Effects of prenatal multimicronutrient supplementation on pregnancy outcomes: a meta-analysis

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The full-text version of this article is available at www.cmaj.ca/cgi/content/full/cmaj.081777.

See related commentary by Bhutta and Haider, page 1188

Abstract

Background: Reduced intake of micronutrients during pregnancy exposes women to nutritional deficiencies and may affect fetal growth. We conducted a systematic review to examine the efficacy of prenatal supplementation with multimicronutrients on pregnancy outcomes.

Methods: We searched MEDLINE, EMBASE, CINAHL and the Cochrane Library for relevant articles published in English up to December 2008. We also searched the bibliographies of selected articles as well as clinical trial registries. The primary outcome was low birth weight; secondary outcomes were preterm birth, small-for-gestational-age infants, birth weight and gestational age.

Results: We observed a significant reduction in the risk of low birth weight among infants born to women who received multimicronutrients during pregnancy compared with placebo (relative risk [RR] 0.81, 95% confidence interval [CI] 0.73–0.91) or iron–folic acid supplementation (RR 0.83, 95% CI 0.74–0.93). Birth weight was significantly higher among infants whose mothers were in the multimicronutrient group than among those whose mothers received iron–folic acid supplementation (weighted mean difference 54 g, 95% CI 36 g–72 g). There was no significant differences in the risk of preterm birth or small-for-gestational-age infants between the 3 study groups.

Interpretation: Prenatal multimicronutrient supplementation was associated with a significantly reduced risk of low birth weight and with improved birth weight when compared with iron–folic acid supplementation. There was no significant effect of multimicronutrient supplementation on the risk of preterm birth or small-for-gestational-age infants.

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Nutrition plays an important role in the growth and development of the fetus. Studies of the nutritional status of pregnant women during the Dutch famine revealed increased risks of infertility, abortion, fetal intrauterine growth restriction and perinatal mortality among malnourished women.[1] In many parts of the world, a similar situation exists for many pregnant women with respect to nutrition. Overall, the diet of pregnant women has been reported to be deficient in calories and micronutrients.[2] Both macro- and micronutrients are important for a woman to sustain pregnancy and for appropriate growth of the fetus.

On the basis of a systematic review performed in 2005, the World Health Organization currently recommends iron–folic acid supplementation for all pregnant women.[3,4] The review reported that multimicronutrient supplementation during pregnancy was more efficacious than 2 or fewer micronutrients in reducing the rates of low birth weight and small-for-gestational-age births. However, when multimicronutrients were compared with iron–folic acid supplementation, no evidence of a difference was noted.[5] Further research in this area was encouraged because information was derived from a few reports. Since then, several randomized controlled trials have evaluated the efficacy of multimicronutrients and have reported varied results. With advancement in our knowledge from recently reported trials,[6] we conducted a systematic review and meta-analysis of the efficacy of supplementation with multimicronutrients during pregnancy in reducing the rates of low birth weight, preterm birth and small-for-gestational-age births compared with placebo or iron–folic acid supplementation.

Methods

We conducted this systemic review to examine whether supplementation with multimicronutrients during pregnancy reduces the risk of low birth weight, preterm birth and small-for-gestational-age births compared with placebo and compared with iron–folic acid supplementation.

Literature search

We searched MEDLINE, EMBASE, CINAHL and the Cochrane Library (from their inception to Dec. 15, 2008) for all relevant studies without language restriction. The search

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terms used for MEDLINE are reported in Appendix 1 (available at www.cmaj.ca/cgi/content/full/cmaj.081777/DC3); they were modified according to database requirements. We reviewed the bibliographies of the identified articles to locate further eligible studies. In addition, we searched 20 clinical trial registries (Appendix 2, available at www.cmaj.ca/cgi/content/full/cmaj.081777/DC3), abstracts of the last 2 years from conferences of the Society of Maternal and Fetal Medicine and the Society of Obstetricians and Gynaecologists of Canada, and Google Scholar™ for ongoing or completed trials.

Study selection and validity assessment

We included randomized and quasi-randomized trials (randomization based on possible identifiers such as date of birth, hospital number or day of the week) that explored the efficacy of supplementation with multimicronutrients during pregnancy and reported any of the outcomes of interest. We included only information available from publications and did not contact primary authors for additional data.

We included studies in which women received multimicronutrient supplementation at any time during pregnancy. A previous systematic review[5] had excluded studies of patients who were HIV positive because of concerns over their background nutritional status. To improve the generalizability of our findings, we included all populations. We planned sensitivity analyses with data for all patients and with data for HIV-positive women.

