

Iodised salt for preventing iodine deficiency disorders (Review)

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[Intervention Review]

Iodised salt for preventing iodine deficiency disorders

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ABSTRACT

Background

Iodine deficiency is the main cause for potentially preventable mental retardation in childhood, as well as causing goitre and hypothyroidism in people of all ages. It is still prevalent in large parts of the world.

Objectives

To assess the effects of iodised salt in comparison with other forms of iodine supplementation or placebo in the prevention of iodine deficiency disorders.

Search methods

We searched *The Cochrane Library*, MEDLINE, the Register of Chinese trials developed by the Chinese Cochrane Centre, and the Chinese Med Database, China National knowledge Infrastructure, and searched reference lists, databases of ongoing trials and the Internet.

Selection criteria

We included prospective controlled studies of iodised salt versus other forms of iodine supplementation or placebo in people living in areas of iodine deficiency. Studies reported mainly goitre rates and urinary iodine excretion as outcome measures.

Data collection and analysis

The initial data selection and quality assessment of trials was done independently by two reviewers. Subsequently, after the scope of the review was slightly widened from including only randomised controlled trials to including non-randomised prospective comparative studies, a third reviewer repeated the trials selection and quality assessment. As the studies identified were not sufficiently similar and not of sufficient quality, we did not do a meta-analysis but summarised the data in a narrative format.

Main results

We found six prospective controlled trials relating to our question. Four of these were described as randomised controlled trials, one was a prospective controlled trial that did not specify allocation to comparison groups, and one was a repeated cross-sectional study comparing different interventions. Comparison interventions included non-iodised salt, iodised water, iodised oil, and salt iodisation with potassium iodide versus potassium iodate. Numbers of participants in the trials ranged from 35 to 334; over 20,000 people were

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included in the cross-sectional study. Three studies were in children only, two investigated both groups of children and adults and one investigated pregnant women. There was a tendency towards goitre reduction with iodised salt, although this was not significant in all studies. There was also an improved iodine status in most studies (except in small children in one of the studies), although urinary iodine excretion did not always reach the levels recommended by the WHO. None of the studies observed any adverse effects of iodised salt.

Authors' conclusions

The results suggest that iodised salt is an effective means of improving iodine status. No conclusions can be made about improvements in other, more patient-oriented outcomes, such as physical and mental development in children and mortality. None of the studies specifically investigated development of iodine-induced hyperthyroidism, which can be easily overlooked if just assessed on the basis of symptoms. High quality controlled studies investigating relevant long term outcome measures are needed to address questions of dosage and best means of iodine supplementation in different population groups and settings.

PLAIN LANGUAGE SUMMARY

Iodised salt for preventing iodine deficiency disorders

Iodine deficiency causes mental retardation in children as well as enlarged thyroid glands (goitre) and deficiencies in thyroid hormones in people of all ages. It still exists in large parts of the world. This review looked at studies of iodised salt in the diet that included a comparison group. Six studies, most of them in children but some also in adults, were included. Iodine in the urine increased in all but one studies, but there was some concern that small children did not eat enough salt to achieve adequate iodine status. Some studies, but not all, also showed a reduction in the enlargement of the thyroid gland (goitre) that can accompany lack of iodine in the diet. Adverse effects were not reported, but these may not have been studied adequately. More high quality long term studies measuring outcomes related to child development, to deaths associated with iodine-deficiency and to adverse effects are needed.

BACKGROUND

Description of the condition

Iodine deficiency (urinary iodine excretion less than 100 µg/day) is the main cause for potentially preventable mental retardation in childhood (WHO 1993). It causes hypothyroidism, resulting in thyroid enlargement, mental retardation, increased neonatal and infant mortality, retardation of growth and development of the central nervous system in children (cretinism), reproductive failure, and an increase of fluid in the tissues (myxoedema) (Delong 1994; Beaufre 2000). There are three main laboratory indicators of iodine deficiency: increased TSH concentration in neonatal blood and cord blood, increased concentration of thyroglobulin, and decreased concentration of iodine in the urine. Development of goitre, i.e. an enlargement of the thyroid gland (due to stimulation of growth by TSH), is common (endemic goitre) and does not need to be accompanied by an abnormality in thyroid hormones (euthyroid goitre).

Iodine deficiency is common, especially in Asia and Africa, but also in large parts of Eastern Europe. Only a small number of

countries currently have sustainable iodine sufficiency, and about a third of the world's population lives in areas with some iodine deficiency. Inland areas, especially mountainous areas like the Alps, Himalayas and the Andes are particularly iodine deficient (Dunn 2004). Iodine deficiency disorders are a global health problem with nearly two billion people at risk (FAO/WHO/IAEA 1996). In countries such as China, the incidence of iodine deficiency diseases in children and pregnant women in areas of iodine deficiency may be up to 50% (Fong 1981; Chen 1984; Lin 1995; Li 1997). In certain Asian, African and Latin American countries iodine deficiency diseases affect more than 200 million people (WHO 1993).

Diagnosis of iodine deficiency disorders

The following recommendations regarding assessment of iodine deficiency disorders are given by the WHO (in collaboration with the United Nations' Children's Fund (UNICEF) and the IC-CIDD) (WHO 2001):

Urinary iodine levels are useful for assessing iodine status as a result of recent iodine intake. Even though intra-individual variation

exists, this tends to even out among populations. Twenty-four hour urine samples and relating urinary iodine to creatinine are not recommended.

One variable often measured is thyroid size. However, the determination of thyroid size is not feasible in neonates and it may be of limited use in school children (8-12 years), a group often studied, as the highest prevalence of goitre occurs during puberty and childbearing age. The two most common methods of measuring thyroid size are by palpation or by ultrasonography. While many studies assess goitre by palpation, the WHO suggests that this is not a very useful technique for determining the impact of iodisation programmes, where thyroid volumes may decrease over time, making the assessment difficult. The technique and classification of measurement of goitre by palpation are specified by the WHO. Ultrasonography is the method of choice for assessing the impact of iodisation programmes on thyroid size, an application of the technique is becoming feasible even in remote areas of the world (the 'thyromobil project').

