REVIEW

Effects of Iodized Salt and Iodine Supplements on Prenatal and Postnatal Growth: A Systematic Review

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ABSTRACT

Hypothyroidism due to iodine deficiency can impair physical development, most visibly in the marked stunting of myxedematous cretinism caused by severe in utero iodine deficiency. Whether iodine repletion improves growth in noncretinous children is uncertain. Therefore, the aim of our systematic review was to assess the effects of iodine fortification or supplementation on prenatal and postnatal growth outcomes in noncretinous children. Following Cochrane methods and PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) reporting guidelines, we searched 10 databases including 2 Chinese databases (latest search February 2017). We included randomized and nonrandomized controlled trials (RCTs; non-RCTs), controlled before-after (CBA) studies, and interrupted time-series studies in pregnant women and children (≤18 y), which compared the effects of iodine (any form, dose, regimen) to placebo, noniodized salt, or no intervention on prenatal and postnatal growth outcomes. We calculated mean differences with 95% CIs, performed random-effects meta-analyses, and assessed the quality of evidence with the use of GRADE (Grading of Recommendations Assessment, Development and Evaluation). We included 18 studies (13 RCTs, 4 non-RCTs, 1 CBA) ($n = 5729$). Iodine supplementation of severely iodine-deficient pregnant women increased mean birthweight [mean difference (MD): 200 g; 95% CI: 183, 217 g; $n = 635$; 2 non-RCTs] compared to controls, but the quality of this evidence was assessed as very low. Iodine repletion across the other groups showed no effects on primary growth outcomes (quality of evidence mostly low and very low). Meta-analyses showed a positive effect in moderate-to-mildly iodine-deficient schoolchildren on insulin-like growth factor-1 (MD: 38.48 ng/mL; 95% CI: 6.19, 70.76 ng/mL; $n = 498$; 2 RCTs, low-quality evidence) and insulin-like growth factor binding protein-3 (MD: 0.46 μg/mL; 95% CI: 0.25, 0.66 μg/mL; $n = 498$; 2 RCTs, low-quality evidence). In conclusion, we identified few well-designed trials examining the effects of iodine repletion on growth. We are uncertain whether prenatal iodine repletion increases infant growth. Postnatal iodine repletion may improve growth factors but has no clear effects on somatic growth. Our systematic review was registered with PROSPERO as CRD42014012940. *Adv Nutr* 2018;9:219–237.

Keywords: iodine, growth, stunting, pregnant, infant, child, adolescent, iodine supplementation, iodized salt, insulin-like growth factor

Introduction

Iodized salt is an effective mass-fortification strategy that provides adequate iodine intakes for all population groups. Following the scale-up of salt iodization programs over the past 30 y, iodine intakes worldwide have substantially improved. However, iodine deficiency (ID) remains a public health problem in several countries (1) and certain population groups are still at risk of low intakes (2–5). Dietary iodine requirements increase during pregnancy (6) and in 2017, 39 countries reported inadequate intakes in pregnant women (1). Vulnerability for ID is high in the first 1000-d period (5). Where salt iodization programs are weak, iodine supplementation is recommended to vulnerable groups to ensure an adequate intake during these critical periods (3, 7). Supplementation may be by daily iodine tablets, e.g. within prenatal multivitamin supplements, or micronutrient powders containing iodine administered to at-risk infants, or iodized oil in cases of moderate to severe ID (3).

Delayed physical development is one of several clinical manifestations resulting from a deficiency in iodine during the first 1000-d period (4, 8–10), most visible in the typical stunted growth associated with myxedematous cretinism following severe ID during pregnancy (1). With a reduction in stunting being the first of the six 2025 global nutrition targets adopted by the World Health Assembly (11), this potential consequence of ID finds itself firmly on the global health agenda (12, 13). Risk of stunting due to ID starts at conception, due to functional changes likely mediated via abnormal thyroid hormone (TH) concentrations. Iodine is an essential component of TH and inadequate iodine intakes may result in low serum TH concentrations. TH are responsible for many central functions of the developmental cycle including growth and development of the skeleton and peripheral tissues. They are also inextricably linked to the actions of growth hormone (GH) and the insulin-like growth factors (IGFs), via both the GH-IGF axis and the effects of TH on the expression and action of GH itself (14–20). Despite plausible mechanistic pathways, the relation between ID and growth has been neglected in the scientific literature, confirmed by our scoping review to identify existing systematic reviews on iodine for prenatal and postnatal growth (21). We did not identify any systematic reviews that investigated as primary outcome the effects of iodine fortification or supplementation on growth and growth-related outcomes in the relevant population groups (i.e. women of childbearing age, pregnant and lactating women, and children of all ages). The objective of this systematic review was therefore to assess the effects of iodized salt or iodine supplements compared to placebo or no intervention on prenatal and postnatal growth of the fetus, infant, and child to 18 y of age.

Methods

Our detailed protocol has been published (22), therefore we briefly report our methods. Minor deviations from the protocol are presented in the discussion. We used Cochrane methodology (23, 24) and this report follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (25) guidelines.

Eligibility criteria

We included randomized controlled trials (RCTs), non-RCTs, controlled before-after (CBA) studies, and interrupted time series (ITS) and ITS with repeated measures studies, which assessed the effect of iodine fortification or supplementation (iodized salt, daily iodine supplements at any dose, or single or repeated oral or intravenous administration of iodized oil at any dose), compared with placebo, non-iodized salt, or no intervention, on prenatal and postnatal growth. To assess the effect of iodine fortification or supplementation on prenatal growth outcomes, eligible study populations included pregnant women or women of reproductive age, and their infants, where the women received the fortification, supplementation, or placebo. For postnatal growth outcomes, eligible participants were lactating women and infants, and children ≤18 y of age, where the lactating women, infants, or children themselves received the fortification, supplementation, or placebo. Studies examining the link between growth and populations affected by congenital hypothyroidism and goiter were excluded, as were studies describing non–iodine-related growth. Data from women who smoke were also excluded, due to confounding factors that may be introduced by the effects of cigarette smoke on thyroid function.

Our primary outcomes were prenatal somatic growth measured at birth, e.g. birthweight (g), birth length (cm), and head circumference (cm); and postnatal somatic growth measured during infancy and childhood, e.g. weight-for-age *z* score (WAZ), height-for-age *z* score (HAZ), length-for-age *z* score, weight-for-height *z* score, BMI (kg/m^2), and mid-upper arm circumference (cm). Secondary outcomes were pregnancy weight gain; surrogate outcomes of somatic growth [e.g. IGF-1 (ng/L); insulin-like growth factor binding protein (IGFBP)-3 (μg/L); GH]; postnatal bone maturation; and malnutrition disorders (e.g. kwashiorkor, marasmus), measured in infants, children, or adolescents.

WAZs, where reported for children >10 y of age, were not included in meta-analyses since WHO does not endorse the use of this indicator above this age (26). WAZ does not distinguish between height and body mass in an age period during which children experience the pubertal growth spurt, and results may therefore be misleading.

Search methods

With no restrictions on date, language, or publication status, we searched 10 electronic databases for published studies and the WHO International Clinical Trials Registry Platform for ongoing studies (latest search date 13 February 2017). For additional ongoing, unregistered, or unpublished studies, we contacted 11 internationally recognized iodine specialists. We also searched the reference lists of the systematic reviews included in our scoping review (21) and other existing systematic reviews identified during screening, and the Chinese literature within a repository of full-text studies yielded from

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Supplemental Methods, Supplemental Tables 1–7, and Supplemental Figures 1 and 2 are available from the "Supplementary data" link in the online posting of the article and from the same link in the online table of contents at https://academic.oup.com/advances/.
Address correspondence to JF (e-mail: jessica.farebrother@hest.ethz.ch).
Abbreviations used: CBA, controlled before-after study; EPOC, Effective Practice and Organisation of Care; GH, growth hormone; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HAZ, height-for-age *z* score; ID, iodine deficiency; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; ITS, interrupted time series study; MD, mean difference; mUIC, median urinary iodine concentration; ppm, parts per million; RCT, randomized controlled trial; TGR, total goiter rate; TH, thyroid hormone; UIC, urinary iodine concentration; WAZ, weight-for-age *z* score.

TABLE 1 Thresholds used to define iodine status of included study populations[1]

Iodine status/degree of deficiency	Sufficient	Mild	Moderate	Severe
mUIC for school-age children, μg/L	>100	50–99	20–49	<20
mUIC for pregnant women, μg/L	>150	75–149	30–74	<30
Total goiter rate, %	0–4.9	5.0–19.9	20.0–29.9	≥30

[1] Data taken from reference 7 and adapted for PW. To calculate the cutoffs for PW, we used the same classification stratification as for SAC, applied to the sufficient/insufficient cutoff of 150 μg/L for PW. Established SAC cutoffs were used for all other groups. mUIC, median urinary iodine concentration; PW, pregnant women; SAC, school-age children.

searches for a previous systematic review (27). All search details and the search strategy are provided in the **Supplemental Methods**.

