Addressing hidden hunger in pregnancy

Current controversies and new evidence on micronutrient supplementation

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Roadmap

The Case for maternal recommendations

Current Recommendations

New Evidence
Nutritious Food Supplements
Calcium Supplementation

Current Controversies & Planned Studies
Multiple Micronutrients

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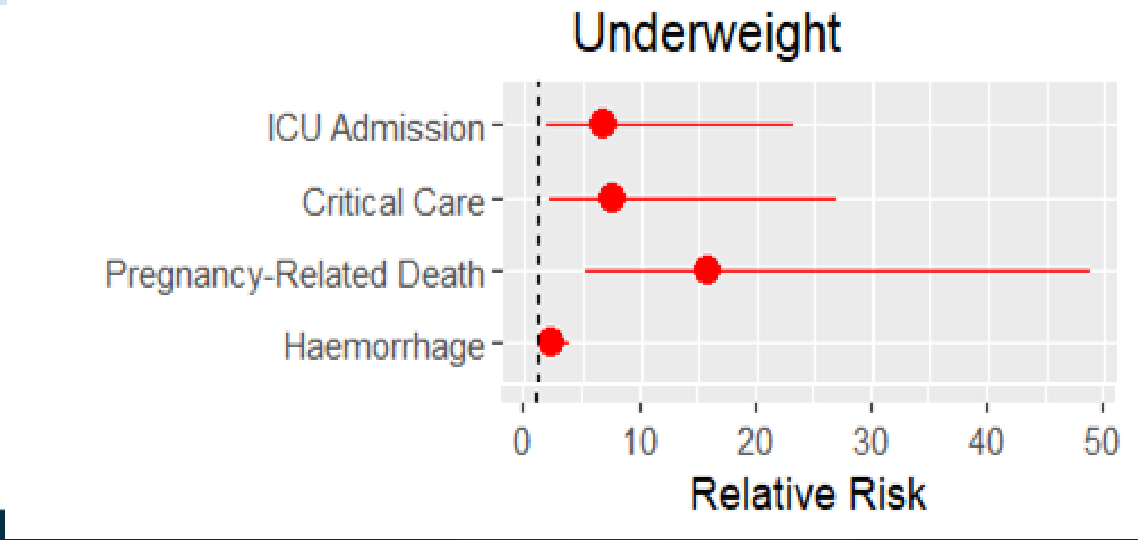
Poor Maternal Nutrition is a Major Cause of Adverse Fetal & Infant Outcomes

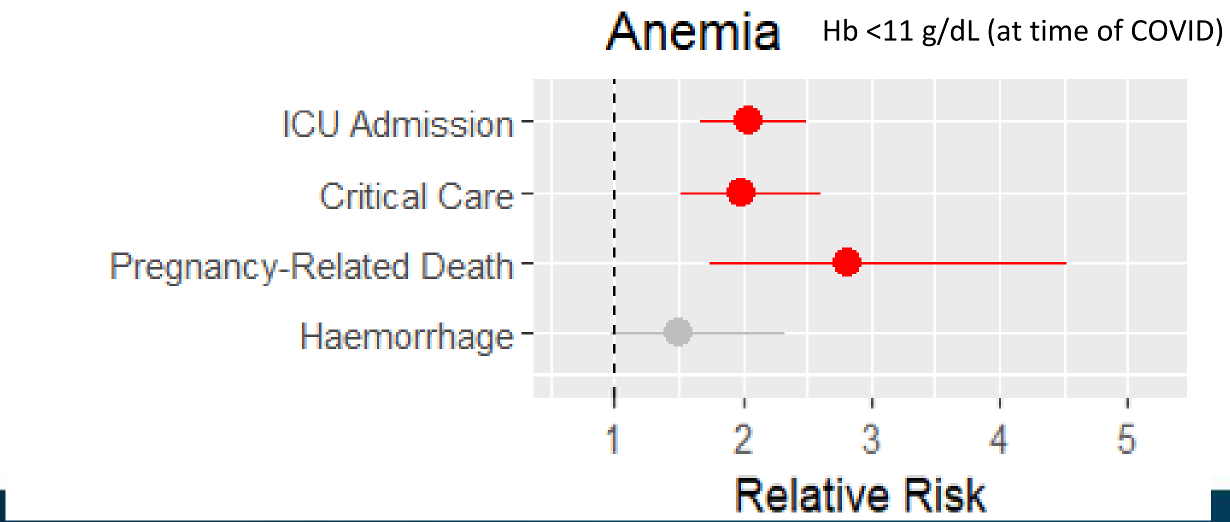
Christian, Smith, & Zaidi, BMJ Global Health, 2020

Poor Maternal Nutritional Status Increases Risk of Maternal Morbidities

Underweight pregnant women with COVID are at higher risk of ICU admission (RR 6.7, 95% CI: 1.9,23.3), critical care (RR 7.5, 95% CI: 2.1,26.9) and pregnancy-related death (RR 15.8, 95% CI:

Anemia at the time of COVID diagnosis is linked to ICU admission (RR 6.7, 95% CI: 1.9,23.3), critical care (RR 7.5, 95% CI: 2.1,26.9) and pregnancy-related death (RR 15.8, 95% CI:





Unpublished update to: Smith et al. AJOG. 2022
Collaboration including data from 100+ collaborators in 36 countries & 186,000+ cases of SARS-CoV-2 infection in pregnancy or postpartum

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WHO recommendations to support nutrition in pregnancy

Iron and Folic Acid

Daily IFA with 30 mg to 60 mg of elemental iron and 400 µg folic acid is recommended for pregnant women to prevent **maternal anaemia, puerperal sepsis, low birth weight, and preterm birth**. (Recommended)

Multiple Micronutrients

MMS is recommended in the context of rigorous research. (Context-specific recommendation – research)

Balanced Energy and Protein

In undernourished populations, BEP is recommended for pregnant women to reduce the risk of **stillbirths and small-for-gestational-age** neonates. (Context-specific recommendation)

Calcium

In populations with low dietary calcium intake, daily calcium supplementation (1.5–2.0 g) is recommended for pregnant women to reduce the risk of **pre-eclampsia**.
(Context-specific recommendation)

Counseling on Healthy Eating & Activity

Counselling about healthy eating and keeping physically active during pregnancy is recommended for pregnant women to stay healthy and to prevent **excessive weight gain** during pregnancy. (Recommended)

Compare data availability for other ANC Nutrition recommendations

	Cochrane Review	N Trials	N
MMS	Keats et al. Cochrane 2019	20 (mostly LMIC)	141,840
IFA	Peña-Rosas et al. Cochrane 2015	44	43,274
Calcium	Buppasiri et al Cochrane 2015	23	18,587
Counseling	Muktabhant et al Cochrane 2015	49 (mostly HIC)	11,444
BEP	Ota et al. Cochrane 2015	12 (mostly HIC)	6,705

Current Nutritional Interventions Should be Scaled Up!

In parallel, research and development can support the next generation of interventions

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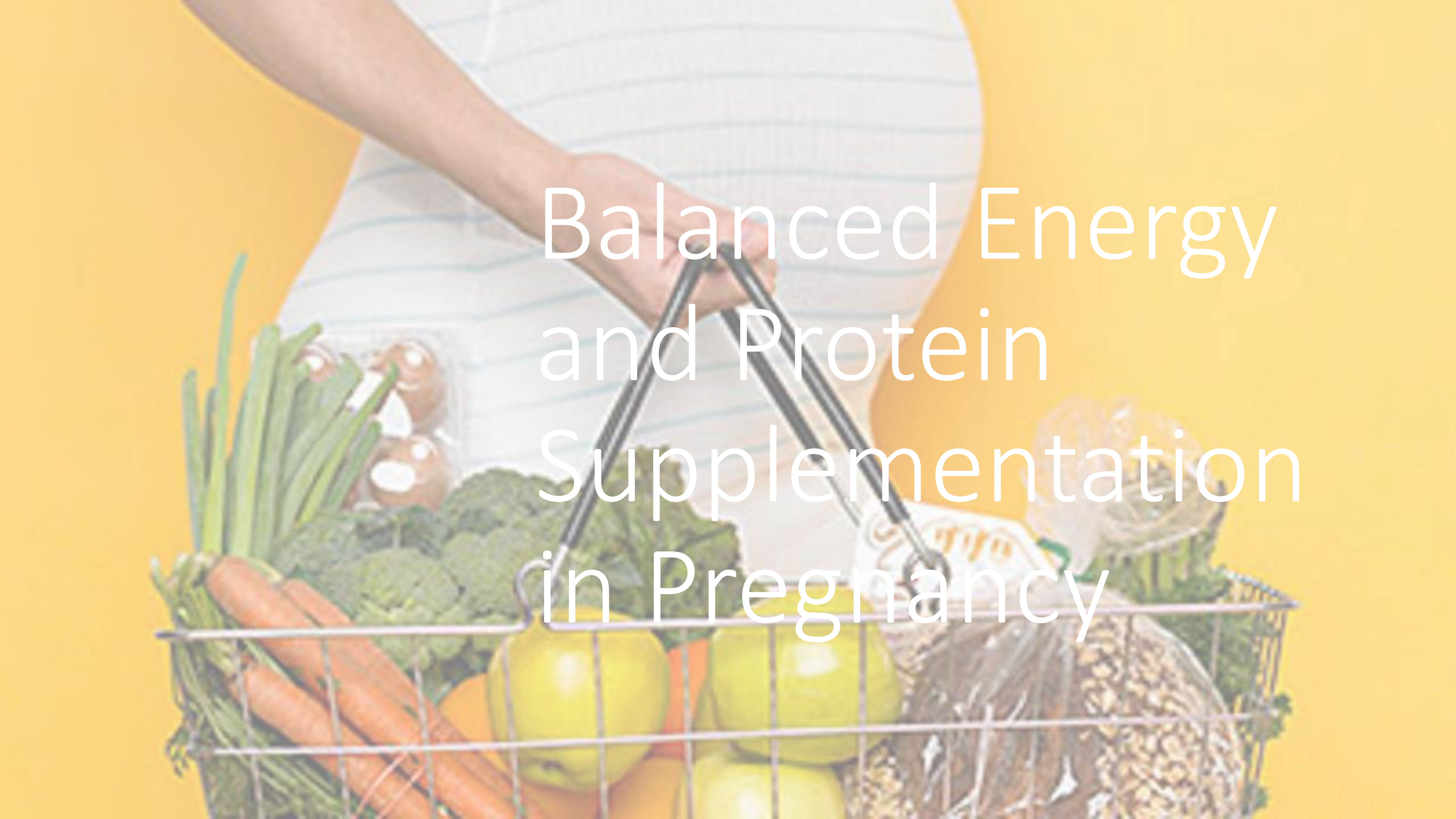
New Evidence,
Data Gaps & Controversies

Balanced Energy and Protein Supplementation in Pregnancy



Types of Nutritious Food Supplements for Pregnant and Lactating Women

High Protein Supplements	Balanced Energy and Protein Supplements	Lipid Nutrient Supplements	Micronutrient Fortified Balanced Energy and Protein Supplements
✗ Not Recommended	✓ WHO Recommended		

