

Original Article

A meta-analysis combining parallel and cross-over randomized controlled trials to assess impact of iodine fortified foods on urinary iodine concentration among children

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The purpose of this analysis was to combine evidence from parallel and cross-over randomized controlled trials to assess the impact of iodine fortified foods on urinary iodine concentration (UIC) in children. A structured search for studies on iodine intervention studies on MEDLINE, Pro Quest, and the Cochrane Library from Jan, 1990 to Dec, 2012 was carried out. Carry-over effect was estimated by general linear model. We explored two methods to pool continuous outcomes in a meta-analysis by combining parallel and cross-over trial designs. The standard mean difference was calculated for net change in UIC. Fixed or random-effects models were used to summaries fortified food response data. Meta-regression and covariate meta-analysis were performed to explore the influence of confounders on the net pooled effect on UIC. The overall pooled estimate, which combined parallel with cross-over trials in the absence of carry-over effect of UIC from 9 studies, showed a significant increase in the fortified group compared with the control group (n=3448; standard mean difference=2.02 µg/L; 95% CI: 1.30, 2.73; I²=99%, τ²=1.81, p<0.01). Meta-regression analysis indicated that dose of the feeding was positively related to the effect size (regression coefficient=0.014; 95% CI: 0.003, 0.026; p<0.019). The net pooled effect size after removing the confounders was 1.59 (95% CI: 0.953, 2.23) µg/L. There was an association between intakes of iodine fortified foods and UIC in children. These results suggest that we can combine parallel with cross-over trials for meta-analysis for nutrients such as iodine when absorption is high.

Key Words: iodine fortification, meta-analysis, carry-over effect, meta-regression, covariate meta-analysis

INTRODUCTION

Deficiencies of micronutrients such as iodine are a major public health problem in developing countries. Iodine is an essential nutrient for the synthesis of thyroid hormones, including thyroxin, that are critical for brain development. Thyroid hormones are also involved in the regulation of the basal metabolic rate and in metabolism.^{1,2} Iodine deficiency disorders (IDD) in utero and in early childhood affect the development of brain and intelligence quotient (IQ), making it one of the most important preventable causes of brain damage in the world. The WHO, International Council for the Control of Iodine Deficiency Disorders (ICCIDD), and UNICEF recommended daily iodine intakes of 90 µg/d for pre-school children, 150 µg/d for adults, reaching 250 µg/d for pregnant and lactating women.^{3,4} Salt iodization is the simplest, least expensive and most efficient strategy to control and prevent iodine deficiency.⁵

An objective biomarker of IDD is UIC, which is an excellent indicator of recent iodine intake because more than 90% of dietary iodine is absorbed and, in healthy,

iodine replete adults, 90% is excreted in the urine within 24-48 hours (hrs).^{6,7} UICs are usually measured in random urine samples because it is difficult to collect 24 hrs samples in field studies.⁸ Sources of dietary iodine are iodized salt, saltwater fish, seaweed, and grains.

In recent years robust study design and systematic review and meta-analysis have advanced significantly and are readily available.⁹ In meta-analysis, combining results from parallel and cross-over trials, raises the query of bias originating from the carry-over effect in cross-over trials. In this paper, we explore the impact of carry-over effect in cross-over trials when these are merged with parallel

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designs. The present review examines the current evidence for the effect of iodine fortified foods on UIC in children through systematic review and meta-analysis. Since we expected heterogeneity among studies, we also explored whether confounders such as age, duration of the study, and dose of fortification could predict the effect of UIC in children.

METHODS

Literature search

The relevant literature was collected as per the PRISMA (Proffered Reporting Items for Systematic reviews and Meta-Analysis) guidelines for meta-analysis.¹⁰ We searched MEDLINE, Pro Quest and the Cochrane Library database from Jan 1990 up to Dec 2012, and reviews and reference lists of the articles, using keywords 'food fortification' paired with 'iodine' or 'UIC' or 'dual fortification' or 'triple fortification' or 'multiple micronutrient fortification' and 'fortification trials'.

Selection criteria

The search was regardless of publication status. For inclusion, studies needed to meet the following criteria; 'involve intervention in children, be randomized (RCTs) or quasi-randomized controlled trials' with control group, or before-after studies, reporting changes in urinary iodine excretion levels, or multiple interventions with other micronutrients administered simultaneously, but whose main outcome measure was the effect on UIC.

