# Effect on birthweight of an antenatal multiple micronutrient supplementation programme compared with iron–folic acid supplementation: a cluster-randomised, controlled trial in 85 698 Ethiopian women

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## Summary

**Background** Prenatal multiple micronutrient supplementation (MMS) including iron, folic acid, and other essential micronutrients, has shown potential to improve birth outcomes in controlled studies. We did an effectiveness study in Ethiopia to determine the effect on mean birthweight of MMS provided as part of routine antenatal care, relative to iron–folic acid supplementation (IFA).

**Methods** A pragmatic, two-arm, facility-based, cluster-randomised controlled trial was conducted across 42 districts in five regions of Ethiopia to determine the effect on birthweight of MMS relative to IFA. Districts were randomly assigned to either retain IFA as part of routine antenatal care or switch to MMS. Randomisation was stratified by region and done using a random number generator within statistical software. All live singleton births at participating health facilities were eligible for inclusion and birthweights were recorded. Additionally, data were collected on maternal receipt and utilisation of MMS or IFA. The primary outcome was birthweight, analysed in the intention-to-treat population. This completed trial is registered at ClinicalTrials.gov, NCT05708183.

**Findings** Between Jan 1, 2023, and Dec 31, 2024, birthweights were recorded for 47 325 babies in the 21 IFA districts and 36 473 babies in the 21 MMS districts. Mean age of mothers was 26·2 years (SD 5·3) and median gestational age of babies at birth was 38 weeks (IQR 38–39). The effect of MMS on birthweight was a mean increase of 38 g (95% CI 20–55) in the MMS arm relative to the IFA arm after adjustment for time, geographical region stratification factor, gestational age, sex of baby, and parity. Among women who reported taking at least 90 tablets of their assigned supplement, the increase in mean birthweight in the MMS arm relative to the IFA arm was 58 g (38–79). Stillbirth risk was 7·5 per 1000 births in the IFA arm and 6·9 per 1000 births in the MMS arm.

**Interpretation** The findings of this trial are consistent with those from efficacy trials in other settings, indicating that the transition from IFA to MMS as part of routine antenatal care in Ethiopia could lead to a small but clear improvement in birthweight, although adherence to supplements and programme sustainability require careful attention.

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## Introduction

Birthweight has been shown consistently to be a strong predictor of infant outcomes.[1–3] Globally, low birthweight (<2500 g) is a major public health problem,[4,5] associated with several short-term and long-term adverse health outcomes.[6–8] Achieving the Global Nutrition Target of reducing low birthweight prevalence is crucial for related Sustainable Development Goals, particularly through scaling up evidence-based interventions. Deficiencies in micronutrients among women in low-income and middle-income countries (LMICs) are a major risk factor for low birthweight.[9,10] Interventions to reduce low birthweight emphasise the optimal utilisation of antenatal care, incorporating micronutrient supplementation as part of a package of essential pregnancy interventions.[11]

Multiple studies have investigated the efficacy and safety of multiple micronutrient supplementation (MMS) during pregnancy to improve birth outcomes, including birthweight. In 2019, a Cochrane review including 19 trials from LMICs reported that, relative to iron–folic acid supplementation (IFA), MMS reduced the number of low birthweight babies by 12% (average risk ratio [RR] 0·88, 95% CI 0·85–0·91).[12] The review also highlighted that MMS could reduce the proportion of babies born small for gestational age or preterm births. In response to this meta-analysis, in 2020, WHO updated its antenatal care guideline to recommend MMS use "in the context of rigorous research", emphasising the need for more implementation research.[11]

## Research in context

### Evidence before this study

We searched PubMed with search terms (antenatal or prenatal) and ("multiple micronutrient supplementation") and (iron or iron-folate or iron-folic) and (birthweight or "birth weight") for research studies published in English (or with a translated version available in PubMed) between database inception and Dec 31, 2022, that evaluated the effect on birthweight of antenatal multiple micronutrient supplementation (MMS) relative to iron–folic acid supplementation (IFA). The search returned 38 manuscripts, including 14 reviews. A 2019 Cochrane review on the effect of MMS for women during pregnancy, relative to IFA, reported that MMS resulted in a decrease in the number of newborn babies identified as low birthweight (high-quality evidence) or small for gestational age (moderate-quality evidence). An earlier 2017 meta-analysis of effect modifiers had reported that early initiation in pregnancy and high adherence to MMS provided greatest overall benefits. A WHO review in 2020 led to a recommendation that countries considering the introduction of MMS as part of routine antenatal care, replacing IFA, should do so alongside implementation research, including on health impact.