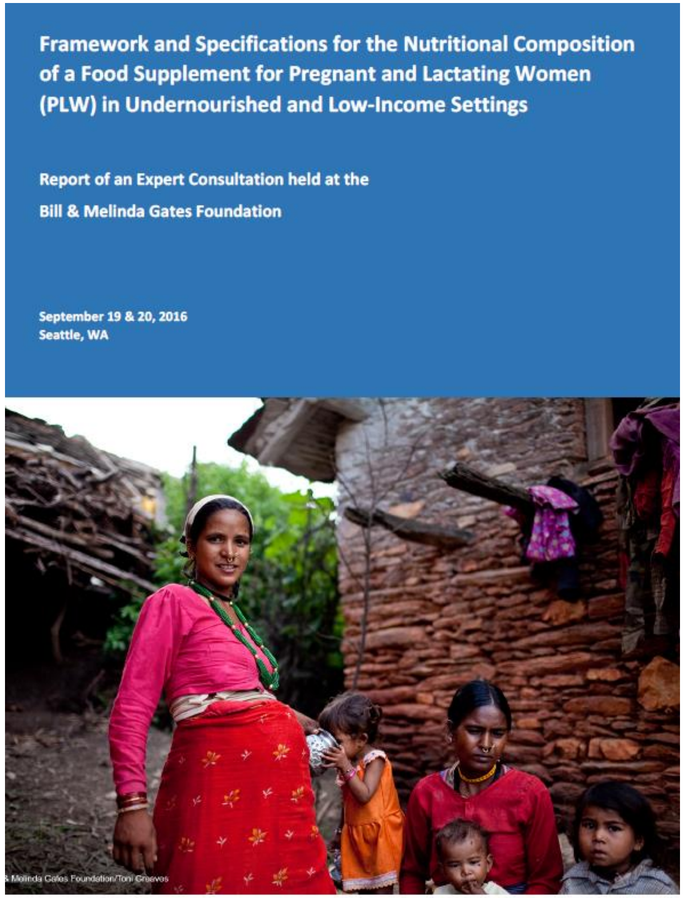
Ciulei &Smith et al, Current Developments in Nutrition, 2023

Evidence for nutritious food supplement for pregnant & lactating women

+ New Niger Trial

	Stillbirth	Low Birthweight	SGA	Preterm	Survival	
LNS vs. IFA[1]	RR 1.14 [0.52, 2.48] N=5575 3 studies	RR 0.87 (0.72 to 1.05) N=4826 3 studies	RR 0.94 (0.89 to 0.99) N=4823 3 studies	RR 0.94 (0.80 to 1.11) N=5924 3 studies	Early neonatal RR 0.70 (0.45, 1.09) N=5555 3 studies	Late neonatal RR 0.96 (0.14, 6.51 N=1617 2 studies
LNS vs. MMN[1]	Unavailable	RR 0.92 (0.74 to 1.14) N=2404 3 studies	RR 0.95 (0.84 to 1.07) N=2393 3 studies	RR 1.15 (0.93 to 1.42) N=2393 3 studies	Unavailable	Unavailable

[1]Das JK, Hoodbhoy Z, Salam RA, Bhutta AZ, Valenzuela-Rubio NG, Weise Prinzo Z, Bhutta ZA (2018). Lipid-based nutrient supplements for maternal, birth, and infant development outcomes. Cochrane Database of Systematic Reviews.



BEP foods/products ranged in calories (118–1017 kcals), protein (3–50 g), fat (6–57 g), and micronutrient content

Ciulei &Smith et al, Current Developments in Nutrition, 2023

Study	Description of Food Supplement	Calories (kcal)	Protein (g)
Atton et al 1990	Flavored milk product packaged in a 200-ml Tetrabrick carton (with choice of flavors)	407	14.6
Blackwell et al 1973	Protein-calorie liquid supplement (milk-based) taken daily plus vitamins and minerals	800	40
Campbell et al 1983	Three different supplement options were offered based on subjects' preference: • 0.5 pint of flavored milk drink • 1 pint of fresh milk • 75 g cheddar cheese	300	14.6
Ceesay et al 1997	High energy groundnut biscuits (2) containing roasted groundnuts, rice flour, sugar and groundnut oil	1017	22
Elwood et al 1981	Free tokens to purchase milk for their families		
Girija et al 1984	50 g of sesame cake, 40 g jaggery and 10 g oil	417	30
Huybregts et al 2009	72 g of a prenatal MMN-fortified spread consisting of 33% peanut butter, 32% soy flour, 15% vegetable oil, 20% sugar and an MMN at 1x RDA	372.6	14.7
Mardones-Santander et al 1988	There were two intervention groups, PUR and V-N • PUR group received powdered milk (an isocaloric supplement) • V-N group received a fortified formula milk (a balanced protein-energy supplement); In addition, through the same program all women received 2 kg of rice monthly	PUR: 498 V-N: 470	PUR: 27.9 V-N: 14.5
Metcoff et al 1985	Monthly WIC vouchers for supplements of milk, egg and cheese	900 – 1000*	40 - 50*
Mora et al 1978	Supplement provided 60 g of dry skim milk, 150 g of enriched bread and 20 g of vegetable cooking oil; plus, a vitamin mineral supplement	856	38
Rush et al 1980	• Supplement: A 16-oz beverage (high protein-energy) • Complement: A 16-oz drink (balanced energy and protein)	Supp: 470 Comp: 322	Supp: 40 Comp: 6
Viegas et al 1982	Flavored carbonated dietary protein energy supplement (PrEnVit): containing 1/3 liquid glucose drink, chocolate flavored skim milk powder (26 g provided daily) along with vitamins	273	30

Evidence for nutritious food supplement for pregnant & lactating women

	Stillbirth	Birthweight	SGA	Preterm	Neonatal Death
Balanced Energy & Protein Supplementation[1] 12 trials, 6705 women	RR = 0.60, 95%CI 0.39,0.94 n = 3408, 5 RCTs	MD 41g, 95%CI 4.66,77.3 n=5385, 11 trials	RR 0.79, 95%CI 0.69,0.9 n = 4408, 7 trials	RR 0.96, 95%CI 0.80,1.16 n=3384, women 5 trials	RR 0.68, 95%CI 0.43,1.07 n=3381, 5 trials

[1]Ota, E., Hori, H., Mori, R., Tobe-Gai, R., & Farrar, D. (2015). Antenatal dietary education and supplementation to increase energy and protein intake. Cochrane Database of Systematic Reviews.

Five recent/ongoing BEP Trials

- Enhancing Nutrition and Antenatal Infection Treatment for Maternal and Child Health [ENAT]),
- Nepal (Mothers and Infants Nutrition Trial [MINT]),
- Burkina Faso (MIcronutriments pour la SAnté de la Mère et de l'Enfant [MISAME-III]),
- Pakistan (Mumta Pregnant Women Trial [MumtaPW]), and
- India (Women and Infants Integrated Interventions for Growth Study [WINGS]

Ciulei &Smith et al, Current Developments in Nutrition, 2023

Who Benefits?
Use Case & Implementation Considerations for Nutritious Food Supplements for PLW

Eligible Population

Prevention

Nutritious Food Supplements for All Women (where low BMI >20%)

✓ WHO Recommended

30 Million

Treatment

Christian, Smith, & Zaidi, BMJ Global Health, 2020

A.3: Calcium supplements

RECOMMENDATION A.3: In populations with low dietary calcium intake, daily calcium supplementation (1.5–2.0 g oral elemental calcium) is recommended for pregnant women to reduce the risk of pre-eclampsia. *(Context-specific recommendation)*

Remarks

- This recommendation is consistent with the 2011 *WHO recommendations for prevention and treatment of pre-eclampsia and eclampsia (57)* (strong recommendation, moderate-quality evidence) and supersedes the WHO recommendation found in the 2013 *Guideline: calcium supplementation in pregnant women (38)*.
- Dietary counselling of pregnant women should promote adequate calcium intake through locally available, calcium-rich foods.
- Dividing the dose of calcium may improve acceptability. The suggested scheme for calcium supplementation is 1.5–2 g daily, with the total dose divided into three doses, preferably taken at mealtimes.
- Negative interactions between iron and calcium supplements may occur. Therefore, the two nutrients should preferably be administered several hours apart rather than concomitantly *(38)*.
- As there is no clear evidence on the timing of initiation of calcium supplementation, stakeholders may wish to commence supplementation at the first ANC visit, given the possibility of compliance issues.
- To reach the most vulnerable populations and ensure a timely and continuous supply of supplements, stakeholders may wish to consider task shifting the provision of calcium supplementation in community settings with poor access to health-care professionals (see Recommendation E.6.1, in section E: Health systems interventions to improve the utilization and quality of ANC).

Ongoing Research for Calcium Supplementation in Pregnancy

The Problem

- Despite WHO recommendation, it is not standard of care
- Barriers to effective coverage: cost, size, regimen complexity

Study Design

Parallel, individually randomized, double-blind, non-inferiority trials in Bangalore, India (n=11,000) and Dar es Salaam, Tanzania (n=11,000)

Hypothesis

A single dose (500mg) of calcium is as effective as higher dose (1500mg)calcium in preventing preeclampsia and preterm birth.

Study Team

Africa Academy of Public Health; Harvard School of Public Health; Ifakara Health Institute; St. John's Research Institute Bangalore

New! Parallel trials in India & Tanzania (n=22,000) find low dose calcium (500 mg) is non-inferior to standard dose (1500 mg)

ORIGINAL ARTICLE

Two Randomized Trials of Low-Dose Calcium Supplementation in Pregnancy

Pratibha Dwarkanath, Ph.D., Alfa Muhihi, M.D., M.P.H., Christopher R. Sudfeld, Sc.D., Blair J. Wylie, M.D., M.P.H., Molin Wang, Ph.D., Nandita Perumal, Ph.D., Tinku Thomas, Ph.D., Shabani M. Kinyogoli, B.Sc., Mohamed Bakari, M.Sc., Ryan Fernandez, M.B.L., John-Michael Raj, M.Sc., Ndeniria O. Swai, M.P.H., Nirmala Buggi, M.D., Rani Shobha, M.D., Mary M. Sando, M.D., M.P.H., Christopher P. Duggan, M.D., M.P.H., Honorati M. Masanja, Ph.D., Anura V. Kurpad, M.D., Ph.D., Andrea B. Pembe, M.D., Ph.D., and Wafaie W. Fawzi, M.B., B.S., Dr.P.H.