Data extraction and quality assessment

The title and abstracts of the studies identified in the web database search were read and those that were not relevant studies were excluded with reason. To avoid the publication bias, the remaining full text studies were retrieved and only peer-reviewed published studies were included. The full text of the articles collected were screened for suitability with an inclusion/exclusion criteria used by a single reviewer with an independent duplicate assessment of second reviewer. Whenever the two reviewers disagreed, the study was discussed and was included only if consensus decision was reached. The extraction of data consisted of obtaining sample size, age, duration of intervention, dose of fortification, and mean change and standard deviation of UIC in the intervention and control groups. The search, data extraction and quality assessment were completed independently by two content experts as per the inclusion criteria and confirmed by using recommended criteria for RCT.^{11,12} Concealment of allocation was classified as 'adequate', 'unclear', 'inadequate' or 'not used', based on randomization, blinding and reporting of withdrawn subjects. Blinding was classified as 'double blinding' 'single blinding' 'no blinding' or 'unclear'. In case of studies that had two or more designs employing different types of intervention groups (different dose of fortification or administration regimens) and a single control group, the sample size of the control group was equally allotted to the number of intervention groups while retaining the same mean value change and its SD. In reporting such designs, each intervention group was analyzed separately. Thus, a few studies contributed more than one intervention component with a single con-

trol group for the statistical analysis and resulted in greater number of trials than the number of studies included.

Statistical analysis

To perform meta-analysis of continuous data, the meta-analyst needs mean and SD in order to pool the data.¹³ The studies included in the analysis reported median and range of UIC. Considering that the studies included had different designs viz parallel, pre-post, and cross-over, three different approaches have been adopted to combine the results. In the first instance, first ordered cross-over trials were combined as parallel trials. In the second step, the general linear model (GLM) technique was used to assess the carry-over effect between two periods of cross-over design trials.¹⁴ The parallel and cross-over trials were combined for ensuring the removal of carry-over effect using appropriate statistical procedures (Tables 1 & 2). The effect size, referred to as the standard mean difference was compiled from the difference in means and divided by pooled SD among the trials between iodine fortified and control groups for the included trials. The overall effect of these trial results was expressed by the Q-statistic and computed with the assumption of homogeneity among the effect sizes and the statistic follows the chi-square distribution with k-1 degrees of freedom, k being the number of interventions. For quantifying the heterogeneity in meta-analysis among the studies, the variance (τ^2) between studies, and the parameter I^2 were employed. The overall standard mean difference of these results was assessed for sampling error (homogeneous, $\tau^2=0$). A fixed-effects meta-analysis was applied to obtain the pooled effect size with 95% confidence intervals or else a random-effects meta-analysis was performed (heterogeneous, $\tau^2 >0$).^{15,16} The results of heterogeneity were represented in the form of a forest plot. The forest plot also represents the Q-statistic value, τ^2 , df, I^2 , Z and p value.

Testing the heterogeneity of the intervention estimate was based on the Q-statistic for all trials. The exploration of heterogeneity could be evaluated for (1) within parallel trials; (2) within cross-over trials; (3) within first order cross-over trials; (4) combine cross-over first order plus parallel trials; and (5) for all trial designs. The computation of a combined design meta-analysis using the random effects method was based on the usual approaches.¹⁵

Publication bias was assessed with the funnel plot and Egger's regression test using a weighted linear regression model with standard error as a covariate.¹⁷ An I^2 value more than 50% is considered to indicate significant heterogeneity between trials.¹⁸ If heterogeneity existed ($I^2 >50\%$), a meta-regression was used to test the study heterogeneity by relating study characteristics. The confounders were identified and a covariate meta-analysis was performed to estimate the net pooled effect size,¹⁹ after removing the effect of confounders.

Statistical analyses were performed with Review Manager (Rev Man) software version 5.2, IBM SPSS version 19.0, SAS 9.1.3 (portable free version) and Comprehensive Meta-Analysis (CMA) software trail version (www.meta-analysis.com).