### Added value of this study

Working with the Ethiopian Ministry of Health and UNICEF, we designed a two-arm, facility-based, cluster-randomised controlled trial in 42 districts of Ethiopia to investigate the programme effectiveness on birthweight of providing MMS as part of routine antenatal care, relative to providing IFA. Analysing data from more than 80 000 births, we observed a mean birthweight improvement in the MMS study arm relative to the IFA study arm, and a larger improvement among those taking at least 90 tablets of MMS compared with at least 90 tablets of IFA.

### Implications of all the available evidence

This randomised study from Ethiopia evaluated the effect on birthweight of MMS when implemented as part of the routine health system for antenatal care. A small but potentially important improvement in mean birthweight was observed, consistent with results from controlled efficacy trials, supporting government decision making for national scale-up of MMS as part of routine antenatal care in Ethiopia. Nonetheless, continued attention is needed to promote adherence to the recommended dose.

In Ethiopia, deficiencies of multiple micronutrients are highly prevalent among women of reproductive age,[10] including pregnant women. In 2022, the Ethiopian Ministry of Health decided to adopt the WHO recommendation by replacing IFA with MMS as part of routine antenatal care in 21 districts across five regions of Ethiopia, alongside a comprehensive evaluation. Here, we report results from a two-arm, 42-district, cluster-randomised trial on the effectiveness of this policy change on birthweight. Specifically, we aimed to estimate the effect of MMS implementation on the mean birthweight of babies born in government health facilities to women living in areas where MMS was implemented, relative to the mean birthweight of babies born in government health facilities to women living in areas where standard antenatal IFA was provided.

## Methods

### Study design

We conducted a facility-based, two-arm, cluster-randomised controlled trial in districts spanning five regions of Ethiopia between January, 2023, and December, 2024, covering a 2-year period from the initial MMS roll-out to the completion of intervention data collection.[13] Clusters, defined as districts, were randomly allocated to one of two groups: continuation of IFA as part of standard antenatal care or a transition to MMS.

The midwives working in participating health facilities were trained to implement standard operating procedures for written informed consent and data collection. Throughout the study period these midwives used uniquely coded paper forms to record birthweight, mode of birth, and sex of all eligible babies. Additionally, within 24 h of birth, midwives recorded self-reported data on the mother's characteristics, use of antenatal care, and exposure to MMS or IFA during the pregnancy leading to the current birth. These midwives received continuous supervision from 13 field supervisors who were deployed to ensure data quality. Field supervisors used digital platforms and conducted site visits to verify digital weight scales, reinterview a proportion of women, and reinforce standard operating protocols, then checked and collected completed paper forms for double data entry and verification. The characteristics of babies born during the roll-out period between January and May, 2023, were used to describe and control for the baseline characteristics of the clusters.

We obtained trial ethical approval from institutional review boards of both the Ethiopian Public Health Institute (EPHI-IRB-455–2022) and the London School of Hygiene & Tropical Medicine (reference 28021). This completed trial is registered at ClinicalTrials.gov, NCT05708183.

### Participants

Ethiopia's administrative system comprises 12 regional states and two city administrations, structured hierarchically from central government to regions, zones, and districts (woredas). District public sector health care is supported by approximately four health centres and one primary hospital, although numbers vary by district.

This study was conducted in 42 districts from five geographically diverse regions of Ethiopia: Gambela,

Sidama, the Southern Nations, Nationalities, and Peoples' region, Somali, and Oromia (appendix 1 p 2).

Health facilities within districts were selected through a two-step process. First, the evaluation team used District Health Information System-2 data to determine the monthly number of births in each public facility in each district. Second, within each district, facilities were ranked by monthly births (highest to lowest), and the top five facilities were visited for record review. 99 health facilities reporting at least 15 births per month were enrolled in the study. Sample selection is described in detail in the published protocol.[13]

All live singleton births at the selected health facilities were eligible for inclusion and birthweights were recorded. Mother–baby dyads were excluded from the study based on the following criteria: mothers who declined to provide informed consent for the documentation of their baby's birthweight data; pregnancies resulting in a stillbirth (although a count was made of the number of stillbirths for the purpose of safety monitoring); and those who encountered an acute medical emergency during the peripartum period that posed a significant threat to their own life or that of their newborn. All participants provided written informed consent.

### Randomisation and masking

Before randomisation, the Ethiopian Ministry of Health generated a list of 286 districts from five regions and, together with UNICEF Ethiopia, selected a shortlist of 42 districts for the study. Randomisation was conducted by the trial statistician, who maintained a degree of independence from other members of the trial team. Stratified randomisation by region (or sub-region in the two geographically large regions) was conducted to guarantee the balanced inclusion of districts from all five regions within both study arms. Consequently, districts were assigned a random number generated in Stata MP (version 17), then the region-specific lists were ranked according to these random numbers. Subsequently, half of the districts within each region—those with the lowest random numbers—were assigned to the intervention arm, with the remaining districts allocated to the comparison arm. A detailed description of this process is provided in appendix 1 (pp 3–5).