We included studies that compared multimicronutrient supplementation with placebo or with iron–folic acid supplementation. We did not restrict the selection of trials on the basis of the specific combination or number of micronutrients. We anticipated that most studies would have used the recommended dietary allowance of individual micronutrients. We planned subgroup analyses to assess the effects of studies in which supplementation of most of the micronutrients were in doses higher or lower than the recommended dietary allowance. Studies of supplementation that started at any time during pregnancy and for any length of time were included. We planned a subgroup analysis to assess the effect of when supplementation was started (before or after 20 weeks' gestation). We report on compliance with supplementation as described by the authors of the studies.

We excluded studies in which prepared food containing macro- and micronutrients was given rather than a unique supplement of micronutrients. We also excluded studies in which the outcomes were not clearly defined. We reviewed studies published only as abstracts and included them only if quality assessment could be completed from the given information. Studies for which quality could not be determined were excluded. We excluded letters, commentaries, reviews and editorials if they did not contain original data.

One of us (P.S.S.) scanned the titles and abstracts of the articles initially. Selected articles were retrieved in full; both of us (P.S.S. and A.O.) assessed them for eligibility. We resolved discrepancies by consensus.

Outcome measures

The primary outcome of interest was the incidence of low birth weight (< 2500 g). Secondary outcomes were preterm birth (birth before 37 weeks' gestation), small-for-gestational-age infants (< 10th centile for gestational age or > 2 standard deviations below the mean for gestational age), birth weight (in grams) and gestational age (in weeks).

Methodologic quality

Both of us (P.S.S. and A.O.) independently assessed the methodologic quality of the studies using a predefined checklist, as suggested for the Cochrane Database of Systematic Reviews[7] (see Appendix 3, available at www.cmaj.ca/cgi/content/full/cmaj.081777/DC3). We resolved discrepancies by consensus.

We assessed statistical heterogeneity using the Cochran Q test and by calculating I^2 values. Clinical heterogeneity was assessed for timing of supplementation, methodologic quality of the studies and characteristics of the study populations. We assessed publication bias using the funnel plot method.

Data extraction and synthesis

Two of us (P.S.S. and A.O.) extracted data from each eligible study using data-collection forms. We resolved discrepancies by consensus. The original data were not modified. At times, calcu-

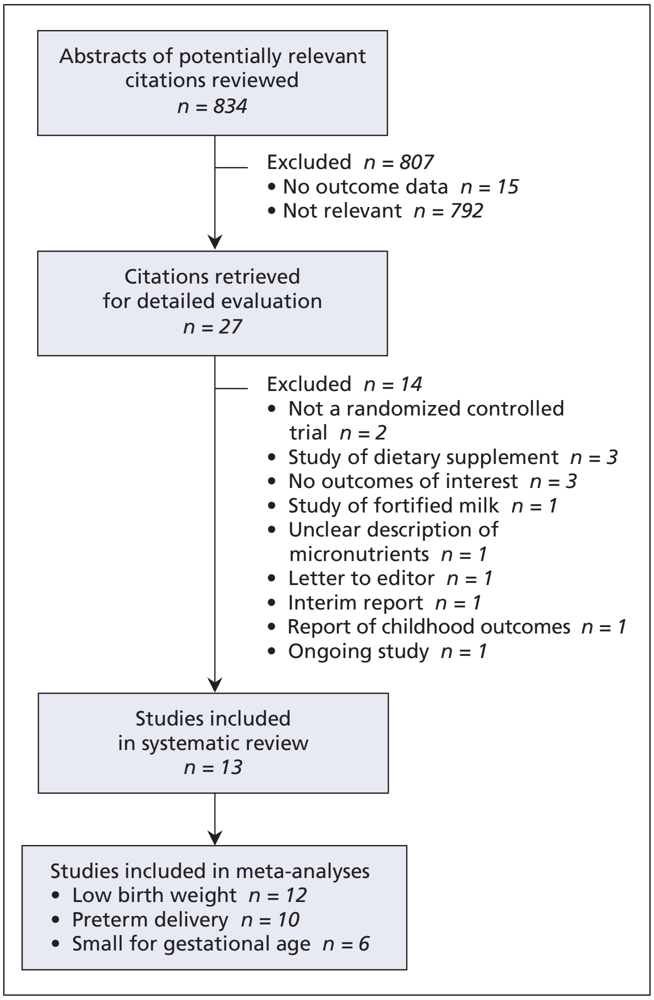

Figure 1: Selection of studies for meta-analysis of the effect of prenatal supplementation with multimicronutrients on pregnancy outcomes.

lations were required from available data for the meta-analysis.