Table 1. Cross-over trials statistics

Source	Estimator	Variance estimator	Weight estimator
Sum of average outcome in sequence j	$S_{ij} = \bar{y}_{ij1} + \bar{y}_{ij2}$		
Average cross-over difference in sequence j	$d_{ij} = \bar{y}_{ij1} - \bar{y}_{ij2}$		
Average sequence difference in period 1	$g_{i1} = \bar{y}_{i11} - \bar{y}_{i21}$		
Average sequence difference in period 2	$g_{i2} = \bar{y}_{i22} - \bar{y}_{i12}$		
Carry-over λ_i	$S_{ij} = s_{i1} - s_{i2} = g_{i1} - g_{i2}$	$V(S_i) = v_{i11} + v_{i12} + v_{i21} + v_{i22} + 2cov_{i112} + 2cov_{i212}$	$W(S_i) = v(S_i)^{-1}$
Treatment effect Cros estimator	$D_i = \frac{1}{2}(d_{i1} - d_{i2}) = \frac{1}{2}(g_{i1} + g_{i2})$	$V(D_i) = \frac{1}{4}(v_{i11} + v_{i12} + v_{i21} + v_{i22} - 2cov_{i112} - 2cov_{i212})$	$W(D_i) = v(D_i)^{-1}$
Treatment effect First estimator	$F_i = \bar{y}_{i11} - \bar{y}_{i21}$	$V(F_i) = v_{i11} + v_{i12}$	$W(F_i) = v(F_i)^{-1}$

Source³⁰.

Table 2. Meta-analysis estimators for cross-over trials in the presence of carry-over effect

Effect	Estimator	Description
Cross-over trials only		
$\lambda^{*\ddagger}$	$\bar{C}_{XO} = \frac{\sum_{i=1}^k W(S_i)S_i}{\sum_{i=1}^k W(S_i)}$	Pooled estimate of carry-over effect
$\theta - \frac{1}{2}\lambda^{**\ddagger}$	$\bar{Y}_{XOCros} = \frac{\sum_{i=1}^k W(D_i)D_i}{\sum_{i=1}^k W(D_i)}$	Pooled estimate of effect treatment of both periods
θ	$\bar{Y}_{XOFirst} = \frac{\sum_{i=1}^k W(F_i)F_i}{\sum_{i=1}^k W(F_i)}$	Pooled estimate of effect treatment of first period
Cross-over and parallel trials		
θ	$\bar{Y}_{CombiFirst} = \frac{\sum_{i=1}^k W(F_i)F_i + \sum_{i=1}^k W(R_i)R_i}{\sum_{i=1}^k W(F_i) + \sum_{i=1}^k W(R_i)}$	Combined estimate from cross-over (first period) and parallel trials
$\tau - \frac{1}{2}\lambda^{***\ddagger}$	$\bar{Y}_{CombiCros} = \frac{\sum_{i=1}^k W(D_i)D_i + \sum_{i=1}^k W(R_i)R_i}{\sum_{i=1}^k W(D_i) + \sum_{i=1}^k W(R_i)}$	Combined estimate from cross-over (both period) and parallel trials

Source³⁰

[‡]Meta-analytic carry-over is defined in different ways according to the weights: $\lambda^* = \frac{\sum_{i=1}^k W(S_i)\lambda_i}{\sum_{i=1}^k W(S_i)}$, $\lambda^{**} = \frac{\sum_{i=1}^k W(D_i)\lambda_i}{\sum_{i=1}^k W(D_i)}$, $\lambda^{***} = \frac{\sum_{i=1}^k W(D_i)\lambda_i}{(\sum_{i=1}^k W(D_i) + \sum_{i=1}^k W(R_i))}$

RESULTS

Search results

A total of 1116 titles and abstracts were identified, of which 274 appeared potentially relevant. Of these, 209 were collected as full-text articles and assessed for inclusion. Only nine articles fulfilled the inclusion criteria and these were submitted to meta-analysis (Figure 1).

Study characteristics and data quality

Characteristics of nine studies²⁰⁻²⁸ included in the meta-analysis are shown in Table 3. All of these were RCTs, out of which seven were double blind, one was longitudinal and one was a pre and post study. At the baseline, all trials had similar UIC in intervention and control groups.