Non-inferiority Margins (RR)

Preeclampsia: 1.54
Preterm Birth: 1.16

Table 2. Primary Efficacy Outcomes in the India and Tanzania Trials.*

Outcome	India Trial				Tanzania Trial			
	500 mg Calcium	1500 mg Calcium	Relative Risk (95% CI)	P Value for Noninferiority	500 mg Calcium	1500 mg Calcium	Relative Risk (95% CI)	P Value for Noninferiority
Preeclampsia								
Primary intention-to-treat analysis	164/5497 (3.0)	196/5503 (3.6)	0.84 (0.68–1.03)	<0.001	165/5503 (3.0)	150/5497 (2.7)	1.10 (0.88–1.36)	<0.001
Preterm birth‡								
Primary intention-to-treat analysis	593/5195 (11.4)	665/5193 (12.8)	0.89 (0.80–0.98)	<0.001	531/5109 (10.4)	493/5081 (9.7)	1.07 (0.95–1.21)	0.10

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MMS

Multiple Micronutrient Supplements

20
Trials

140,000+
Participants

IFA

Nutrient	Dose
Folic acid	400 ug
Iron	30-60 mg

MMS

Nutrient	Dose
Vitamin A	800 µg
Vitamin D	5 µg
Vitamin E	10 mg
Vitamin C	70 mg
Vitamin B1	1.4 mg
Vitamin B2	1.4 mg
Niacin	18 mg
Vitamin B6	1.9 mg
Vitamin B12	2.6 µg
Folic acid	400 ug
Iron	30-60 mg
Zinc	15 mg
Copper	2 mg
Selenium	65 µg
Iodine	150 µg

Clinical trials compare MMS vs IFA

WHO considers UNIMAPP formulation with 30mg of iron as 'standard' formulation

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MMS vs IFA Summary of Findings (Maternal)

Outcome	Number of participants (Studies)	Certainty of Evidence (Grade)	Relative Effect RR (95% CI)
Maternal mortality	*(6 trials)	low-certainty**	RR 1.06 (0.72 to 1.54)
Maternal anemia at term	*(9 trials)	high-certainty evidence**	RR 1.04 (0.94 to 1.15)

* Cochrane & Guideline do not included participant numbers
** GRADE from 2020 WHO Guideline. No GRADE is given in the Cochrane Review

MMS vs IFA Summary of Findings (Infant)

Keats et al. Cochrane Database Syst Review. 2019

Outcomes	**Number of participants (Studies)**	**Certainty of Evidence (Grade)**	**Relative Risk (95% CI)**
Preterm Births	91,425 (18 RCTs)	⊕⊕⊕⊖ **Moderate**	RR 0.95 (0.90 to 1.01)
Small-for-Gestational Age	57,348 (17 RCTs)	⊕⊕⊕⊖ **Moderate**	RR 0.92 (0.88 to 0.97)
Low Birth-weight	68,801 (18 RCTs)	⊕⊕⊕⊕ **High**	RR 0.88 (0.85 to 0.91)
Perinatal Mortality	63,922 (15 RCTs)	⊕⊕⊕⊕ **High**	RR 1.00 (0.90 to 1.11)
Stillbirths	97,927 (17 RCTs)	⊕⊕⊕⊕ **High**	RR 0.95 (0.86 to 1.04)
Neonatal Mortality	80,964 (14 RCTs)	⊕⊕⊕⊕ **High**	RR 1.00 (0.89 to 1.12)

Cochrane Conclusion

“Our findings suggest a positive impact of MMN supplementation with iron and folic acid on several birth outcomes. MMN supplementation in pregnancy led to a reduction in babies considered LBW, and probably led to a reduction in babies considered SGA. In addition, MMN probably reduced preterm births. No important benefits or harms of MMN supplementation were found for mortality outcomes (stillbirths, perinatal and neonatal mortality). These findings may provide some basis to guide the replacement of iron and folic acid supplements with MMN supplements for pregnant women residing in low- and middle-income countries.”

Keats et al. Cochrane Database Syst Review. 2019

MMS: Who Benefits?

THE LANCET
Global Health

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, ScD • Anuraj H Shankar, ScD • Lee S-F Wu, MHS • Said Aboud, PhD • Seth Adu-Afarwuah, PhD • Hasmot Ali, MPH • Rina Agustina, PhD • Shams Arifeen, DrPH • Per Ashorn, PhD • Zulfiqar A Bhutta, PhD • Parul Christian, DrPH • Delanjathan Devakumar, PhD • Kathryn G Dewey, PhD • Henrik Friis, PhD • Exnevia Gomo, PhD • Piyush Gupta, MD • Pernille Kæstel, PhD • Patrick Kolsteren, PhD • Hermann Lanou, MD • Kenneth Maleta, PhD • Aissa Mamadoultaibou, MS • Gernard Msamanga, ScD • David Osrin, PhD • Lars-Åke Persson, PhD • Usha Ramakrishnan, PhD • Juan A Rivera, PhD • Arjumand Rizvi, MSC • H P S Sachdev, FRCPCH • Willy Urassa, PhD • Keith P West Jr, DrPH • Noel Zagre, PhD • Lingxia Zeng, PhD • Zhonghai Zhu, MSc • Wafaie W Fawzi, DrPH • Dr Christopher R Sudfeld, ScD • Show less

Open Access • • Published: November, 2017 • DOI: https://doi.org/10.1016/S2214-109X(17)30371-6

Global collaboration to address raised by the 2016 WHO GDG

Burkina Faso
Ghana
Guinea-Bissau
Malawi
Niger
Tanzania (2)
Zimbabwe

Mexico

Bangladesh (2)
China
India
Indonesia
Nepal (2)
Pakistan

35 Investigators

112,000 women

17 trials

14 outcomes

10 subgroups

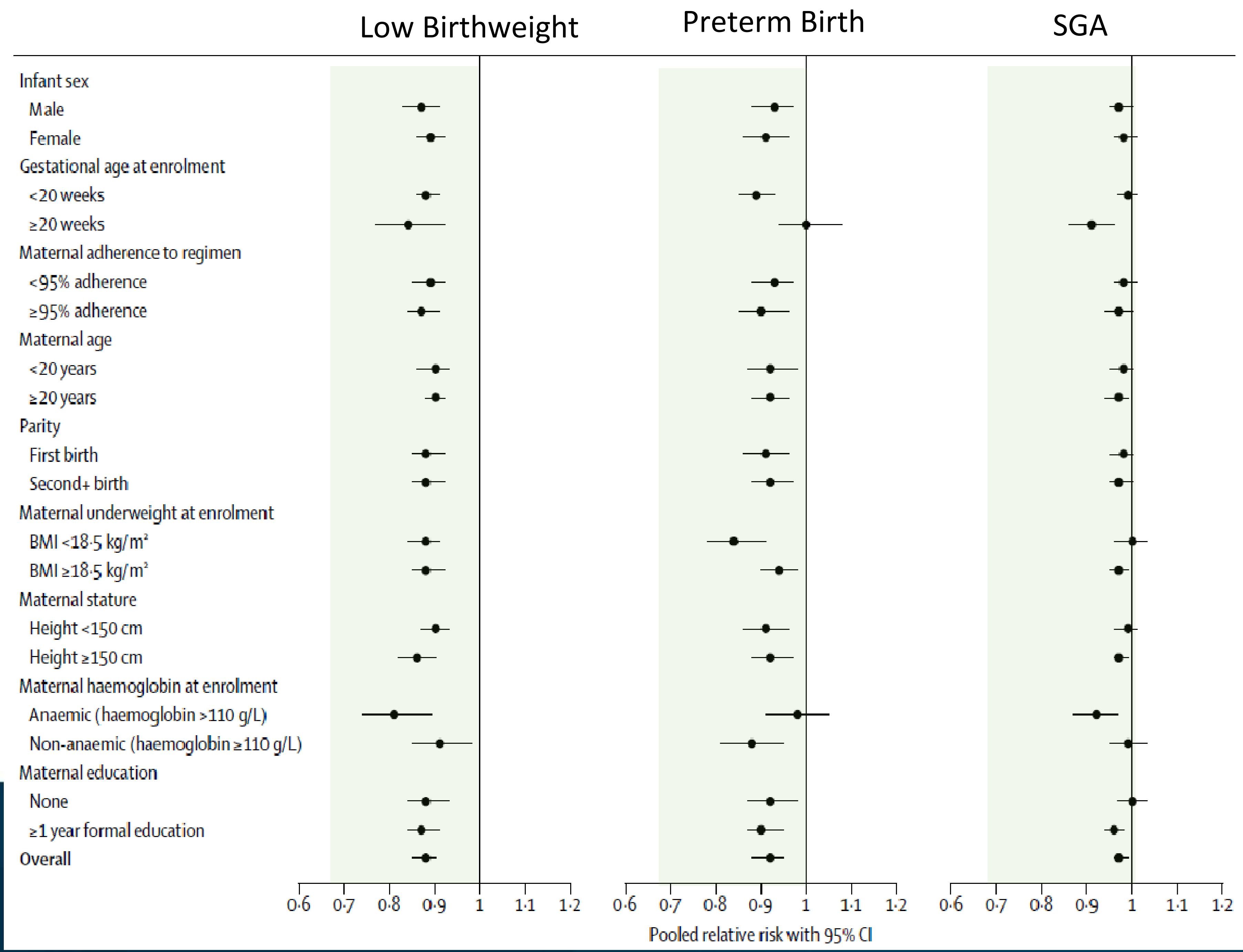
Stillbirth, Infant Mortality, Birthweight, Gestational Age, Size for Gestational Age

Infant Sex, Parity, Maternal Age, Maternal Anthropometry, Maternal Anemia, Gestational Age at Supplementation, Adherence

Consistent Benefits

Benefit apparent in most subgroups
Larger gains for undernourished women
No harmful effects observed

Smith et al. *Lancet Global Health.* 2017



Overall, MMS probably slightly reduces the risk of stillbirth, but does not reduce mortality for the general population.

IPD results consistent with the 2019 Cochrane Review.

	Stillbirth		Neonatal Death	
	N Studies	RR (95% CI)	N Studies	RR (95% CI)
IPD[1]	16	0.92 (0.86 to 0.99)	12	0.99 (0.89 to 1.09)
Cochrane[2]	17	0.95 (0.86 to 1.04)	14	1.00, (0.89 to 1.12)

5% 8%

Overall Null Effect

1 Smith et al. Lancet Global Health. 2017
2 Keats et al. Cochrane Database Syst Review. 2019

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MMS probably reduces the risk of mortality for female infants through the first year of life.