Data collection and analysis

All search results were screened independently and in duplicate through the use of the Covidence online systematic review platform (28). Reasons for excluding full-texts were documented. Discrepancies were resolved through discussions within the author team. Using the Cochrane Risk of Bias domains (29) and the Cochrane Effective Practice and Organisation of Care (EPOC) Group Risk of Bias domains for RCTs, non-RCTs, CBA, and ITS studies (30), we assessed the risk of bias of included studies, independently and in duplicate. We were not able to assess risk of publication bias as per our protocol due to an insufficient number of studies per meta-analysis.

Data were extracted independently and in duplicate with the use of a standardized, piloted data extraction form developed by the authors. Non-English data were translated. For trials reporting data in more than 1 publication, we extracted relevant data from all publications as comprehensively as possible, and designated 1 publication as the key reference. Applicable data from non-smoking women contained in trials including smokers were extracted; authors were contacted where necessary to facilitate extraction. Data were exported into Review Manager 5.1 (Cochrane Collaboration) for data and statistical analyses (31). For measures of treatment effect for dichotomous outcomes we calculated the RR, and for continuous variables, the mean difference (MD) with 95% CI.

Where data were missing or unclear, we contacted study authors wherever possible. Where SEs or 95% CIs were reported for means, SDs were calculated as follows: SD = SEM × square root of sample size. Where missing data were not able to be obtained, we reported the results as presented in the published full text with an appropriate disclosure statement. Results reported in the single included cluster RCT were correctly adjusted for clustering (as confirmed by a biostatistician) and thus we extracted and presented the published results.

Where possible and appropriate, we performed meta-analyses using random-effects, as we anticipated heterogeneity between studies. Studies were assessed for clinical heterogeneity by examining variability in the study participant baseline characteristics, type of intervention, and outcome parameters. We assessed statistical heterogeneity using the chi-square test (significance level $P < 0.1$) and the I^2 statistic (22, 32). We stratified our analyses by participant age groups (life stage), namely pregnant women (offspring measured at birth and/or during infancy), infants (0–24 mo), preschool children (2–5 y), school-age children (6–12 y), and adolescents (13–18 y). We analyzed intervention effects across subgroups of baseline iodine status of the intervention group, namely "severe", "moderate to mild", or "sufficient", based on median urinary iodine concentration (mUIC) or total goiter rate (TGR) (**Table 1**). If urinary iodine concentration (UIC) was reported as μg/24 h or μmol/L we converted participant baseline UIC to μg/L. We used the following algorithm to assign studies to these subgroups: *1*) where mUIC of participants in the intervention group was measured and reported at study baseline, WHO cutoffs (Table 1) were applied; *2*) where mUIC of participants in the intervention group was not measured or reported at baseline but TGR in this group was measured and reported, TGR was used and WHO cutoffs were applied; *3*) where options 1 and 2 were not possible, but the mUIC or TGR from schoolchildren from the study population (i.e. the specific area from which the participants were taken) were available and within 2 y of the date given for sample collection, these data were used and WHO cutoffs applied; *4*) where options 1–3 were not possible, but data for the general population, e.g. TGR of the entire population at the study site, were reported, WHO cutoffs were applied; *5*) if none of the aforementioned data were specified, or if a discordance between UIC and TGR in the same study was revealed, descriptive reports taken from the study manuscript were used.

We had planned to conduct sensitivity analyses based on study design (RCT compared with non-RCT), iodine vehicle, and risk of bias of the included studies to assess the robustness of our results. However, in most cases sensitivity analyses were not feasible, because of the small number of studies in the meta-analysis and the large degree of uncertainty around key aspects of study methodology due to incomplete reporting.

Quality of evidence

We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) (33) approach to assess the quality of the included evidence. We reported our results and quality assessment for the most important outcomes in Summary of Findings tables.

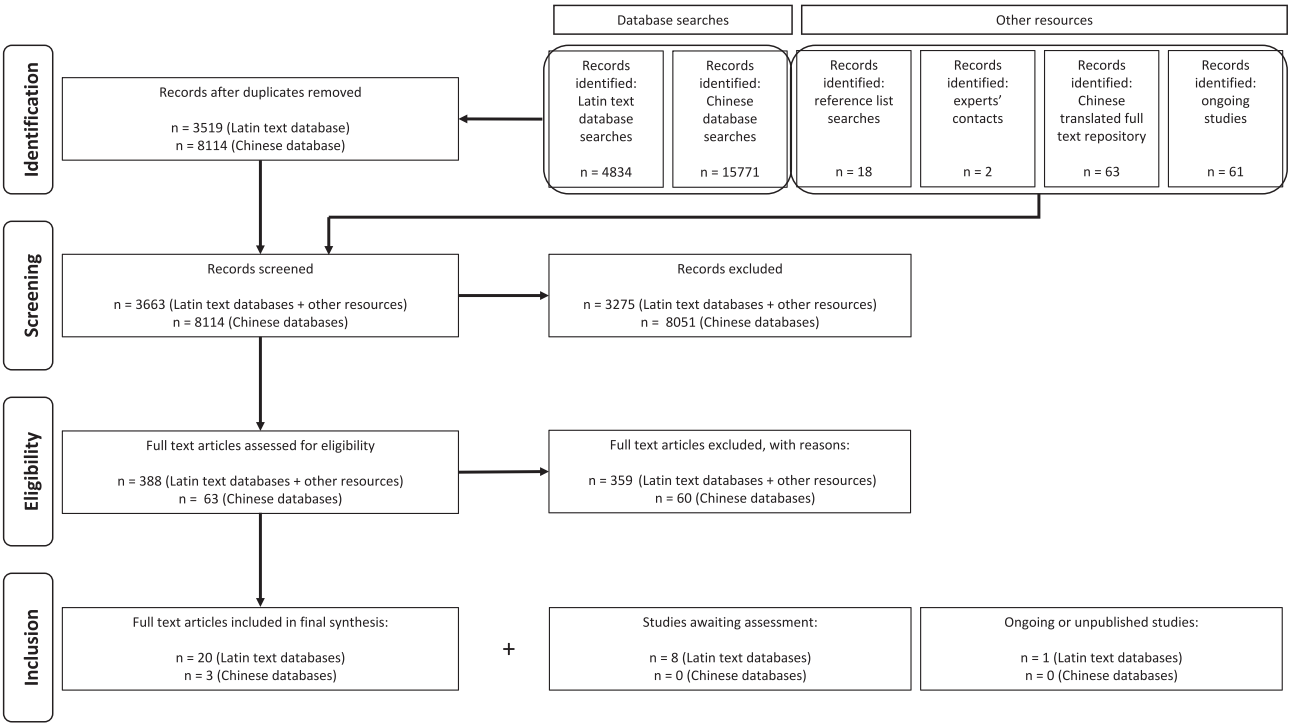


FIGURE 1 Flow chart illustrating the search results and study selection procedure.

Results

From an initial search yield of 20,749, we included 18 studies with 5729 participants, reported in 23 full-text articles published between 1969 and 2016 (**Figure 1**, **Table 2**). Further details including reasons for exclusion of potentially eligible full-text articles are provided in **Supplemental Table 1**. **Supplemental Table 2** details potentially eligible ongoing studies and studies awaiting assessment owing to insufficient information being provided in the published full text and receiving no reply after attempts to contact the relevant authors.

Prenatal growth outcomes measured at birth were reported in 6 studies and postnatal outcomes measured during infancy, childhood, and adolescence were reported in 12 studies (Table 2). There were no studies reporting on growth of offspring after fortification or supplementation in women of reproductive age. Owing to poor reporting practices in many of the included studies, the risk of bias was unclear in several domains, but particularly in the allocation concealment category. A high risk of attrition bias was identified in 8 studies (34, 35, 37, 39, 41–43, 45) classified as high risk. Risk of bias from selective reporting of outcomes was low in all but 1 study (42). Full details of risk of bias assessments are found in **Supplemental Figures 1 and 2** and **Supplemental Table 3**.

Primary outcomes

Prenatal somatic growth outcomes measured at birth

Interventions in pregnant women: iodized oil or iodine tablet compared with placebo or no intervention. These interventions include 2 non-RCTs in severely iodine-deficient pregnant women and 4 RCTs in moderate-to-mild iodine-deficient pregnant women. **Figure 2** shows the forest plots for birthweight, length, and head circumference at birth, respectively, subgrouped by baseline iodine status of the intervention group. **Table 3** provides the summary of findings for these prenatal growth outcomes.