For binary outcome variables (low birth weight, preterm birth and small for gestational age), we calculated the relative risks (RRs), risk differences and numbers needed to benefit and to harm, as well as respective 95% confidence intervals (CIs). For continuous measures (birth weight and gestational age), we calculated the mean differences or standardized mean differences as appropriate. Weighting of the studies in the meta-analyses was calculated based on the inverse variance of the study. We expected clinical and statistical heterogeneity among the studies. Thus, we used the random-effect model for meta-analyses because it accounts for random variability both within and among studies. We planned sensitivity analyses to assess the effects of the quality of the studies on the results. No adjustment for multiple analyses was made.

Results

Literature search

We identified 13 trials (8 randomized trials, 1 factorial randomized trial and 4 cluster-randomized trials) of prenatal multimicronutrient supplementation for inclusion in the meta-analysis (Figure 1).[8–20] We excluded 14 reports (the reasons for exclusion are given in Appendix 4, available at www.cmaj.ca/cgi/content/full/cmaj.081777/DC3).

Study participants and interventions

The baseline characteristics of the women in the included studies and the timing of initiation of micronutrient supplementation are reported in Table 1 of the the full-text version of this article (available at www.cmaj.ca/cgi/content/full/cmaj.081777). The composition of micronutrients in the different studies is reported in Table 1 of this article and online Appendix 5 (available at www.cmaj.ca/cgi/content/full/cmaj.081777/DC3).

Methodologic quality

The results of our assessment of the risk of bias among included studies and compliance rates are reported in Appendix 6 (available at www.cmaj.ca/cgi/content/full/cmaj.081777/DC3). All of the studies were of high quality.

Outcomes

Details of the outcomes reported in the individual studies are reported in Appendix 7 (available at www.cmaj.ca/cgi/content/full/cmaj.081777/DC3).

Twelve of the studies reported on the outcome of low birth weight (Figure 2). Four compared multimicronutrient supplementation with a placebo (n = 6097) and 10 compared it with iron–folic acid supplementation (n = 29 889); 2 studies reported on both comparisons. The risk of low-birth-weight infants was significantly lower among women given multimicronutrients than among those given placebo (RR 0.81, 95% CI 0.73 to 0.91; risk difference –0.03, 95% CI –0.05 to –0.01; number needed to benefit 33, 95% CI 20 to 100). The same was true for the comparison with iron–folic acid supplementation (RR 0.83, 95% CI 0.74 to 0.93; risk difference –0.02, 95% CI –0.03 to –0.01; number needed to benefit 50, 95% CI 33 to 100).

Ten studies reported on preterm birth as an outcome measure (Figure 3). Three studies compared multimicronutrient supplementation with placebo and 9 compared it with iron–folic acid supplementation; 2 studies reported on both comparisons. The risk of preterm birth was not significantly lower among women given multimicronutrient supplementation during pregnancy than among those given placebo or iron–folic acid supplementation.

Table 1: Composition of micronutrients in studies included in the meta-analysis

Study	Vitamin A, IU	Vitamin B_1, mg	Vitamin B_6, mg	Folic acid, mg	Zinc, mg	Iron, mg	Copper, mg	Total no. of micronutrients*
Christian et al.,[9] 2003	1000	1.6	2.2	400	30	60	2.0	16
Fawzi et al.,[10] 1998	5000	20	25	800	–	–	–	10
Fawzi et al.,[8] 2007		20	25	800	–	–	–	8
Friis et al.,[11] 2004	3000	1.5	2.2	–	15	–	1.2	13
Gupta et al.,[12] 2007	2500	1.0	1.0	150	15	10	2	28
Hininger et al.,[13] 2004		1.4	–	200	15			12
Kaestal et al.,[14] 2005 (micronutrient-1)	800	1.4	1.9	400	15	30	2	15
Kaestal et al.,[14] 2005 (micronutrient-2)	1600	2.8	3.8	800	30	30	4	15
Osrin et al.,[15] 2005	2640	1.4	1.9	400	15	30	2	15
Ramakrishnan et al.,[16] 2003	2150	0.93	1.94	215	12.9	62.4	–	13
Roberfroid et al.,[17] 2008	2640	1.4	1.9	400	15	30	2	15
Shankar et al.,[18] 2008	2640	1.4	1.9	400	15	30	2	14
Zagre et al.,[19] 2007	2640	1.4	1.9	400	15	30	2	15
Zeng et al.,[20] 2008	2640	1.4	1.9	400	15	30	2	15

*A detailed description of other micronutrients in each study appears in Appendix 5 (available at www.cmaj.ca/cgi/content/full/cmaj.081777/DC3).

