognition in mildly iodine-deficient children | Supplementation in child |
| Iodine supplementation in pregnancy and its effect on child cognition | Not child neurodevelopment |
| Iodine: it's important in patients that require parenteral nutrition. | Not supplementation |
| Iron deficiency and cognitive functions | Not iodine          |
| Malnutrition, brain development, learning, and behavior, | Not iodine          |
| Maternal iodine status is associated with offspring language skills in infancy and toddlerhood. | Not iodine          |
| Micronutrient adequacy and morbidity: Paucity of information in children with cerebral palsy. | Not iodine          |
| Micronutrient interventions on cognitive performance of children aged 5-15 years in developing countries. | Is revision          |
| Micronutrient supply and health outcomes in children. | Not iodine          |
| Micronutrients in pregnancy in low- and middle-income countries. | Not iodine          |
| Mild iodine deficiency in pregnancy in Europe and its consequences for cognitive and psychomotor development of children: A review, | Is revision          |
| Multiple micronutrient supplementation for improving cognitive performance in children: Systematic review of randomized controlled trials, | Is revision          |
| Neurocognitive outcomes of children secondary to mild iodine deficiency in pregnant women, | Not child neurodevelopment |
| Nutrient supplementation and neurodevelopment timing is the key, | Not iodine          |
| Nutrition and brain development in early life, | Not iodine          |
| Nutrition and development: Other micronutrients’ effect on growth and cognition, | Not iodine          |
| Nutrition and neurodevelopment in children: Focus on NUTRIMENTHE project, | Not iodine          |
| Nutritional deficiencies and later behavioral development, | Not supplementation |
| Overall child development: Beyond pharmacological iodine supplementation | Is revision          |
| Prevention and control of iron deficiency anemia amongst young children, | Not iodine          |
| Promoting early child development with interventions in health and nutrition: A systematic review | Is revision          |
| Role of iodine-containing multivitamins during pregnancy for children and brain function: protocol of an ongoing Randomized controlled trial: the SWIDDICH study, | Not child neurodevelopment |
| Suggested use of sensitive measures of memory to detect functional effects of maternal iodine supplementation on hippocampal development, | Not in human          |
| Summary of the public affairs committee symposium at the teratology society 2011 annual meeting: The thyroid and iodine: Impacts on pregnancy and child health | Not article          |
| Systemic endocrinopathies (thyroid conditions and diabetes): impact on postnatal life of the offspring. | Not supplementation |
| Teratology public affairs committee position paper: Iodine deficiency in pregnancy | Not supplementation |
| The adverse effects of mild-to-moderate iodine deficiency during pregnancy and childhood: A review, | Is revision          |
| The Assessment of Cognitive Performance in Children: Considerations for Detecting Nutritional Influences, | Not iodine          |
| The Effect of Intermittent Antenatal Iron Supplementation on Maternal and Infant Outcomes in Rural Viet Nam: A Cluster Randomized Trial | Not iodine          |
| The effect of iodine supplementation in pregnancy on early childhood neurodevelopment and clinical outcomes: Results of an aborted randomized placebo-controlled trial, | Not child neurodevelopment |
| The effects of iodine deficiency in pregnancy and infancy, | Not supplementation |
| The importance of adequate iodine during pregnancy and infancy, | Not iodine          |
| The influence of dietary status on the cognitive performance of children, | Not iodine          |
### Supplemental Table 2. Description of the interventions applied in the evaluated studies

| Author/ Year | Dosage | Supplementation interval | Form of supplementation |
|--------------|--------|--------------------------|-------------------------|
| Velasco et al., 2009<sup>24</sup> | 300 µg/day of iodine | ≤13<sup>th</sup> week of pregnancy to lactation | Potassium iodide (KI) |
| Murcia et al., 2011<sup>27</sup> | <100 µg/day, 100–149 µg/day, ≥150 µg/day | ≤13<sup>th</sup> week of pregnancy to delivery | Different supplementary sources of iodine |
| Santiago et al., 2013<sup>26</sup> | 200 µg/day, 300 µg/day | ≤10<sup>th</sup> week of pregnancy to delivery | KI |
| Rebagliato et al., 2013<sup>29</sup> | <100 µg/day of KI, 100–149 µg/day, ≥150 µg/day | ≤13<sup>th</sup> week of pregnancy to delivery | KI or vitamin/mineral preparations containing iodine |
| Zhou et al., 2015<sup>31</sup> | 150 µg/day | ≤20<sup>th</sup> week of pregnancy to delivery | KI |
| Gowachirapant et al., 2017<sup>30</sup> | 200 µg/day | ≤14<sup>th</sup> week of pregnancy to delivery | KI |
| Markhus et al., 2018<sup>25</sup> | 150 – 200 µg/day | ≤26<sup>th</sup> week of pregnancy to delivery | Different supplementary sources of iodine |
| Abel et al., 2019<sup>28</sup> | NA | Week 0-26 before pregnancy GW: 0–12 GW: 12–22 | Different supplementary sources of iodine |

