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[Intervention Protocol]

Iodine supplementation for preventing iodine deficiency disorders in children and adolescents

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ABSTRACT

Objectives

This is a protocol for a Cochrane Review (intervention). The objectives are as follows:

To assess the efficacy and safety of iodine supplementation for preventing iodine deficiency in children and adolescents.

BACKGROUND

Description of the condition

Iodine is an essential micronutrient for thyroid hormone synthesis, which is mainly dependent on the level of dietary iodine intake. The thyroid hormone, in turn, is needed for normal growth and neurodevelopment (Rohner 2014). Iodine is primarily obtained from dietary sources, therefore, the iodine nutritional status of the population depends on an adequate micronutrient intake. The primary dietary sources of iodine are iodised salt, seafood (animals and plants concentrate iodine from seawater), grains from iodine-rich soils (NIH 2020), and dairy products (due to enrichment of livestock's feed with iodine-containing mineral mixtures, or through the use of iodophor antiseptics (Eveleigh 2020; Friesen 2020)).

Iodine is ingested in a range of forms, which are reduced to iodide in the gut before absorption. Recommended daily allowances (RDA) vary for different ages groups of children and adolescents, and depending on the source: 90 µg/day for children aged one to three years; 90 to 120 µg/day for children aged four to eight years; and 120 to 150 µg/day for children aged 9-13 years. Adequate intake levels have been set at 110 µg/day for infants aged zero to six months, and 130 µg/day for infants aged 6 to 12 months (Krela-Kaźmierczak 2021; Pearce 2014). The World Health Organization (WHO), United Nations Children's Fund (UNICEF), and the International Council for the Control of Iodine Deficiency Disorders (ICCIDD) recommend a daily intake of 150 µg for adolescents (WHO 2007a; WHO 2007b).

Iodine is crucial in the early stages of human development, since it is essential for synthesising thyroid hormones, which are particularly involved in somatic growth and neurodevelopment (Zimmermann 2009). Therefore, children are particularly vulnerable to iodine deficiency disorders, and school-age children (six years or older) have traditionally been regarded as a reference group to monitor iodine nutrition in the population (Wassie 2019). Iodine deficiency disorders involve a broad spectrum of consequences, ranging from endemic goitre (enlargement of the thyroid gland, occurring in geographical areas with low iodine content in soils or water), retardation of growth and development of the central nervous system in children (cretinism), intellectual impairment, neonatal hypothyroidism (insufficient thyroid function in newborns), pregnancy loss, and infant mortality (Pearce 2013). A cause and effect relationship has been established between the dietary intake of iodine and its contribution to normal cognitive development (EFSA 2014). Iodine deficiency disorders represent a global health threat to individuals and societies, and significantly burden public healthcare systems (The Krakow Declaration 2018).

For a long time, iodine deficiency was determined by the prevalence of goitre in the population, expressed as the total goitre rate. Goitre is a reflection of chronic iodine deficiency. It can be used as a baseline assessment of a region's iodine status and as a sensitive, long-term indicator of the success of an iodine programme (WHO 2007a). A total goitre rate of 5% or more in school-age children signals a public health problem (WHO 2014a). However, palpation of goitre size may lead to high misclassification rates, especially with the size estimation of smaller glands, particularly in children (Pearce 2014; Vanderpump 2017). The most distressing clinical consequence of iodine deficiency, which was not clear until the 1980s, is brain damage in children. This brain damage and its subsequent mental impairment in the population has resulted in a substantial change in the way of assessing iodine deficiencies (Li 2012a). Hence nowadays, the measurement of urinary iodine concentration (UIC) in casual urine specimens is recommended for monitoring iodine status (WHO 2007a). UIC is highly sensitive to recent changes in iodine intake, as up to 90% of iodine is absorbed and excreted in the urine. A recent meta-analysis suggested that UIC could be a promising biomarker for predicting goitre among school children, which could facilitate interventions to address iodine excess or deficiency (Xiu 2017). Therefore, the WHO recommends using median urinary iodine concentration as the leading indicator for assessing and monitoring the iodine nutritional status of a population (Zimmermann 2012).

According to recommendations by the WHO, a median urinary iodine concentration of 100 µg/L to 199 µg/L in samples from school-age children indicates adequate iodine intake and optimal iodine nutrition (WHO 2013). The use of this indicator to monitor iodine deficiency disorders, and the Universal Salt Iodization programmes implemented, have redefined the epidemiology and distribution of iodine deficiency (IGN 2019; Li 2012a).

Iodine deficiency prevention is feasible, and should be addressed throughout life, by providing an adequate iodine supply from the early stages of development and childhood (Vanderpump 2017; Yakoob 2017). Iodising all salt for human and animal consumption (known as Universal Salt Iodization (USI)) is the recommended strategy to control iodine deficiency (Untoro 2010), but household coverage with adequately iodised salt varies greatly between countries, depending on product availability and affordability (Knowles 2017; Untoro 2010). However, a high salt intake is a top dietary risk factor for cardiovascular disease, all-cause mortality, and other conditions, such as kidney disease, stomach cancer, and osteoporosis. Salt reduction programmes are cost-effective, and should be implemented or accelerated in all countries (He 2020; Rutigliano 2020). So, public health policies face an emergent challenge: to synergise USI programmes to eradicate iodine deficiency disorders, and to reduce population salt intake to prevent and decrease the burden of cardiovascular disease (WHO 2014b). Although successful USI programmes should continue and be sustained, it is also mandatory to implement programmes to reduce the population's salt intake to less than 5 g/day (WHO 2014b). The combination of both goals emphasises the importance of tailoring iodine programmes, and advocates for complementary strategies, including increased iodine intake through fortification or supplementation to ensure optimal iodine nutrition in relevant groups, such as pregnant women and children (Eastman 2012). The dose-response relationship between iodine intake and biomarkers of iodine status (urinary iodine concentration, goitre rate) may help to provide complementary evidence to support recommendations for iodine intake in different population groups (Ristić-Medić 2014).