Measurement of TSH levels, which are expected to be elevated in iodine deficiency, is not a reliable indicator in school children and adults as differences to normal levels are small and there is a large overlap between values in people who are iodine sufficient and those who are iodine deficient. However, TSH levels are a good indicator of iodine deficiency in neonates. Increased thyroglobulin levels are a good indicator of thyroid hyperplasia resulting from iodine deficiency. Thyroglobulin levels reflect iodine nutrition over months and years, whereas urinary iodine levels measure the more immediate effects of increased iodine intake on iodine status. Measurement of thyroid hormones (T3 and T4) is not recommended, as the tests are difficult and expensive and the measurements are not very reliable indicators of iodine deficiency.

Description of the intervention

Iodine

Iodine is a trace element which is an integral part of the thyroid hormones thyroxine (T4) and triiodothyronine (T3), produced by the thyroid gland, a small butterfly-shaped organ situated in the neck. Thyroid hormones are essential for regulating and stimulating metabolism, temperature control, and normal growth and development (Larsen 1981). Synthesis and release of thyroid hormones are stimulated by thyroid-stimulating hormone (TSH, thyrotropin), which is released from the pituitary gland; this regulation is subject to feedback inhibition.

History of prevention of iodine deficiency disorders

Large programmes for the prevention of iodine deficiency - or more specifically endemic goitre - using iodised salt were already initiated in Switzerland and in the USA in the 1920s, where large sur-

veys of goitre incidence before and after the intervention showed the use of iodised salt to be an effective preventative intervention. New Zealand followed in 1941 but only very low iodisation levels were used in the first 20 years. Then in the 1950s and the 1960s a number of European countries followed, with associated reductions in endemic goitre rates. Before 1960, interventions for iodine deficiency disorders were pursued by every country independently. Between 1961 and 1973, the Pan-American Health Organization (PAHO) and the World Health Organisation (WHO) had four international meetings regarding interventions for iodine deficiency. At the fourth meeting in 1973, diagnostic criteria, measures of intervention, and directions of research were suggested. At the fifth meeting in 1983, these diagnostic criteria were revised. In 1986, the International Council for the Control of Iodine Deficiency Disorders (ICCIDD) was established in Kathmandu, Nepal. Based on the proposal of the ICCIDD, the 39th World Health Congress in 1986, declared that iodine deficiency disorders should be controlled within the following ten years. Since its establishment in 1986, the ICCIDD's work focused on Africa and South-East Asia. The 43rd World Health Congress in 1990 declared that iodine deficiency disorders should have disappeared from the earth by 2000. Also in 1990, the 71 heads of States and 80 other officials from 150 governments who attended the World Summit for Children held in New York in 1990 adopted the goal of virtual elimination of iodine deficiency disorders by the year 2000. In response to this recommendation, most of the countries with iodine deficiency problems agreed to try to iodise 90% of all edible salt by 1995. However, iodine deficiency disorders have not yet been eliminated and 36 affected countries have not yet introduced salt iodisation programmes (see [Delange 2001](#)).

Salt iodisation

Iodised salt, iodised bread, iodised water and injecting iodine oil are commonly used for preventing iodine deficiency disorders. Iodised salt is considered the most appropriate means of iodine supplementation for the following reasons: 1. It is consumed by nearly everyone at roughly equal amounts throughout the year, 2. Salt production is limited to a few centres, facilitating quality control, 3. Addition of iodate or iodide does not affect the taste or smell of the salt, and 4. Iodisation is cheap (less than 0.01 US Dollar a day for the estimated amount of salt intake). However, there have been problems with implementing salt iodisation in countries with numerous scattered salt deposits and complex distribution systems, so alternatives are sometimes required ([Dunn 2004](#)).

Salt is commonly iodised using potassium iodate (KIO₃) or potassium iodide (KI). Potassium iodate is the more stable and less soluble form, making it the recommended form, especially for use in moist tropical locations. The WHO recommends a daily intake of 90 µg of iodine for infants (0-59 months), 120 µg for schoolchildren (6-12 years), 150 µg for adolescents and adults

and 200 µg for pregnant and lactating women. The appropriate level of salt iodisation will depend on the individual consumption of salt, the degree of iodine deficiency in the area and the loss of iodine from producer to consumer. All these factors will be different in different countries, and levels of salt iodisation have varied substantially between countries and over time. Currently, iodisation levels of 20–40 mg iodine per kg of salt are recommended. In addition, the response to supplemental iodine may be reduced by other factors in the environment, such as consumption of specific goitrogenic foods (for example, cassava (manioc)), and deficiency of other trace elements in the diet, such as selenium (Yang 1997; Köhrle 1999) or iron (Zimmermann 2000).

Why it is important to do this review

Many large surveys on goitre prevalence have been carried out worldwide, but only few controlled trials on the effectiveness of iodised salt for goitre prevention have been done. A Cochrane review (Mahomed 2001) investigates the effect of maternal iodine supplementation in pregnant women. The review suggests that iodine supplementation leads to improved outcomes in the children of the mothers having received the supplements (decreased mortality, decreased prevalence of cretinism and increased scores of psychomotor development). However, as the review only included pregnant women and outcomes in their children, and as none of the included studies used iodised salt, conclusions cannot be drawn regarding the effects of supplementation with iodised salt in the general population. A small number of controlled trials have suggested that iodised salt may be effective at preventing iodine deficiency disorders. There remains some uncertainty whether goitre rates are reduced by the supply of iodised salt (Hintze 1988; Foo 1996; Yang 1997). Furthermore, there is some evidence that correcting for iodine deficiency with excessive supplementation of iodine increases the risk of iodine-induced hyperthyroidism (Delange 1999) and thyroid auto-immunity (Kahaly 1997).

In light of this incomplete evidence and the possibility of adverse effects, a systematic review of controlled trials of iodised salt in comparison to other forms of iodine supplementation in the general population is needed.

