Effect and safety of salt iodization to prevent iodine deficiency disorders: *a systematic review with meta-analyses*

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Abstract

Background: Iodine deficiency, one of the most prevalent micronutrient deficiencies globally, is the main cause of potentially preventable mental retardation in childhood, as well as a spectrum of morbidities referred to as iodine deficiency disorders. Iodization of salt is recommended to prevent and treat many of these disorders.

Objective: To assess the effects and safety of consumption of iodized salt in the prevention of iodine deficiency disorders.

Data sources: The following databases were searched: China National Knowledge Infrastructure, the Cochrane Library, EMBASE, MEDLINE, VIP (the register of Chinese trials developed by the Chinese Cochrane Centre), The Virtual Health Library of the Pan-American Health Organization, WANFANG, the World Health Organization (WHO) International Clinical Trials Platform search portal, and the WHO Global Health Library regional databases. Relevant agencies were contacted, and the reference lists were reviewed.

Study appraisal and synthesis methods: Randomized controlled trials (RCTs), non-RCTs, quasi-experimental, cohort, and multiple cross-sectional studies were included. All studies compared a group of individuals with exposure to iodized salt to a group without exposure to iodized salt. Two or more reviewers independently screened potential studies, extracted study characteristics and outcomes and, when possible, conducted meta-analyses to estimate the effect of iodized salt relative to non-iodized salt. Results are presented as mean differences (MDs), risk ratios (RRs), prevalence ratios (PRs), or odds ratios (ORs), with 95% confidence intervals (CIs).

Results: Two RCTs, 6 non-RCTs, 20 quasi-experimental studies, 16 cohort studies, 42 multiple cross-sectional studies, and 3 studies with mixed designs were included. The numbers of participants ranged from 30 in a cohort study to over 5 000 000 in a multiple cross-sectional registry study. Iodized salt significantly reduced the risk of goitre (non-RCTs RR = 0.59 [95% CI = 0.36 to 0.95]; cohort RR = 0.30 [95% CI = 0.23 to 0.41]; multiple cross-sectional PR = 0.18 [95% CI = 0.14 to 0.22]), cretinism (multiple cross-sectional OR = 0.13 [95% CI = 0.08 to 0.20]), low intelligence (quasi-experimental RR = 0.28 [95% CI = 0.21 to 0.36]; multiple cross-sectional PR = 0.24 [95% CI = 0.07 to 0.82]), and low urinary iodine excretion (multiple cross-sectional PR = 0.45 [95% CI = 0.34 to 0.59]). Iodized salt significantly increased intelligence quotient (quasi-experimental MD = 8·18 [95% CI = 6·71 to 9·65]; multiple cross-sectional MD = 10.45 [95% CI = 4·79 to 16·11]) and urinary iodine excretion (cohort MD = 59.22 [95% CI = 50.40 to 68.04]; multiple cross-sectional MD = 72·35 [95% CI = 44·54 to 100.17]). The results regarding the potential adverse effect of hypothyroidism showed no relationship (cohort OR = 1.14 [95% CI = 0.84 to 1.53]; multiple cross-sectional OR = 1.13 [95% CI = 0.94 to 1.36]), and the results for hyperthyroidism were inconsistent and dependent on study design (cohort OR = 1.36 [95% CI = 1.12 to 1.66]; multiple cross-sectional OR = 0.96 [95% CI = 0.92 to 1.00]). The quality of evidence varied from very low to moderate, depending on outcome and study design.

Conclusions: This review showed that iodized salt has a large effect on reducing the risk of goitre, cretinism, low cognitive function and iodine deficiency. Robust monitoring of salt iodization programmes is important, to ensure safe and effective levels of iodine consumption, especially as countries implement programmes to reduce population salt intake.

Plain language summary

Iodine deficiency causes a spectrum of disorders, from poor growth, retarded development, low urinary iodine excretion and poor cognitive function and goitre, to severe cognitive disability and death. Consistent consumption of small quantities of iodine can prevent these disorders and reverse some, but not all, of the negative effects of iodine deficiency. In 1993, the World Health Organization (WHO), the United Nations Children's Fund (UNICEF) and the International Council for the Control of Iodine Deficiency Disorders (ICCIDD) recommended universal iodization of salt to prevent and treat iodine deficiency disorders, and this recommendation remains today. Salt is a good vehicle for iodization because it is consumed almost universally without seasonal variation; there are relatively few production facilities, simplifying quality control; technology for iodization is well established; consumer acceptability of iodized salt is high; and iodization is very inexpensive. However, elevated salt intake results in elevated blood pressure and is associated with cardiovascular disease, and globally most populations consume salt at levels far exceeding needs. Therefore, public health policies based on WHO recommendations seek to reduce population salt intakes.