Six studies reported on the risk of small-for-gestational-age infants (Figure 4). Three studies compared multimicronutrient supplementation with placebo and 5 compared it with iron–folic acid supplementation; 2 studies reported on both comparisons. There was no statistically significant reduction in the risk of this outcome among women given multimicronutrient supplementation compared with women given placebo or iron–folic acid supplementation.

Results of our meta-analysis concerning birth weight and gestational age appear in the full-text version of this article (available at www.cmaj.ca/cgi/content/full/cmaj.081777).

Heterogeneity and publication bias

Clinical heterogeneity among the studies is described in Table 1 of the full-text version of this article (available at www.cmaj.ca/cgi/content/full/cmaj.081777). There was moderate statistical heterogeneity for low birth weight (I^2 = 55%–64%) but not for preterm birth (I^2 = 0%).

Visual inspection of the funnel plot suggested publication bias for the outcomes low birth weight and preterm birth for studies of small effect size showing both positive and negative results (Appendix 8, available at www.cmaj.ca/cgi/content/full/cmaj.081777/DC3). We believe that this bias is unlikely to change the overall results, since the majority of included studies were of high quality and precision. However, this should be interpreted with caution in face of heterogeneity in studies.[21]

Subgroup and sensitivity analyses

In a subgroup analysis based on the timing of initiation of supplementation, we found no difference in the risk of low-birth-weight infants when multimicronutrient supplementation was compared with iron–folic acid supplementation (RR 0.89, 95% CI 0.72 to 1.08 for initiation before 20 weeks' gestation; RR 0.80, 95% CI 0.69 to 0.91 for initiation anytime after 12 weeks' gestation). However, the majority of the studies in the later category had entry criteria of 12–27 weeks' gestation.

We found that the effect of multimicronutrient supplementation was more pronounced for low-birth-weight and small-for-gestational-age infants in randomized trials (low birth weight: RR 0.74, 95% CI 0.62 to 0.89; small for gestational age: RR 0.82, 95% CI 0.73 to 0.92) than in cluster randomized trials (low birth weight: RR 0.91, 95% CI 0.82 to 1.02; small for gestational age: RR 0.98, 95% CI 0.84 to 1.14).

We performed a post-hoc stratified analysis to identify an effective minimal composition of micronutrients that can be suggested for practical use and to explore heterogeneity in the composition of micronutrients. We selected a group of studies that used a homogeneous combination of water and fat-soluble vitamins and minerals (vitamin A ≥ 2640 IU, vitamin D ≥ 200 IU, vitamin E ≥ 10 mg, vitamin B_1 ≥ 1.4 mg, folic acid ≥ 400 µg, vitamin C ≥ 70 mg, zinc ≥ 15 mg and iron ≥ 30 mg). We observed a reduction in the risk of low-birth-weight infants in this subgroup analysis (RR 0.85, 95% CI 0.78 to 0.93, I^2 = 0%). Despite

Study	Study group, *n/N*: Micronutrients	Study group, *n/N*: Control	Relative risk (95% CI)
Micronutrients v. placebo			
Christian et al., 2003[9]	249/705	297/685	0.81 (0.71–0.93)
Kaestel et al., 2005[14]	83/750	51/373	0.81 (0.58–1.12)
Ramakrishnan et al., 2003[16]	27/318	28/315	0.96 (0.58–1.58)
Zeng et al., 2008[20]	57/1 406	82/1 545	0.76 (0.55–1.06)
Overall	*416/3 179*	*458/2 918*	*0.81 (0.73–0.91)*
Micronutrients v. iron–folic acid supplementation			
Christian et al., 2003[9]	249/705	218/635	1.03 (0.89–1.19)
Fawzi et al., 1998[8]	36/410	62/390	0.55 (0.38–0.81)
Fawzi et al., 2007[10]	306/3 937	368/3 929	0.83 (0.72–0.96)
Friis et al., 2004[11]	54/564	62/542	0.84 (0.59–1.18)
Gupta et al., 2007[12]	12/74	31/72	0.38 (0.21–0.67)
Osrin et al., 2005[15]	101/529	133/523	0.75 (0.60–0.94)
Roberfroid et al., 2008[17]	77/526	82/526	0.94 (0.71–1.25)
Shankar et al., 2008[18]	510/5 695	567/5 406	0.85 (0.76–0.96)
Zagre et al., 2007[19]	96/1 328	103/1 222	0.86 (0.66–1.12)
Zeng et al., 2008[20]	57/1 406	66/1 470	0.90 (0.64–1.28)
Overall	*1 498/15 174*	*1 692/14 715*	*0.83 (0.74–0.93)*