Providing iodine supplementation (as oral or intramuscular iodized oil, or iodine tablet; see Table 2) to severely iodine-deficient pregnant women resulted in a 200-g greater birthweight on average compared with the control group (95% CI: 183, 217 g; $I^2 = 0\%$; $n = 635$; 2 non-RCTs; very low-quality evidence) (34, 35), but no difference in birthweight was observed in moderate-to-mild ID (MD: −14 g; 95% CI: −212, 185 g; $I^2 = 93\%$; $n = 783$; 4 RCTs; very low-quality evidence) (37–39, 41). In the pooled result across all 6 studies, iodine supplementation during pregnancy had no overall effect on birthweight (very low-quality evidence) (Figure 2A). We found no effect of iodine supplementation during pregnancy on infant birth length in severe ID (35), in moderate-to-mild ID (37–39), or in the overall pooled result of the 4 RCTs (very low-quality evidence) (Figure 2B). In 1 non-RCT in severely iodine-deficient pregnant women, iodine supplementation increased head circumference at birth by 0.4 cm (95% CI: 0.1, 0.7 cm; $n = 568$; 1 non-RCT; very low-quality evidence) (35), but no effect was seen in moderate-to-mildly iodine-deficient pregnant women (MD: 0.3 cm; 95% CI: −0.7, 1.2 cm; $I^2 = 79\%$; $n = 612$; 2 RCTs; very low-quality evidence) (37, 38), nor in the pooled analysis of the 3 studies (very low-quality evidence) (Figure 2C). Additional details

TABLE 2 Characteristics of included studies[1]

Authors, year (ref), country, study design	Primary outcomes of study	Baseline iodine status of sample or study group	Study population	Participants, *n*	Form of iodine intervention vs. control	Iodine exposure (dose, duration)	Duration of follow-up, d	Relevant endpoint data reported
Prenatal somatic growth outcomes measured at birth								
Interventions in pregnant women: iodized oil or iodine tablet vs. placebo or no intervention								
Severe ID								
Anees et al., 2015 (34), Pakistan, non-RCT	Birth outcome; thyroid function	Severe deficiency Intervention: 100% TGR Control: 83% TGR	PW and their infants at birth	Total: 304 Intervention: 150 Control: 154	Iodized oil vs. no intervention	400 mg, once	No follow-up past birth	Birthweight
Pretell et al., 1972 (35) [including Kevany et al., 1969 (36)], Peru, non-RCT	Goiter prophylaxis	Severe deficiency Population TGR >30%	PW and their infants, to age 5 y	Total: 456 Intervention: 254 Control: 202	Iodized oil (IM injection) vs. no intervention	475 mg/mL, 2-mL dose, except in the case of women with nodular goiter (0.2 mL), once	Newborn infants followed until age 5 y	Birthweight, length, head circumference; placental weight
Moderate to mild ID								
Gowachirapant et al., 2017 (37),[2] India and Thailand, RCT	Infant cognitive and early motor development at ages 1 and 2 y; verbal and performance intelligence, executive functions, and internalizing/externalizing difficulties at age 5 y	Mild deficiency Intervention: 135 μg/L Control: 125 μg/L	PW and their infants, to age 2 y	Total: 615 Intervention: 303 Control: 312	Iodine tablet vs. placebo tablet	200 μg/d until delivery, average gestational week at trial entry: Intervention: 10.8 ($\pm$2.7), Control: 10.7 ($\pm$2.8)	Infants followed until age 2 y	Birthweight, length, head circumference; weight, length, head circumference age 12 and 24 mo
Zhou et al., 2015 (38), Australia, RCT	Child neurodevelopment	Mild deficiency Baseline iodine status of intervention and controls <150 μg/L but >100 μg/L	PW and their infants, to age 18 mo	Total: 46 Intervention: 21 Control: 25 (trial was stopped early)	Iodine tablet vs. placebo tablet	150 μg/d from randomization (<20 wk of gestation) until delivery	548 (18 mo)	Birthweight, length, head circumference
Hiéronimus et al., 2013 (39) [including Brucker-Davis et al., 2015 (40)], France, RCT	Comparison of maternal thyroglobulin concentrations at delivery between intervention and control	Mild deficiency Intervention: 111 μg/L Control: 103 μg/L	PW and their infants at birth	Total: 67 Intervention: 25 Control: 42	Iodine in prenatal multivitamins vs. multivitamins without iodine	150 μg/d, from enrollment (before 12 wk of gestation) until 3 mo postpartum	Infants followed until age 2 y	Birthweight, length

(*Continued*)

TABLE 2 (*Continued*)

Authors, year (ref), country, study design	Primary outcomes of study	Baseline iodine status of sample or study group	Study population	Participants, *n*	Form of iodine intervention vs. control	Iodine exposure (dose, duration)	Duration of follow-up, d	Relevant endpoint data reported
Zhuang and Wang, 1998 (41),[3] China, RCT	Thyroid function; infant birthweight	Moderate deficiency Intervention: moderate deficiency: UIC <100 μg/L; generated median: 69 μg/L Control: sufficient: UIC >100 μg/L; generated median 191 μg/L	PW and their infants at birth	Total: 80 Intervention: 39 Control: 41	Iodine tablet vs. no intervention	177.9 μg/d, 30 d	30	Birthweight
Postnatal somatic growth outcomes measured during infancy, childhood, and adolescence								
Interventions in pregnant women: iodized oil vs. placebo or no intervention								
Severe ID								
Pharoah and Connolly, 1991 (42), Papua New Guinea, non-RCT	Child development	Severe deficiency (descriptive data from manuscript: "Endemic cretinism… widely prevalent in the highlands of New Guinea [study site] in association with severe iodine deficiency.")	PW and their offspring at age 15 y	Total: 29 Intervention: 13 Control: 16	Iodized oil (IM injection) vs. placebo injection (physiologic saline)	475 mg/mL, 4 mL (= 1900 mg), once during pregnancy	15 y	Height (age 15 y)
Ramirez et al., 1969 (43) [including Ramirez et al., 1972 (44) and Kevany et al., 1969 (36)], Ecuador, non-RCT	Cretinism prophylaxis	Severe deficiency (descriptive data from manuscript: "Chronic iodine deficiency is severe in both [intervention and control] villages.")	PW and their infants, to age 5 y	Total: 267 Intervention: 90 Control: 177	Iodized oil (IM injection) vs. no intervention	475 mg/mL, 2-mL dose, except in the case of women with nodular goiter (0.2 mL), once	Newborn infants followed until age 5 y	Length, weight, and head circumference reported descriptively from ages 1.25–60 mo
Moderate to mild ID								
Gowachirapant et al., 2017 (37),[2] India and Thailand, RCT	Infant cognitive and early motor development at ages 1 and 2 y; verbal and performance intelligence, executive functions, and internalizing/externalizing difficulties at age 5 y	Mild deficiency Intervention: 135 μg/L Control: 125 μg/L	PW and their infants, to age 2 y	Total: 615 Intervention: 303 Control: 312	Iodine tablet vs. placebo tablet	200 μg/d until delivery; average gestational week at trial entry: Intervention: 10.8 (±2.7), Control: 10.7 (±2.8)	Infants followed until age 2 y	Birthweight, length, head circumference; weight, length, head circumference age 12 and 24 mo

(*Continued*)

TABLE 2 (*Continued*)

Authors, year (ref), country, study design	Primary outcomes of study	Baseline iodine status of sample or study group	Study population	Participants, *n*	Form of iodine intervention vs. control	Iodine exposure (dose, duration)	Duration of follow-up, d	Relevant endpoint data reported
Huang et al., 1995 (45) [including Zhu et al. 1995 (46)], China, RCT	Physical and cognitive development of infants	Moderate deficiency Intervention: 64 μg/L Control: 91 μg/L	PW and their infants at 6 mo	Total: 76 Intervention: 39 Control: 37	Iodized oil vs. no intervention	400 mg, once	180	Weight, height, head circumference (at age 6 mo; standardized mean difference used as mean age of infants was different between groups)
Infants (0–24 mo) High-iodine formula vs. low-iodine formula								
Rogahn et al., 2000 (47), England, RCT	Thyroid status	Not reported	Premature infants <33 wk of gestation (median age 30 wk in intervention and control groups)	Total: 121 Intervention: 61 Control: 60	High-iodine formula vs. standard formula (lower iodine content)	40–50 μg/kg daily, 70 d	Median 70 d. Final follow-up at 40–41 wk postconception; days of treatment depended upon exact age at enrollment	Weight, weight gain, head circumference, head circumference gain, lower leg length, lower leg length gain
Preschool children (2–5 y) Iodized salt vs. non-iodized salt								
Aboud et al., 2017 (48), Ethiopia, Cluster-RCT	Cognitive development	Severe deficiency Intervention: 14 μg/L Control: 10 μg/L	Preschool children 54–60 mo of age	Total: 1376 Intervention: 671 Control: 705	Iodized salt >15 ppm vs. noniodized salt	4 mo: July–October 2012	"Approximately 365 d intervention group received approximately 4 to 6 months more exposure to iodized salt than controls"	HAZ, WAZ
School-age children (6–12 y) Iodized oil vs. placebo or no intervention								
Severe ID								
Furnee et al., 2000 (49), Malawi, RCT	Efficacy of oral iodized oil	Severe deficiency Intervention: 19 μg/L Control: 24 μg/L	Ages 8–10 y	Total: 230 Intervention: 197 Control: 33	Iodized oil capsule vs. placebo oil capsule	490 mg, once	280	Height, weight, HAZ
Moderate to mild ID								
Zimmermann et al., 2007 (50) [including Zimmermann et al., 2007 (51)], South Africa, RCT	Safety and efficacy of iodine repletion	Mild deficiency Intervention: 70 μg/L Control: 78 μg/L	Ages 5–14 y	Total: 188 Intervention: 100 Control: 88	Iodized oil capsule vs. placebo oil capsule	191 mg, twice in 90-d period	180	Height, weight, HAZ, IGF-1, IGFBP-3

(*Continued*)

TABLE 2 (*Continued*)