Over the last two decades, USI programmes have been implemented in more than 120 countries, the number of iodine-deficient countries decreased from 54 to 19, and the number of countries with adequate iodine intake increased from 67 to 111 (Gizak 2018). But despite the existence of iodine deficiency disorders elimination programmes, iodine deficiency still affects relevant percentages of the population worldwide (Bali 2018; Bali 2019; Bhattacharya 2019; Carvalho 2018; Cesar 2020; Gärtner 2016; Gyamfi 2020; Hassen 2019; Ittermann 2020; Ovadia 2017;

Randremanana 2019; Rezaie 2020; Shetty 2019; Wallborn 2020; Wassie 2018; Yao 2020).

Description of the intervention

Iodine supplementation, providing additional amounts of iodine to the daily intake, can be done through intramuscular oil injections (Azizi 2007), or orally, using oral tablets or gelatin capsules (Untoro 2007). Iodine can be administered in either a high-dose of iodised oil, administered only once or annually, or by potassium iodine tablets, capsules, or drops, which can be dosed more accurately (low-dose administered daily or weekly (Harding 2017)).

Intramuscular injections of high doses of iodised oil (from 150 mg to 600 mg of iodine) can meet iodine needs for a year or more in a single dose (Azizi 2007), but are currently reserved for communities in which it is unlikely that USI will be introduced within the foreseeable future (and such areas are disappearing), and areas where the need is urgent, and USI is unlikely to reach the target population immediately (Pharoah 1993). In the last decades, iodised oil has been progressively replaced as a vehicle of iodine supplementation by orally administered potassium iodine tablets, capsules, or drops that can be dosed more accurately (low dose of 100 mcg to 300 mcg of iodine administered daily or weekly (Harding 2017; Untoro 2007)).

Adverse effects of the intervention

Optimal iodine intake in children should be kept within a relatively narrow interval, as both iodine deficiency and excess may lead to thyroid dysfunction (Chen 2018; Zimmermann 2013). The Tolerable Upper Intake Level (UL) for iodine intake is 1100 µg/day for adults. In children, the dosages were derived by adjusting the adult UL, based on body surface area (Institute of Medicine 2001). Additionally, the WHO's epidemiological criteria define a median urinary iodine concentration, which is 300 µg/L or higher, as excessive in a population of school-age children (six years or older (WHO 2013)).

The spectrum of thyroid disorders concerning iodine intake is U-shaped (Farebrother 2019). Iodine excess attributable to iodine supplementation has been described in some vulnerable individuals, particularly in those previously exposed to iodine deficiency, pregnant women, or infants (Katagiri 2017; Pearce 2016). Excessive intrathyroidal concentrations can cause opposing effects. The Wolff-Chaikoff effect consists of a transient decrease in thyroid hormone synthesis, as an autoregulatory mechanism in response to excess iodide intake. In normal conditions, thyroid hormone concentrations remain within normal ranges, and in a few days, most people recover their hormonal synthesis (and escape the phenomenon). However, people with impaired autoregulation (with thyroid disease, or even subclinical thyroid dysfunction) are unable to escape from the Wolff-Chaikoff effect, and are at risk of developing iodine-induced hypothyroidism. The Jod-Basedow phenomenon is a significant increase in the production of thyroid hormones due to a failure of the acute autoregulatory mechanisms, which leads to iodine-induced hyperthyroidism that can be transient or permanent (Leung 2014).

A sudden increase in iodine supply to those in an iodine-deficient region may enhance thyroid autoimmunity through a cellular and humoral immune response. In individuals with a damaged thyroid gland, this may result in hypothyroidism or hyperthyroidism in those with an underlying multinodular goitre or Graves' disease (Vanderpump 2017). However, this enhanced thyroid autoimmunity may be reversible, and may improve over time (Mazziotti 2003). In countries with long-standing iodine deficiency disorders, the intake should not exceed 500 µg/day in adults, to avoid the occurrence of hyperthyroidism (EFSA 2006).

Excessive iodine intake in children has been associated with goitre (Li 2012b), and thyroid dysfunction, especially subclinical hypothyroidism (Sang 2013). Goitre begins to appear in children when iodine intake increases above 400 µg/day to 500 µg/day (Zimmermann 2013). On the other hand, excessive iodine intake may induce thyroid autoimmunity, or worsen autoimmunity in children genetically predisposed to thyroid autoimmunity, which may contribute to thyroid failure during childhood (Huber 2002). In addition, the prevalence of subclinical hypothyroidism is significantly increased in children with positive thyroid autoantibodies exposed to high iodine levels (Sang 2013).

The sources identified for excess iodine intake in children related to iodine supplementation are insufficiently monitored USI programmes and fortified foods consumption (Katagiri 2017). Excessive prenatal maternal iodine intake from nutritional supplements can also cause transient hypothyroidism or persistent hyperthyrotropinemia in neonates (Connelly 2012).

How the intervention might work

Ideally, iodine supplementation in children should begin as soon as possible. In this regard, maternal iodine supplementation protects against in-utero iodine deficiency, and provides this essential micronutrient at the early stages of development (Taylor 2017).

Although iodine sufficiency in infancy cannot completely overcome the effects of in-utero iodine deficiency, iodine supplements are expected to improve intellectual and physical development when administered at early stages, or for prolonged periods during infancy (Mattei 2019). It is generally accepted that the period between conception and the age of two (1000 days) is sensitive to nutrient effects on child growth, cognition, and subsequent school attainment (Black 2017; Velasco 2018). Another study has also shown that infants in these first 1000 days are more vulnerable to iodine deficiency than their mothers, and programmes should prioritise iodine prophylaxis for this group (Stinca 2017).

The potential benefits of iodine supplementation in children and adolescents are closely related to the health consequences of iodine deficiency at the early stages of development: perinatal and infant mortality, impaired mental function, delayed physical development, or iodine-induced hyperthyroidism.