KI- Potassium iodide; GW: Gestational Week; NA- Not available.
### Supplemental Table 3. Effects of iodine supplementation in pregnancy on neurocognitive development on offspring

| Trial          | Iodine Status of region | Mental development (MDI) | Psychomotor development (PDI) | Behaviour development (BDI) | Sound response time (T) | Verbal IQ (WPPSI – III) | IQ performance (WPPSI – III) | IQ reasoning (WPPSI – III) |
|---------------|------------------------|--------------------------|-------------------------------|-----------------------------|-------------------------|-------------------------|-----------------------------|-----------------------------|
| Velasco et al., 2009 (24) | Maternal MUIC during pregnancy: MUIC 263.0 ± 120.9 µg/L iodine (n=133) > control 87.6 ± 62.1 µg/L (n=31). | Infant: NA | Maternal intake of 300 µg/day of iodine in supplements compared with control group (n=19) associated with a 6.1±0.9 point high in PDI with control. High PDI in child was associated with lower FT4 in third trimester of pregnancy in mother in supplemented group (r=0.50; P <0.001). | Mother intake 300 µg/day of iodine in supplements compared with control group was associated with a 6.1±0.9 point high in PDI with control. High PDI in child was associated with lower FT4 in third trimester of pregnancy in mother in supplemented group (r=0.50; P <0.001). | Infant: NA | Maternal intake of 300 µg/day of iodine in supplements compared with control group (n=19) associated with a 6.1±0.9 point high in PDI with control. | Infant: NA | Maternal intake of 300 µg/day of iodine in supplements compared with control group (n=19) associated with a 6.1±0.9 point high in PDI with control. |
| Murcia et al., 2011 (27) | Maternal MUIC during pregnancy: NA. | Infant: NA | Maternal intake of 300 µg/day of iodine in supplements compared with control group (n=19) associated with a 6.1±0.9 point high in PDI with control. | Maternal intake of 300 µg/day of iodine in supplements compared with control group was associated with a 6.1±0.9 point high in PDI with control. High PDI in child was associated with lower FT4 in third trimester of pregnancy in mother in supplemented group (r=0.50; P <0.001). | Maternal intake of 300 µg/day of iodine in supplements compared with control group was associated with a 6.1±0.9 point high in PDI with control. High PDI in child was associated with lower FT4 in third trimester of pregnancy in mother in supplemented group (r=0.50; P <0.001). | Infant: NA | Maternal intake of 300 µg/day of iodine in supplements compared with control group (n=19) associated with a 6.1±0.9 point high in PDI with control. | Infant: NA | Maternal intake of 300 µg/day of iodine in supplements compared with control group (n=19) associated with a 6.1±0.9 point high in PDI with control. |
| Trial                          | Iodine status of region | Mental development (MDI) | Psychomotor development (PDI) | Behaviour development (BDI) | Sound response time (T) | Verbal IQ (WPPSI – III) | IQ performance (WPPSI – III) | IQ reasoning (WPPSI – III) |
|-------------------------------|-------------------------|--------------------------|-------------------------------|-----------------------------|-------------------------|--------------------------|-----------------------------|----------------------------|
| Santiago et al., 2013 (26)   | Maternal MUIC during pregnancy: NA | Maternal supplementation with 200 or 300 μg/day was related with lower PDI than the iodized salt group (NA). The results showed that the age at which this psychometric test was performed correlated significantly with a scales MDS ($r = 0.93, P < 0.001$) and the PDS ($r = 0.90, P < 0.001$), but not with indices (MDI and DPI). The showing a age to be important factor of measured its testes. | NA | NA | NA | NA | NA |
| Rebagliato et al., 2013 (29) | Maternal MUIC during pregnancy: | A negative association of iodine supplementation with low development. | NA | NA | NA | NA | NA |

Objective of this study was assessment iodine intake and their consequences in health in area with iodine deficiency.