Authors, year (ref), country, study design	Primary outcomes of study	Baseline iodine status of sample or study group	Study population	Participants, *n*	Form of iodine intervention vs. control	Iodine exposure (dose, duration)	Duration of follow-up, d	Relevant endpoint data reported
Zimmermann et al., 2006 (52) [including Zimmermann et al., 2007 (51)], Albania, RCT	Cognition	Moderate deficiency Intervention: 42 μg/L Control: 44 μg/L	Ages 10–12 y	Total: 303 Intervention: 157 Control: 146	Iodized oil capsule vs. placebo oil capsule	400 mg, once	168	Height, weight, HAZ, IGF-1, IGFBP-3
Huda et al., 2001 (53),[4] Bangladesh, RCT	Cognition	Moderate deficiency Intervention: 35 μg/L Control: 36 μg/L (TGR >30% in both groups: severe deficiency)	Age 10 y	Total: 305 Intervention: 156 Control: 149	Iodized oil capsule vs. placebo oil capsule	400 mg, once	112	Weight
Bautista et al., 1982 (54), Bolivia, RCT	Cognition, thyroid status, somatic growth	Moderate deficiency Intervention: 29 μg/L Control: 34 μg/L	Ages 5–12 y	Total: 189 Intervention: 95 Control: 94	Iodized oil capsule vs. placebo oil capsule	475 mg, once	154	Height, weight (change data)
Iodized salt, iodized water, and iodized condiment compared with placebo								
Pongpaew et al., 1998 (55), Thailand, CBA	Nutritional status (HAZ, WAZ, WHZ)	Mild deficiency to sufficient Intervention: 96, 123, 108 μg/L Control: 129 μg/L	Ages 6–12 y	Total: 263 Intervention: 200 (68, 75, 57) Control: 63	Salt, water, fish sauce vs. no intervention	Water: 200 μg/d Salt: 100–150 μg/d Fish sauce: 120–160 μg/d	365	Height, weight, HAZ
Adolescents (13–18 y)								
Iodized oil compared with placebo								
Eftekhari et al., 2006 (56), Iran, RCT	Thyroid status	Sufficient Intervention: 130 μg/L Control: 110 μg/L	Ages 14–18 y	Total: 47 Intervention: 25 Control: 22	Iodized oil capsule vs. placebo oil capsule	190 mg, once	96	Height, weight, BMI

[1] CBA, controlled before-after study; HAZ, height-for-age *z* score; ID, iodine deficiency; IGF, insulin-like growth factor; IGFBP, insulin-like growth factor binding protein; IM, intramuscular; mUIC, median urinary iodine concentration; ppm, parts per million; PW, pregnant women; RCT, randomized controlled trial; ref, reference; TGR, total goiter rate; UIC, urinary iodine concentration; WAZ, weight-for-age *z* score; WHZ, weight-for-height *z* score.

[2] The study by Gowachirapant et al. (37) reported outcomes at birth and, in addition, postnatal outcomes after supplementation in pregnant women. It is therefore listed under both prenatal and postnatal outcomes.

[3] This study did not specify a baseline mUIC; instead the authors chose to show the UIC distribution of the study population, from which an intervention (mUIC <100 μg/L) and a control (mUIC >100 μg/L) group were designated. In order to best classify this study, we used this distribution figure to generate random numbers based on the number of participants in each UIC echelle. We then took the median of the groups <100 μg/L, and >100 μg/L, as stated in the manuscript, repeated 10 times, and took the mean result for the final median and thus classification of iodine status, using the R statistics software (57).

[4] We believe that Huda et al. (53) have a typographic error in their manuscript; the UIC values may correctly read μmol/dL not per L. The authors state: "In this study, both groups would be classified as moderately iodine deficient by urinary iodine excretion." The TGR was >30%.

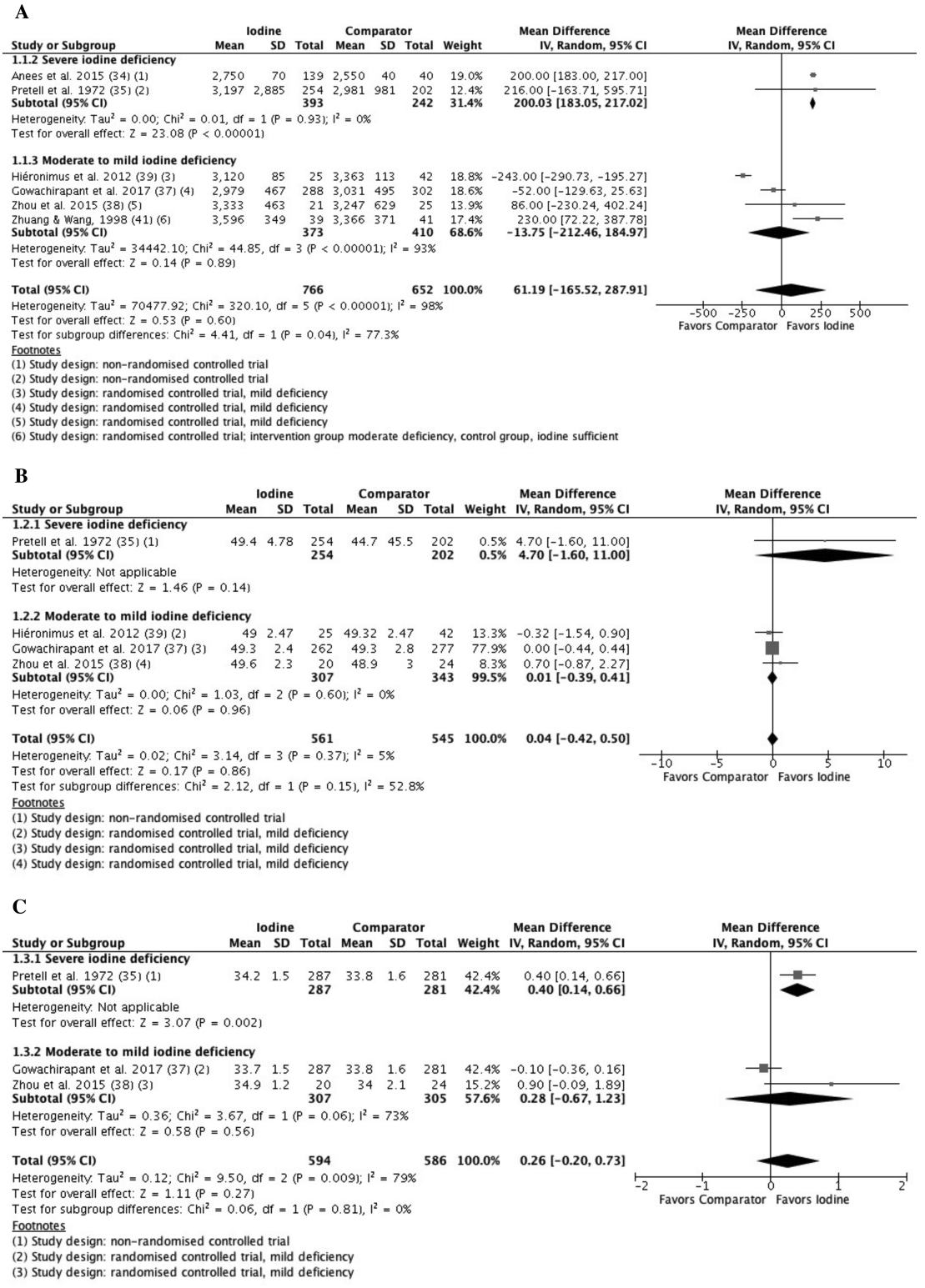


FIGURE 2 Forest plots of iodine supplementation during pregnancy compared with placebo or no intervention for the prenatal growth outcomes: (A) birthweight (g), (B) birth length (cm), and (C) head circumference at birth (cm). IV, inverse variance; Random, random effects model.

TABLE 3 Summary of findings for iodine supplementation during pregnancy compared with placebo or no intervention for the prenatal growth outcomes: birthweight, birth length, and head circumference at birth[1]