A total of 3448 participants (children) of average age range of 7.0 to 10.5 years, with intervention duration ranging between 4 to 30 months, with levels of iodine fortification of 25 to 200 µg, were studied.

Four studies^{22,23,25,28} of multiple interventions with multiple micronutrients, each one had more than one trial. The trial involving deworming with multiple micronutrients fortification was considered as multiple interventions with multiple micronutrients. In each trial, the number of participants, mean and SD of UIC were assessed for conducting meta-analysis.

Effects of iodine fortification on UIC

The results indicate that there was no carry-over effect in

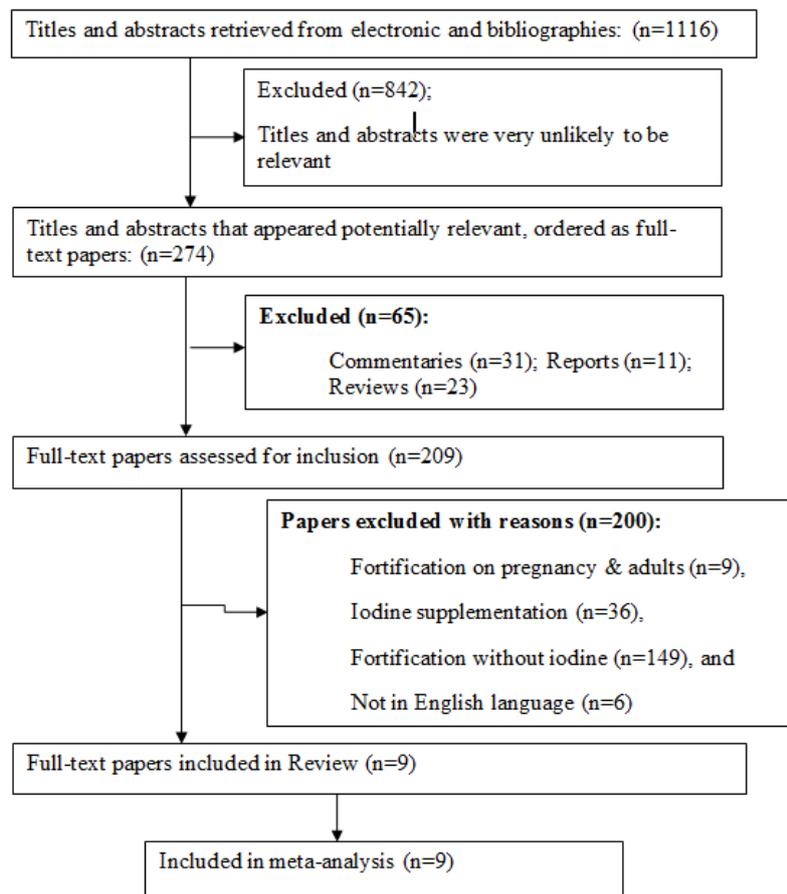


Figure 1. Flow diagram for inclusion of randomized controlled trials (RCTs)

Table 3. Summary of prospective controlled trials assessing the effect of iodine fortified foods on mean UIC in children

Study	Year	Study duration (months)	Average age (years)	Dose of fortification (µg/L)	Food vehicle	Study design
Van Stuijvenberg et al ²⁰	1999	12	8.5	67.2	Biscuits	RCT/DB
Van Stuijvenberg et al ²¹	2001	30	8.5	60	Biscuits	Longitudinal
Zimmermann et al ²²	2002	9.4	10.5	200	Meals	RCT/DB
Zimmermann et al ²³	2004	10	10.5	25	Meals	RCT/DB
Kumar et al ²⁴	2007	12	9	40	Meals	PP
Anderson et al ²⁵	2008	10	10	114	Meals	RCT/DB
Kumar et al ²⁶	2009	12	10	42.2	Meals	RCT/DB
Lien et al ²⁷	2009	6	7.5	37	Milk	RCT/DB
Nga et al ²⁸	2009	4	7	35	Biscuits	RCT/DB

RCT: randomized controlled trial; DB: double blind; PP: pre-post.