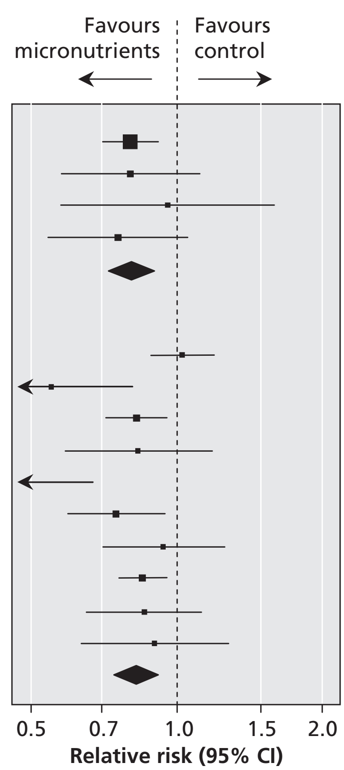

Figure 2: Random-effect meta-analysis of the risk of low-birth-weight infants among women given multimicronutrient supplementation versus control (placebo or iron–folic acid supplementation) during pregnancy. Values less than 1.0 indicate decreased risk of outcome with multimicronutrient supplementation. Note: CI = confidence interval.

the exclusion of studies that did not satisfy one or more criteria, we found no clear discernible pattern to indicate that one or more micronutrients in addition of iron and folic acid would suffice.

When we examined results for women with known HIV infection from 2 studies (n = 1160), we found no evidence of a difference in the risk of low-birth-weight infants between women given multimicronutrient supplementation and those given iron–folic acid supplementation (RR 0.73, 95% CI 0.40 to 1.33).

Interpretation

In this systematic review, we identified a significantly reduced risk of low-birth-weight infants among women given multimicronutrient supplementation during pregnancy compared with women given placebo or iron–folic acid supplementation. The birth weight of infants was 54 g higher on average among those whose mothers were given micronutrients than among those whose mothers received iron–folic acid supplementation. We found no evidence of a significant difference in the risk of preterm birth or small-for-gestational-age infants between the study groups.

There was a certain degree of clinical and statistical heterogeneity among the studies included in the meta-analysis. This was not beyond what one could have predicted from the outset. The most important aspects of heterogeneity were the underlying population and the time of onset of supplementation.

The included trials were of very good quality. Although they all had missing data for birth outcomes for a proportion of patients, the results were unlikely affected because the numbers with missing data were small and were proportionally distributed. In some studies, the micronutrient supplementation was started at the earliest detection of pregnancy, whereas in other studies it was started as late as in the third trimester. One might have expected stronger evidence of a difference in outcomes with supplementation started before 20 weeks' gestation; however, Shankar and associates[18] reported a higher efficacy in terms of reduced infant mortality among participants whose supplementation was initiated in their third trimester. Our subgroup analyses did not reveal an advantage with earlier initiation of supplementation; however, the number of studies in each subgroup was small, and there was overlap of the timing of initiation in various studies.

Variation in the composition of micronutrients between the studies was minor except in the study by Fawzi and colleagues,[10] in which the amount of certain micronutrients was significantly higher than the recommended dietary allowance (Table 1). Our exploratory post-hoc analyses to identify the minimum number of additional nutrients that can be added to an iron–folic acid supplement to identify beneficial effects revealed a combination rather than a particular ingredient that may be essential to observe benefit. However, these results were from a subset of studies that assessed virtually identical compositions of micronutrients. Post-hoc exploration to assess heterogeneity in the treatment effect revealed that treatment effect had no relation with consistent pattern of inclusion or exclusion of vitamin A or zinc, or with particular