This is an example of “effect modification”. In this case pooled estimates lack meaning; stratified results are most appropriate

Smith et al. *Lancet Global Health.* 2017

	Neonatal Mortality		Infant Mortality	
	RR (95% CI)	P value heterogeneity	RR (95% CI)	P value heterogeneity
Male	1.06 (0.95-1.17)	0.007	1.05 (0.93-1.18)	0.04
Female	0.85 (0.75-0.96)		0.87 (0.77-0.99)	

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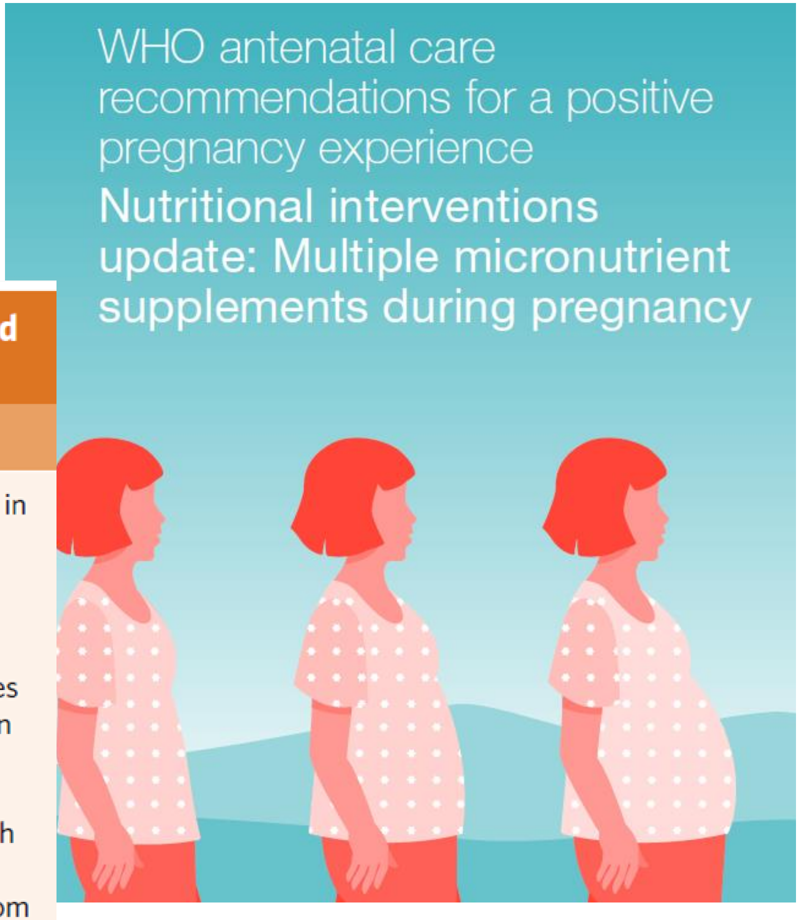
Current MMS Guidelines

2020 Update

Antenatal multiple micronutrient supplements that include iron and folic acid are recommended in the context of rigorous research[1]. *(Context-specific recommendation – research)*

Remarks

- This recommendation updates and supersedes the WHO recommendation found in the WHO ANC guideline issued in 2016 *(1)*.
- The evidence is derived from trials using MMS containing 13 to 15 micronutrients (including iron and folic acid) and the widely available United Nations International Multiple Micronutrient Antenatal Preparation (UNIMMAP), which contains 15 micronutrients, including 30 mg of iron and 0.4 mg of folic acid (see Box 2).
- As the evidence was mainly derived from low- and middle-income countries, its applicability to high-income countries or to populations not at risk of micronutrient deficiencies – for example, due to an adequate diet and food fortification programmes – is unclear.
- Research in this context therefore includes:
  - controlled clinical trials in which early pregnancy ultrasound is used to establish gestational age with certainty,[2] with assessment of critical maternal and perinatal outcomes, and follow-up of infants sustained into childhood; and
  - where programmes of MMS are being considered, implementation research to establish the impact of switching from iron and folic acid supplements to MMS, including evaluation of acceptability, feasibility, sustainability, equity and cost-effectiveness.
- Many MMS contain 30 mg or less of elemental iron and WHO recommends antenatal iron and folic acid supplements containing 60 mg of elemental iron in populations where anaemia is a severe public health problem (a prevalence of 40% or higher) *(2)*. Therefore, countries should consider their population magnitude and distribution of anaemia, its nutritional determinants (i.e. iron deficiency), as well as the magnitude and distribution of the complex low birthweight and its component parts (i.e. preterm, small for gestational age [SGA] or a combination of these) *(3)*, when undertaking any research in the context of this recommendation.
- Pregnant women should be supported and encouraged to receive adequate nutrition, which is best achieved through consumption of a healthy, balanced diet consistent with guidelines on healthy eating *(4)*.



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BMJ Global Health

WHO recommendations on antenatal nutrition: an update on multiple micronutrient supplements

Özge Tuncalp,[1] Lisa M Rogers,[2] Theresa Anne Lawrie,[1,3] María Barreix,[1] Juan Pablo Peña-Rosas,[2] Maurice Bucagu,[4] James Neilson,[5] Olufemi T Oladapo[1]

"Evidence on the effects of MMS on the component parts of low birthweight is inconsistent and controlled clinical trials are needed in which early pregnancy ultrasound is used to establish gestational age with certainty, to understand where the effect on low birth weight is derived."

"National policies in low-income and middle-income countries commonly recommend the 60 mg dose of elemental iron,14 where the higher dose of iron may be indicated due to a high anaemia prevalence. Therefore, more research is needed on the effects of switching from daily IFA supplements containing a 60 mg dose of elemental iron to daily MMS containing a lower dose (30 mg) of elemental iron in these settings."

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Consistent effects of MMS
regardless of GA assessment method

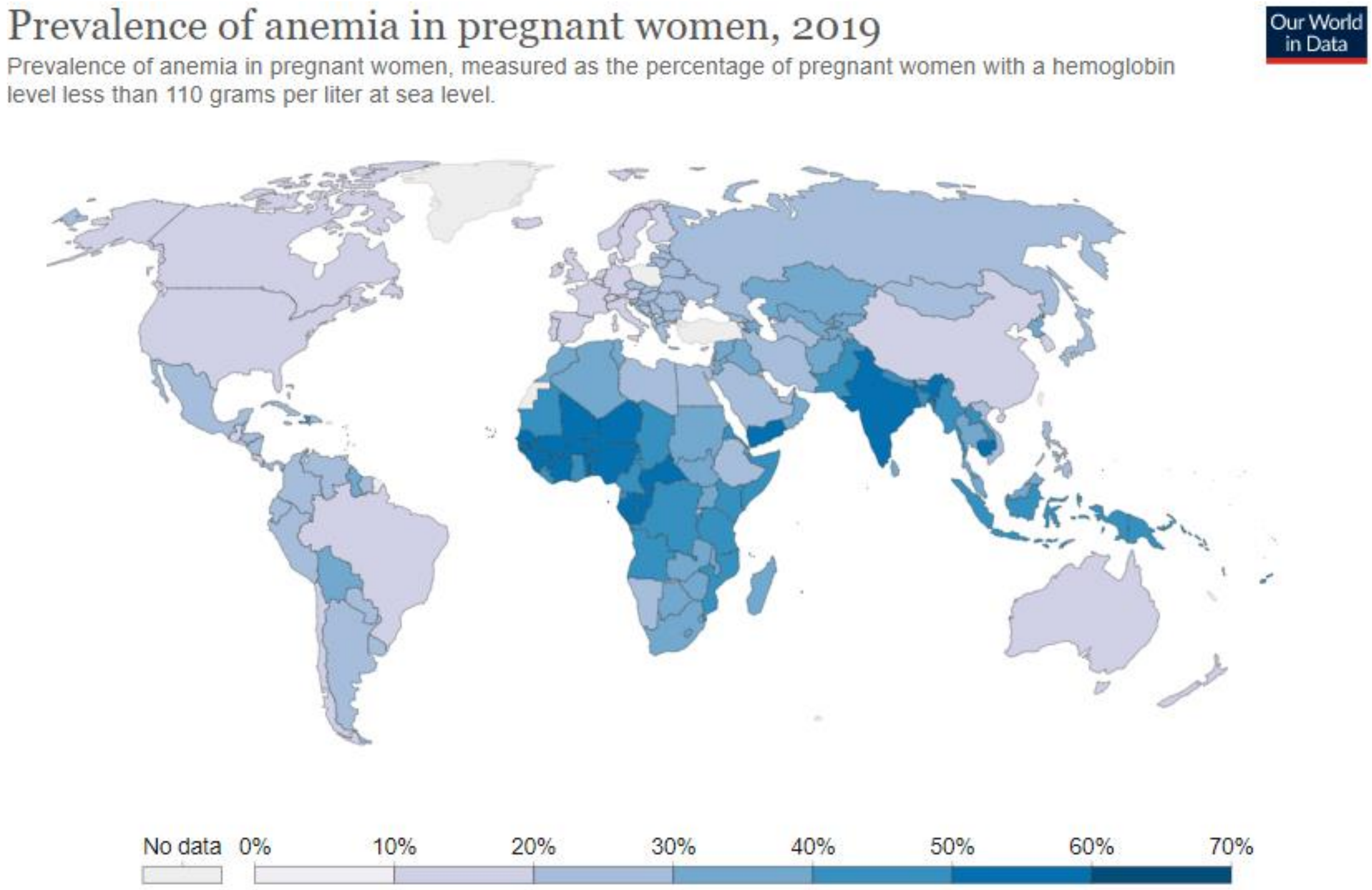
Trend towards larger benefit with better GA method

Consistent with expectation that nondifferential measurement error biases estimates towards the null

Method used for gestational age assessment	Effect of MMS versus IFA on LBW RR (95% CI) *n* trials	Effect of MMS versus IFA on preterm birth RR (95% CI) *n* trials	Effect of MMS versus IFA on SGA RR (95% CI) *n* trials
Overall analyses	**0.88 (0.86–0.91)** 16 trials	0.94 (0.88–1.00) 16 trials	0.98 (0.86–1.00) 15 trials
Subgroup analyses (three groups)			
p Value (subgroup differences)	0.82	0.23	0.32
1—Ultrasound	**0.87 (0.78–0.97)** 7 trials	0.90 (0.79–1.03) 7 trials	**0.90 (0.83–0.99)** 7 trials
2—Prospective date of LMP collection and confirmation of pregnancy by urine test	**0.89 (0.84–0.95)** 4 trials	0.92 (0.82–1.04) 4 trials	0.98 (0.92–1.05) 4 trials
3—Recall of date of LMP	**0.86 (0.76–0.97)** 5 trials	0.99 (0.99–1.04) 5 trials	0.93 (0.84–1.04) 4 trials

Gomes et al. Maternal & child nutrition. 2023

Current IFA Guidelines Recommend 60mg iron where anemia >40%



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Optimal Iron Dose

What do we know?

Evidence from Iron trials & MMS trials

For most micronutrients there are <u>zero</u> studies from pregnant or lactating women used to select the indicator or set the upper limit for Nutrient Reference Values

Smith ER, et al. Science advances. 2021

Micronutrient	Indicators Section			Life Stages Section			UL Section		
	# Studies	Included Women (%)	Included Pregnant or Lactating Women (%)	# Studies	Included Women (%)	Included Pregnant or Lactating Women (%)	# Studies	Included Women (%)	Included Pregnant or Lactating Women (%)
Vitamin A	3	67%	0%	9	89%	33%	5	100%	40%
Vitamin B1 (Thiamin)	7	57%	0%	10	60%	10%	0	0%	0%
Vitamin B2 (Riboflavin)	10	70%	10%	23	87%	30%	0	0%	0%
Vitamin B3 (Niacin)	2	0%	0%	5	80%	0%	8	50%	0%
Vitamin B5 (Pantothenic Acid)	3	33%	0%	7	100%	71%	0	0%	0%
Vitamin B6 (Pyridoxine)	17	65%	18%	17	94%	24%	4	75%	0%
Vitamin B7 (Biotin)	10	70%	0%	1	100%	0%	0	0%	0%
Vitamin B9 (Folate)	33	64%	12%	46	80%	33%	20	80%	5%
Vitamin B12 (Cobalamin)	9	100%	0%	47	74%	15%	0	0%	0%
Choline	5	80%	0%	4	75%	0%	4	0%	0%
Vitamin C	1	0%	0%	8	100%	13%	1	100%	0%
Vitamin D & Calcium	33	100%	0%	28	39%	32%	9	67%	0%
Vitamin E	1	0%	0%	10	80%	20%	5	80%	0%
Vitamin K	0	0%	0%	10	100%	20%	0	0%	0%
Carotenoids	33	48%	0%	0	0%	0%	0	0%	0%
Copper	4	75%	0%	6	50%	17%	5	80%	0%
Iodine	16	69%	6%	5	80%	40%	4	75%	0%
★ Iron	12	83%	17%	15	87%	13%	8	88%	25%
Magnesium	8	38%	0%	26	100%	58%	10	90%	10%
Phosphorus	1	0%	0%	9	100%	89%	5	60%	0%
Selenium	5	100%	20%	9	78%	22%	6	83%	0%
Zinc	20	50%	0%	41	78%	29%	8	63%	13%
All micronutrients	233	67%	5%	336	80%	29%	102	74%	7%