Adolescence is a stage in life as critical as childhood, and adequate nutrition is a crucial contributor to the proper growth and development of individuals and their offspring. Consequently, there has been a growing interest in adolescent girls' nutrition as a means to improve the health of women and children, as maternal preconception nutritional deficiencies have profound consequences for fetal and infant development, with the effects extending to neonatal and early childhood development and mortality (Lassi 2017).

Why it is important to do this review

Several systematic reviews have assessed the impact of strategies other than direct iodine supplementation for children to prevent

iodine deficiency-related problems in children: iodised salt (Aburto 2014; Farebrother 2018; Wu 2002); iodine fortification in foods and condiments other than salt (Santos 2019); iodine supplementation for women in the preconception, pregnancy, and postpartum period (Harding 2017); multiple-micronutrient supplementation for women during pregnancy (Keats 2019); and iodine supplementation in preterm infants (Walsh 2019), a group not covered in our review.

We have found few published systematic reviews that addressed the population and objectives of this review. One is a Cochrane Review published in 2004, that examined the effects of iodine supplementation on preventing iodine deficiency disorders in children, which included studies published up to spring 2003 (Angermayr 2004). A research group has published several reviews that only partially covered the objectives of our review, including the evaluation of iodine supplements in children on postnatal growth, but they did not evaluate the impact on other relevant outcomes, such as cognitive function, health-related quality of life, or adverse events (Farebrother 2015a; Farebrother 2015b; Farebrother 2018).

In summary, it is important to have an updated evaluation of the evidence on the impact or efficacy of iodine supplementation in children and adolescents in terms of cognitive function, growth, adverse effects, and health-related quality of life in both severe and mild-to-moderate iodine deficiency regions and populations.

OBJECTIVES

To assess the efficacy and safety of iodine supplementation for preventing iodine deficiency in children and adolescents.

METHODS

Criteria for considering studies for this review

Types of studies

We will include randomised controlled trials (RCTs) and cluster-randomised controlled trials.

Types of participants

Children up to 18 years of age at risk of iodine deficiency, considering this micronutrient deficiency is a contributor to poor growth, intellectual impairments, perinatal complications, and increased risk of morbidity and mortality.

We will exclude studies on iodine interventions during pregnancy, since these were included in a previous Cochrane Review (Harding 2017).

If we identify studies in which only a subset of participants is relevant to this review, we will include them if data are available separately for the relevant subset, or if the majority of participants (> 80%) meet the inclusion criteria.

Types of interventions

Intervention

- Iodine supplementation alone (orally or by injection) or in combination with vitamins and minerals (orally or by injection)

Comparisons

- Placebo or no intervention

Concomitant interventions will have to be identical in both the intervention and comparator groups to establish fair comparisons.

If a study includes multiple arms, we will include any arm that meets the review inclusion criteria for this review.

Minimum duration of intervention

We will include studies that used single or periodic high-dose therapy, or continuous interventions with a minimum duration of eight weeks.

Eight weeks is considered a reasonable lapse of time to assess substantial changes in neurodevelopmental milestones in children, growth, and adverse events (Spittle 2015).

Minimum duration of follow-up

We will include studies with a minimum of three months of follow-up.

Summary of specific exclusion criteria

- Studies on preterm and low birth weight neonates
- Studies on fortification interventions in water, salt or food
- Studies on iodine interventions during pregnancy

We will exclude interventions that fortify water, salt, or food. However, we will include studies in which interventions with specifically iodine-fortified water or salt are considered as co-interventions of the main iodine supplementation in children and/or adolescents.

Types of outcome measures

We will not exclude a study if it fails to report one or more of our primary or secondary outcome measures. We will only exclude studies if none of the outcomes relevant to this review were measured, provided that there is supporting documentation for this (e.g. contact with trial authors, access to the original protocol, etc.).

Primary outcomes

- Cognitive function: assessed by validated scales, such as Bayley Mental Development Index (MDI), Bayley Psychomotor Development Index (PDI); Standford-Binet Test; DENVER II Developmental Screening Test
- Growth: defined as differences in height (centimetres), weight (kilograms), height for age, weight for age, and weight for height scores
- Hypothyroidism; overt, subclinical, or myxoedema: overt primary hypothyroidism is defined as thyroid-stimulating hormone (TSH) concentrations above the reference range and free thyroxine concentrations below the reference range. Subclinical hypothyroidism is defined by TSH concentrations above the reference range and free thyroxine concentrations within the normal range (even as a transient expected effect of the improvement of iodine status). Myxoedema (skin changes) includes other clinical manifestations, such as tiredness, lethargy, slowing in mental function, cold intolerance, and others.

- Adverse events: i.e. iodine-induced hyperthyroidism, thyroid auto-antibodies

Secondary outcomes

- Health-related quality of life: assessed by validated scales, such as the Short Form 36 questionnaire (SF-36), Quality Adjusted Life Years (QALY), and Disability-Adjusted Life Years (DALYs)
- All-cause mortality: defined as death from any cause
- Goitre: defined as enlargement of the thyroid gland by palpation or by measuring thyroid size. Thyroid palpation, using a grading system (grades 0, 1, and 2); World Health Organization (WHO) classification: grade 0: no goitre is palpable or visible; grade 1: palpable goitre, not visible when the neck is held in normal position; grade 2: a clearly swollen neck, also visible in the normal position of the neck, which is consistent with a goitre on palpation (WHO 2014a).

Timing of outcome measurement

- Short-term: three months from the onset of the intervention
- Medium-term: from the fourth month to the first year after the intervention
- Long-term: at least one year after the intervention

For specific outcomes.

- Cognitive function: measured at least three months after the intervention
- Growth: measured at least at one year after commencement of therapy
- Adverse events, hypothyroidism, health-related quality of life, all-cause mortality, thyroid size, or goitre: measured at any time

If a study reports more than one time point of measurement, we will use the longest follow-up results to assess the effect on the outcomes, and shorter periods for subgroups analyses.

Search methods for identification of studies

Electronic searches

We will search the following sources from inception of each database to the date of search; we will place no restrictions on the language of publication.