Outcome, *n* participants (studies)	Relative effect (95% CI)	Illustrative comparative effect		Quality of the evidence (GRADE)	What happens
		Without iodine supplement	Effect difference with iodine supplements		
Birthweight (g)—Severe ID, 635 participants (2 non-RCTs)	—	The mean birthweight in control groups was 2765 g	200-g higher birthweight on average (could be 183–217 g higher)	⊕◯◯◯ VERY LOW[2]	We are uncertain whether iodine supplementation of severely iodine-deficient pregnant women improves birthweight
Birthweight (g)—Moderate to mild ID, 783 participants (4 RCTs)	—	The mean birthweight in control groups was 3252 g	14-g lower birthweight on average (could be 212 g lower to 185 g higher)	⊕◯◯◯ VERY LOW[3,4]	We are uncertain whether iodine supplementation of moderate to mildly iodine-deficient pregnant women improves birthweight
Birthweight (g)—Pooled result, 1418 participants (4 RCTs, 2 non-RCTs)	—	The mean birthweight in control groups was 3163 g	61-g higher birthweight on average (could be 166 g lower to 288 g higher)	⊕◯◯◯ VERY LOW[5,6]	We are uncertain whether iodine supplementation of pregnant women improves birthweight
Birth length (cm)—Severe ID, 456 participants (1 non-RCT)	—	The mean birth length in control groups was 44.7 cm	4.7-cm higher birth length on average (could be 1.6 cm lower to 11.0 cm higher)	⊕◯◯◯ VERY LOW[7]	We are uncertain whether iodine supplementation of severely iodine-deficient pregnant women improves infant birth length
Birth length (cm)—Moderate to mild ID, 650 participants (3 RCTs)	—	The mean birth length in control groups was 49.2 cm	0.0-cm difference in birth length on average (could be 0.4 cm lower to 0.4 cm higher)	⊕⊕◯◯ LOW[8]	Iodine supplementation during pregnancy in moderate to mild ID settings may make little or no difference to infant birth length
Birth length (cm)—Pooled result, 1106 participants (1 non-RCT, 3 RCTs)	—	The mean birth length in control groups was 48.1 cm	0.0-cm difference in birth length on average (could be 0.4 cm lower to 0.5 cm higher)	⊕⊕◯◯ LOW[9]	Iodine supplementation during pregnancy may make little or no difference to infant birth length
Head circumference at birth (cm)—Severe ID, 568 participants (1 non-RCT)	—	The mean head circumference at birth in control groups was 33.8 cm	0.4-cm higher head circumference on average (could be 0.1–0.7 cm higher)	⊕◯◯◯ VERY LOW[7]	We are uncertain whether iodine supplementation of severely iodine-deficient pregnant women improves birth head circumference
Head circumference at birth (cm)—Moderate to mild ID, 612 participants (2 RCTs)	—	The mean head circumference at birth in control groups was 33.9 cm	0.3-cm higher head circumference on average (could be 0.7 cm lower to 1.2 cm higher)	⊕◯◯◯ VERY LOW[10,11]	We are uncertain whether iodine supplementation of moderate to mildly iodine-deficient pregnant women improves birth head circumference
Head circumference at birth (cm)—Pooled result, 1180 participants (1 non-RCT, 2 RCTs)	—	The mean head circumference at birth in control groups was 33.9 cm	0.3-cm higher head circumference on average (could be 0.2 cm lower to 0.7 cm higher)	⊕◯◯◯ VERY LOW[12,13]	We are uncertain whether iodine supplementation of pregnant women improves birth head circumference

[1] Patient or population: infants of pregnant women who did or did not receive iodine supplementation during pregnancy. Setting: pooled and nonpooled results of studies in participants with severe and moderate-to-mild ID at baseline. Intervention: iodized oil (oral: 400 mg once or intramuscular: 475 mg/mL, 2 mL or 4 mL dose once) or iodine tablet [150 μg (alone or in a multivitamin) or 200 μg/d until delivery from enrollment, or 177.9 μg/d for 30 d] administered during pregnancy. Comparison: placebo, noniodized multivitamin tablet, or no intervention. The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). GRADE Working Group grades of evidence: High quality: We are very confident that the true effect lies close to that of the estimate of the effect; Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different; Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect; Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. GRADE, Grading of Recommendations Assessment, Development and Evaluation; ID, iodine deficiency; RCT, randomized controlled trial.

[2] Downgraded by 2 for risk of bias: 2 non-RCTs with >10% loss to follow-up (high risk of selection and attrition bias).

[3] Downgraded by 2 for risk of bias: 3/4 trials with >10% loss to follow-up (high risk of attrition bias); 2 trials with small sample size ($n = 46$; $n = 67$).

[4] Downgraded by 1 for inconsistency: significant unexplained heterogeneity ($I^2 = 93\%$).

[5] Downgraded by 2 for risk of bias: pooled result includes 2 non-RCTs and 1 open-label RCT (high risk of selection and performance bias) and 5/6 trials had >10% loss to follow-up (high risk of attrition bias).

[6] Downgraded by 1 for inconsistency: significant level of unexplained heterogeneity (pooled $I^2 = 98\%$).

[7] Downgraded by 2 for risk of bias: non-RCT with >10% loss to follow-up (high risk of selection and attrition bias).

[8] Downgraded by 2 for risk of bias: 2/3 trials with >10% loss to follow-up (high risk of attrition bias); 2 trials with small sample size ($n = 44$; $n = 67$).

[9] Downgraded by 2 for risk of bias: pooled result includes 1 non-RCT and 1 open-label RCT (high risk of selection and performance bias); 3/4 trials with >10% loss to follow-up (high risk of attrition bias).

[10] Downgraded by 2 for risk of bias: >10% loss to follow-up in 1 trial (high risk of attrition bias); small sample size ($n = 44$) in 1 trial.

[11] Downgraded by 1 for inconsistency: significant level of unexplained heterogeneity ($I^2 = 73\%$).

[12] Downgraded by 1 for risk of bias: pooled result includes 1 non-RCT (high risk of selection bias).

[13] Downgraded by 1 for inconsistency: significant level of unexplained heterogeneity (pooled $I^2 = 79\%$).

on these data and analyses are presented in **Supplemental Table 4**.

One non-RCT ($n = 456$) reported on placental weight (35), a measure of intrauterine growth. There was no effect on placental weight at birth after iodine supplementation in severely iodine-deficient pregnant women (MD: −75 g; 95% CI: −398, 248 g; $n = 456$; 1 non-RCT; very low-quality evidence) (35).

Postnatal somatic growth outcomes measured during infancy, childhood, and adolescence

Interventions in pregnant women: iodized oil compared with placebo or no intervention. Postnatal growth outcomes of infants born to iodine supplemented or nonsupplemented pregnant women were reported in 3 RCTs (moderate-to-mild ID) and 2 non-RCTs (severe ID) (Table 2) (42, 43). Data could not be pooled due to disparate reporting. Outcomes included length, head circumference, and weight at 6, 12, and 24 mo, and height at 15 y. Iodine supplementation during pregnancy had little or no effect on these postnatal growth outcomes (low or very low quality of evidence) (Supplemental Table 4).

Interventions in infants (0–24 mo): high-iodine compared with standard infant formula. One RCT (47) ($n = 121$) investigated whether a high-iodine infant formula containing 40–50 $\mu g \cdot kg^{-1} \cdot d^{-1}$, compared to standard formula containing 12–16 $\mu g \cdot kg^{-1} \cdot d^{-1}$, would be more beneficial for the subsequent growth of preterm infants (enrolment at <33 wk gestational age) at 40 wk postconception. There was no difference in median infant weight (g), weight gain (g/d), lower leg length (mm), lower leg length gain (mm/d), head circumference, or head circumference growth between groups (low quality of evidence) (Supplemental Tables 4 and **5**). The results are not generalizable to infants born at term.

Interventions in preschool children (2–5 y): iodized compared with non-iodized salt. One cluster RCT (48) reported growth outcomes in preschool children aged 4.5–5 y after exposure to iodized salt [>15 parts per million (ppm) for ∼4 mo; see Table 2] compared with non-iodized salt in a severely iodine-deficient area of Ethiopia. There was no difference in mean HAZ between children who received iodized salt and controls (MD: 0.11; 95% CI: −0.01, 0.23; $n = 1376$; 1 cluster RCT; very low-quality evidence); however, on average, children in clusters receiving iodized salt had a 0.13 greater WAZ than children in control clusters (95% CI: 0.03, 0.23; $n = 1376$; 1 cluster RCT; very low-quality evidence) (Supplemental Tables 4 and **6**).

Interventions in school-age children (6–12 y): iodized oil or iodine fortification compared with placebo or no intervention. We identified 6 studies that included growth outcome measurements in school-age children: 5 RCTs (49, 50, 52–54) that compared oral iodized oil capsules, containing between 400 and 490 mg iodine given once, or 191 mg twice, with a placebo oil capsule; and 1 CBA (55) that compared iodized salt, iodinated drinking water, or iodine-fortified fish paste with no intervention, for which data could not be pooled (Table 2).

Iodized oil compared with placebo: **Figure 3** shows the forest plots for height, HAZ, and weight after iodine supplementation in school-age children, subgrouped by iodine status of the intervention group at baseline. Overall, there was no difference in the pooled or subgrouped results for any of these growth outcomes (Figures 3A–C) at 112–180 d post-intervention. The quality of evidence for these outcomes was either low or very low (**Table 4**).

Iodine fortification compared with no intervention: One CBA study (55) ($n = 263$) assessed the effects of iodized salt, water, or food condiment (fish sauce) compared with no intervention in school-age children with mild ID, over the period of 1 y (Table 2). The study authors report: "a significant difference in the weight and height of children from the 4 schools investigated [3 intervention and 1 control school], before and after supplementation within each school". Medians and ranges are reported in this study and the authors did not reply to our correspondence attempts, thus the data could not be meta-analyzed. Further details are included in Supplemental Table 4.

Interventions in adolescents (13–18 y): iodized oil compared with placebo: One RCT ($n = 47$) (56) assessed the effect of 190 mg oral iodized oil compared with placebo on height, weight, and BMI of iodine-sufficient adolescent girls. At 12 wk postsupplementation, there was no mean difference in height, weight, or BMI (moderate-quality evidence) (56) between the intervention and control groups (Supplemental Tables 4 and **7**).