Current IFA Guidelines

A.2: Iron and folic acid supplements

A.2.1: Daily iron and folic acid supplements

RECOMMENDATION A.2.1: Daily oral iron and folic acid supplementation with 30 mg to 60 mg of elemental iron[a] and 400 μg (0.4 mg) folic acid[b] is recommended for pregnant women to prevent maternal anaemia, puerperal sepsis, low birth weight, and preterm birth.[c] *(Recommended)*

Remarks

- This recommendation supersedes the 2012 WHO *Guideline: daily iron and folic acid supplementation in pregnant women (36)* and should be considered alongside Recommendation A.2.2 on intermittent iron.
- In settings where anaemia in pregnant women is a severe public health problem (i.e. where at least 40% of pregnant women have a blood haemoglobin [Hb] concentration < 110 g/L), a daily dose of 60 mg of elemental iron is preferred over a lower dose.
- In the first and third trimesters, the Hb threshold for diagnosing anaemia is 110 g/L; in the second trimester, the threshold is 105 g/L *(50)*.
- If a woman is diagnosed with anaemia during pregnancy, her daily elemental iron should be increased to 120 mg until her Hb concentration rises to normal (Hb 110 g/L or higher) *(34, 51)*. Thereafter, she can resume the standard daily antenatal iron dose to prevent recurrence of anaemia.
- Effective communication with pregnant women about diet and healthy eating – including providing information about food sources of vitamins and minerals, and dietary diversity – is an integral part of preventing anaemia and providing quality ANC.
- Effective communication strategies are vital for improving the acceptability of, and adherence to, supplementation schemes.
- Stakeholders may need to consider ways of reminding pregnant women to take their supplements and of assisting them to manage associated side-effects.

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Cochrane Library

Cochrane Database of Systematic Reviews

Daily oral iron supplementation during pregnancy (Review)

Peña-Rosas JP, De-Regil LM, Garcia-Casal MN, Dowswell T

44 trials including 43,274 infants

Iron vs Placebo Summary of Finding (Maternal)

Outcomes	Number of participants (Studies)	Certainty of Evidence (GRADE)	Relative Effect (95% CI)
Maternal anaemia at term (Hb <110 g/L)	2,199 (14 RCTs)	⊕⊕⊖⊖ low [1,2]	RR 0.30 (0.19 to 0.46)
Maternal iron deficiency at term (as defined by as defined trialists)	1,256 (7 RCTs)	⊕⊕⊖⊖ low [2,3]	RR 0.43 (0.27 to 0.66)
Maternal severe anaemia at any time during second and third trimester (Hb <70 g/L)	2,125 (9 RCTs)	⊕⊖⊖⊖ very low [3,6,7]	RR 0.22 (0.01 to 3.20)
Maternal death	12,560 (2 RCTs)	⊕⊖⊖⊖ very low [4,5]	RR 0.33 (0.01 to 8.19)
Infection during pregnancy (including urinary tract infections)	727 (1 RCT)	⊕⊕⊖⊖ low [5]	RR 1.21 (0.33 to 4.46)

Pena-Rosas et al. Cochrane Database Syst Review. 2015

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Iron vs Placebo Summary of Finding (Infant)

Outcomes	Number of participants (Studies)	Certainty of Evidence (Grade)	Relative Effect (95% CI)
Low birthweight (<2500 g)	17,613 (11 RCTs)	⊕⊕⊖⊖ low [1,2]	RR 0.84 (0.69 to 1.03)
Birthweight (g)	18,590 (15 RCTs)	⊕⊕⊕⊖ moderate [1]	Mean Difference +23.75 (-3.02 to 50.51)
Preterm birth (<37 weeks of gestation)	19,286 (13 RCTs)	⊕⊕⊕⊖ moderate [1]	RR 0.93 (0.84 to 1.03)
Neonatal death (<28 days)	16,603 (4 RCTs)	⊕⊕⊖⊖ low [1,2]	RR 0.91 (0.71 to 1.18)
Congenital anomalies	14,636 (4 RCTs)	⊕⊕⊖⊖ low [1,2]	RR 0.88 (0.58 to 1.33)

Pena-Rosas et al. Cochrane Database Syst Review. 2015

Iron vs Placebo
Cochrane Review Conclusions

“Supplementation reduces the risk of maternal anaemia and iron deficiency in pregnancy but the positive effect on other maternal and infant outcomes is less clear. Implementation of iron supplementation recommendations may produce heterogeneous results depending on the populations' background risk for low birthweight and anaemia, as well as the level of adherence to the intervention.”

Pena-Rosas et al. Cochrane Database Syst Review. 2015

Compare effect size & data availability for other ANC Nutrition recommendations

	Low Birthweight <2500g	Preterm Birth <37 weeks	Small-for-Gestational Age <10th percentile
IFA vs Placebo	11 trials; 17,613 infants **RR: 0.84 (95% CI: 0.69-1.03)** low-certainty evidence	13 trials; 19,296 infants RR: 0.93 (95% CI: 0.84-1.03) moderate-certainty evidence	Not available
MMS vs IFA	16 trials; 68,801 infants RR: 0.88 (95% CI: 0.86-0.91) high-certainty evidence	18 trials; 91,425 infants RR: 0.95 (95% CI: 0.90 to 1.01) moderate-certainty evidence	15 trials; 57,348 infants RR: 0.98 (95% CI:0.96, 1.00) moderate-certainty evidence
Calcium	6 trials, 14,162 infants RR: 0.93 (95% CI: 0.81–1.07) moderate-certainty evidence	13 trials, 16,139 infants RR: 0.86 (95% CI: 0.70–1.05) low-certainty evidence	Not available
BEP	Not available	5 trials, 3,384 infants; RR: 0.96 (95% CI: 0.80–1.16) moderate-certainty evidence	7 trials, 4408 infants; RR:0.79 (95% CI: 0.69–0.90) moderate-certainty evidence
Counseling	Very uncertain	16 trials, 5,923 infants; RR: 0.91 (95% CI: 0.68–1.22) low-certainty evidence	Very uncertain

GDG decision-making generally based on birth outcomes

Iron Dose Response Evidence

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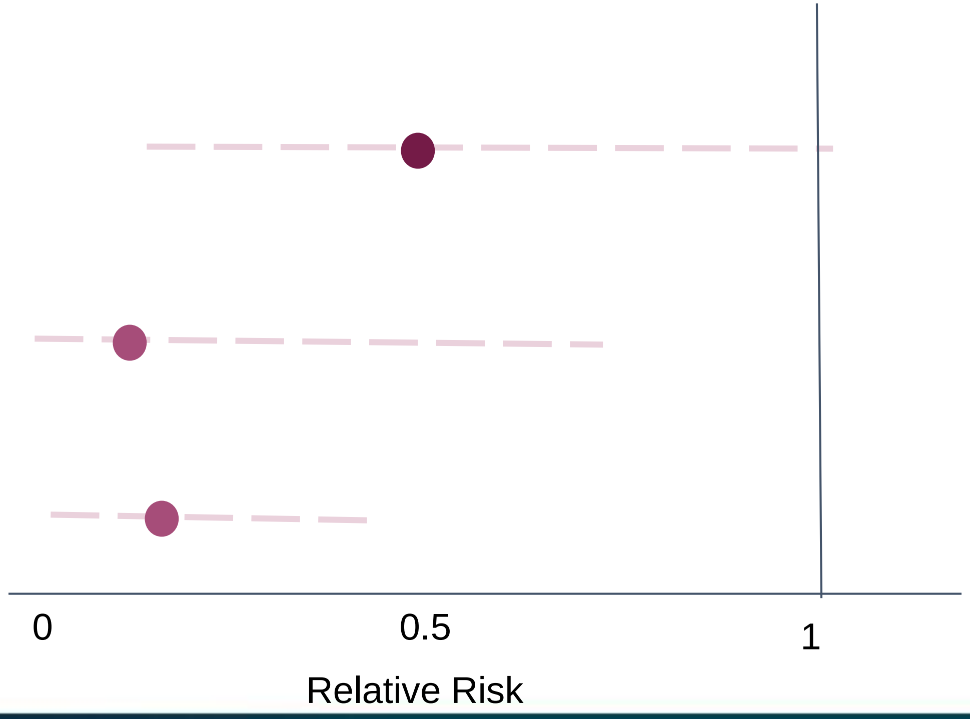
Iron vs Placebo Dose Response

Cochrane Review of RCTs[1]

Possible dose-response relationship, but not enough data for definitive conclusion.

	Maternal Anemia at Term*
Low Dose (≤30 mg)	3 trials 2,199 women 0.49 [0.24,1.03]
Moderate Dose (31-59 mg)	1 trial 590 women 0.21 [0.06,0.73]
High Dose (≥60 mg)	10 trials 1,540 women 0.25 [0.14,0.45]