Table 4. Meta-analytic estimators from trials of iodine fortified food

Estimators	Number of trials	Pooled effect size	95% CI	τ^2 (Tau) value
Parallel ^{20,21,24,26-28}	7	2.17	0.96, 3.39	2.65
Cross-over ^{22,23,25}	7	1.86	0.95, 2.78	1.50
Cross-over first order ^{22,23,25}	7	0.92	-0.06, 1.91	1.75
Combine first order ²⁰⁻²⁸	14	1.55	0.78, 2.31	2.12
Combine cross-over ²⁰⁻²⁸	14	2.02	1.30, 2.73	1.81

Pooled estimates of combined standard mean differences are significant ($p < 0.01$).

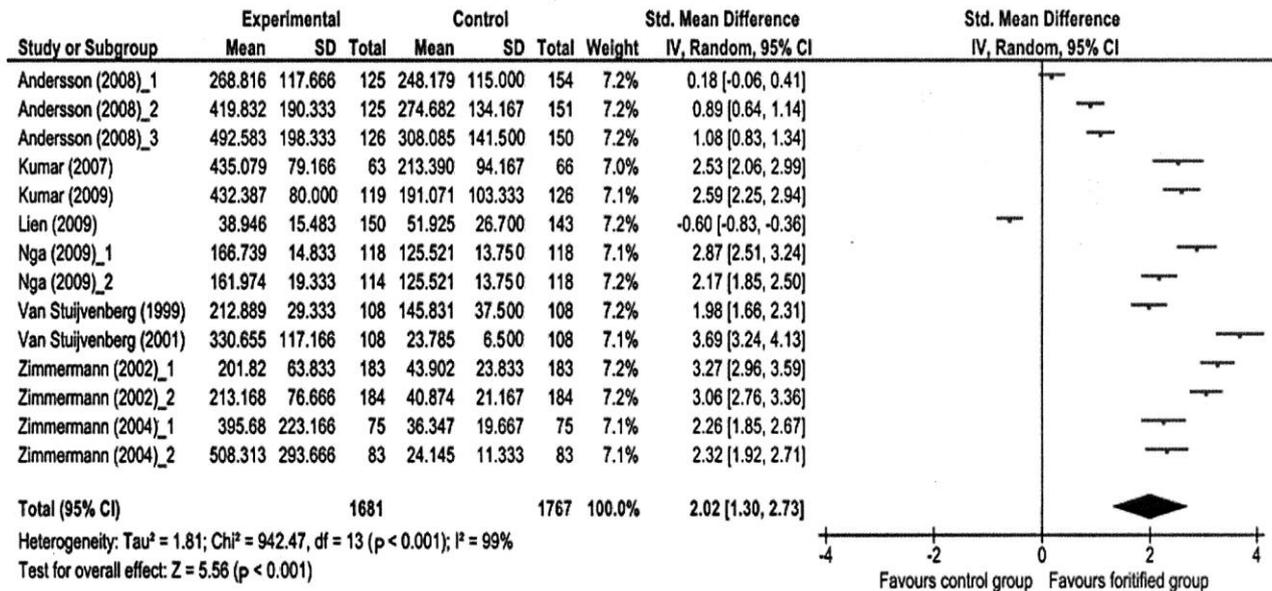


Figure 2. Forest plot of impact of iodine fortification on standard mean difference in UIC $\mu\text{g/L}$ in comparison with no intervention or placebo control in children (Combined cross-over plus parallel). Random-effects meta-analysis of standard mean difference with 95% CI on UIC with iodine fortified food intervention compared with control group. The size of data markers indicates the weight of each study in the analysis. Horizontal lines represent 95% CI. Blob indicates best estimate and diamond indicates the pooled estimate of the standard mean difference.

cross-over trials [i.e. $\lambda^* = 1.378$ and $\lambda^* \sim N(0,1)$]. Hence, the parallel and cross-over trials were combined. Table 4 presents the results of heterogeneity (τ) of trials for parallel, cross-over, combined designs using standard mean difference. The forest plot indicated that the standard mean change in UIC was significantly higher in the fortified group than the control group ($N=3448$, standard mean difference = $2.02 \mu\text{g/L}$, 95% CI 1.30, 2.73; $I^2=99\%$, $\tau^2=1.81$, $p < 0.001$) (Figure 2). There was significant heterogeneity in the mean UICs reported in the included trials. Overall statistical results of heterogeneity such as the Q-statistic ($Q=942.47$, $\text{df}=13$), τ^2 more than zero ($\tau^2=1.81$); and I^2 greater than 75% ($I^2=99\%$) were higher than the expected values, indicating heterogeneity among the trials. Meta-regression analysis performed to detect the source of heterogeneity indicated that the dose (levels) of fortification of the intake of foods was positively related to the effect size (regression coefficient = 0.014 , 95% CI 0.003, 0.026; $p < 0.019$).