OBJECTIVES

To assess the effects of iodised salt in comparison with placebo and other forms of iodine supplementation on the incidence of iodine deficiency disorders.

Additional questions were as follows:

- if iodised salt is effective, what is the optimum level of salt iodisation under given conditions?

- are there any adverse effects associated with salt iodisation (e.g. iodine-induced hyperthyroidism, iodine-induced anaphylaxis)?

METHODS

Criteria for considering studies for this review

Types of studies

Originally we had intended to include only randomised controlled trials in this review. However, after becoming better acquainted with the literature, we felt that it would be appropriate also to include other types of prospective comparative epidemiological studies. We therefore included in this review any prospective study that had a control group and studied the prevention of iodine deficiency disorders using iodised salt. We were particularly interested in randomised and quasi-randomised trials of a duration of at least one year, but other controlled trials were also considered. Trials using indicators for assessment of iodine deficiency disorders that are approved by the WHO, UNICEF and the ICCIDD were preferred.

Types of participants

The review includes trial participants (adults and children) living in areas with low iodine intake (iodine deficiency). Controlled trials of iodine supplementation before or during pregnancy with outcomes referring only to the neonate were excluded as these have already been included in another Cochrane review (Mahomed 2001).

Types of interventions

We were interested in comparisons of iodised salt (using iodide or iodate) with placebo or with other forms of iodine supplementation (for example, iodised oil, iodised water).

Types of outcome measures

Primary outcomes

- mortality related to iodine deficiency disorders;
- goitre (thyroid size);
- physical and mental development in children;
- symptoms of hypothyroidism (for example, reproductive failure/infertility, myxoedema, tiredness, lethargy, slowing of mental function, cold intolerance, cardiac complications).

Secondary outcomes

- urinary iodine concentration;
- thyroid-stimulating hormone (TSH) concentration in blood and neonatal cord blood;
- serum thyroglobulin concentration;
- adverse effects (for example, iodine-induced hyperthyroidism);
- health-related quality of life (ideally using a validated instrument);
- costs;
- compliance;
- socioeconomic and related effects (for example, school performance, per capita income).

Timing of outcome assessment

We had planned to assess outcomes in the short (up to six months), medium (seven months to one year) and long (more than one year) term.

Search methods for identification of studies

Electronic searches

For the update of the review, we searched the following electronic databases:

- *The Cochrane Library* (Issue 3, 2004), including the Cochrane Controlled Trials Register;
- MEDLINE (PubMed 1966 to 8, 2004);
- The Register of Chinese trials developed by the Chinese Cochrane Centre,
- The Chinese Med Database;
- China National knowledge Infrastructure, and searched reference lists, databases of ongoing trials and the Internet.

For detailed search strategies please see under [Appendix 1](#).

We also used a simplified search strategy for searching the LILACS and the PAHO (Pan-American Health Organisation) database (www.bireme.br - August 2004), the meta-register of ongoing trials (www.current-trials.com) and the Internet (www.google.com). We also searched the following web sites' references: International Council for the Control of Iodine Deficiency Disorders, Thyroid Disease Manager, and World Health Organisation. In addition, we contacted one trialist (Dr Köbberling) and the Executive Director of the ICCIDD (Dr Delange) for overlooked or unpublished trials

Searching other resources

We handsearched the Chinese Journal of Control of Endemic Diseases, the Chinese Journal of Epidemiology, and the Chinese Journal of Preventive Medicine, and Studies of Trace Elements and

Health up to August 2004. We also scanned the reference lists of papers identified for further trials.

Data collection and analysis

Selection of studies

The title, abstract and keywords of every record retrieved were scanned independently by two reviewers (TW, GL) to determine which studies required further assessment. The full article was retrieved when the information given in the titles, abstracts and keywords suggested that: 1. The study used iodised salt as an intervention, 2. The study had a prospective design and a control group. When there was any doubt regarding these criteria from scanning the titles and abstracts, the full article was retrieved for clarification. Disagreements were resolved by discussion. A third reviewer (CC) performed additional searches and trials selection independently.

Data extraction and management

Data concerning details of study population, intervention and outcomes were extracted independently by three reviewers (TW, GL, CC) using a standard data extraction form specifically adapted for this review. Data on participants, interventions, and outcomes, as described above, were abstracted. The data extraction form included the following items.

- general information: published/unpublished, title, authors, reference/source, contact address, country, urban/rural etc., language of publication, year of publication, duplicate publications, sponsor, setting.
- trial characteristics: design, duration of follow up, method of randomisation, allocation concealment, blinding (patients, people administering treatment, outcome assessors).
- intervention(s): placebo included, interventions(s) (dose, route, timing), comparison intervention(s) (dose, route, timing), co-medication(s) (dose, route, timing), verification of salt iodisation, measurement of other sources of iodine.
- participants: sampling (random/convenience), exclusion criteria, total number and number in comparison groups, sex, age, baseline characteristics, diagnostic criteria, duration of iodine deficiency disorders, similarity of groups at baseline (including any co-morbidity), assessment of compliance, withdrawals/losses to follow-up (reasons/description), subgroups.
- outcomes: outcomes specified above, any other outcomes assessed, other events, length of follow-up, quality of reporting of outcomes.
- results: for outcomes and times of assessment (including a measure of variation), if necessary converted to measures of effect specified below; intention-to-treat analysis.

Assessment of risk of bias in included studies

The quality of reporting of each trial was assessed independently by three reviewers (TW, GL, CC) according to a modification of the quality criteria specified by Schulz (Schulz 1995) and by Jadad (Jadad 1996) and in Cochrane Reviewer's Handbook 4.2.2.

In particular, the following quality criteria were assessed.

1. Minimisation of selection bias - a) was the randomisation procedure adequate? b) was the allocation concealment adequate?
2. Minimisation of performance bias - were the participants and people administering the treatment blind to the intervention?
3. Minimisation of attrition bias - a) were withdrawals and drop-outs completely described? b) was analysis by intention-to-treat?
4. Minimisation of detection bias - were outcome assessors blind to the intervention?