1. Pena-Rosas et al. Cochrane Database Syst Review. 2015

* At ≥ 37 weeks gestation

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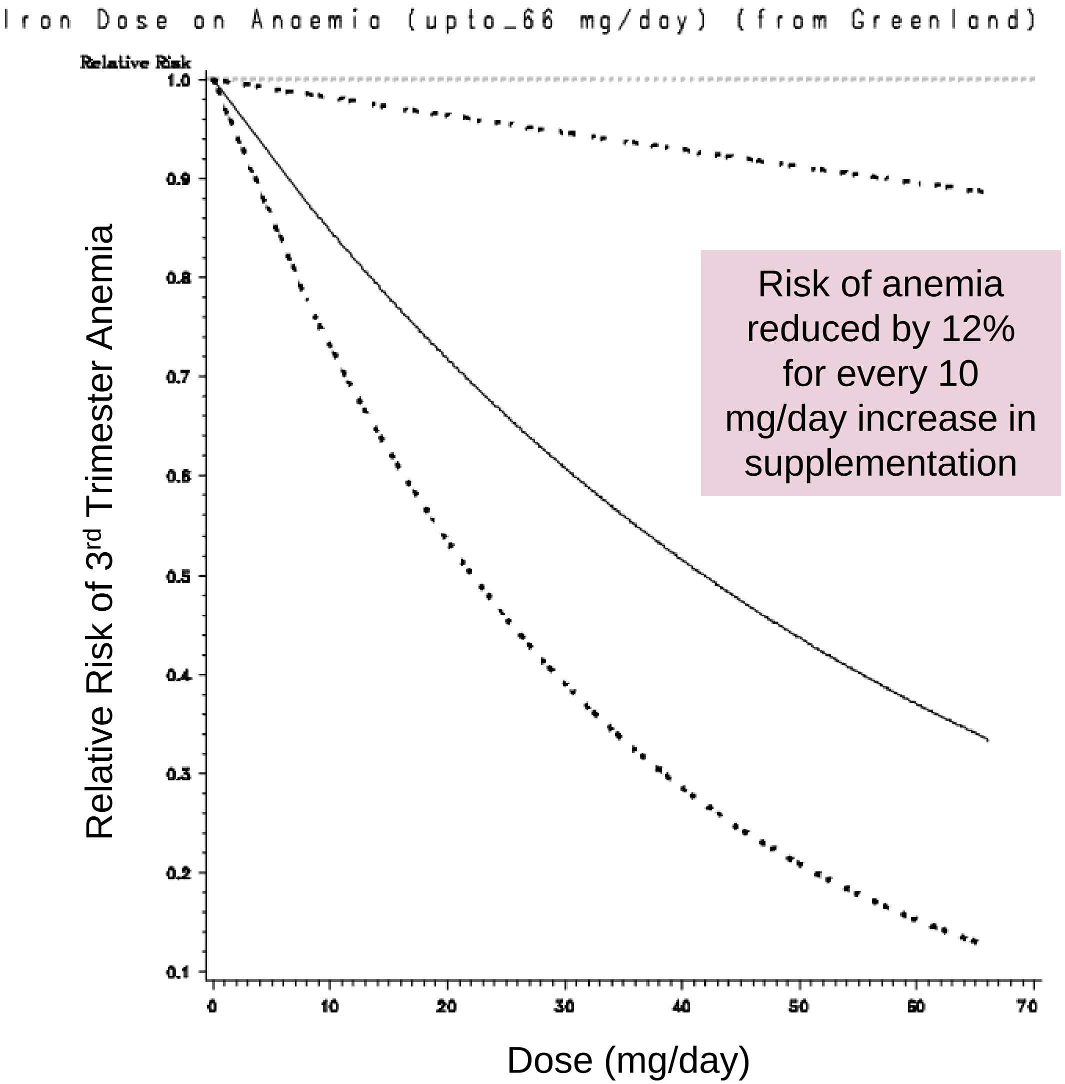
Iron Dose Response

Meta-Regression[1]

Higher iron dose may be linked to lower risk of maternal anemia at 3rd trimester* or delivery

An exposure-response analysis[1] of randomized trials of iron supplementation indicated that for every 10 mg increase in iron dose/day (up to 66 mg/day), the relative risk of maternal anemia was 0.88 (95% CI: 0.84 to 0.92).



1. Haider et al. BMJ. 2013
* At >27 weeks gestation

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Iron Dose vs Placebo Dose Response

Cochrane Review of RCTs[1]

No significant difference on birth outcomes, but insufficient data

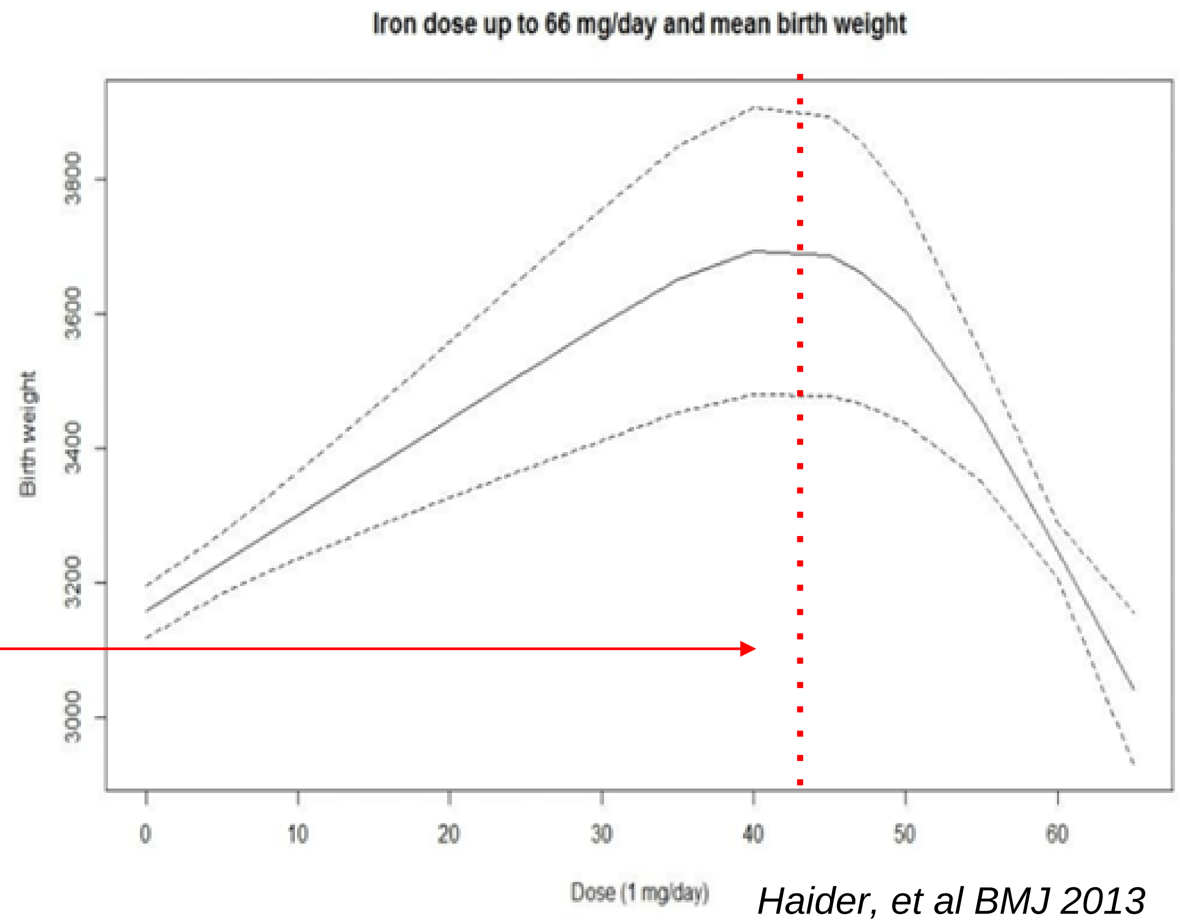
	Birthweight	**Low Birthweight**	**Preterm**	**SGA**
Low Dose (≤30 mg)	7 trials 13,729 infants 33.94 g [-13.42,81.29]	5 trials 12,858 infants RR: 0.70 [0.38,1.32]	6 trials 13,649 infants RR: 0.89 [0.76,1.05]	Not reported
Moderate Dose (31-59 mg)	1 trial 727 infants 10.0 g [-51.92,71.92]	1 trial 727 infants RR: 1.21 [0.57,2.54]	1 trial 727 infants RR: 1.26 [0.62,2.56]	
High Dose (≥60 mg)	8 trials 4,134 infants 19.18 g [-26.63,64.99]	5 trials 4,028 infants RR: 0.82 [0.72,0.94]	6 trials 4,910 infants RR: 0.95 [0.81,1.12]	

1. Pena-Rosas et al. Cochrane Database Syst Review. 2015

Iron Dose Effects on Birthweight

Meta-Regression[1]

A meta-analysis dose-response analysis[1] also suggests an inverted U-shaped relationship between iron dose and birthweight; iron doses above 45 mg/day appear to negatively affect birthweight



Haider, et al BMJ 2013

1. Haider et al. BMJ. 2013

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Iron Dose Summary of Findings Cochrane Review[1]

	Neonatal Mortality
Low Dose (≤30 mg)	1 trial 11,832 infants RR: 1.10 [0.67,1.82]
Moderate Dose (31-59 mg)	1 trial 727 infants RR: 0.48 [0.12,1.91]
High Dose (≥60 mg)	2 trials 4,044 infants RR: 0.88 [0.65,1.19]

Unable to conclude if iron dose impacts neonatal mortality

1. Pena-Rosas et al. Cochrane Database Syst Review. 2015

Data from Iron vs. Placebo trials suggests that the relationship between iron dose and maternal hemoglobin--compared to iron dose and other outcomes like birthweight or side effects--may be different.

MMS trials have varied iron in both MMS and IFA arms

Iron Dose in Trials

- 10 trials used the same iron dose in MMS and IFA arms
  - MMS-30 vs IFA-30
  - MMS-60 vs IFA-60
- 9 trials used lower dose iron in the MMS arm compared to IFA
  - MMS-15/30 vs IFA-60

How to consider dose subgroups

RCTs tell us the causal effect of whatever thing is different between the intervention & control group.

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IFA

Nutrient	Dose
Folic acid	400 ug
Iron	30 mg

MMS

Nutrient	Dose
Vitamin A	800 µg
Vitamin D	5 µg
Vitamin E	10 mg
Vitamin C	70 mg
Vitamin B1	1.4 mg
Vitamin B2	1.4 mg
Niacin	18 mg
Vitamin B6	1.9 mg
Vitamin B12	2.6 µg
Folic acid	400 ug
Iron	30 mg
Zinc	15 mg
Copper	2 mg
Selenium	65 µg
Iodine	150 µg

Since the iron and folic acid doses are THE SAME in both arms - the results of this trial tells the effect of adding 13 additional micronutrients

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IFA

Nutrient	Dose
Folic acid	400 μg
Iron	60 mg

MMS

Nutrient	Dose
Vitamin A	800 μg
Vitamin D	5 μg
Vitamin E	10 mg
Vitamin C	70 mg
Vitamin B1	1.4 mg
Vitamin B2	1.4 mg
Niacin	18 mg
Vitamin B6	1.9 mg
Vitamin B12	2.6 μg
Folic acid	400 μg
Iron	30 mg
Zinc	15 mg
Copper	2 mg
Selenium	65 μg
Iodine	150 μg

Since only the folic acid doses are THE SAME in both arms - the results of this trial tells the effect of adding 13 additional micronutrients AND also less 30 mg of iron.