- Cochrane Central Register of Controlled Trials (CENTRAL) via the Cochrane Register of Studies Online (CRSO (Cochrane 2020));
- MEDLINE Ovid (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE; 1946 onwards);
- WHO International Clinical Trials Registry Platform (ICTRP; www.who.int/trialsearch);
- ClinicalTrials.gov (www.clinicaltrials.gov);
- Scopus;
- WHO Global Index Medicus;
- Trials Register of promoting Health Interventions (TRoPHI);
- Open Grey.

We will also search the following Chinese databases:

- China Network Knowledge Infrastructure (CNKI; cnki.net);
- Chinese Scientific Journals Database (VIP; cqvip.com);
- Wan Fang data (wanfangdata.com.cn/index.html);
- SinoMed (sinomed.ac.cn).

For detailed search strategies, see Appendix 1.

Searching other resources

We will search the reference lists of publications (including trials, reviews, meta-analyses, and reports) identified through our searches of electronic databases, and will consider any relevant trials included in these reference lists.

We will not use abstracts or conference proceedings for data extraction unless full data are available from the study authors, because this information source does not fulfil the CONSORT requirements (CONSORT 2018; Scherer 2018). We will present information on abstracts or conference proceedings that appear to meet the inclusion criteria for this systematic review in the Characteristics of studies awaiting classification table.

Data collection and analysis

Selection of studies

Two review authors (IV and MRE) will independently screen the abstract, title, or both of every record retrieved by the literature searches. We will obtain the full text of all potentially relevant records. We will resolve disagreements through consensus, or by recourse to a third review author (NN). If we cannot resolve a disagreement, we will categorise the study as awaiting classification, and will contact the study authors for clarification. We will present a PRISMA flow diagram to show the process of study selection (Page 2021). We will list all articles excluded after full-text assessment in a Characteristics of excluded studies table, and will provide the reasons for exclusion (Page 2022). We will use Covidence software for study selection (Covidence).

Data extraction and management

For trials that fulfil our inclusion criteria, pairs of the review authors (IV and MRE, MR and JR) will independently extract key information on participants, interventions, and comparators. We will extract the following data from reports.

- Methods
  - Study design
- Participants
  - Inclusion and exclusion criteria
  - Participant details, baseline demographics (sex, age)
  - The number of participants by study and by study arm
- Interventions and comparisons according to the Template for intervention description and replication (TIDieR) checklist (Hoffmann 2014)
  - Name of the intervention
  - Why: rationale, theory, or goal of the elements essential to the intervention
  - What: physical or informational materials used in the intervention; procedures, activities, or processes used in the intervention
  - Who provided: expertise, background, and specific training given

- How: describe modes of deliveryWhere: describe the location where the intervention occurred, including infrastructure and features
- When/how much: the number of times the intervention was delivered over a period of time
- Tailoring: describe if personalisation or adaptations were plannedModifications: during the course of the study
- How well: measurements of adherence or fidelity; adherence to treatment, measured by urine iodine levels

- Outcomes:
  - Definitions of relevant outcomes, method and timing of outcome measurement, and any relevant subgroups to the review
- Study dates (start date to end date; if dates are not available, then report this as such)
- Study settings and country, language of publication, and study identifier
- Study funding sources
- Declarations of interest by primary investigators

These data will be reported in the Characteristics of included studies and in summary tables in the main text.

We will contact all authors of included studies to enquire whether they would be willing to answer questions regarding their studies. We will document these communications. Thereafter, we will request relevant missing information on the study from the primary study author(s), if required.

Dealing with duplicate and companion publications

In the event of duplicate publications, companion documents, or multiple reports of a primary study, we will maximise the information yield by collating all available data, and use the most complete dataset, aggregated across all known publications. We will list duplicate publications, companion documents, multiple reports of a primary study, and study documents of included studies (such as trial registry information) as secondary references under the study ID of the included study. We will also list duplicate publications, companion documents, multiple reports of a study, and trial documents of excluded studies (such as trial registry information) as secondary references under the study ID of the excluded study.

Data from clinical trials registers

If data from included studies are available as study results in clinical trials registers, such as ClinicalTrials.gov, or similar sources, we will make full use of this information and extract the data. If there was also a full publication of the study, we will collate and critically appraise all available data. If an included study was marked as a completed study in a clinical trial register, but no additional information was available, we will add this study to the Characteristics of studies awaiting classification table.

Assessment of risk of bias in included studies

Two pairs of the review authors (IV and MRE, MR and JR) will independently assess the risk of bias for the results of the main outcomes (those included in the summary of findings table, listed below) in each study, using the RoB 2 tool (Higgins 2022). We will resolve disagreements by consensus or consultation with a third review author (MT or PT). If adequate information is unavailable from the publications, trial protocols, clinical study reports, or other sources, we will contact the study authors for more details, and to request missing data on risk of bias items. We will assess the risk of bias according to the following domains, focusing on the effect of assignment to the intervention at baseline:

- the randomisation process;
- deviations from intended interventions;
- missing outcome data;
- measurement of the outcome;
- selection of the reported results.

Answers to signalling questions and supporting information will collectively lead to a domain-level judgement of low risk, some concerns, or high risk of bias. We will use these domain-level judgements to inform an overall risk of bias judgement for a single result as (a) low risk, if we judge all domains at low risk; (b) some concerns, if we judge one or more domains as raising some concerns; and (c) high risk, if we judge one or more domains at high risk, or four domains as raising some concerns. We will provide a quote from the study report, together with a justification for our judgement in the risk of bias table. We will summarise the risk of bias judgements across different studies for each of the domains listed. We will aim to source trial registries, protocols and analysis plans for the assessment of selective reporting. When information on the risk of bias relates to unpublished data or correspondence with a trialist, we will note this in the risk of bias table.

When considering treatment effects, we will take into account the risk of bias for the studies that contribute to that outcome. We will construct summary assessments of the risk of bias for each important outcome (across domains) within and across studies (Higgins 2022).