Covariate meta-analysis was performed to eliminate the effect of the confounder (moderator), dose of fortification of the trial. The net effect of fortification on UIC in children was found to be 1.59 (95% CI 0.953, 2.23) $\mu\text{g/L}$, after removal of confounder effect, as compared with the calculated pooled effect size of 2.02 (95% CI 1.30, 2.73) $\mu\text{g/L}$.

Publication bias

The funnel plot (Figure 3) was asymmetrical, indicating the probable presence of publication bias which was confirmed using Egger's weighted regression analysis (Egger's test, $p=0.001$). This may be due to the fact that the publications with statistically significant results are more likely to be submitted and published than the studies with non-significant results.

DISCUSSION

We have considered the issue of meta-analyses which combine parallel with cross-over trials in the presence/absence of carry-over effect.²⁹⁻³² The carry-over effect, that is the persistence of the effect of a treatment beyond the period during which it is given, can potentially bias the estimated treatment effect in cross-over trials. Our meta-analysis has demonstrated that iodine fortified foods improved UIC in children. The present meta-analysis of nine studies confirmed the effect of iodine fortified foods in increasing UIC, which is an effective biomarker reflecting changes in iodine status.

The present study adopted design by intervention approaches to verify the impact of interventions of iodine fortified foods on UIC among the children. This paper presents two methods to pool treatment estimates from cross-over and parallel trials with continuous outcomes

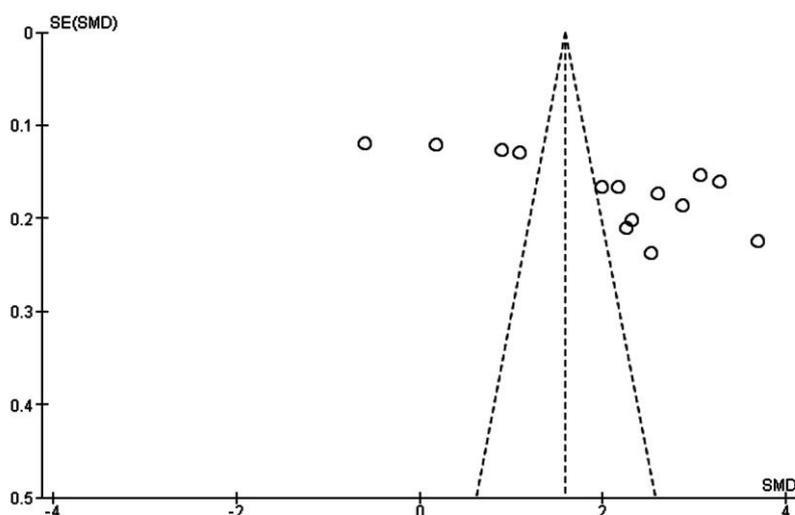


Figure 3. Funnel plot of all individual studies in the meta-analysis. Studies that evaluated the effect of iodine fortification on UIC in children were their standard mean difference on the x-axis and the corresponding standard error of the standard mean difference along the y-axis.

into a combined-design meta-analysis.³⁰ The potential problem in crossover design is that carry-over effects may bias the direct treatment effects. Carry-over (or residual) effect is defined as the effect of the treatment from the previous time period on the response at the current time period. It occurs when the effect of a treatment given in the first time period persists into the second period and distorts the effect of the second treatment. The incorporation of washout period in the design can diminish the impact of carry-over effects. A washout period should be long enough to minimize the carry-over effects. The combination of the two trial designs uses the meta-analysis formulae based on the weighted average of trial estimates of treatment effect.