Study	Study group, *n/N* Micronutrients	Control	Relative risk (95% CI)
Micronutrients v. placebo			
Christian et al., 2003[9]	145/704	140/685	1.01 (0.82–1.24)
Ramakrishnan et al., 2003[16]	24/321	21/321	1.14 (0.65–2.01)
Zeng et al., 2008[20]	78/1 494	102/1 666	0.85 (0.64–1.14)
Overall	*247/2 519*	*263/2 672*	*0.97 (0.82–1.13)*
Micronutrients v. iron–folic acid supplementation			
Christian et al., 2003[9]	145/704	146/633	0.89 (0.73–1.09)
Fawzi et al., 1998[8]	96/410	106/390	0.86 (0.68–1.09)
Fawzi et al., 2007[10]	676/3 993	666/4 003	1.02 (0.92–1.12)
Friis et al., 2004[11]	85/564	99/542	0.83 (0.63–1.08)
Gupta et al., 2007[12]	1/74	1/72	0.97 (0.06–15.26)
Osrin et al., 2005[15]	47/571	54/568	0.87 (0.60–1.26)
Roberfroid et al., 2008[17]	86/607	81/604	1.06 (0.80–1.40)
Shankar et al., 2008[18]	3 736/14 373	3 654/14 053	1.00 (0.96–1.04)
Zeng et al., 2008[20]	78/1 494	76/1 537	1.06 (0.78–1.44)
Overall	*4 950/22 790*	*4 883/22 402*	*0.99 (0.96–1.03)*

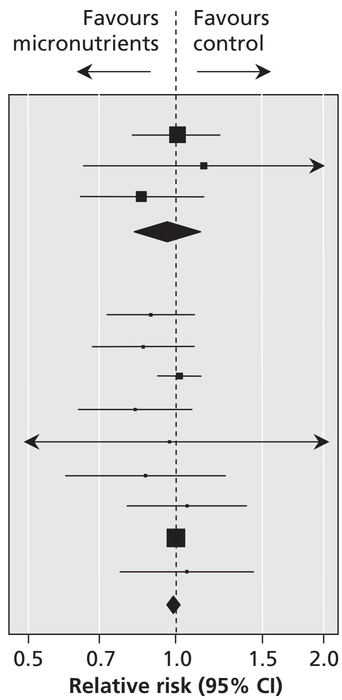

Figure 3: Random-effect meta-analysis of the risk of preterm birth among women given multimicronutrient supplementation versus control (placebo or iron–folic acid supplementation) during pregnancy. Values less than 1.0 indicate decreased risk of outcome with multimicronutrient supplementation. Note: CI = confidence interval.

doses of vitamin A or zinc. We explored these 2 ingredients only because other ingredients of interest were present in similar doses in most formulations of micronutrients.

Our findings differ substantially from those reported previously.[4,5] Haider and Bhutta[5] concluded that the evidence was not adequate to replace the current global strategy of iron–folic acid supplementation with multimicronutrient supplementation. Our findings showed that multimicronutrient supplementation was more efficacious than iron–folic acid supplementation in reducing the incidence of low birth weight and in improving birth weight. However, the collection of data differed slightly between the reviews. We included the study by Fawzi and colleagues,[10] which had been excluded by Haider and Bhutta.[5] They included a study from Pakistan that we did not include because we could not locate a peer-reviewed article or any other reference for the study. We incorporated new findings from 7 recently completed randomized trials in different countries. We were unable to match some of the numbers for the outcomes included in the Haider and Bhutta review for the study by Christian and colleagues.[9] We used methods for our meta-analyses that were similar to those used by Haider and Bhutta. As well, we searched clinical trial registries extensively. The variation in multimicronutrient compounds used in the studies was relatively greater in studies conducted before 2003 (those included in Haider and Bhutta's review) than in more recent studies included in our review. This was because micronutrient supplementation during pregnancy was highlighted as a research priority and was subsequently investigated with a rather similar approach at the suggestions of UNICEF.

One of the criticisms of any health intervention that is multicomponent in nature is not knowing with certainty which of the components works. It will be difficult to tease out which components of multimicronutrient supplementation were responsible for the improvement in low birth weight that we observed. Therefore, it is not unreasonable to recommend a composite of micronutrients for supplementation because it would be impossible to identify and target individual deficiencies in every pregnant women. The effect of multimicronutrient supplementation on birth weight was relatively smaller than the effect on low birth weight. However, supplementation probably affected infants at a borderline weight around the cutoff of 2500 g.

With the possibility of reducing the incidence of low birth weight by 17%, as shown in our meta-analysis, we believe that providing pregnant women with multimicronutrient supplementation offers the highest possible return for the investment. Current estimates indicate that 15.5% of about 133 million births worldwide each year are of low-birth-weight infants. We estimate that 75 million births occur in developing countries, where mothers at best receive iron–folic acid supplementation. If all of these women were given multimicronutrient supplementation, our most conservative calculations indicate that about 1.5 million (95% CI 0.75 million to 2.25 million) births of low-birth-weight infants could be averted worldwide every year.