For cluster-RCTs, we will use the RoB 2.0 tool and add a domain specific to cluster-RCTs, from the archived version of the tool (Domain 1b. Bias arising from the timing of identification and recruitment of participants and its corresponding signalling questions (www.riskofbias.info/)). We will follow the guidance in section 23.1.2 and table 23.1.a in the Handbook of Systematic Review of Interventions (Higgins 2022).

We will use the RoB 2 Excel tool to manage the data supporting the answers to the signalling questions and risk of bias judgements (available at www.riskofbias.info/). All these data will be publicly available as supplementary material in a public repository (Flemyng 2023).

Measures of treatment effect

We will express dichotomous data as a risk ratio (RR) with 95% confidence intervals (CIs); we will express continuous data as the mean difference (MD) or standardised mean difference (SMD) with 95% CIs. When combining data across studies for continuous outcomes measured on the same scale, we will estimate the intervention effect using the MD with 95% CIs. When combining data across studies for outcomes that measure the same underlying concept (e.g. health-related quality of life) but use different measurement scales, we will calculate the SMD with 95% CI. We will express time-to-event data as a hazard ratio (HR) with 95% CIs.

Unit of analysis issues

We will consider if there are multiple observations for the same outcome. If more than one comparison from the same study is eligible for inclusion in the same meta-analysis, we will either combine groups to create a single pair-wise comparison, or we will appropriately reduce the sample size, so that the same participants do not contribute data to the meta-analysis more than once (splitting the shared group into two or more groups). Although the latter approach offers some solutions for adjusting the precision of the comparison, it does not account for correlation arising from the inclusion of the same set of participants in multiple comparisons (Higgins 2022).

We will attempt to re-analyse cluster-RCTs that have not appropriately adjusted for the potential clustering of participants within clusters in their analyses. The variance of the intervention effects will be inflated by a design effect. Calculation of a design effect involves the estimation of an intracluster correlation coefficient (ICC). We will obtain estimates of ICCs by contacting study authors, or by imputing ICC values, using either estimate from other included studies that report ICCs or external estimates from empirical research (Bell 2013). We plan to examine the impact of clustering by performing sensitivity analyses.

Dealing with missing data

If possible, we will obtain missing data from the authors of included studies. We will carefully evaluate important numerical data, such as screened and randomly assigned participants, as well as intention-to-treat, as-treated, and per-protocol populations. We will investigate attrition rates (e.g. dropouts, losses to follow-up, withdrawals), and we will critically appraise issues concerning missing data and the use of imputation methods (e.g. last observation carried forward).

For studies in which the standard deviation (SD) of the outcome is not available at follow-up, or we cannot recreate it, we will standardise by the mean of the pooled baseline SD from studies that reported this information.

When included studies do not report means and SDs for outcomes, and we do not receive requested information from study authors, we will impute these values by estimating the mean and the variance from the median, the range, and the size of the sample (Hozo 2005).

We will investigate the impact of imputation on meta-analyses by performing sensitivity analyses, and for every outcome, we will report which studies had imputed SDs.

Assessment of heterogeneity

In the event of substantial clinical or methodological heterogeneity, we will not report study results as the pooled effect estimate in a meta-analysis.

We will take into account a visual examination of the variability in point estimates and the overlap in confidence intervals. We will use the I^2 statistic to estimate the degree of heterogeneity present among the trials in each analysis. If we identify substantial or considerable unexplained heterogeneity, we will report it and explore possible causes by prespecified subgroup analysis. We will use the rough guide to interpretation, as outlined in Chapter 10 of the *Handbook*, as follows (Higgins 2022):

- 0% to 40%: might not be important;
- 30% to 60%: may represent moderate heterogeneity;
- 50% to 90%: may represent substantial heterogeneity;
- 75% to 100%: considerable heterogeneity.

We will avoid the use of absolute cutoff values but interpret I^2 in relation to (a) the size and direction of effects and (b) the strength of evidence for heterogeneity, e.g. P value from the Chi^2 test or CI for I^2.

Assessment of reporting biases

If we include 10 or more studies that investigate a particular outcome, we will use funnel plots to assess small-study effects. Several explanations may account for funnel plot asymmetry, including true heterogeneity of effect with respect to study size, poor methodological design (and hence bias of small studies), selective non-reporting (Kirkham 2010), and publication bias (Page 2022). Therefore, we will interpret the results carefully (Sterne 2011).

Data synthesis

We plan to undertake a meta-analysis only if we judge the participants, interventions, comparisons, and outcomes to be sufficiently similar to ensure a result that is clinically meaningful. Unless good evidence shows homogeneous effects across studies of different methodological quality, we will primarily summarise data using a random-effects model (Wood 2008). We will interpret random-effects meta-analyses with due consideration for the whole distribution of effects, and will present a confidence interval. We will perform statistical analyses according to the statistical guidelines presented in the Handbook (Deeks 2022).

Subgroup analysis and investigation of heterogeneity

We expect the following characteristics to introduce clinical heterogeneity, and we plan to carry out the following subgroup analyses, including an investigation of interactions (Altman 2003).

- By gender: some studies have found a greater proportional prevalence of goitre for females than males (Malboosbaf 2013)
- By age groups: children under six years of age; school-age children (6 to 12 years); adolescents (12 to 17 years). Schoolchildren are a particular group to monitor iodine deficiency, and the effect of iodine supplementation programmes (Lazarus 2021; Wainwright 2019).
- By iodine dosage: milligrams/micrograms
- By administration form: oral versus intramuscular via (Phillips 1988; Sankar 1995)
- By duration of intervention: single or periodic high-dose therapy, and continuous interventions with a minimum duration of eight weeks
- By studies in regions with concomitant active policies on iodine fortification in water, salt or food, or on preterm fortification, and studies in places without these policies

Sensitivity analysis

We plan to perform sensitivity analyses to explore the influence of the following factors (when applicable) on effect sizes, by restricting the analysis to the following.