Based on these criteria, studies were subdivided into one of the following three categories:

A - all quality criteria met: low risk of bias.

B - one or more of the quality criteria only partly met: moderate risk of bias.

C - one or more criteria not met: high risk of bias.

We had intended to use this classification as the basis of a sensitivity analysis. Additionally, we were going to explore the influence of individual quality criteria in a sensitivity analysis.

After reviewing the literature, we also decided that the following two quality criteria were important.

- similarity of the groups at baseline
- measurement of the level of salt iodisation and of other potential sources of iodine accessible to the participants

Data synthesis

As we did not identify enough high quality randomised controlled trials and as outcome measures were reported in various different ways that could not easily be converted into a standard measure, we decided against doing a meta-analysis. Data were summarised in a narrative format. Different comparisons were analysed separately. If there are data available for meta-analysis in future, we will proceed as follows: Data will be included in a meta-analysis if they are of sufficient quality and sufficiently similar. We expect both event (dichotomous) data and continuous data. Dichotomous data will be expressed as odd ratios (OR). The relative risk (RR) may be used as an alternative to the OR as interpretation is easier, especially if the outcome is a negative event. Continuous data will be expressed as weighted mean differences (WMD). Overall results will be calculated based on the random effects model. Heterogeneity will be tested for using the Z score and the Chi square statistic with significance being set at $P < 0.1$. Possible sources of heterogeneity will be assessed by sensitivity and subgroup analyses as described below. Small study bias will be tested for using the funnel plot or other corrective analytical methods depending on the number of clinical trials included in the systematic review.

Subgroup analysis and investigation of heterogeneity

We will aim to perform subgroup analyses in order to explore effect size differences as follows, if there is a significant result for one of the main outcome measures:

- different comparison interventions (iodised oil capsule, iodised water, and so on - based on data);
- dose (low, medium, high - based on data);
- duration of intervention (short, medium, long - based on data).

Sensitivity analysis

We will perform sensitivity analyses in order to explore the influence of the following factors on effect size:

- repeating the analyses excluding any unpublished studies;
- repeating the analyses taking account of study quality, as specified above;
- repeating the analyses excluding any very long or large studies to establish how much they dominate the results;
- repeating the analyses excluding studies using the following filters: diagnostic criteria, language of publication, source of funding (industry versus other), country.

The robustness of the results will also be tested by repeating the analyses using different measures of effects size (risk difference, odds ratio etc.) and different statistical models (fixed and random effects models).

RESULTS

Description of studies

See: [Characteristics of included studies](#); [Characteristics of excluded studies](#).

Results of the search

The initial MEDLINE search using the electronic search strategy listed above yielded 2019 studies. After scanning the studies identified and doing the other searches specified, we identified twelve studies which appeared to fulfil the inclusion criteria. Of these, the MEDLINE search identified six, three further references were found scanning reference lists (Marine 1917/20; Kimball 1937; Sooch 1965), another through searching the PAHO database (Scrimshaw 1953), another through handsearching (Yang 1997), and the last one through searching the Internet and consequent personal contact with the department of the author (l'Ons 2000). Most of the studies were published in English, one in Chinese (Yang 1997) and one in Spanish (Scrimshaw 1953).

Retrieval of missing data

Some missing data were obtained for the study by Zhao et al (Zhao 1999).

Included studies

Design

Details of the characteristics of the included studies are shown in Appendix 2. All studies included were of a parallel design, single centre and had a control group. Four of them (Hintze 1988; Romano 1991; Foo 1996; Zhao 1999) were clearly identified as randomised. Units for allocation of the treatment were either individuals (Hintze 1988; Romano 1991; Zhao 1999) or groups [schools (l'Ons 2000), villages (Foo 1996) or other geographical regions (Sooch 1965)]. The two studies not mentioning randomisation (Sooch 1965; l'Ons 2000) were of this latter category. Trial duration ranged from four months to five years. Trials came both from the high incomes countries (Hintze 1988; Romano 1991) and the low incomes countries (Sooch 1965; Foo 1996; Zhao 1999; l'Ons 2000).

Participants

Numbers of participants of the studies ranged from 35 to over 20,000. Most studies had over hundred participants. Most studies examined children (5 years and younger to 16 years) (Sooch 1965; Hintze 1988; Foo 1996; Zhao 1999) one study examined women of childbearing age (Foo 1996), one studied pregnant women (Romano 1991), and one the general population (Sooch 1965). Studies were all carried out in areas of known iodine deficiency with substantial goitre rates (9.5-83%). Some studies had substantial differences in baseline goitre rates and urinary iodine excretion (Foo 1996; l'Ons 2000).

Interventions

Four of the studies included a control group where no iodine supplementation was used (Sooch 1965; Hintze 1988; Romano 1991; l'Ons 2000). In one study, iodised water was used as a comparison (Foo 1996), one study used iodised oil (Zhao 1999), and two studies compared different forms of iodised salt (specially prepared iodised salt versus commercially available iodised salt in the trial by Zhao et al (Zhao 1999), and salt fortified with potassium iodide versus salt fortified with potassium iodate in the trial by Sooch and Ramalingaswami (Sooch 1965)). Levels of iodisation were 12 to 53 parts per million (ppm). All interventions were given orally. In some studies the salt was supplied to the participants directly (Foo 1996; Zhao 1999; l'Ons 2000) in others the salt that was available for the participants to buy was either iodised or non-iodised (Hintze 1988; Sooch 1965; Zhao 1999).

Salt consumption was not prescribed but was that used in normal household consumption.

Outcome measures

None of the studies assessed mortality, physical and mental development in children, symptoms of hypothyroidism, adverse effects, health-related quality of life, or socioeconomic effects. All studies reported goitre rates or a related measure (thyroid volume, neck circumference). Goitre was generally measured by palpation. All studies measured iodine content of the urine. Iodine excretion was measured in a number of different units, which could not always be converted to a unit allowing comparison between studies, due to missing data.

A number of studies (Hintze 1988; Sooch 1965; Zhao 1999) reported on quality checks of their outcome measurements (duplicate measurements, assessment of samples of outcome measurements before the main outcome assessment, etc.).