Strengths and limitations

The strengths of this systematic review include a focused question, an extensive literature search, a large sample of the studied population, inclusion of studies from various parts of the world and the precision of the results. Limitations include clinical heterogeneity in the studies, including the timing and duration of supplementation, the composition of micronutrients and the characteristics of the study populations. All of these features could have an impact on pregnancy outcomes. Further studies are needed to differentiate effects from these perspectives.

Study	Study group, *n/N*		Relative risk (95% CI)
	Micronutrients	Control	
Micronutrients v. placebo			
Christian et al., 2003[12]	379/704	402/685	0.92 (0.84–1.01)
Fawzi et al., 1998[5]	39/410	66/390	0.56 (0.39–0.81)
Zeng et al., 2008[23]	238/1 406	280/1 545	0.93 (0.80–1.09)
Overall	*656/2 520*	*748/2 620*	*0.85 (0.71–1.02)*
Micronutrients v. iron–folic acid supplementation			
Christian et al., 2003[12]	379/704	327/633	1.04 (0.94–1.15)
Fawzi et al., 2007[13]	407/3 827	523/3 823	0.78 (0.69–0.88)
Gupta et al., 2007[15]	23/74	31/72	0.72 (0.47–1.11)
Roberfroid et al., 2008[20]	194/518	213/512	0.90 (0.77–1.05)
Zeng et al., 2008[23]	238/1 406	278/1 470	0.90 (0.77–1.05)
Overall	*1 241/6 529*	*1 372/6 510*	*0.89 (0.77–1.01)*

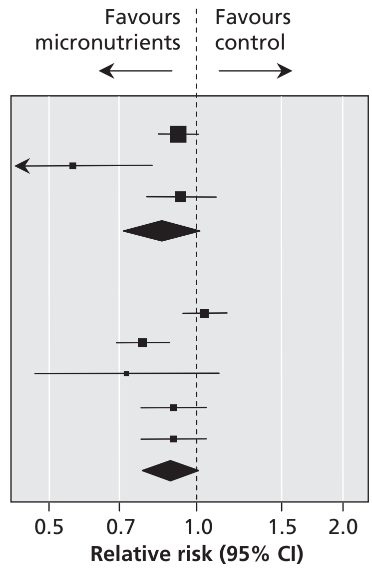

Figure 4: Random-effect meta-analysis of the risk of small-for-gestational-age infants among women given multimicronutrient supplementation versus control (placebo or iron–folic acid supplementation) during pregnancy. Values less than 1.0 indicate decreased risk of outcome with multimicronutrient supplementation. Note: CI = confidence interval.

Implications for practice and research

Potential implications for practice include the need to ensure that pregnant women receive multimicronutrient supplementation during the prenatal period. The current strategy recommended by the World Health Organization of providing only iron–folic acid supplementation to pregnant women needs to be challenged in light of the evidence from our review.

Further research is needed to answer certain critical questions. Will a reduction in the risk of low-birth-weight infants associated with multimicronutrient supplementation result in an overall reduction in mortality and related complications among these children? Does multimicronutrient supplementation lead to improved neurodevelopmental outcomes? Do we need different approaches for different populations based on their underlying nutritional status? Will multimicronutrient supplementation at the time of conception improve placentation and prevent preeclampsia sufficiently to improve fetal growth?[22]

Conclusion

We found that prenatal supplementation with multimicronutrients was associated with a significantly reduced risk of low-birth-weight infants and with improved birth weight when compared with iron–folic acid supplementation. We found no effect of multimicronutrient supplementation on the risk of preterm birth or small-for-gestational-age infants.

This article has been peer reviewed.

Competing interests: None declared.

Contributors: Prakesh Shah and Arne Ohlsson participated in writing the original grant application and contributed to all drafts of the manuscript. Prakesh Shah was the principal investigator and led the Knowledge Synthesis group. He contributed to analyzing and interpreting the data, wrote the first draft, and is guarantor for this paper. Arne Ohlsson contributed to the conception of the study and protocol, interpreted the data, and revised the first and subsequent drafts of this manuscript. Both authors approved the final version submitted for publication.