- Studies with an overall low risk of bias, as specified in the Assessment of risk of bias in included studies section

- Very long or large studies, to establish the extent to which they dominate the results
- Cluster-randomized studies
- Studies without imputed data

Summary of findings and assessment of the certainty of the evidence

We will present the overall certainty of the evidence for each outcome specified below, according to the GRADE approach, which takes into account issues related to internal validity (overall risk of bias, inconsistency, imprecision, and publication bias) and external validity (such as directness of results). Two review authors (IV and MRE, MR and JR) will independently rate the certainty of the evidence for each outcome. We will resolve any differences in assessment by discussion or by consultation with a third review author (MT or PT).

We will present a summary of the evidence in a summary of findings table. This will provide key information about the best estimate of the magnitude of effect, in relative terms and as absolute differences, for each relevant comparison of alternative management strategies; the numbers of participants and studies addressing each important outcome; and a rating of overall confidence in effect estimates for each outcome. We will create the summary of findings table using the methods described in the Handbook (Schünemann 2022), using Review Manager (RevMan Web 2023), and GRADEpro GDT software (GRADEpro GDT).

If meta-analysis is not possible, we will present the results in a narrative format in the summary of findings table. We will justify all decisions to downgrade the certainty of the evidence by using informative footnotes, and we will use GRADE guidelines for informative statements (Santesso 2016; Santesso 2020).

We will create summary of findings tables for the following comparison/s and outcomes.

Comparison/s

- Iodine supplements versus placebo or no intervention

Outcomes, measured at the longest time of follow-up

- Cognitive function
- Growth
- Adverse events
- Hypothyroidism
- Health-related quality of life
- All-cause mortality
- Thyroid size or goitre

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The following people conducted the editorial process for this article:

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APPENDICES

Appendix 1. Search strategies

Cochrane Central Register of Controlled Trials (Cochrane Register of Studies Online)

#1 MESH DESCRIPTOR Congenital Hypothyroidism EXPLODE ALL TREES

#2 (iodine deficiency):TI,AB,KY

#3 (hypothyroid* or thyroid deficien* or TSH deficien* or thyroid stimulating hormone deficien*):TI,AB,KY

#4 MESH DESCRIPTOR Goiter EXPLODE ALL TREES

#5 MESH DESCRIPTOR Goiter, Endemic EXPLODE ALL TREES

#6 MESH DESCRIPTOR Iodine EXPLODE ALL TREES WITH QUALIFIERS AE,DF

#7 (goiter or goitre or goitrous):TI,AB,KY

#8 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7

#9 MESH DESCRIPTOR Iodine

#10 (iodine? or iodi?ed or iodi?ation):TI,AB,KY

#11 #9 OR #10

#12 MESH DESCRIPTOR Adolescent

#13 MESH DESCRIPTOR Child EXPLODE ALL TREES

#14 MESH DESCRIPTOR Infant

#15 MESH DESCRIPTOR Pediatrics

#16 minors:TI,AB,KY

#17 (boy or boys or boyhood):TI,AB,KY

#18 girl*:TI,AB,KY

#19 infant*:TI,AB,KY

(Continued)

#20 (baby or babies or neonat*):TI,AB,KY

#21 toddler?:TI,AB,KY

#22 (kid or kids):TI,AB,KY

#23 (child or childs or children* or childhood* or childcare* or schoolchild*):TI,AB,KY

#24 adolescen*:TI,AB,KY

#25 juvenil*:TI,AB,KY

#26 youth*:TI,AB,KY

#27 (teen* or preteen*):TI,AB,KY

#28 (underage* or under age*):TI,AB,KY

#29 pubescen*:TI,AB,KY

#30 p?ediatric*:TI,AB,KY

#31 #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30

#32 #8 AND #11 AND #31

MEDLINE (state platform/delete as appropriate: Ovid SP/PubMed/other)

MEDLINE (OvidSP)

Part 1: Condition

1. Congenital Hypothyroidism/

2. Iodine/df [Deficiency]

3. Iodine/ae [Adverse Effects]

2. iodine deficiency.tw.

3. Hypothyroidism/

4. (hypothyroid*.tw. or thyroid deficien*.tw. or TSH deficien*.tw. or thyroid stimulating hormone deficien*.tw.

5. Goiter/

6. Endemic Goiter/

7. (goiter or goitre or goitrous).tw.

8. or/1-7

Part 2: Intervention

10. Iodine/

11. (iodine? or iodi?ed or iodi?ation).tw.

12. or/10-11

(Continued)

Part 3: Population [adapted from Leclercq 2013]

13. Adolescent/

14. exp Child/

15. Infant/

16. Pediatrics/

17. minors.tw.

18. (boy or boys or boyhood).tw.

19. girl*.tw.

20. infant*.tw.

21. (baby or babies or neonat*).tw.

22. toddler?.tw.

23. (kid or kids).tw.

24. (child or childs or children* or childhood* or childcare* or schoolchild*).tw.

25. adolescen*.tw.

26. juvenil*.tw.

27. youth*.tw.

28. (teen* or preteen*).tw.

29. (underage* or under age*).tw.

30. pubescen*.tw.

31. p?ediatric*.tw.

32. or/13-31

Part 4: Condition + Intervention + Population

33. 8 and 12

34. 32 and 33

Part 5: Cochrane Handbook 2008 RCT filter –sensitivity max. version

35. randomized controlled trial.pt.

36. controlled clinical trial.pt.

37. randomi?ed.ab.

38. placebo.ab.

39. drug therapy.fs.

40. randomly.ab.

(Continued)

41. trial.ab.

42. groups.ab.