Excluded studies

Of the twelve studies, six were excluded upon further scrutiny. Reasons for exclusion of studies are given in Characteristics of excluded studies. Reasons for exclusion included studies not being prospective controlled comparisons (Kimball 1937), iodised salt not being the primary intervention (Marine 1917/20; Scrimshaw 1953; van den Briel 2000; Yang 1997), and implausible results (Saowakhontha 1994).

Risk of bias in included studies

Most studies were of poor methodological quality ('C'). Only one study was of higher quality (Zhao 1999) ('B') and described methodological issues in some detail (for example, power calculation, randomisation method, flow of participants, blinding of outcome assessment). An overview of study quality can be found in Appendix 2.

Allocation

Four studies were described as randomised (see above). Only one study mentioned the method of randomisation (Zhao 1999), although not in much detail. None of the studies mentioned allocation concealment.

Blinding

Only one study (l'Ons 2000) mentioned blinding of participants and only one study (Zhao 1999) mentioned blinding of outcome assessment.

Incomplete outcome data

Withdrawals and losses to follow-up were described by two studies (Hintze 1988; l'Ons 2000). One study mentioned that there were no losses to follow-up (Zhao 1999). None of the studies mentioned an intention-to-treat analysis.

Other potential sources of bias

Compliance assessment

A number of studies used methods to ensure compliance, for example, notices in schools and reminders (Hintze 1988; l'Ons 2000), and to check compliance, for example, checking amounts of iodised salt requested or collecting left-overs of previous deliveries of iodised salt (Zhao 1999; l'Ons 2000).

Similarity of comparison groups at baseline

In two studies (Foo 1996; l'Ons 2000), there were significant differences between the comparison groups in baseline urinary iodine excretion and goitre rates.

Check of iodisation levels and iodine contamination

In four studies, the iodine content of the salt and of other iodine supplements (for example, iodised water) was checked (Sooch 1965; Foo 1996; Zhao 1999; l'Ons 2000). In three cases (Sooch 1965; Zhao 1999; l'Ons 2000) some of the salt samples were found to contain different levels (generally lower) of iodine than intended. A number of studies (Sooch 1965; l'Ons 2000) also studied other sources of iodine the participants might be exposed to (for example, iodine in food generally consumed, in the drinking water, in the soil), as well as potential goitrogens in the diet (for example, there were high levels of cassava leaves and tubers (which have a known goitrogenic effect) in the diet of the participants of study by Foo et al (Foo 1996)).

Effects of interventions

The effects of the interventions on goitre prevalence and urinary iodine excretion are shown in [Appendix 3](#).

Goitre

All studies measuring goitre rates (or thyroid volume) showed a trend towards reduction in goitre rates (or prevention of occurrence of goitre) with the use of iodised salt. These reductions were significant in the studies by Sooch and Ramalingaswami (Sooch 1965), Zhao et al (Zhao 1999) (at least for specially distributed salt and for market salt plus iodised oil), and Foo et al (Foo 1996) (women only). The prevention of increase in thyroid volume in

pregnancy with use of iodised salt in the study by Romano et al (Romano 1991) was a significant effect. No significant effects of iodised salt on goitre rates were seen in the study by Hintze et al (Hintze 1988) and the (short term) study by l'Ons et al (l'Ons 2000).

Urinary iodine excretion

In almost all studies measuring urinary iodine, iodine excretion was significantly increased with use of iodised salt. The only exception was the study by Foo et al (Foo 1996), where iodine excretion was not significantly increased in small children (of less than six years). The WHO target value of iodine excretion of at least 100 µg/L was reached in at least three studies (Foo 1996 (women only); Zhao 1999; l'Ons 2000). It was clearly not reached in the study by Hintze et al (Hintze 1988) and in the children in the study by Foo et al (Foo 1996). From the data, no clear relation can be seen between dose of iodine in the salt and urinary iodine excretion. Similarly, the data do not allow any conclusions regarding differences in iodine excretion rates following salt fortification using KI or KIO₃.

Different forms of iodine supplementation

The study by Sooch showed no differences in the decrease of goitre rates after fortification of salt with either KI or KIO₃. In the study by Foo et al (Foo 1996), iodised salt was about as effective as iodised water in women aged 15–40 years, but iodised water was more effective in children below six years. In the study by Zhao et al (Zhao 1999), iodised salt with a carefully controlled iodine content and commercially available iodised salt with a supplementation of iodised oil were more efficient than commercially available iodised salt alone (which had a very variable iodine content).

Children versus adults children versus adults

In the study by Sooch and Ramalingaswami (Sooch 1965), children benefited from iodised salt to a similar extent as adults. However, in the study by Foo et al (Foo 1996), small children (below six years) benefited less than adults. The conclusion of that study is similar to the one given by Hintze et al (Hintze 1988), who suggested that salt consumption in children is lower than that of adults and that therefore children might benefit less from salt iodised at a relatively low level.

DISCUSSION

Summary of main results

We only found one randomised controlled trial relating to our question that was of fairly good quality, the other studies examined were of fairly poor quality and some of them were not randomised. The studies did not assess many of the outcome measures we had considered important. The studies identified used differing levels of salt iodisation and different units of measurement, and were therefore not easily comparable. There was a tendency towards goitre reduction with iodised salt, although this was not significant in all studies. There was also an improved iodine status in most studies (except in small children in one of the studies), although this did not always reach the levels recommended by the WHO.