This systematic review and the corresponding meta-analyses provide the first comprehensive synthesis of available data comparing consumption of, or exposure to, iodized salt on an entire array of iodine deficiency disorders, including goitre, urinary iodine excretion, cretinism, cognitive function and potential adverse effects such as hypothyroidism and hyperthyroidism. Because this review comprised diverse study designs, including randomized controlled trials, non-randomized controlled trials, quasi-experimental, cohort observational, and multiple cross-sectional studies, the study was large enough to explore the effectiveness of iodized salt for preventing iodine deficiency disorders by a number of subgroups, such as age, physiological status, concentration of iodine in the salt, and risk of iodine deficiency disorders at baseline. The additional information on the large number of outcomes and on potential effect modifiers provides important information for assessing and informing an update of the current WHO guidelines on salt iodization, especially in the context of renewed efforts to reduce salt consumption globally.

Background

Iodine deficiency, one of the most prevalent micronutrient deficiencies globally *(1)*, is the main cause of potentially preventable cognitive disability in childhood *(2)*. Iodine is a trace element that is an integral part of the thyroid hormones essential for fetal development, regulation of metabolic activities of cells, and proper growth and development *(3)*. When iodine requirements go unmet, synthesis of thyroid hormones is impaired, resulting in a spectrum of growth, developmental and functional abnormalities referred to as iodine deficiency disorders *(4)*. Goitre, swelling of the thyroid gland, is the most common manifestation of iodine deficiency in both children and adults *(4, 5)*. Severe iodine deficiency during pregnancy results in fetal death or cretinism, marked by severe mental and physical growth retardation. Mild and moderate deficiency during pregnancy hinders fetal development, and offspring are at high risk of speech and hearing defects and impaired motor and physical growth. Iodine deficiency during infancy and early childhood can also cause irreversible deficits in cognitive development.

The World Health Organization (WHO) estimates that approximately 37% of school-age children, 285 million, and nearly 2 billion individuals worldwide, have insufficient iodine intake *(6, 7)*. Mountainous areas are particularly susceptible to iodine deficiency, owing to low levels of iodine in the soil and, thus, the locally grown and raised food *(8)*. However, iodine deficiency is common in many contexts globally and is considered a public health problem in more than 50 countries *(6)*.

WHO, the United Nations Children's Fund (UNICEF) and the International Council for the Control of Iodine Deficiency Disorders Global Network (ICCIDD) promote salt iodization for the control of iodine deficiency disorders because: (i) salt is widely consumed by virtually all population groups in all countries, with little seasonal variation in consumption; (ii) salt production is generally limited to a few centres, facilitating quality control; (iii) technology for salt iodization is well established and relatively easy to transfer to less developed countries; (iv) iodization does not affect the organoleptic properties of salt and, therefore, consumer acceptability is high; and (v) iodization is very inexpensive. To date, more than 120 countries with all levels of deficiency risk are implementing large-scale salt iodization *(9)*. Despite the known benefits of appropriate consumption of iodine, some concern exists that widespread salt iodization could potentially lead to excess iodine intake *(10)*. Furthermore, though policies to support salt iodization and reduce sodium intake are compatible, there is concern that, as populations reduce salt intake to reduce the risk of elevated blood pressure, hypertension and stroke, there may be an increase in iodine deficiency disorders *(11–13)*.

A systematic review of the effectiveness of iodization of salt in preventing iodine deficiency disorders, published in 2002, included data from populations at high risk of iodine deficiency, and controlled trials, and concluded that salt iodization was an effective means of improving iodine status *(14)*. Because it included only six studies, it could not address many outcomes of interest, nor explore potential effect modifiers. The objective of the current systematic review and meta-analyses is to assess the effect and safety of iodized salt compared to non-iodized salt, to prevent the numerous outcomes comprising iodine deficiency disorders. Furthermore, it aims to explore whether results are affected by age, physiological status, concentration of iodine in salt, population salt consumption, or underlying risk of iodine deficiency.

Methods

Study characteristics

Randomized controlled trials (RCTs), non-RCTs, quasi-experimental studies, cohort observational studies and multiple cross-sectional observational studies were included. The participants could be adults (>15 years of age) and children of any age (0–15 years) and of either sex. Populations could be in the general population (free living) or part of specific populations, such as refugees. Studies in apparently healthy populations that may or may not have been at risk or suffered from iodine deficiency were considered. The review also included studies that compared outcomes between groups consuming iodized salt and groups consuming non-iodized salt. Salt could have been fortified with other micronutrients if the only difference between groups was the inclusion of iodine in the fortificant. An attempt was made to collect the following outcomes: all-cause mortality, goitre, mental or physical development, cretinism, cognitive function, urinary iodine concentration, thyroid-stimulating hormone (TSH) concentration, serum thyroglobulin concentration, hypothyroidism, hyperthyroidism, and adverse effects reported by study authors.