43. or/35-42

44. exp animals/ not humans/

45. 43 not 44

Part 6:

46. 34 and 45

WHO ICTRP Search Portal (Standard search)

WHO ICTRP Search Portal (*Standard search*)

(hypothyroidism OR "iodine deficien*" OR "TSH deficien*" OR "thyroid deficien*" OR goiter OR goitre OR goitrous) AND (child OR children OR childhood OR schoolchild* OR adolescent* OR minors OR juvenile* OR youth* OR teenager* OR pubescen* OR pediatric* OR paediatric* OR underage OR baby OR babies OR toddler* OR boy OR boys OR boyhood OR girl* OR infant* OR kids)

ClinicalTrials.gov (Advanced search)

ClinicalTrials.gov (*Advanced Search*)

Condition: hypothyroidism OR "iodine deficiency" OR "TSH deficiency" OR "thyroid deficiency" OR goiter OR goitre OR goitrous

Other terms: child OR children OR childhood OR schoolchildren OR adolescents OR minors OR juvenile OR youths OR teenagers OR pubescence OR pediatrics OR paediatrics OR underage OR baby OR babies OR toddlers OR boy OR boys OR boyhood OR girls OR infants OR kids

SinoMed (Advanced search)

1) "先天性甲状腺功能减退症"[不加权: 不扩展] OR "碘/副作用/缺乏"[不加权:扩展] OR "甲状腺功能减退症"[不加权: 不扩展]

2) "甲状腺肿"[不加权: 不扩展] OR "甲状腺肿, 地方性"[不加权: 不扩展]

3) "碘缺乏"[常用字段:智能] OR "缺碘"[常用字段:智能]

4) "甲状腺功能减退"[常用字段:智能] OR "甲状腺机能减退"[常用字段:智能] OR "甲减"[常用字段:智能]

5) "甲状腺低能"[常用字段:智能] OR "甲状腺激素缺乏"[常用字段:智能] OR "促甲状腺激素缺乏"[常用字段:智能] OR "TSH缺乏"[常用字段:智能]

6) "甲状腺肿"[常用字段:智能]

7) (#6) OR (#5) OR (#4) OR (#3) OR (#2) OR (#1)

8) "碘"[不加权: 不扩展]

9) "碘"[常用字段:智能]

10) (#9) OR (#8)

11) "青少年"[不加权: 不扩展] OR "儿童"[不加权: 扩展] OR "婴儿"[不加权: 不扩展] OR "儿科学"[不加权: 不扩展]

(Continued)

12) "未成年"[常用字段:智能] OR "低龄"[常用字段:智能] OR "幼年"[常用字段:智能] OR "学童"[常用字段:智能] OR "学龄"[常用字段:智能] OR "小学生"[常用字段:智能]

13) "青年"[常用字段:智能] OR "少年"[常用字段:智能] OR "青少年"[常用字段:智能] OR "青春期"[常用字段:智能] OR "年轻"[常用字段:智能]

14) "婴儿"[常用字段:智能] OR "幼儿"[常用字段:智能] OR "婴幼儿"[常用字段:智能] OR "新生儿"[常用字段:智能] OR "早产儿"[常用字段:智能] OR "儿童"[常用字段:智能] OR "幼童"[常用字段:智能] OR "年幼"[常用字段:智能] OR "小儿"[常用字段:智能] OR "儿科"[常用字段:智能] OR "患儿"[常用字段:智能]

15) "少男"[常用字段:智能] OR "少女"[常用字段:智能] OR "男婴"[常用字段:智能] OR "女婴"[常用字段:智能] OR "幼女"[常用字段:智能] OR "幼男"[常用字段:智能] OR "女孩"[常用字段:智能] OR "男孩"[常用字段:智能] OR "未婚女性"[常用字段:智能] OR "未婚男性"[常用字段:智能]

16) (#15) OR (#14) OR (#13) OR (#12) OR (#11)

17) (#16) AND (#10) AND (#7)

18) "随机"[常用字段:智能] OR "对照组"[常用字段:智能] OR "安慰剂"[常用字段:智能] OR "对照"[中文标题:智能] OR "比较"[中文标题:智能] OR "试验"[中文标题:智能]

19) "药物疗法"[不加权: 不扩展]

20) "动物"[不加权:扩展] NOT "人类"[不加权:扩展]

21) (#19) OR (#18)

22) #21 NOT #20

23) (#22) AND (#17)

CNKI (Expert search)

((SU %= 先天性甲状腺功能减退症+碘缺乏+甲状腺功能减退症+甲状腺肿) or

(TKA = 甲状腺功能减退症+甲状腺功能减退病+甲状腺功能减退+甲状腺机能减退+甲减+

碘缺乏+缺碘+

甲状腺低能+甲状腺激素缺乏+促甲状腺激素缺乏+TSH缺乏+甲状腺肿)) and

(SU %= 碘 or TKA = 碘) and

((SU %= 青少年+儿童+婴儿+儿科) or

(TKA = 未成年+低龄+幼年+学童+学龄+小学生+

青年+少年+青少年+青春期+年轻+

婴儿+幼儿+婴幼儿+新生儿+早产儿+儿童+幼童+年幼+小儿+儿科+患儿+

少男+少女+男婴+女婴+幼女+幼男+女孩+男孩+未婚女性+未婚男性)) and

((TKA = 随机+对照组+安慰剂) or

(TI = 对照+比较+试验)) not

(TI = 大鼠+小鼠+鼠+兔)

WanFang (Expert search)

全部: ("先天性甲状腺功能减退症" or "甲状腺功能减退症" or "甲状腺功能减退病" or "甲状腺功能减退" or "甲状腺机能减退" or "甲减" or

"碘缺乏" or "缺碘" or

(Continued)

"甲状腺低能" or "甲状腺激素缺乏" or "促甲状腺激素缺乏" or "TSH缺乏" or "甲状腺肿") and

全部: ("碘") and

全部: ("未成年" or "低龄" or "幼年" or "学童" or "学龄" or "小学生" or "儿科" or

"青年" or "少年" or "青少年" or "青春期" or "年轻" or

"婴儿" or "幼儿" or "婴幼儿" or "新生儿" or "早产儿" or "儿童" or "幼童" or "年幼" or "小儿" or "儿科" or "患儿" or

"少男" or "少女" or "男婴" or "女婴" or "幼女" or "幼男" or "女孩" or "男孩" or "未婚女性" or "未婚男性") and

