



Modifiers of the effect of maternal multiple micronutrient supplementation on stillbirth, birth outcomes, and infant mortality: a meta-analysis of individual patient data from 17 randomised trials in low-income and middle-income countries

Emily R Smith, Anuraj H Shankar, Lee S-F Wu, Said Aboud, Seth Adu-Afarwuah, Hasmat Ali, Rina Agustina, Shams Arifeen, Per Ashorn, Zulfiqar A Bhutta, Parul Christian, Delanjathan Devakumar, Kathryn G Dewey, Henrik Friis, Exnevia Gomo, Piyush Gupta, Pernille Kæstel, Patrick Kolsteren, Hermann Lanou, Kenneth Maleta, Aissa Mamadoulaibou, Gerard Msamanga, David Osrin, Lars-Åke Persson, Usha Ramakrishnan, Juan A Rivera, Arjumand Rizvi, H P S Sachdev, Willy Urassa, Keith P West Jr, Noel Zagre, Lingxia Zeng, Zhonghai Zhu, Wafaie W Fawzi, Christopher R Sudfeld



Summary

Background Micronutrient deficiencies are common among women in low-income and middle-income countries. Data from randomised trials suggest that maternal multiple micronutrient supplementation decreases the risk of low birthweight and potentially improves other infant health outcomes. However, heterogeneity across studies suggests influence from effect modifiers. We aimed to identify individual-level modifiers of the effect of multiple micronutrient supplements on stillbirth, birth outcomes, and infant mortality in low-income and middle-income countries.

Methods This two-stage meta-analysis of individual patient included data from 17 randomised controlled trials done in 14 low-income and middle-income countries, which compared multiple micronutrient supplements containing iron-folic acid versus iron-folic acid alone in 112 953 pregnant women. We generated study-specific estimates and pooled subgroup estimates using fixed-effects models and assessed heterogeneity between subgroups with the χ^2 test for heterogeneity. We did sensitivity analyses using random-effects models, stratifying by iron-folic acid dose, and exploring individual study effect.

Findings Multiple micronutrient supplements containing iron-folic acid provided significantly greater reductions in neonatal mortality for female neonates compared with male neonates than did iron-folic acid supplementation alone (RR 0.85, 95% CI 0.75–0.96 vs 1.06, 0.95–1.17; p value for interaction 0.007). Multiple micronutrient supplements resulted in greater reductions in low birthweight (RR 0.81, 95% CI 0.74–0.89; p value for interaction 0.049), small-for-gestational-age births (0.92, 0.87–0.97; p=0.03), and 6-month mortality (0.71, 0.60–0.86; p=0.04) in anaemic pregnant women (haemoglobin <110g/L) as compared with non-anaemic pregnant women. Multiple micronutrient supplements also had a greater effect on preterm births among underweight pregnant women (BMI <18.5 kg/m²; RR 0.84, 95% CI 0.78–0.91; p=0.01). Initiation of multiple micronutrient supplements before 20 weeks gestation provided greater reductions in preterm birth (RR 0.89, 95% CI 0.85–0.93; p=0.03). Generally, the survival and birth outcome effects of multiple micronutrient supplementation were greater with high adherence ($\geq 95\%$) to supplementation. Multiple micronutrient supplements did not significantly increase the risk of stillbirth or neonatal, 6-month, or infant mortality, neither overall or in any of the 26 examined subgroups.

Interpretation Antenatal multiple micronutrient supplements improved survival for female neonates and provided greater birth-outcome benefits for infants born to undernourished and anaemic pregnant women. Early initiation in pregnancy and high adherence to multiple micronutrient supplements also provided greater overall benefits. Studies should now aim to elucidate the mechanisms accounting for differences in the effect of antenatal multiple micronutrient supplements on infant health by maternal nutrition status and sex.