Adverse effects

There have been concerns about adverse effects of iodine supplementation, including iodised salt supplementation. Iodine-induced hyperthyroidism has been observed in a number of iodine supplementation programmes, including programmes using iodised salt (Galofre 1994; Todd 1995; Bourdoux 1996). In the cases cited, iodisation levels were much higher than those recommended (Todd 1995; Bourdoux 1996) or iodisation occurred in an area of iodine sufficiency (Galofre 1994), however, iodine-induced hyperthyroidism has also been observed when lower levels of iodine were given. An associated increase in cardiovascular mortality has been reported. The data suggest that iodine-induced hyperthyroidism mainly occurs in people over forty years of age with nodular goitres, in whom some thyroid autonomy has developed, i.e. thyroid hormone production is not inhibited by increased levels of iodine (Corvilain 1998). The risk of developing iodine-induced hyperthyroidism seems to be higher when initial iodine deficiency was severe and when the initial rise in iodine intake was great. Increases in cases of iodine-induced hyperthyroidism are often only temporary after the introduction of iodisation programmes, but there are also cases in which the disorder persists. As symptoms of iodine-induced hyperthyroidism are often not very severe and very non-specific, it is easy to overlook the problem unless investigators specifically study hormone levels (Stanbury 1998), which was done in none of the studies included in this review. While surveys suggest that the benefits of iodine supplementation outweigh the risks, the potentially fatal nature of iodine-induced hyperthyroidism places an increased importance on adequate monitoring of the levels of iodine in supplements, on adequate monitoring of the iodine status of populations and on early detection of iodine-induced hyperthyroidism (Dunn 1998b).

Overall completeness and applicability of evidence

The review included studies from countries of the developing as well as the developed world. It becomes apparent that delivery and quality control of iodised salt is probably more difficult in remote

areas in developing countries and this method of iodine supplementation is therefore not without problems. However, the impression also arises that it is the most practicable and well accepted means of providing iodine supplementation.

The studies identified focussed mainly on children and women of childbearing age. While these are probably the most vulnerable to iodine deficiency disorders, future studies should also include other population groups. The question also arises of the most adequate way of iodine supplementation in newborn babies and infants. They will not consume any iodised salt at all. If they are breast fed, it would be interesting to establish if any iodised salt consumed by the mother to achieve an adequate iodine status is also enough to achieve an adequate iodine status in the child.

Studies generally concentrated on measuring iodine status by measuring urinary iodine levels - presumably because these measurements can be easily and quickly obtained. However, these values will not reflect long term iodine status and therefore other indicators should be used, for example, thyroglobulin levels or iodine excretion profiles, to get a more accurate picture of iodine status.

Potential biases in the review process

There was only a small number of studies included in this review, none of which abided by the criteria laid down in the CONSORT statement (CONSORT 2001). The only study of slightly higher quality study (Zhao 1999) was faced with the problem that the commercially available iodised salt had a very unreliable iodine content. This may demonstrate that in certain parts of the world the quality control of iodisation programmes is a problem, but does not allow any conclusions regarding the effectiveness of salt iodisation per se. Most of the other studies were also faced with major confounders, such as differences in baseline goitre rates (Foo 1996; l'Ons 2000), presence of goitrogens in the diet (Foo 1996), levels of iodisation not reaching the recommended level of iodine intake (Hintze 1988; Foo 1996 (children)), and restriction to pregnant women, in whom iodine requirements are different to those of the general population (Romano 1991). In the study by Sooch and Ramalingaswami (Sooch 1965) the populations studied at the different time points did not consist entirely of the same people, even though the populations studied were fairly well isolated and increases in numbers in the groups at the end of the study may have been due to internal effects (for example, children below five years at the beginning of the study growing older). However, all this means that none of the studies were ideally suited to investigate the effectiveness of iodised salt in preventing iodine deficiency disorders and any conclusions must be treated with great caution. This review focussed on iodised salt as a means of iodine supplementation. While iodised salt is undoubtedly the form of iodine supplementation most widely used and most practical for global use, the results of the review also suggest that it is not suitable for all situations. It may therefore be more useful to compare all the different forms of iodine supplementation, to give a more com-

plete picture. We intend to do this in a future version of this review.

AUTHORS' CONCLUSIONS

Implications for practice

The results suggest that iodised salt is an effective means of improving iodine status and support the current endeavours to achieve universal salt iodisation. Variations in the iodine levels in the salt used by some studies suggest that particular care must be taken to ensure the quality of the production and storage of iodised salt - and that there may be situations in which other forms of iodine supplementation may be more appropriate. There was also a suggestion that forms of iodine supplementation should be reassessed in small children, as their salt intake may not be high enough to guarantee adequate iodine levels through the use of iodised salt. There was no suggestion from the studies that the use of iodised salt with the levels of iodine studied had any unwanted side effects, although this point must be regarded with caution as most studies did not specifically consider adverse effects.

Implications for research

More high quality controlled trials (following the CONSORT criteria) are required for assessing the effects of iodised salt in comparison to other forms of iodine supplementation. These studies should also address the question of the most effective dose to be used (under given conditions). Studies should be large and long term, lasting at least two years, including participants of all ages. The outcomes studied should not be restricted to goitre rates and urinary iodine excretion, but should include the other outcome measures specified above, such as mental and physical development in children, mortality, etc. Special attention should be paid to adverse effects. The effects of iodised salt should be assessed separately for children (including very young children who may have a relatively low salt consumption) and adults.

ACKNOWLEDGEMENTS

We thank Sally Green and Steve McDonald of the Australasian Cochrane Centre for helping develop this review, and the China Medical Board of New York for supporting this review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

Characteristics of included studies [ordered by study ID]

Foo 1996

Methods	Randomised controlled trial, blinding not mentioned Units of comparison: Villages Duration: One year Location: Sarawak	
Participants	101 women (15-50 years) and 65 young children (<= 6 years) Goitre prevalence: (women) 83% (but large consumption of goitrogenic food)	
Interventions	1. Iodised salt (47.1±9.7 ppm iodine - unclear if iodate or iodide used) (N=48 women, 33 children) 2. Iodised water (138.6±43.2 µg/l) (N=53 women, 32 children)	
Outcomes	1. Urinary iodine excretion 2. Goitre palpation (women only)	
Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Hintze 1988

Methods	Randomised controlled trial - not blinded Units of comparison: Individuals Duration: Four years Location: Germany	
Participants	334 children (166 female, 168 male), 10 years at the beginning of the study Goitre prevalence: 30.5%	
Interventions	1. Iodised salt (iodate, 20 ppm iodine) (N=146) 2. Plain salt (N=188)	
Outcomes	1. Goitre (palpation) 2. Neck circumference 3. Urinary iodine excretion	
Notes		
<i>Risk of bias</i>		