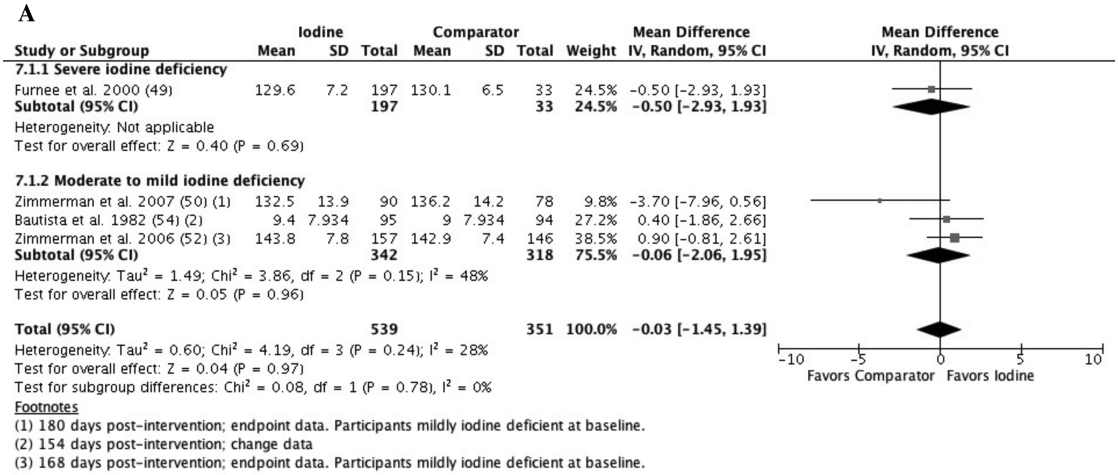
Secondary outcomes

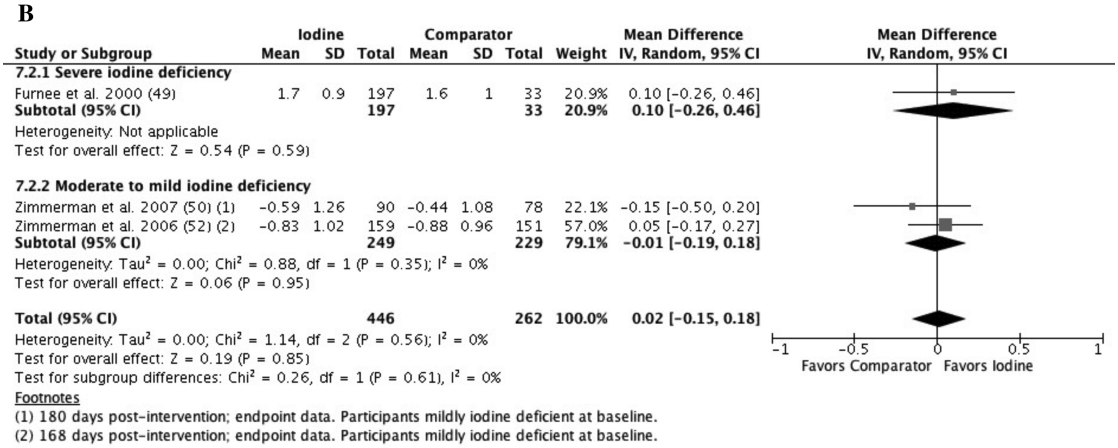
Postnatal somatic growth outcomes measured during childhood

Interventions in school-age children (6–12 y): iodized oil compared with placebo. Two RCTs reported on the biochemical markers IGF-1 and IGFBP-3 after oral iodized oil supplementation, as 400 mg iodine once or 191 mg iodine twice in 90 d, in school-age children (Table 2) (50, 52). Compared to controls, iodine supplementation increased mean IGF-1 and IGFBP-3 concentrations in moderate-to-mildly iodine-deficient school-age children, by 38.48 ng/mL (95% CI: 6.19, 70.76 ng/mL; $I^2 = 65\%$; $n = 498$; 2 RCTs; low-quality evidence) (50, 52) (**Figure 4**A) and 0.46 μg/mL (95% CI: 0.25, 0.66 μg/mL; $I^2 = 0\%$; $n = 498$; 2 RCTs; low-quality evidence) (50, 52) (Figure 4B), respectively. Table 4 provides the summary of findings for these secondary outcomes.

Discussion

This systematic review assessed 18 studies (12 RCTs, 1 cluster RCT, 4 non-RCTs, and 1 CBA study), including 5729 participants across a range of settings and age groups, to investigate the effect of iodine supplementation or fortification on prenatal or postnatal growth outcomes. For most reported





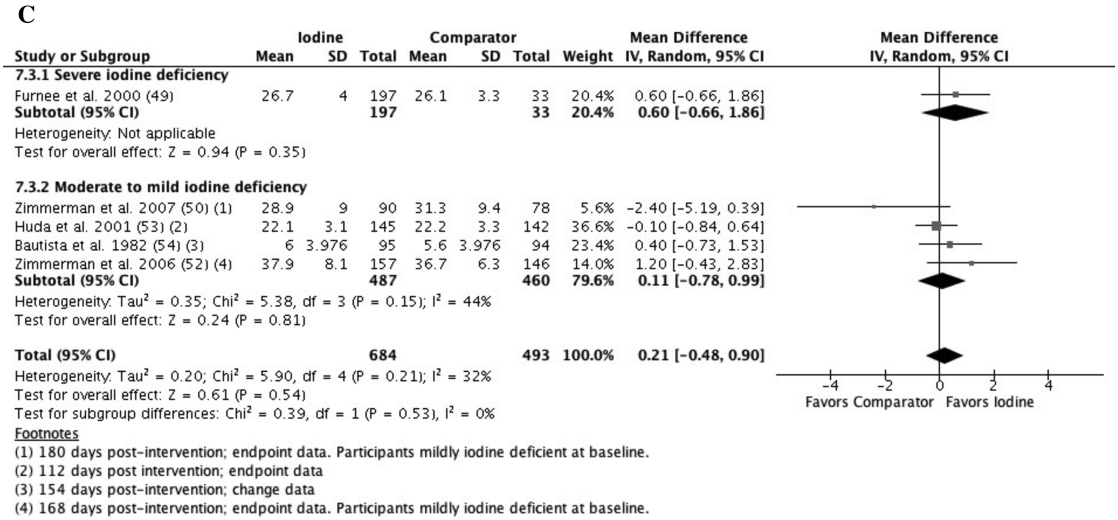


FIGURE 3 Forest plots of iodine supplementation in school-age children compared with placebo for the postnatal growth outcomes: (A) height (cm), (B) height-for-age *z* score, and (C) weight (kg). IV, inverse variance; Random, random effects model.

TABLE 4 Summary of findings for iodine supplementation in school-age children compared with placebo for the postnatal growth outcomes: height, HAZ, weight, IGF-1, and IGFBP-3[1]

Outcome, *n* participants (studies)	Relative effect (95% CI)	Illustrated comparative effect		Quality of the evidence (GRADE)	What happens
		Without iodine supplement	Effect difference with iodine supplements		
Height (cm) 280 d post-intervention—Severe iodine deficiency, 230 participants (1 RCT)	—	The mean height at 280 d post-intervention in control groups was 130.1 cm	0.5 cm lower height on average (could be 2.9 cm lower to 1.9 cm higher)	⊕◯◯◯ VERY LOW[2,3]	We are uncertain whether giving iodized oil to severely iodine-deficient school-age children improves height at 280 d post-intervention
Height (cm) 154–180 d post-intervention—Moderate to mild iodine deficiency, 660 participants (3 RCTs)	—	The mean height at 154–180 d post-intervention in control groups was 211.0 cm	0.1 cm lower height on average (could be 2.1 cm lower to 2.0 cm higher)	⊕⊕◯◯ LOW[4]	Giving iodized oil to moderate to mildly iodine-deficient school-age children may make little or no difference to height at 154–180 d post-intervention
Height (cm) 154–280 d post-intervention—Pooled result, 890 participants (4 RCTs)	—	The mean height at 154–280 d post-intervention in control groups was 136.4 cm	0.0 cm in height on average (could be 1.5 cm lower to 1.4 cm higher)	⊕⊕◯◯ LOW[5]	Giving iodized oil to school-age children may make little or no difference to height measured at 154–280 d post-intervention
HAZ 280 d post-intervention—Severe iodine deficiency, 230 participants (1 RCT)	—	The mean HAZ at 280 d post-intervention in control groups was 1.6	0.1 higher HAZ on average (could be 0.3 lower to 0.5 higher)	⊕◯◯◯ VERY LOW[6,7]	We are uncertain whether giving iodized oil to severely iodine-deficient school-age children improves HAZ at 280 d post-intervention
HAZ 168–180 d post-intervention—Moderate to mild iodine deficiency, 478 participants (2 RCTs)	—	The mean HAZ at 168–280 d post-intervention in control groups was –0.7	0.2 lower HAZ on average (could be 0.5 lower to 0.2 higher)	⊕⊕◯◯ LOW[8]	Giving iodized oil to moderate to mildly iodine-deficient school-age children may make little or no difference to HAZ at 168–180 d post-intervention
HAZ 168–280 d post-intervention—Pooled result, 708 participants (3 RCTs)	—	The mean HAZ at 168–280 d post-intervention in control groups was 0.1	0.0 difference in HAZ on average (could be 0.2 lower to 0.2 higher)	⊕⊕◯◯ LOW[9]	Giving iodized oil to school-age children may make little or no difference to HAZ at 168–280 d post-intervention
Weight (kg) 280 d post-intervention—Severe iodine deficiency, 230 participants (1 RCT)	—	The mean weight at 280 d post-intervention in control groups was 26.1 kg	0.6 kg higher weight on average (could be 0.7 kg lower to 1.9 kg higher)	⊕◯◯◯ VERY LOW[10,11]	We are uncertain whether giving iodized oil to severely iodine-deficient school-age children improves children's weight at 280 d post-intervention
Weight (kg) 112–180 d post-intervention—Moderate to mild iodine deficiency, 947 participants (4 RCTs)	—	The mean weight at 112–180 d post-intervention in control groups was 30.1 kg	0.1 kg higher weight on average (could be 0.8 kg lower to 1.0 kg higher)	⊕⊕◯◯ LOW[12]	Giving iodized oil to moderate to mildly iodine-deficient school-age children may make little or no difference to weight at 112–180 d post-intervention
Weight (kg) 112–280 d post-intervention—Pooled result, 1177 participants (5 RCTs)	—	The mean weight at 112–280 d post-intervention in control groups was 29.1 kg	0.2 kg higher weight on average (could be 0.5 kg lower to 0.9 kg higher)	⊕⊕◯◯ LOW[13]	Giving iodized oil to school-age children may make little or no difference to the children's weight at 112–280 d post-intervention
IGF-1 180–280 d post-intervention—Moderate to mild iodine deficiency, 498 participants (2 RCTs)	—	The mean IGF-1 at 180–280 d post-intervention in control groups was 184.5 ng/mL	38.5 ng/mL higher IGF-1 on average (could be 6.2–70.8 ng/mL higher)	⊕⊕◯◯ LOW[14]	Giving iodized oil to moderate to mildly iodine-deficient school-age children may improve IGF-1 concentrations at 180–280 d post-intervention