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Introduction

Micronutrient deficiencies are common among women in low-income and middle-income countries mainly due to inadequate dietary intake and limited diversity of fruits,

vegetables, animal protein, and fortified foods.¹ The burden and severity of micronutrient deficiencies are exacerbated during pregnancy because of increased demands of both the mother and the growing fetus.² It is

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Department of Global Health and Population (E R Smith ScD, W W Fawzi DrPH, C R Sudfeld ScD), Department of Nutrition (A H Shankar ScD), Harvard T.H. Chan School of Public Health, Boston, MA, USA; Division of Gastroenterology, Hepatology and Nutrition, Boston Children's Hospital, Boston, MA, USA (E R Smith); Summit Institute of Development, Mataram, Indonesia (A H Shankar, R Agustina PhD); The JiVitA Project, Johns Hopkins University in Bangladesh, Gaibandha, Bangladesh (L S-F Wu MHS, H Ali MPH, P Christian DrPH, K P West Jr DrPH); Center for Human Nutrition, Department of International Health, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD, USA (L S-F Wu, H Ali, P Christian, K P West Jr); Department of Microbiology and Immunology, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania (S Aboud PhD, W Urassa PhD); Department of Nutrition and Food Science, University of Ghana, Legon, Accra, Ghana (S Adu-Afarwuah PhD); Department of Nutrition, Faculty of Medicine, Universitas Indonesia – Dr. Cipto Mangunkusumo General Hospital, Jakarta, Indonesia (R Agustina); International Centre for Diarrhoeal Diseases Research Bangladesh (ICDDR,B), Dhaka,

Bangladesh (S Arifeen DrPH); Centre for Child Health Research and Department of Paediatrics, University of Tampere School of Medicine and Tampere University Hospital, Tampere, Finland (P Ashorn PhD); Center for Global Child Health, Hospital for Sick Children, Toronto, ON, Canada (Z A Bhutta PhD); Center of Excellence in Women and Child Health, The Aga Khan University, Karachi, Pakistan (Z A Bhutta, A Rizvi MSC); UCL Institute for Global Health, London, UK (D Devakumar PhD, D Osrin PhD); Department of Nutrition and Program in International and Community Nutrition, University of California-Davis, Davis, CA, USA (K G Dewey PhD); Department of Nutrition Exercise and Sports, University of Copenhagen, Copenhagen, Denmark (H Friis PhD, P Kaestel PhD); College of Health Sciences, University of Zimbabwe, Harare, Zimbabwe (E Gomo PhD); Department of Pediatrics, University College of Medical Sciences, Delhi, India (P Gupta MD); Nutrition and Child Health Unit, Department of Public Health, Prince Leopold Institute of Tropical Medicine, Antwerp, Belgium (P Kolsteren PhD); Faculty of Bio-science engineering, Ghent University, Belgium (P Kolsteren); Institut de Recherche en Sciences de la Santé, Ministry of Scientific Research and Innovation, Ouagadougou, Burkina Faso (H Lanou MD); School of Public Health and Family Medicine, University of Malawi College of Medicine, Blantyre, Malawi (K Maleta PhD); Food and Agriculture Organization of the United Nations, Libreville, Gabon (A Mamadoulaibou MS); Department of Community Health, Muhimbili University of Health and Allied Sciences, Dar es Salaam, Tanzania (G Msamanga ScD); Department of Women's and Children's Health, International Maternal and Child Health, Uppsala University, Uppsala, Sweden (L-Å Persson PhD); Hubert Department of Global Health, Rollins School of Public Health, Emory University, Atlanta, USA (U Ramakrishnan PhD); Instituto Nacional de Salud Publica, Cuernavaca, Mexico (J A Rivera PhD); Pediatric and

Research in context

Evidence before this study

Micronutrient deficiencies are common in pregnant women in low-income and middle-income countries. However, debate persists regarding the current WHO recommendation to provide pregnant women with iron-folic acid supplementation alone, rather than multiple micronutrient supplements containing other essential micronutrients in addition to iron-folic acid during routine antenatal care. In the past two decades, more than 20 randomised trials have examined the effect of multiple micronutrient supplements during pregnancy, compared with iron-folic acid alone, on maternal and child health outcomes. The 2017 Cochrane review and meta-analysis established that provision of daily oral multiple micronutrient supplements reduced the risk of low birthweight (<2500 g) and small-for-gestational-age births, but had no overall effect on perinatal and neonatal mortality as compared with iron-folic acid alone.