The presence of heterogeneity is an important attribute of meta-analysis, and can influence the results, which is tested by the Q-statistic, τ^2 and I^2 . The analysis showed that the standard mean difference in UIC (2.02 $\mu\text{g/L}$) favoured the intervention group, suggesting that the iodine fortification improved the mean UIC levels of children. We found the value of Q was more than degrees of freedom, indicating the heterogeneity and suggesting that the variation in the mean change in UIC between intervention and control groups was due to systematic underlying difference.^{16,33} Similarly, τ^2 , also indicated that the variance of standard mean difference was more than zero, which confirmed that heterogeneity existed among the trials. A third measure of heterogeneity, I^2 , which was derivative of Q-statistic, was 99% also suggesting heterogeneity among the trials.^{34,35} The significant difference of the improvement of UIC as reported in forest plot could be due to different time periods of feeding regimens of iodine fortified foods to the children. Increased dose of feeding of fortified foods might have resulted in higher levels of UIC. We observed that there was higher heterogeneity among the trials as some of the trials did not fit into the funnel plot. However, Egger's weighted regression test suggested that there was a publication bias ($p=0.01$).

Since there was heterogeneity among the trials, fixed-effects meta-analysis could not be performed. We applied

the random-effects meta-analysis. This showed a significant impact of iodine fortification on UIC among the child beneficiaries. Thus, this analysis provided evidence to combine studies that have carry-over effect. Meta-regression analysis was also performed to explain the influence of moderators such as study characteristics like age, duration of intervention, dose of fortification.³⁶ Among the moderators, the dose of fortification of the iodine in the trial was the only confounder. This observation is in line with excretion of iodine in urine, which is a function of amount of iodine ingested through fortified salt. The covariate meta-analysis showed that the net effect of standard mean difference was 1.59 $\mu\text{g/L}$ after eliminating the effect of confounder. There was publication bias which is another critical step which can lead to inflated estimates of efficacy. This bias may be the tendency of journals to accept only strong effects or statistically significant results, and this may lead to an upward bias in magnitude of reported results.

In this paper, attempt has been made to combine the studies from different designs viz., parallel and cross-over. There was an insignificant carry-over effect and therefore such studies can be pooled for meta-analysis. In conclusion, present study suggests that iodine fortified foods significantly impact on UIC in children and efforts should concentrate on the elimination of IDD in developing countries.

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AUTHOR DISCLOSURES

There are no conflicts of interest declared by authors.

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Original Article

A meta-analysis combining parallel and cross-over randomized controlled trials to assess impact of iodine fortified foods on urinary iodine concentration among children

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碘强化食品对儿童尿碘浓度的影响评估：一项结合平行和交叉随机对照试验的 meta 分析

本分析的目的是结合平行和交叉随机对照试验的证据，评估碘强化食品对儿童尿碘浓度（UIC）的影响。进行结构化搜索 MEDLINE、Pro Quest 和 Cochrane 数据库中收录的 1990 年 1 月份到 2012 年 12 月份发表的碘干预研究。采用一般线性模型评估延滞效应。我们通过将平行和交叉试验设计相结合，在一个 meta 分析中探讨出两种合并连续结果的方法。计算 UIC 净变化的标准平均差。用固定或随机模型汇总强化食品反应数据。用 meta 回归和协变量 meta 分析探讨混杂因素对 UIC 净合并效应的影响。结合没有 UIC 延滞效应的 9 个平行和交叉试验分析结果显示：与对照组相比，强化组整体综合评估显著增加（ $n=3448$ ，标准平均差=2.02 $\mu\text{g/L}$ ；95% CI：1.30，2.73； $I^2=99\%$ ， $\tau^2=1.81$ ， $p<0.01$ ）。Meta 回归分析表明，干预剂量与影响大小成正相关（回归系数=0.014，95% CI：0.003，0.026； $p<0.019$ ）。去除混杂因素后的净合并效应为 1.59（95% CI：0.953，2.23） $\mu\text{g/L}$ 。碘强化食品摄入与儿童 UIC 有关。这些结果表明，当营养素（比如碘）吸收率高时，我们可以将平行和交叉试验结合起来进行 meta 分析。

关键词：碘强化、meta 分析、延滞效应、meta 回归、协变量 meta 分析