(*Continued*)

TABLE 4 (*Continued*)

Outcome, *n* participants (studies)	Relative effect (95% CI)	Illustrated comparative effect		Quality of the evidence (GRADE)	What happens
		Without iodine supplement	Effect difference with iodine supplements		
IGFBP-3 180–280 d post-intervention—Moderate to mild iodine deficiency, 498 participants (2 RCTs)	—	The mean IGFBP-3 at 180–280 d post-intervention in control groups was 4.4 μg/mL	0.46 μg/mL higher IGFBP-3 on average (could be 0.3–0.7 μg/mL higher)	⊕⊕◯◯ LOW[14]	Giving iodized oil to moderate to mildly iodine-deficient school-age children may improve IGFBP-3 concentrations at 180–280 d post-intervention

[1] Patient or population: school-age children (5–14 y). Setting: pooled results of studies in participants with severe and moderate-to-mild iodine deficiency at baseline. Intervention: oral iodized oil (191 mg administered twice in 90 d; 400 mg once or 475 mg once). Comparison: placebo. One CBA study (263 participants) compared iodized salt, iodized water, and iodized fish paste with no intervention in school-age children with a mildly deficient or sufficient iodine status. Growth outcomes measured included height, weight, and HAZ. Medians (ranges) were reported; the author did not provide further data upon request. Data cannot be pooled or meta-analyzed. See Supplemental Table 4 for further details on outcome measures. The GRADE of these data was assessed as very low quality of evidence. The risk in the intervention group (and its 95% CI) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI). GRADE Working Group grades of evidence: High quality: We are very confident that the true effect lies close to that of the estimate of the effect. Moderate quality: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect. Very low quality: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect. CBA, controlled before-after study; GRADE, Grading of Recommendations Assessment, Development and Evaluation; HAZ, height-for-age *z* score; IGF-1, insulin-like growth factor-1; IGFBP-3, insulin-like growth factor binding protein-3; MD, mean difference; RCT, randomized controlled trial.

[2] Downgraded by 2 for risk of bias: random sequence generation and allocation concealment not reported (high risk of selection bias); unclear risk of contamination.

[3] Downgraded by 1 for imprecision: wide CI (2.4 cm on either side of the mean).

[4] Downgraded by 2 for risk of bias: random sequence generation and allocation concealment either not reported or not conducted in 2/3 trials; significant difference in baseline characteristics in 1 trial (high risk of selection bias); high or unclear risk of contamination in all studies.

[5] Downgraded by 2 for risk of bias: random sequence generation and allocation concealment either not reported or not conducted in all studies and significant difference in baseline characteristics of study groups in 1 trial (high risk of selection bias); high or unclear risk of contamination in all studies.

[6] Downgraded by 2 for risk of bias: random sequence generation and allocation concealment either not reported or not conducted (high risk of selection bias); unclear risk of contamination.

[7] Downgraded by 1 for imprecision: wide CI (0.4 *z* scores on either side of the mean).

[8] Downgraded by 2: random sequence generation and allocation concealment either not reported or not conducted in both trials (high risk of selection bias); unclear risk of contamination in both trials.

[9] Downgraded by 2 for risk of bias: random sequence generation and allocation concealment either not reported or not conducted in all of the trials (high risk of selection bias); unclear risk of contamination in all 3 trials.

[10] Downgraded by 2 for risk of bias: random sequence generation and allocation concealment either not reported or not conducted (high risk of selection bias); unclear risk of contamination.

[11] Downgraded by 1 for imprecision: wide CI (1.3 kg on either side of the mean).

[12] Downgraded by 2 for risk of bias: random sequence generation and allocation concealment either not reported or not conducted in all of the trials and significant difference in baseline characteristics in 1 trial (high risk of selection bias); high risk of contamination in 2/4 trials.

[13] Downgraded by 2 for risk of bias: random sequence generation and allocation concealment either not reported or not conducted in all of the trials and significant difference in baseline characteristics in 1 trial (high risk of selection bias); high risk of contamination in 2/5 trials.

[14] Downgraded by 2 for risk of bias: random sequence generation and allocation concealment either not reported or not conducted in both trials (high risk of selection bias); unclear risk of contamination in both trials; baseline characteristics not reported in 1 trial.

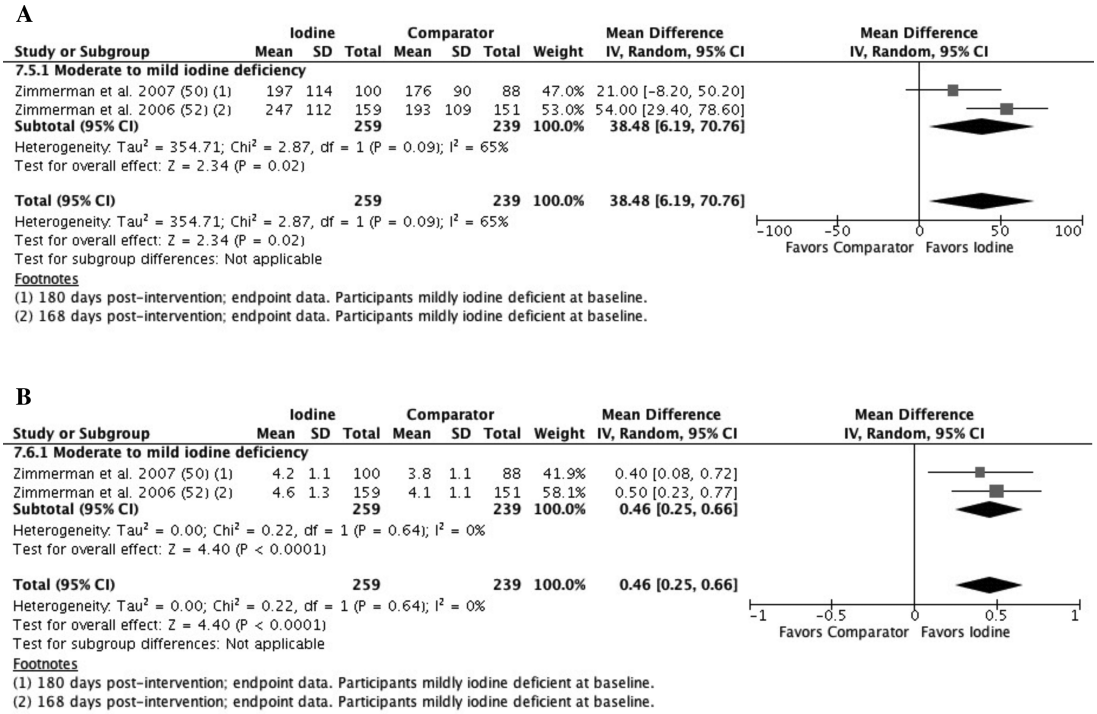


FIGURE 4 Forest plots of iodine supplementation in school-age children compared with placebo for the postnatal growth outcomes: (A) IGF-1 (ng/mL) and (B) IGFBP-3 (μg/mL). IV: inverse variance; Random: random effects model.

outcomes, the quality of the available evidence (GRADE) was low or very low and therefore we remain uncertain of the effects of iodine supplementation or fortification on prenatal or postnatal growth outcomes.