The recently updated 2016 WHO antenatal care recommendations acknowledged that policy makers in populations with a high prevalence of maternal nutritional deficiencies might wish to provide multiple micronutrient supplements. However, WHO does not universally recommend multiple micronutrient supplements, noting: "There is some evidence of additional benefit of multiple micronutrient supplements containing 13–15 different micronutrients

(including iron and folic acid) over iron and folic acid supplements alone, but there is also some evidence of risk, and some important gaps in the evidence".

Added value of this study

This study uses the most detailed approach to analysing existing trial data on multiple micronutrient supplements. Previous meta-analyses identified overall benefits of multiple micronutrient supplements in terms of birth size, but our findings show that specific subgroups experience mortality benefits, notably female neonates. Women with indicators of malnutrition during pregnancy who took multiple micronutrient supplements also had greater reductions in low birthweight, preterm, and small-for-gestational-age births. We found no evidence that multiple micronutrient supplements significantly increased the risk of stillbirth or neonatal, 6-month, or infant mortality, neither overall or in any of the 26 examined subgroups.

Implications of the available evidence

This novel analysis identified subgroups of mothers and infants that might benefit the most from multiple micronutrient supplements. This new evidence suggests that WHO might wish to re-evaluate the balance of benefits and harms of universal multiple micronutrient supplementation in their antenatal care recommendations.

well established that iron-deficiency anaemia in pregnancy can lead to decreased birthweight, and insufficient folate concentrations in the periconceptional period increases the risk of neural tube defects and other adverse outcomes.^{3–5} Deficiencies in other micronutrients including vitamins A, B-complex, D, E, zinc, calcium, copper, magnesium, selenium, and iodine are also prevalent in low-income and middle-income countries and can lead to poor pregnancy, fetal growth, and child health outcomes.^{3,6–8} As such, maternal multiple micronutrient supplementation including iron-folic acid is a potential intervention to improve maternal and child health as compared with iron-folic acid supplementation alone.

The 2017 Cochrane Systematic Review and meta-analysis that assessed the effect of maternal multiple micronutrient supplements in pregnancy on infant mortality identified 19 randomised controlled trials and pooled data from 17 of these studies.⁶ Provision of multiple micronutrient supplements in combination with iron-folic acid during pregnancy reduced the risk of low birthweight (<2500 g; relative risk [RR] 0·88, 95% CI 0·85–0·91) and small-for-gestational-age births (0·92, 0·86–0·98), but had no significant effect on perinatal (1·01, 0·91–1·13) and neonatal mortality (1·06, 0·92–1·22) as compared with iron-folic acid supplementation alone.⁶ There was moderate heterogeneity, as measured by I^2 , of the effect of multiple micronutrient supplements on some birth outcomes across published trials but

substantial heterogeneity for perinatal mortality. A previously published pooled analysis of 12 multiple micronutrient supplements trials also indicated the effect of multiple micronutrient supplements on birthweight may be greater in pregnant women with higher BMI.⁹

In 2016, WHO reviewed their antenatal care recommendations and acknowledged that policy makers in populations with a high prevalence of nutritional deficiencies might wish to provide multiple micronutrient supplements containing iron and folic acid. However, WHO did not universally recommend multiple micronutrient supplements, noting that there was evidence of benefit but also some evidence of harm.¹⁰ The existing data also precluded definitive conclusions if any subgroups experience greater benefits or harm due to multiple micronutrient supplements.

In this study we aimed to elucidate individual-level effect modifiers that might alter the impact of maternal multiple micronutrient supplements on stillbirth, birth outcomes, and infant mortality. We aimed to identify subgroups of pregnant women and infants who might experience greater benefit or harm from multiple micronutrient supplements and explore the sources of the heterogeneity across randomised trials.

Methods

In this two-stage meta-analysis of individual patient data, we identified potential studies for inclusion

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