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Cochrane MMS iron dose analysis on birth outcomes

Cochrane suggests that for birth outcomes there is no clear trend by iron dose

	Birthweight	Low Birthweight	Preterm	SGA
MMS-30 vs IFA-60	Not available	Not available	6 trials RR: 1.05 (0.94,1.17)	7 trials RR: 0.89 (0.81, 0.97)
MMS-15-20 vs IFA-60			3 trials RR 0.90 (0.64, 1.27)	2 trials RR: 0.91 (0.75, 1.09)
MMS-60 vs IFA-60			5 trials RR: 0.96 (0.88, 1.05)	5 trials RR: 0.88 (0.72, 1.08)
MMS-30 vs IFA-30			5 trials RR 0.92 (0.84, 1.02)	3 trials RR: 0.98 (0.96, 1.00)

Keats et al. Cochrane Database Syst Review. 2019

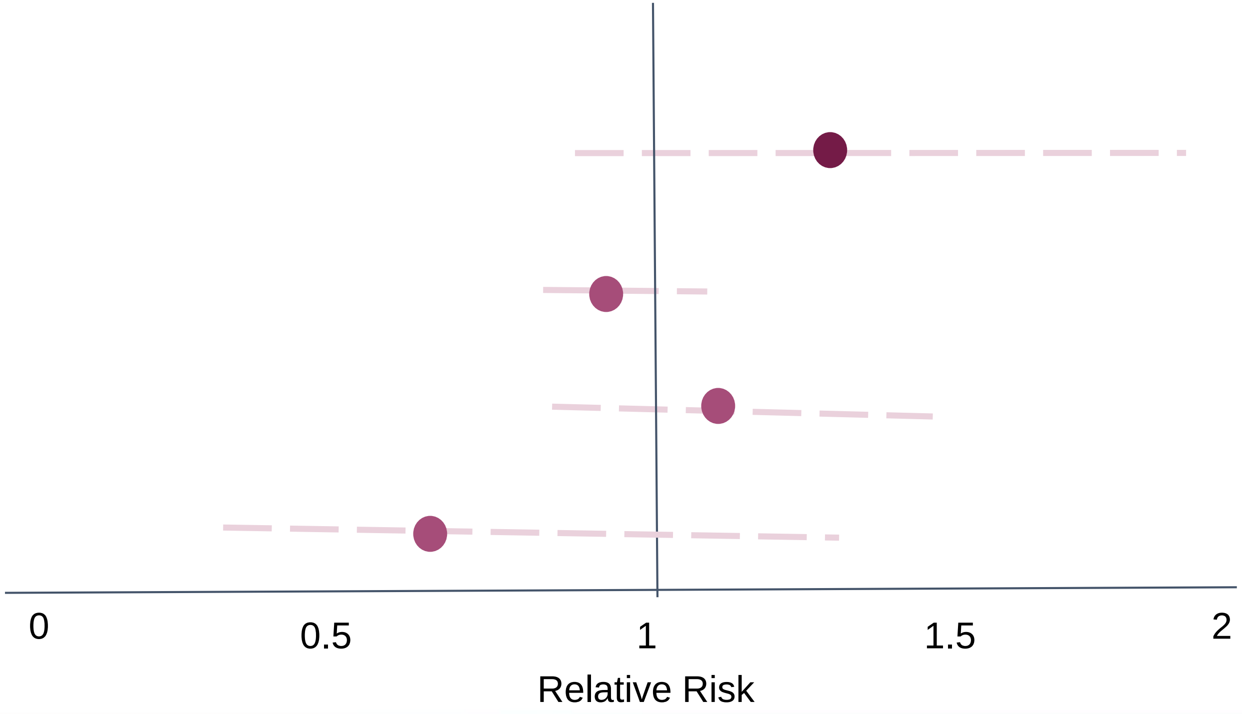
2020 WHO Guidelines Neonatal Mortality

MMS Technical Advisory Group
Updated Analysis

The MMS Technical Advisory Group reanalysed the data presented in therein using four comparison groups according to iron dose

1. **60 mg MMS *v.* 60 mg IFA**
   - Two trials
   - RR: 1.29, 95% CI: 0.90 to 1.85
1. **30 mg MMS *v.* 30 mg IFA**
   - Four trials
   - RR: 0.95, 95% CI: 0.87 to 1.04
1. **30 mg MMS *v.* 60 mg IFA**
   - Seven trials
   - RR: 1.12, 95% CI: 0.83 to 1.50
1. **20 mg MMS *v.* 60 mg IFA**
   - Two trials
   - RR: 0.67, 95% CI: 0.32 to 1.41

Neonatal mortality did not differ between MMS and IFA regardless of Fe dose in either supplement.



Limited data to inform MMS Iron Dose analysis for maternal anemia outcome

Table 4. Summary of results: subgroup analyses for maternal hemoglobin

Effect of MMS versus IFA on **hemoglobin (third trimester), g/L**	Random effects model		*P* value (subgroup differences)	Included studies
	n comparisons	Mean difference (95% CI)		
Subgroup analysis by iron dose				
MMS 60 mg iron versus IFA 60 mg iron	3	−0.68 (−3.56, 2.20)	0.78	12, 19, 28
MMS 30 mg iron versus IFA 30 mg iron	4	0.14 (−0.71, 0.99)		20, 22, 27, 30
MMS 30 mg iron versus IFA 60 mg iron	4	−0.26 (−1.41, 0.89)		21, 23, 30, 40

Gomes et al. Ann. N.Y. Acad. Sci. 2022

No evidence of harm from addition of MMS alone

Suggestion from low-iron-dose MMS vs high-iron-dose IFA trials: higher iron may be better for some outcomes.

Supplemental Table 7. Effect of MMS on stillbirth, mortality, and birth outcomes stratified by iron dose provided in the MMS arm as compared to the IFA comparison arm

	Trials using same dose iron in MMS and IFA control arms[2]		Trials using lower dose iron in MMS arm as comared to IFA control arm[3]		p-value for heterogeneity by iron dose
	N[1]	Relative risk (95% CI)	N[1]	Relative risk (95% CI)	
Stillbirth	7	0.90 (0.83-0.97)	8	1.08 (0.90-1.30)	0.07
Early neonatal mortality	6	0.95 (0.97-1.04)	7	1.24 (0.96-1.60)	0.06
Neonatal mortality	4	0.96 (0.88-1.04)	7	1.16 (0.92-1.45)	0.12
Six month mortality	3	0.92 (0.84-1.00)	5	1.14 (0.85-1.52)	0.17
Infant mortality	2	0.96 (0.87-1.05)	5	1.15 (0.89-1.49)	0.19
Low birthweight (<2500g)	8	0.88 (0.85-0.90)	8	0.85 (0.77-0.95)	0.62
Very low birthweight	8	0.77 (0.70-0.84)	8	0.94 (0.70-1.26)	0.18
Very preterm birth	7	0.85 (0.77-0.95)	6	0.97 (0.74-1.25)	0.39
Preterm birth	8	0.92 (0.89-0.96)	7	0.97 (0.88-1.06)	0.30
SGA Oken	8	0.98 (0.96-1.00)	7	0.90 (0.85-0.96)	0.01
SGA Intergrowth	8	0.94 (0.91-0.96)	7	0.92 (0.85-1.00)	0.64
LGA Oken	7	1.05 (0.95-1.17)	5	1.02 (0.80-1.30)	0.82
LGA Intergrowth	7	1.10 (1.02-1.18)	6	1.21 (1.06-1.40)	0.20

[1] Number of studies included in subgroup analysis

[2] Christian 2003, Friis 2004, Gupta 2007, Fawzi 2007, Fawzi 1998, Ramakrishnan 2003, SUMMIT 2008, West 2014

[3] Ashorn 2015, Adu-Afarwuah 2015, Bhutta 2009, Kaestel 2005, Osrin 2005, Roberfroid 2008, Zagre 2007, Zeng 2008

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Ongoing work to identify optimal iron dose for MMS

MMS-MAP Tanzania Trial

Three Arm Superiority Trial

experimental treatment		control treatment
MMS - 60 mg Iron	vs	MMS - 30 mg Iron
MMS - 45 mg Iron		

Is MMS with higher iron better than MMS unimapp?

Launching soon! Individually randomized, quadruple blinded superiority trial of daily antenatal MMS in Dar es Salaam, Tanzania (n=6381 pregnant women)

Primary Endpoint
Moderate or Severe Anemia (<10g/dL) at 32 weeks

MMS Acceptability Cross-over Trial

We propose an acceptability trial using mixed methods to identify barriers and enablers of adherence, and assess side effects, for MMS with 30, 45, and 60 mg iron among women accessing standard of care counseling during ANC.

Each woman will receive 1-month supply of each MMS iron dose.

N~200

Randomization Pattern

Month 1	Month 2	Month 3
30mg	45mg	60mg
30mg	60mg	45mg
45mg	60mg	30mg
45mg	30mg	60mg
60mg	30mg	45mg
60mg	45mg	40mg

The order in which women receive these supplements will be randomized. Given three regimens, there are six different randomization patterns.

MMS-MAP Collaboration

ISO 9001: 2015 certified
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AAPH Africa Academy for Public Health
Research | Training | Practice

Milken Institute School of Public Health
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Thank you!

Let’s chat!

Email me at EmilySmith@gwu.edu

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Reference Material

Compare effect size & data availability for other ANC Nutrition recommendations

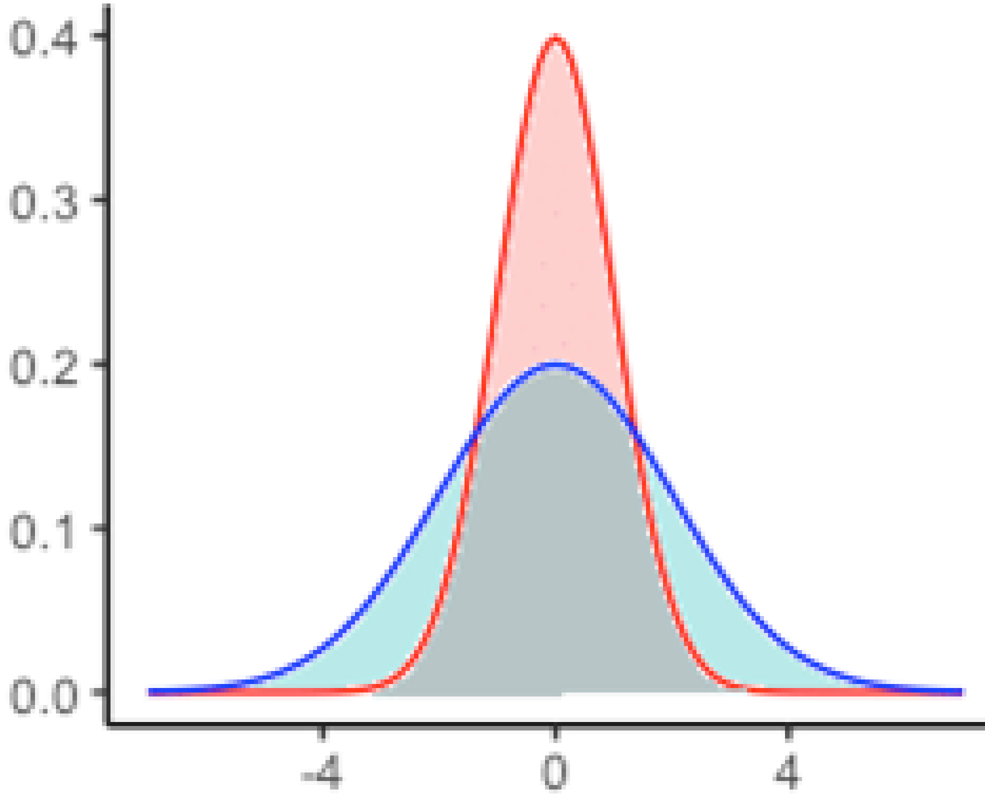
Larger benefits at the extreme end of the birthweight tail (most vulnerable)

	Low Birthweight <2500g	Birthweight <2000g
IFA	11 trials; 17,613 infants RR: 0.84 (95% CI: 0.69-1.03) low-certainty evidence	Not Reported
MMS vs IFA	16 trials; 68,801 infants RR: 0.88 (95% CI: 0.86-0.91) high-certainty evidence	16 trials, RR 0.78 (95% CI: 0.72-0.85) no grade (IPD)

Preterm vs very preterm (or LBW vs LBW <2000g) suggests important biological effect on the lower tail of the distribution

Nutritional interventions may “pull up” the lower end of the birthweight and gestational age distribution.