Iodine supplementation and prenatal growth outcomes

TH concentration in utero regulates fetal growth, development, and viability through several pathways (58), making an adequate supply of iodine paramount during pregnancy. Maternal iodine supplementation (59) or an adequate iodine status (60, 61) has been positively associated with infant birthweight in previous intervention and observational studies (studies ineligible for inclusion in this review; see Supplemental Table 1). The pooled results of 6 studies (2 non-RCTs and 4 RCTs) in our review showed no difference in the weight, length, or head circumference at birth of infants born to iodine-supplemented iodine-deficient pregnant women, compared with non-supplemented women. As a collective, these studies had high risks of performance, detection, and attrition bias, and considerable heterogeneity. When looking only at severely iodine-deficient pregnant women, findings from 2 non-RCTs suggest, on average, a 200-g greater weight and 0.4-cm greater head circumference at birth in infants born to supplemented women compared with controls. This finding is, however, likely subject to attrition bias and confounding from lack of randomization, which results in an imbalance in prognostic factors associated with these outcomes that may severely compromise its validity (29).

Iodine supplementation and postnatal growth outcomes

The results on postnatal growth outcomes of infants born to women who received iodine or a placebo supplement or no intervention during pregnancy could unfortunately not be pooled, and the designs of 3 of these 4 studies were open to substantial bias. The fourth study, a recent RCT (37) ($n = 613$) in which mildly iodine-deficient pregnant women were supplemented with 200 μg iodine daily from approximately week 10 of gestation until delivery, was judged as low risk of bias in most domains. This study reported no differences between infants of iodine-supplemented women and controls, on infant length, weight, and head circumference at 12 and 24 mo postnatally. The positive effect of iodized salt in preschool children reported in the only cluster-RCT (48) should be interpreted with caution because of a high risk of bias from contamination between intervention and control clusters, and statistically significant differences in baseline characteristics and outcomes between the 2 groups.

In schoolchildren, iodine supplementation may make little or no difference to height, HAZ, or weight, as the quality of the evidence retrieved for these outcomes was very low. The main reason for downgrading the evidence was a high risk of bias due to contamination between the intervention and control groups and high risk of selection bias as evidenced by the statistically significant differences in baseline characteristics and outcomes.

In adolescents, mean differences between intervention and control groups for height, weight, and BMI were trivial

and based upon 1 small trial only (56), which was considerably underpowered to appropriately detect any differences in anthropometric measurement.

Although somatic growth was reported as a primary outcome in 1 study (54), it is important to note that a hypothesis measuring a difference in growth outcomes with iodine supplementation was the main objective of none of the 18 studies. As a result, no study, nor subsequent meta-analysis, was sufficiently powered to detect an effect of iodine on somatic growth as the primary outcome. Previous RCTs measuring the effects of nutrition interventions on growth as the primary outcome have included >800 participants to sufficiently detect an effect in growth outcome with a difference of 0.2 SD, a 90% power ($1-\beta$), and 95% confidence level (α) (62–64). Furthermore, although the follow-up period of trials included in this systematic review was generally longer than 100 d, this may be too short to detect measurable differences in growth with respect to the intervention.

The methodological quality of most studies included in this review was questionable when considering existing study design standards that seek to minimize systematic errors that threaten the internal validity of comparative studies. This was exacerbated by incomplete reporting in some studies (and lack of response when authors were contacted), which impacted negatively on the assessment of the quality of evidence.

Positive associations between salt fortification, household iodized salt availability, and child growth have been previously described (65). Although causality was not established by Krämer et al. (65), there are physiologically plausible links between both inadequate iodine intake and severe stunting, and adequate iodine intake and age-appropriate growth. However, somatic growth from in utero to adulthood is a complex process influenced by numerous direct and indirect factors. Most studies did not provide a comprehensive description of the nutrition status and/or dietary intake of the study participants. This is a significant limitation with respect to the interpretation of the results of this systematic review, yet this factor could be integrated into study designs. Appropriately designed intervention trials seeking to investigate the effect of iodine repletion on prenatal or postnatal growth are needed. Such studies should be adequately powered, conducted in iodine-deficient populations, and, depending on the participant age group and growth rate, cover a substantial follow-up period (e.g., greater than 2 y).

Indirect biochemical growth markers such as IGF-1 and IGFBP-3 are more sensitive measures of growth. There is an intricate relation between TH and the GH-IGF axis, and normal GH secretion is dependent upon normal thyroid function (66, 67). The main function of GH is to promote the synthesis and secretion of IGFs, which enhance cell growth and differentiation (68). IGFs circulate in the plasma in complexes with structurally related IGFBPs, of which IGFBP-3 is the most common (51, 68). The synthesis of TH requires the presence of IGF-1 (69), and IGF-1 is necessary for the anabolic effect of triiodothyronine, the active TH metabolite (66). In addition, GH accelerates the peripheral conversion of thyroxine to triiodothyronine (70). Given this interrelation, and that normal thyroid function depends upon an adequate iodine intake, the pooled results from the 2 RCTs (50, 52) in our review are aligned with this mechanistic pathway and the plausible contributory effect of iodine on growth, mediated by both TH and the GH-IGF axis. This interpretation is, however, limited by the lack of trials investigating these outcomes, and our results should be confirmed in further rigorous and appropriately designed studies.

The IGFs have been described as the principal fetal growth factors (71), and correlations between human fetal IGF-1 concentrations in utero and fetal weight (72, 73) have been previously described. During childhood, beginning from between 6 mo and 3 y to puberty, the GH-IGF-1 axis and TH become more influential on growth, and at puberty, GH and IGF-1 concentrations increase significantly in both males and females (71).

In a cross-sectional study in Turkey, pubertal children living in an area affected by severe ID had significantly lower IGF-1 and IGFBP-3 values than their counterparts living in an area with mild deficiency ($P < 0.0001$) (16). In our review, a meta-analysis of 2 RCTs (50, 52) in school-age children ($n = 498$) showed that iodized oil compared to placebo in a moderate or mildly iodine-deficient setting increased IGF-1 and IGFBP-3 concentrations. A similar effect was observed after the introduction of iodized salt (to 25 ppm) to school-age children in a severely iodine-deficient area of Morocco (51, 74). This study (RCT, $n = 71$) compared the IGF-1 of 7–10-y-old school-age children whose families either did or did not (retrospective control) make use of iodized salt at household level. Over 10 mo of iodized salt use, median IGF-1 concentrations in the intervention children were higher compared with the control children (202 ng/mL for intervention children compared with 134 ng/mL for control children; $P < 0.05$). In this study, there was also a greater increase in HAZ in children exposed to iodized salt compared with controls (median baseline value –0.98 for intervention children compared with –0.93 for control children; median endpoint value –0.69 for intervention children compared with –1.04 for control children, $P < 0.05$). The Moroccan study was not included in this review because the data for the control group were collected retrospectively; see Supplemental Table 1.

To our knowledge, this is the first systematic review to investigate the effects of iodized salt or iodine supplements on both prenatal and postnatal somatic growth. In the limited discussion on growth in the 2 systematic reviews (75, 76) included in our scoping review (21) that assessed studies measuring growth and development, we note a consistency in findings. These include a higher birthweight with superior iodine status (UIC of 50–99 μg/L compared to <50 μg/L during pregnancy) (76), and a slightly greater (but nonsignificant) body weight or height in iodine-supplemented groups compared with control groups, across 3 and 4 studies, respectively (meta-analyses not performed) (75). Similar to our findings, a recently published Cochrane Review (77) found no difference between iodine or no iodine

groups for the outcome of low birthweight. A forthcoming Cochrane review (78) will investigate the effect of iodine fortification of foods and condiments other than salt on the prevention of disorders related to ID, and includes physical development as an outcome measure.

With the aim of generating evidence that could guide healthcare decisions and due to the nature of our question that makes undertaking RCTs challenging, we incorporated data from non-RCTs, CBA, and ITS studies to complement the RCT evidence-base, in line with reports from the field of comparative effectiveness research (79–82). Strengths of our review include a comprehensive search for both published and unpublished literature, and methods directed by our previously published protocol in which we sought to follow recommendations for good conduct, adapted specifically for inclusion of non-randomized studies. The minor deviations from our protocol are described next and are also reported on the PROSPERO International Register of Prospective Systematic Reviews (83), number CRD42014012940. We acknowledge that there is an abundance of cross-sectional and ecological literature on iodine that may elucidate some interesting and potentially relevant findings about the effect of iodine repletion on prenatal and postnatal growth outcomes in infants, children, and adolescents.

Minor deviations from the protocol

We excluded cretinism as a secondary outcome due to the irreversible manifestation of stunted growth with this condition that would confound our comparisons. Our decision to subgroup outcome data by baseline iodine status of the intervention group was a deviation from our protocol. This decision was based on evidence from the iodine literature, which suggests that the physiologic response to iodine repletion would be different depending upon the degree of ID before treatment.

Conclusions

We identified few adequately designed trials investigating the effect of iodine repletion on human growth. Importantly, our review does not show "evidence of no effect", rather "no evidence of an effect"—which is distinctly different. Based on our findings, current best evidence remains too uncertain to fully answer our research question. Thus, we cannot firmly conclude that maternal iodine repletion has an effect on growth outcomes at birth, nor confidently identify clear effects on somatic growth outcomes in infants, children, and adolescents after postnatal iodine repletion. That said, pooling of results of 2 trials in the review showed that postnatal iodine supplementation may improve concentrations of growth factors and their binding proteins (IGF-1 and IGFBP-3), which can be regarded as indirect markers of growth. This finding must be confirmed by further rigorous RCTs, sufficiently powered to detect a clinically significant difference in such growth factors, or physical indicators of somatic growth, as primary outcomes.

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