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REFERENCES

1. Smith CA. Effects of maternal undernutrition upon the newborn infant in Holland (1944–45). *J Pediatr* 1947;30:229-43.
2. Gopalan C. Multiple micronutrient supplementation in pregnancy. *Nutr Rev* 2002;60:S2-6.
3. *Composition of a multi-micronutrient supplement to be used in pilot programmes among pregnant women in developing countries*. New York (NY): UNICEF; 1999.
4. Lumbiganon P. Multiple-micronutrient supplementation for women during pregnancy [commentary]. Geneva (Switzerland): Reproductive Health Library, World Health Organization; 2007 Available: www.who.int/rhl/pregnancy_childbirth/antenatal_care/nutrition/plcom2/en/index.html (last revised 2007 Aug. 23; accessed 2009 Apr. 29).
5. Haider BA, Bhutta ZA. Multiple-micronutrient supplementation for women during pregnancy [review]. *Cochrane Database Syst Rev* 2006;(4):CD004905.
6. de Onis M, Villar J, Gülmezoglu M. Nutritional interventions to prevent intrauterine growth retardation: evidence from randomized controlled trials. *Eur J Clin Nutr* 1998;52(Suppl 1):S83-93.
7. Higgins PT, Green S, editors. *Cochrane handbook for systematic reviews of interventions*. The Cochrane Collaboration; 2008. Available: www.cochrane-handbook.org (accessed 2008 Jan. 3).
8. Fawzi WW, Msamanga GI, Urassa W, et al. Vitamins and perinatal outcomes among HIV-negative women in Tanzania. *N Engl J Med* 2007;356:1423-31.
9. Christian P, Khatry SK, Katz J, et al. Effects of alternative maternal micronutrient supplements on low birth weight in rural Nepal: double blind randomised community trial. *BMJ* 2003;326:571.
10. Fawzi WW, Msamanga GI, Spiegelman D, et al. Randomised trial of effects of vitamin supplements on pregnancy outcomes and T cell counts in HIV-1-infected women in Tanzania. *Lancet* 1998;351:1477-82.
11. Friis H, Gomo E, Nyazema N, et al. Effect of multimicronutrient supplementation on gestational length and birth size: a randomized, placebo-controlled, double-blind effectiveness trial in Zimbabwe. *Am J Clin Nutr* 2004;80:178-84.
12. Gupta P, Ray M, Dua T, et al. Multimicronutrient supplementation for undernourished pregnant women and the birth size of their offspring: a double-blind, randomized, placebo-controlled trial. *Arch Pediatr Adolesc Med* 2007;161:58-64.
13. Hininger I, Favier M, Arnaud J, et al. Effects of a combined micronutrient supplementation on maternal biological status and newborn anthropometrics measurements: a randomized double-blind, placebo-controlled trial in apparently healthy pregnant women. *Eur J Clin Nutr* 2004;58:52-9.
14. Kaestel P, Michaelsen KF, Aaby P, et al. Effects of prenatal multimicronutrient supplements on birth weight and perinatal mortality: a randomised, controlled trial in Guinea-Bissau. *Eur J Clin Nutr* 2005;59:1081-9.
15. Osrin D, Vaidya A, Shrestha Y, et al. Effects of antenatal multiple micronutrient supplementation on birthweight and gestational duration in Nepal: double-blind, randomised controlled trial. *Lancet* 2005;365:916-7.
16. Ramakrishnan U, Gonzalez-Cossio T, Neufeld LM, et al. Multiple micronutrient supplementation during pregnancy does not lead to greater infant birth size than does iron-only supplementation: a randomized controlled trial in a semirural community in Mexico. *Am J Clin Nutr* 2003;77:720-5.
17. Roberfroid D, Huybregts L, Lanou H, et al. Effects of maternal multiple micronutrient supplementation on fetal growth: a double-blind randomized controlled trial in rural Burkina Faso. *Am J Clin Nutr* 2008;88:1330-40.
18. Shankar AH, Jahari AB, Sebayang SK, et al. Effect of maternal multiple micronutrient supplementation on fetal loss and infant death in Indonesia: a double-blind cluster-randomised trial. *Lancet* 2008;371:215-27.
19. Zagre NM, Desplats G, Adou P, et al. Prenatal multiple micronutrient supplementation has greater impact on birthweight than supplementation with iron and folic acid: a cluster-randomized, double-blind, controlled programmatic study in rural Niger. *Food Nutr Bull* 2007;28:317-27.
20. Zeng L, Dibley MJ, Cheng Y, et al. Impact of micronutrient supplementation during pregnancy on birth weight, duration of gestation, and perinatal mortality in rural western China: double blind cluster randomised controlled trial. *BMJ* 2008;337:a2001.
21. Ioannidis JP, Trikalinos TA. The appropriateness of asymmetry tests for publication bias in meta-analyses: a large survey. *CMAJ* 2007;176:1091-6.
22. Catov JM, Bodnar LM, Ness RB, et al. Association of periconceptional multivitamin use and risk of preterm or small-for-gestational-age births. *Am J Epidemiol* 2007;166:296-303.

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