(全部: ("随机" or "对照组" or "安慰剂") or

题名: ("对照" or "比较" or "试验")) not

题名: ("大鼠" or "小鼠" or "鼠" or "兔")

VIP (Expert search)

(U = "先天性甲状腺功能减退症" or "甲状腺功能减退症" or "甲状腺功能减退病" or "甲状腺功能减退" or "甲状腺机能减退" or "甲减" or

"碘缺乏" or "缺碘" or

"甲状腺低能" or "甲状腺激素缺乏" or "促甲状腺激素缺乏" or "TSH缺乏" or "甲状腺肿") and

(U = "碘") and

(U = "未成年" or "低龄" or "幼年" or "学童" or "学龄" or "小学生" or "儿科" or

"青年" or "少年" or "青少年" or "青春期" or "年轻" or

"婴儿" or "幼儿" or "婴幼儿" or "新生儿" or "早产儿" or "儿童" or "幼童" or "年幼" or "小儿" or "儿科" or "患儿" or

"少男" or "少女" or "男婴" or "女婴" or "幼女" or "幼男" or "女孩" or "男孩" or "未婚女性" or "未婚男性") and

((U = "随机" or "对照组" or "安慰剂") or

(T = "对照" or "比较" or "试验")) not

(T = "大鼠" or "小鼠" or "鼠" or "兔")

Other databases and resources

Scopus (Elsevier) (*Advanced Search*)

1. TITLE-ABS("iodine deficien*" OR hypothyroid* OR "thyroid deficien*" OR "TSH deficien*" OR "thyroid stimulating hormone deficien*" OR goiter OR goitre OR goitrous)

2. TITLE-ABS(iodine? OR iodi?ed OR iodi?ation)

3. TITLE-ABS(child OR childs OR children* OR childhood* OR childcare* OR schoolchild* OR adolescent* OR juvenile* OR youth* OR teen* OR preteen* OR underage* OR "under age" OR pubescen* OR p?ediatric* OR minors OR boy OR boys OR boyhood OR girl* OR infant* OR baby OR babies OR toddler* OR neonat* OR kid OR kids OR child OR childs OR children* OR childhood* OR childcare* OR schoolchild* OR adolescen* OR juvenil* OR youth* OR teen* OR preteen* OR underage* OR "under age*" OR pubescen* OR p?ediatric*)

4. TITLE-ABS(random* OR "double blind*") OR TITLE-ABS-KEY(placebo*)

5. #1 AND #2 AND #3 AND #4

WHO Global Index Medicus (*Advanced Search*)

(Continued)

tw:((tw:(hypothyroidism OR "iodine deficiency" OR "TSH deficiency" OR "thyroid deficiency" OR "thyroid stimulating hormone deficiency" OR goiter OR goitre OR goitrous)) AND (tw:(child OR children OR childhood OR schoolchild* OR adolescen* OR minors OR juvenile* OR youth* OR teen* OR preteen* OR pubescen* OR pediatric* OR paediatric* OR underage OR "under age" OR baby OR babies OR toddler* OR boy OR boys OR boyhood OR girls OR infant* OR kid OR kids)) AND (tw:(random* OR "double blind" OR "double blinded" OR placebo*)))

TRoPHI (EPPI) (*Freetext search*)

1. "hypothyroidism" OR "iodine deficien*" OR "TSH deficien*" OR "thyroid deficien*" OR "thyroid stimulating hormone deficien*" OR "goiter" OR "goitre" OR "goitrous"

2. "iodine" OR "iodized" OR "iodised" OR "iodization" OR "iodisation"

3. "child" OR "childs" OR "children" OR "childhood" OR "childcare" OR "schoolchild*" OR "adolescen*" OR "juvenile*" OR "youth*" OR "teen*" OR "preteen*" OR "underage" OR "under age" OR "pubescen*" OR "paediatric*" OR "pediatric*" OR "minors" OR "boy" OR "boys" OR "boyhood" OR "girls" OR "infant*" OR "baby" OR "babies" OR "toddler*" OR "neonate*" OR "kid" OR "kids"

4. "random*" OR "double blind*" OR "placebo*"

5. #1 AND #2 AND #3 AND #4

Open Grey (*Freetext search*)

(hypothyroidism OR iodine deficien* OR TSH deficien* OR thyroid deficien* OR goiter OR goitre OR goitrous) AND (child OR children OR childhood OR childcare OR schoolchild* OR adolescen* OR juvenile* OR youth* OR minors OR juvenile* OR youth* OR teen* OR preteen* OR pubescen* OR pediatric* OR paediatric* OR underage OR "under age" OR baby OR babies OR toddler* OR boy OR boys OR boyhood OR girls OR infant* OR kid OR kids)

CONTRIBUTIONS OF AUTHORS

Ines Velasco (IV): Review, analysis and writing.

Mikel Rueda-Etxebarria (MRE): Review, analysis and writing.

Peter Taylor (PT): Writing and correction.

Montserrat Rabassa Bonet (MRB): Review, analysis and writing.

José-Ramón Rueda (JRR): Review, analysis and writing.

Yuan Chi (YC): Search strategy, analysis of Chinese data.

Heidrun Janka (HH): Search strategy. HJ is a member of the Cochrane Metabolic and Endocrine Disorders Group, but she was excluded from the editorial process of the review.

All protocol authors contributed to, read and approved the final protocol draft.

DECLARATIONS OF INTEREST

Ines Velasco (IV): none known.

Mikel Rueda-Etxebarria (MRE): none known.

Maria Angelica Trak-Fellermeier (MTF): none known.

Peter Taylor (PT): none known.

Montserrat Rabassa Bonet (MRB): none known.

José-Ramón Rueda (JRR): none known.

Heidrun Janka (HJ): none known. HJ is a member of the Cochrane Metabolic and Endocrine Disorders Group, but she was excluded from the editorial process of the review.

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  salary for M Rueda-Etxebarria

External sources

- none to declare, Other

  none

NOTES

We have based parts of the Methods of this Cochrane Protocol on a standard template established by the CMED Group.