Hintze 1988 (Continued)

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

P'Ons 2000

Methods	Prospective controlled study, randomisation unclear, participants were blind to the intervention Units of comparison: Schools Duration: Four months Location: South Africa	
Participants	112 school children (7-16 years) (102 at follow-up) Goitre prevalence: 9.5-28.2%	
Interventions	1. Iodised salt (first 2 batches 18 and 12 ppm iodine, last batch (last 4-5 weeks) 53 ppm (unclear if iodide or iodate)) (N=39) 2. Plain salt (N=63)	
Outcomes	1. Goitre (palpation) 2. Urinary iodine excretion	
Notes		

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Romano 1991

Methods	Randomised trial - blinding not mentioned Units of comparison: Individuals Duration: Nine months of pregnancy Location: Italy	
Participants	35 pregnant women (27.1±3.8 years) Goitre prevalence: unknown for the given sample, 41% in the 8-15 year olds in the area	
Interventions	1. Iodised salt (20 ppm iodide, i.e. 15.27 ppm iodine) (N=17) 2. Control - plain salt, but not specifically distributed (N=18)	
Outcomes	1. Thyroid volume (ultrasono-graphy) 2. Urinary iodine excretion 3. Serum TSH levels	
Notes		

Romano 1991 (Continued)

Risk of bias		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Sooch 1965

Methods	Prospective controlled study, randomisation and blinding unclear Units of comparison: Geographical regions Duration: Five years Location: Himalayan endemic goitre belt, Punjab
Participants	Over 20,000 villagers, includes specific investigations of school children 5-16 years, boys versus girls, men versus women Goitre prevalence: 37.6-47%
Interventions	1. Iodised salt (20 ppm KI, i.e. 15.27 ppm iodine) (N over 6000) 2. Plain salt (N over 7000) 3. Iodised salt (25 ppm KIO ₃ , i.e. 14.83 ppm iodine) (N over 6000)
Outcomes	1. Goitre (visual and palpation) 2. [¹³¹ I] uptake by the thyroid and subsequent excretion
Notes	

Risk of bias

Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Zhao 1999

Methods	Randomised controlled trial, participants not blinded, outcome assessment blinded Duration: 18 months Location: China
Participants	205 children 8-10 years (50% male) Goitre prevalence: 26.1-26.5%
Interventions	1. Iodised salt (42.25 g/kg KIO ₃ , 25 ppm iodine) (N=69) 2. Market iodised salt (iodine content varied, 13-47 ppm) (N=68) 3. Market iodised salt (iodine content varied, 13-47 ppm) plus oral iodised oil 400 mg (N=68)
Outcomes	1. Goitre (palpation) 2. Thyroid volume (ultrasonography) 3. Urinary iodine concentration

Zhao 1999 (Continued)

Notes		
<i>Risk of bias</i>		
Item	Authors' judgement	Description
Allocation concealment?	Unclear	B - Unclear

Characteristics of excluded studies [ordered by study ID]

Study	Reason for exclusion
Carella 2002	The objective of the trial is to investigate whether the addition of iodized salt to daily diet in thyroidectomized patients for nontoxic goitre could influence the effectiveness of nonsuppressive L-thyroxine (L-T4) therapy on thyroid remnant size after thyroid surgery, was not for preventing IDD's
Hess 2002	The comparison in this controlled trial is iodised salt plus iron versus iodised salt alone - so this is not assessing the effects of iodised salt
Kimball 1937	Not a prospective controlled study but a case-control study comparing goitre rates in children having used iodised salt and those not having used iodised salt
Marine 1917/20	Possibly a prospective controlled study, but the intervention was not iodised salt but a syrup of hydriodic acid or ferrous iodide
Saowakhontha 1994	Prospective controlled study comparing iodised fish sauce, iodised salt, iodised water and placebo. The outcome assessed was urinary iodine excretion only, and the values given seem very implausible, by several orders of magnitude
Scrimshaw 1953	The intervention was potassium iodide or potassium iodate given as tablets and not in salt
Simescu 2002	It's not a randomised controlled trial, but a 'random selection' cross-sectional study and no control group. Also, the intervention was iodised oil combined with iodised salt
van den Briel 2000	Although the abstract suggests involvement of iodised salt, the primary intervention of this randomised controlled trial was in fact iodised oil
Yang 1997	The comparison in this controlled trial is iodised salt plus sodium selenite versus iodised salt alone - so this is not assessing the effects of iodised salt
Zhao 2002	Duplicate publication with Zhao 1999.

DATA AND ANALYSES

This review has no analyses.

APPENDICES

Appendix I. Search strategy

Search terms

Unless otherwise stated, search terms are free text terms; MeSH = Medical subject heading (Medline medical index term); exp = exploded MeSH; the dollar sign (\$) stands for any character(s); the question mark (?) = to substitute for one or no characters; tw = text word; pt = publication type; sh = MeSH; adj = adjacent

Iodine deficiency/supplementation

- (1) IODINE/ [MeSH term, all subheadings included]
- (2) iod* [in abstract or title]
- (3) explode IODIZED-OIL/ [MeSH term, all subtrees and subheadings included]
- (4) #1 or #2 or #3
- (5) DIETARY-SUPPLEMENTS/ [MeSH term, all subheadings included]
- (6) supplement* [in abstract or title]
- (7) THYROID-GLAND/ [MeSH term, all subheadings included]
- (8) explode HYPOTHYROIDISM/ [MeSH term, all subtrees and subheadings included]
- (9) explode GOITER/ [MeSH term, all subtrees and subheadings included]
- (10) goit* [in abstract or title]
- (11) (hypo thyroid* or hypothyroid*) [in abstract or title]
- (12) explode MENTAL-DISORDERS-DIAGNOSED-IN-CHILDHOOD/ [MeSH term, all subtrees and subheadings included]
- (13) (intelligen* or development*) [in abstract or title]
- (14) #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13
- (15) #4 and #14
- (16) cretin* [in abstract or title]
- (17) CRETINISM/ [MeSH term, all subheadings included]
- (18) ((IDD or IDD) not diabet*) [in abstract or title]
- (19) (iod* and (defic* or poor or poverty or lack* [in abstract or title]
- (20) #15 or #16 or #17 or #18 or #19