No difference with groups, site of study and user of iodized salt or supplement. But consumption during pregnancy of 150 μg/day or more of iodine was related to a decrease in Psychomotor development score, although only significantly so in Asturias less than 85 (OR = 1.7, 95% CI: 1.1, 2.6).
## Iodine effect on neurocognitive development

| Trial | Iodine Status of region | Mental development (MDI) | Psychomotor development (PDI) | Behaviour development (BDI) | Sound response time (T.) | Verbal IQ (WPPSI – III) | IQ performance (WPPSI – III) | IQ reasoning (WPPSI – III) |
|-------|-------------------------|--------------------------|-------------------------------|-----------------------------|-------------------------|--------------------------|-----------------------------|-----------------------------|
| Zhou et al., 2015 (31) | Maternal MUIC during pregnancy: 3rd trimester: 200 µg/L in supplemented group > (n=27), with 150 µg/L in control. Iodine in breast milk: 6 weeks after birth was 1.1 (0.8–1.5) µg/100ml in both groups. 150 µg/day of KI (n=27) for supplemented group, with without iodine supplements in control (n=30). Infant MUIC: NA. | Infant: NA | Infant: NA | Infant: NA | NA | NA | NA | NA |
| Gowachirapan et al., 2017 (30) | Maternal MUIC during pregnancy: NA. 200 µg/day of KI group (n=303) Placebo (n=312). Infant MUIC: NA. In INNA Study, the authors found in a sample of women from the Valencia region, an iodine-sufficient areas, that maternal consumption of multivitamins containing iodine was related to lower psychomotor achievement of their infants at 1 year of age. | Infant: no diff iodine vs control (n=unclear, means not presented). | Infant: All the scores in the primary outcomes were higher in mean in the placebo than in the intervention group (not significant). | Infant: no diff iodine vs control (n=unclear, means not presented). | Infant: A negative association of iodine supplementation with expressive language (BSID) at 1 year in the first one | Infant: NA | Infant: NA | Infant: no congenital goitre was found in either group |
| Markhus, M. W., 2018 (25) | Maternal MUIC during pregnancy 1st trimester: Median 92 (56.200) µg/L in supplemented group (n=658) > and 77 (50.130) µg/L in control (n=155). In total: 79% of women had a MUIC < 150 µg/L and 28% < 50 µg/L. 175 µg/day of KI (n=155) for supplemented group, with without iodine supplements in control (n=658). Infant MUIC: NA. | Infant: NA | Supplementation with 150 µg/day was associated with poorer gross motor skills, standardized beta = −0.18 (95% CI = −0.33, −0.03, p = 0.02). | Infant: NA | NA | NA | NA | NA |
| Trial | Iodine Status of region | Mental development (MDI) | Psychomotor development (PDI) | Behaviour development (BDI) | Sound response time (T) | Verbal IQ (WPPSI – III) | IQ performance (WPPSI – III) | IQ reasoning (WPPSI – III) |
|-------|-------------------------|--------------------------|-------------------------------|----------------------------|-------------------------|--------------------------|-----------------------------|-----------------------------|
| Abel M.H. et al., 2018 (28) | Maternal MUIC during pregnancy 1st and 2nd trimester: Median 83 (43, 138) µg/L in supplemented group (n=14,665) > and 59 (32, 101) µg/L in control (n=24,806). 175 µg/day of KI (n=14,665) for supplemented group, with 175 µg/day KI given with iodine supplements in control (n=24,806). Infant MUIC: NA | The results are consistent in demonstrating no beneficial effects of iodine supplement use in pregnancy. Not have any associations between maternal use of iodine-containing supplements and child outcomes. But in sample, 6.9% of the 8-year old were granted special education at school. According to the mother, 28% had suboptimal or low score on the mandatory mapping test in school in reading, and 18% had suboptimal or low score in mathematics. | NA | NA | But in control: Maternal iodine intake was associated with child language skills at age 3 years. Children with mild to moderate language delay at 3 years (3.1%) scored on average 1.2 SD higher on the language score (CCC-S) at 8 years (95% CI 1.1, 1.3), and those with severe language delay at 3 years (0.7%) scored 2.8 SD higher (95% CI 2.3, 3.2). Higher scores at 8 years indicated poorer language skills. | NA | NA |

NA, Not available; MUIC, median urinary iodine concentration; n, number; KI, iodide potassium; No diff, no difference; UI, urinary iodine; CCC-S: Children's Communication Checklist-Short.