The mean can stay the same, but we avoid the extreme outcomes.



Supplemental Table 1. Nutrient composition of control and intervention group by study

	Control Group		MMS Intervention Group																
	Iron (mg)	Folic Acid (mcg)	Iron (mg)	Folic Acid (mcg)	A (mcg)	D (IU)	E (mg)	C (mg)	B1 (mg)	B2 (mg)	Niacin (mg)	B6 (mg)	B12 (mcg)	Zinc (mg)	Copper (mg)	Selenium (mcg)	Iodine (mcg)	K (mcg)	Others
Fawzi 1998	120	5 mg folate	120	5 mg folate	A: 5000 IU B: 0		30	500	1.4	20	100	25	50			-	-	-	-
Christian 2003	60	400	60	400	1000	10 mcg	10	100	1.6	1.8	20	2.2	2.6	-	2	-	-	65	a
Ramakrishnan 2003	60	215	60	215	2150 IU	309	5.73 IU	66.5	0.93	1.87	15.5	1.94	2.04	12.9		-	-	-	b
Friis 2004					3000	10 mcg	10	80	1.5	1.6	17	2.2	4	15	1.2	65	-	-	c
Fawzi 2007	60	250	60	250	-	25 mg	30	500	-	-	100	-	50			-	-	-	
Gupta 2007	60	500	60	500	2500 IU	1 mg	7.5	50	1.5	1	-	-	1	15	2	-	-	-	d
Kaestel 2005	60	400	30	A:400 B:800	A:800 B:1600	A:200 B:400	A:10 B:20	A:70 B:140	A:1.4 B:2.8	A:1.4 B:2.8	A:18 B:36	A:1.9 B:3.8	A:2.6 B:5.2	A:15 B:30	A:2 B:4	A:65 B:130	A:150 B:300	-	-
Osrin 2005	60	400	30	400	800	5 mcg	10	70	1.4	1.4	18	1.9	2.6	15	2	65	150	-	-
Zagre 2007	60	400	30	400	800	200	10	70	1.4	1.4	18	1.9	2.6	15	2	65	150	-	-
Roberfroid 2008	60	400	30	400	800	200	10	70	1.4	1.4	18	1.9	2.6	15	2	65	150	-	-
Shankar 2008	30	400	30	400	800	200	10	70	1.4	1.4	18	1.9	2.6	15	2	65	150	-	-
Zeng 2008	60	400	30	400	800	200	10	70	1.4	1.4	18	1.9	2.6	15	2	65	150	-	-
Bhutta 2009	60	400	30	400	800	200	10	70	1.4	1.4	18	1.9	2.6	15	2	65	150	-	-
Persson 2012	A: 60 B: 30	400	30	400	800	200	10	70	1.4	1.4	18	1.9	2.6	15	2	65	150	-	-
West 2014	27	600	27	600	800	200	10	70	1.4	1.4	18	1.9	2.6	15	2	65	150	-	-
Ashorn 2015	60	400	20	400	800	400	20	100	2.8	2.8	36	3.8	5.2	30	4	130	250	45	e
Adu-Afarwuah2015	60	400	20	400	800	400	20	100	2.8	2.8	36	3.8	5.2	30	4	130	250	45	e

[a] magnesium 100 mg
[b] magnesium 252 mg
[c] beta carotene 3.5 mg
[d] vitamin D 200IU, vitamin E 7.5mg, calcium patothenate 5mg, ferrous fumarate 10mg, folic acid 0.15 mg, nicotinamide 20mg, biotin 30 mcg, potassium iodide 0.15mg, manganese sulfate 2.5 mg, calcium 162 mg, phosphorus 125 mg, potassium 40 mg, chloride 36.3mg, chromium 25mcg, molybdenum, 25 mcg, sodium selenate 30 mcg, nickel 5 µg, silicon dioxide 2 mg, vanadium 10 mcg, boron 150mcg
[e] pantothenic acid 7mg, manganese 2.6mg

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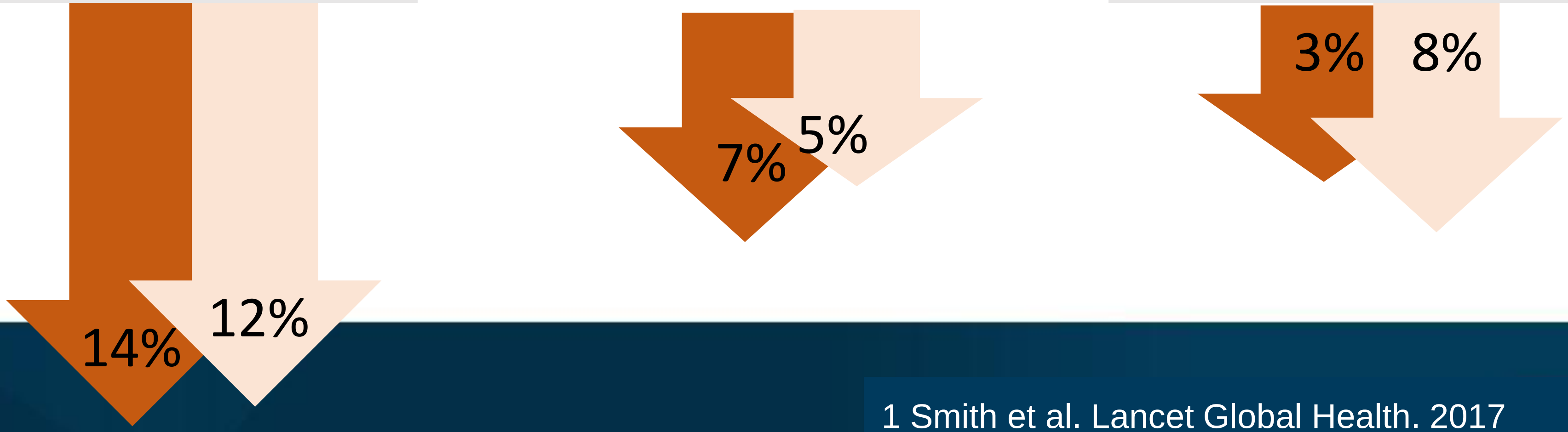
Overall, MMS reduces the risk of low birthweight, and probably reduces the risk of preterm birth, SGA.

IPD results consistent with the 2019 Cochrane Review.

	Low Birthweight		Preterm Birth		SGA	
	N Studies	RR (95% CI)	N Studies	RR (95% CI)	N Studies	RR (95% CI)
IPD[1]	17	0.86 (0.81 to 0.92)	16	0.93 (0.87 to 0.98)	16	0.97 (0.96 to 0.99)
Cochrane[2]	18	0.88 (0.85 to 0.91)	18	0.95 (0.90 to 1.01)	17	0.92 (0.88 to 0.97)



1 Smith et al. Lancet Global Health. 2017
2 Keats et al. Cochrane Database Syst Review. 2019

How many trials used ultrasound?

Nondifferential measurement error biases estimates towards the null

Study	Relative Effect (95% CI)	Method used to assess Gestational Age?
Ashorn 2010	RR 0.81 (0.52 to 1.26)	**Ultrasound**
Bhutta 2009a	RR 1.07 (0.82 to 1.40)	**Ultrasound**
Dewey 2009	RR 0.65 (0.37 to 1.14)	**Ultrasound**
Moore 2009	RR 0.67 (0.15 to 2.93)	**Ultrasound**
Osrin 2005	RR 0.87 (0.60 to 1.26)	**Ultrasound**
Roberfroid 2008	RR 1.06 (0.80 to 1.40)	**Ultrasound**
Tofail 2008	RR 0.77 (0.59 to 0.99)	**Ultrasound** & urine test

Study	Relative Effect (95% CI)	Method used to assess Gestational Age?
Chrisitan 2003	RR 0.87 (0.73 to 1.04)	Date of last menstruation & week of pregnancy tests
Fawzi 2007	RR 1.01 (0.91 to 1.12)	Date of last menstruation
Friis 2004	RR 0.79 (0.55 to 1.13)	Date of last menstruation or fundal height
Kaestel 2005	RR 1.04 (0.77 to 1.41)	Date of last menstruation
Lui 2013	RR 0.91 (0.78 to 1.06)	Date of last menstruation- collected prospectively
Ramakrishnan 2003	RR 1.14 (0.65 to 2.01)	Date of last menstruation & pregnancy surveillance
SUMMIT 2008	RR 1.00 (0.96 to 1.04)	Date of last menstruation
Sunawang 2009	RR 1.08 (0.89 to 1.31)	Date of last menstruation
West 2014	RR 0.85 (0.80 to 0.90)	Date of last menstruation & pregnancy surveillance with urine tests
Zagre 2007	RR 1.03 (0.91 to 1.15)	Date of last menstruation & urine tests
Zeng 2008	RR 1.06 (0.76 to 1.49)	Date of last menstruation & pregnancy surveillance with urine tests

Gomes et al. Maternal & child nutrition. 2023

Compare effect size & data availability for other ANC Nutrition recommendations

Larger benefits at the extreme end of the gestational age tail (most vulnerable)

	Preterm Birth <37 weeks	Very Preterm Birth <34 weeks	GDG Conclusion
IFA vs Placebo	13 trials; 19,296 infants RR: 0.93 (95% CI:0.84-1.03) moderate-certainty evidence	5 trials, 3,749 infants RR: 0.51 (95% CI: 0.29-0.91) high-certainty evidence	"is recommended for pregnant women to prevent maternal anaemia, puerperal sepsis, low birth weight, and **preterm birth**"
MMS vs IFA	18 trials; 91,425 infants RR: 0.95 (95% CI: 0.90-1.01) moderate-certainty evidence	4 trials, 37,701 infants RR: 0.81 (95% CI: 0.71-0.93) no grade (cochrane) 14 trials RR: 0.87 (95% 0.79-0.95) no grade (IPD)	"The evidence suggests that MMS probably make little or no difference to preterm birth compared with IFA supplements"

Molecular Methods for Maternal Nutrition **(MM4MN)**

Project Objectives

<u>**#1**</u> Enhance our understanding of vitamin B12 bioavailability during pregnancy in people with sufficient and insufficient baseline B12 status;

<u>**#2**</u> Identify priority dose regimens of vitamin B12 in pregnancy for investigation in later phase clinical trials and

<u>**#3**</u> Identify novel biomarkers of vitamin B12 intake appropriate for pregnancy.

	B12 Dose	2.6 ug	10 ug	50 ug
Sufficient Baseline B12 Status	1x daily	🤰👧	🤰	🤰
	2x daily	-	-	🤰
Low Baseline B12 Status	1x daily	🤰👧	🤰	🤰
	2x daily	-	-	🤰

Partner organizations

1. GWSPH Department of Global Health
2. GWSPH Exercise & Nutrition Sciences
3. GWSPH Biostatistics & Computational Biology
4. GWMFA
5. Penn State University
6. Baylor College of Medicine
7. University of Maryland School of Pharmacy
8. Ifakara Health Institute
9. Muhimbili University of Health & Allied Sciences

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