This was combined with a sensitive search strategy for identifying controlled clinical trials:

Randomised controlled trials and controlled clinical trials

- 21 See search strategy of the Metabolic and Endocrine Disorders Group

Appendix 2. Risk of bias

Study	Randomisation	Alloc. concealment	Blinding	Drop-outs	Simil. at baseline	Iodine measured	Compliance checks
Foo 1996	Yes	Not mentioned	Not mentioned	Not mentioned	No	Intervention iodine levels checked	Not mentioned
Hintze 1988	Yes	Not mentioned	Not mentioned	Described, 14%	Yes	No checks	Reminders
L'Ons 2000	Allocation not described	Not mentioned	Participants	Described, 9%	No	Intervention iodine levels and external iodine contamination checked	Reminders, check of salt used
Romano 1991	Yes	Not mentioned	Not mentioned	Not mentioned	Yes	No checks	Not mentioned
Sooch 1965	Allocation not described	Not mentioned	Not mentioned	Not mentioned	Yes	Intervention iodine levels and external iodine contamination checked	Not mentioned
Zhao 1999	Yes	Not mentioned	Outcome assessors	No drop-outs	Yes	Intervention iodine levels checked	Check of salt used

Appendix 3. Effects of the intervention on goitre rates and urinary iodine

Study	Goitre	Goitre	Urinary iodine	Urinary iodine	Notes
	POST-INTERVENTION	CHANGE FROM BASELINE	POST-INTERVENTION	CHANGE FROM BASELINE	
Foo 1996	Women:		Women: (median)		
	Iodised salt: 27.1%	-33.3%	Iodised salt: 168.2 µg/L	+131.4 µg/L	
	Iodised water: 47.2%	-35.8%	Iodised water: 114.2 µg/L	+102.9 µg/L	

(Continued)

			Children		
			Iodised salt: 33.4 µg/L	+5.3 µg/L	
			Iodised water: 97.6 µg/L	+87.0 µg/L	
Hintze 1988	KIO3 salt: 23.8%	-9.1%	KIO3 salt: 60.1 ± 24.1 µg/g creatinine (-74 µg/L)	+13.1 µg/g creatinine (-16 µg/L)	
	Plain salt: 22.5%	-6.2%	Plain salt: 45.1 ± 18.6 µg/g creatinine (-56 µg/L)	+2.3 µg/g creatinine (-3 µg/L)	
L'Ons 2000	Iodised salt: 12.8%	-15.4%	Iodised salt:		
	Plain salt: 6.3%	-3.2%	86.9% ≥ 100 µg/L 65% ≥ 200 µg/L	+25% +49.4%	
			Plain salt:		
			46.1% ≥ 100 µg/L 15.9% ≥ 200 µg/L	+3.3% +8%	
Romano 1991	KI salt: thyroid volume ~10.2±2.2 ml	+4%	KI salt: 100.0 ± 39.0 µg/day	+63.0 µg/day	Numbers preceded by '-' were estimates derived from a graph
	Plain salt: thyroid volume ~11.7±2.4 ml	+16.25%	Plain salt: 50.0 ± 37.0 µg/day	+19.5 µg/day	
Sooch 1965	Children:				As the units of comparison were regions, the numbers of people examined varied between the groups and sometimes increased at follow-up
	KI salt (N = 3495): 19.1%	-18.5% (N = 2529 pre-intervention)			
	KIO3 salt (N = 3420): 14.6%	-23.8% (N = 2964 pre-intervention)			

(Continued)

	Plain salt (N = 4544) : 40.3%	+2.5% (N = 2027 pre-intervention)			
	General population:				
	KI salt (N = 3290): 18.1%	-24.3% (N = 4400 pre-intervention)			
	KIO3 salt (N = 2821) : 16.8%	-23.3% (N = 4151 pre-intervention)			
	Plain salt (N = 4046) : 45.7%	-1.3% (N = 5076 pre-intervention)			
Zhao 1999	Distributed KIO3 salt: 8.7%	-17.4%	Distributed KIO3 salt: 238 µg/L (95% CI 146-264)	+146 µg/L	
	Market KIO3 salt: 19.1%	-7.4%	Market KIO3 salt: 302 µg/L (274-347)	+207 µg/L	
	Market KIO3 salt plus iodised oil: 8.8%	-17.7%	Market KIO3 salt plus iodised oil: 295 µg/L (248-346)	+201 µg/L	

WHAT'S NEW

Last assessed as up-to-date: 30 August 2004.

Date	Event	Description
8 November 2008	Amended	Converted to new review format.

HISTORY

Protocol first published: Issue 3, 2001

Review first published: Issue 3, 2002

Date	Event	Description
31 August 2004	New search has been performed	This is an update of the original Cochrane Review published in issue 3, 2002: new studies found and included or excluded

CONTRIBUTIONS OF AUTHORS

TAIXIANG WU: protocol development, searching for trials, quality assessment of trials, data extraction, data analysis, review development, review update.

GUANJIAN LIU: quality assessment of trials, data analysis, statistical advice.

PING LI: quality assessment of trials, searching for trials, data extraction, data analysis.

CHRISTINE CLAR: searching for trials, quality assessment of trials, data extraction, review development.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

- Chinese Cochrane Centre, China.

External sources

- Australia Cochrane Centre, Australia.

INDEX TERMS

Medical Subject Headings (MeSH)

Cross-Sectional Studies; Dietary Supplements; Intellectual Disability [prevention & control]; Iodine [*administration & dosage; *deficiency]; Prospective Studies; Sodium Chloride, Dietary [*administration & dosage]

MeSH check words

Humans