Search methods

The following sources were searched: The China National Knowledge Infrastructure (May 2011); the Cochrane Library (Issue 5, 2011), including the Cochrane Controlled Trials Register; EMBASE (1966 to 18 June, 2011); MEDLINE (PubMed 1966 to 31 May, 2011); The Virtual Health Library of the Pan-American Health Organization (May 2011); VIP (the register of Chinese trials developed by the Chinese Cochrane Centre); WANFANG; the WHO International Clinical Trials Registry Platform (18 June 2011); and the WHO Global Health Library regional databases (June 2011). For the detailed search strategy used for the electronic search, see Annex 1. The following websites were also searched: Google, ICCIDD, Thyroid Disease Manager, and the WHO Department of Nutrition for Health and Development. The following organizations were contacted: the Sprinkles Global Health Initiative, the Home Fortification Technical Advisory Group, the nutrition section of UNICEF, the United Nations World Food Programme (WFP), the Micronutrient Initiative (MI), the Global Alliance for Improved Nutrition (GAIN), Helen Keller International (HKI), Sight and Life Foundation, the United States (US) Centers for Disease Control and Prevention (CDC), the Iodine Network, and ICCIDD. The following journals were hand searched: *Chinese Journal of Control of Endemic Diseases*, *Chinese Journal of Epidemiology*, *Chinese Journal of Preventive Medicine* and *Studies of Trace Elements and Health*. The reference lists of identified papers were also scanned.

Data collection and analysis

Selection of studies

Two reviewers independently assessed references for potential relevance. The full manuscript was retrieved when the title, abstract and keywords suggested that the study: (i) compared a group consuming iodized salt to a group consuming non-iodized salt; (ii) reported on an outcome of interest; or (iii) was unclear regarding these criteria. Two reviewers independently assessed all potentially eligible studies, according to the above prespecified inclusion criteria, while two other reviewers assessed the relevance of one third of those selected for full review. An adapted preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart was used to depict the selection of studies for inclusion *(15)*.

Data extraction and management

Two reviewers independently extracted relevant characteristics of the populations and interventions of each study. A third reviewer checked the data, and disagreements were resolved through consensus. In the case of articles originally published in the Chinese language, studies were screened and data extracted in duplicate before translation, and then again after translation to English. Any relevant missing information was requested from the original study authors. In the case of companion papers of a primary study, all available data were simultaneously evaluated, to maximize the yield of information. For RCTs, the risk of bias associated with the method of sequence generation, allocation concealment, blinding, selective reporting, loss to follow-up, and completeness of outcome data was assessed. For observational studies, the risk of bias associated with the method of measuring exposure, collecting outcome data, and selecting participants was also evaluated. The risk of bias was rated as low, unclear or high, according to established criteria *(16, 17)*. A risk of bias graph and a risk of bias summary were generated. The quality of the entire body of evidence was assessed, using the grading of recommendations assessment, development and evaluation (GRADE) methodology *(18)* and GRADEProfiler software (version 3.6, 2011).

Statistical analysis

An overall effect estimate for dichotomous data was calculated as a risk ratio (RR) with 95% confidence interval (CI), or an odds ratio (OR), in the case of rare events *(19)*. For multiple cross-sectional studies, prevalence ratios (PRs) were reported for the overall effect estimate from dichotomous outcomes. For continuous variables, the overall effect estimate was calculated as the difference in means, with 95% CI, between the group consuming iodized salt (intervention) and the group consuming non-iodized salt (control/comparison). To combine data and generate overall effect estimates, RRs, PRs, and mean differences (MDs) were calculated, using the inverse variance method, random effects, and, for ORs, the Peto method, fixed effects meta-analysis in Review Manager software (Copenhagen, 2011) *(17, 19)* was used. When a study reported results for multiple intervention groups with multiple control groups, all comparisons were included in the pooled analysis. When outcomes were assessed at more than one time point, data from the latest time point were used for the pooled analysis, and all relevant time points were used for subgrouping by study duration.

Results were considered to be statistically significant at $\alpha = 0.05$. Evidence was considered conclusive and the estimate precise if the point estimate suggested a benefit or harm and the 95% CI did not overlap a threshold of relevance. If the point estimate was near the null value and the CI did not overlap a threshold of relevance, evidence was considered conclusive of no effect. Conversely, evidence was considered to be inconclusive, and the point estimate imprecise, if the point estimate suggested a