Owing to the nature of the study interventions, masking of study participants and investigators was not possible. Nonetheless, to minimise potential bias during the data analysis phase, the trial statistician was masked to treatment group identity until the trial dataset was locked.

### Procedures

The intervention has been described elsewhere.[14] Briefly, implementation of the switch from IFA to MMS as part of routine antenatal care was integrated within Ethiopia's existing government health-care system and supported by UNICEF Ethiopia. Capacity building activities were undertaken across the 42 districts to emphasise the importance of supply chain management, health education, counselling, and monitoring, ensuring that antenatal care providers were equipped to support pregnant women to adhere to the supplement provided in their district.

See Online for appendix 1

In the MMS arm, antenatal care users were instructed to take one MMS tablet daily starting on their first antenatal care contact. The UN International Multiple Micronutrient Antenatal Preparation was used, containing 15 essential vitamins and minerals: retinol (as vitamin A acetate) 800 µg; vitamin E (as vitamin E acetate) 10 mg; vitamin D (as cholecalciferol) 200 IU; vitamin B1 (as thiamine mononitrate) 1·4 mg; vitamin B2 (as riboflavin) 1·4 mg; vitamin B3 (as nicotinamide) 18 mg; vitamin B6 (as pyridoxine 1·9 mg; vitamin B12 (as cyanocobalamin) 2·6 µg; folic acid 400 µg; vitamin C (as ascorbic acid) 70 mg; iron (as ferrous sulphate) 30 mg; zinc (as zinc sulphate) 15 mg; copper (as copper sulphate) 2 mg; selenium (as sodium selenite) 65 µg; and iodine (as potassium iodate) 150 µg. In the IFA arm, antenatal care users were instructed to take one IFA tablet daily starting on their first antenatal care contact. The IFA tablets contained 60 mg of elemental iron and 400 µg of folic acid. Both nutritional supplements were provided free of charge to antenatal care users.

A data and safety monitoring board (DSMB) was established to safeguard the wellbeing of trial participants, and to ensure the integrity of investigators and the sponsor, assess the safety of the intervention, and monitor the overall conduct, validity, and credibility of the trial. The DSMB operated independently of the trial, with its members having no other involvement in the study. It was a multidisciplinary team comprising a research ethics specialist, a nutrition and public health expert, a paediatrician, and a statistician. The DSMB's responsibilities encompassed a review of the trial design and analysis plan, as well as an assessment of adverse effects. The DSMB reviewed the incidence of stillbirths by study arm, using data extracted from maternity registers at enrolled health facilities. Furthermore, the board provided recommendations for supplementary analyses and addressed ethical implications arising during the trial's execution.

### Outcome

Birthweight (in g) was the primary outcome. Each study facility received calibrated digital weight scales (SECA 384 and SECA 354; UNICEF Supply Division, Copenhagen, Denmark), with batteries, standard weights (50 g, 100 g, or 200 g), and laminated written standard operating procedures for using the scales. Before the study began, all midwives and facility in-charges were briefed on the study and participated in on-the-job training that covered the use of scales and standard weights. The standard weights were regularly used before measurement of birthweight and calibration was rechecked during supervision visits.

### Statistical analysis

To calculate sample size, we extrapolated the expected effect size on birthweight to evidence on birthweight distributions in the Ethiopian population.[12,15–17] We estimated that 21 districts in each of the two study arms would provide 80% power to detect a 35 g or greater difference in mean birthweight, assuming a mean birthweight of 3000 g (SD 500) in the comparison group, and an intracluster correlation coefficient of 0·003 within district, corresponding to a design effect of 2·0, based on a two-sided test of between-group difference in means at the 5% level of statistical significance. Because the evaluation was to be conducted over 2 years, we estimated that birthweight measurements from at least 15 babies in each month in each of the 42 clusters (ie, 15 120 babies over 24 months) would be sufficient to detect this effect if the between-month autocorrelation of cluster-level birthweights of babies was 0·9 at the slightly larger intracluster correlation of 0·0055. To ensure a sufficient sample of babies from all health facilities, including the smallest, birthweight data were collected from a census of babies born in 99 health facilities.

Statistical analyses were performed according to a prespecified statistical analysis plan based on the published trial protocol.[13] The locked dataset was shared with the DSMB chair before the analysis. The analysis was based on complete cases, and was conducted at the individual mother–baby dyad level, with appropriate adjustments for clustering within district, controlling for region stratification factor and time in the crude analysis, and additionally for gestational age (including a quadratic term for gestational age to allow for non-linearity in its relationship with the outcome), parity, and baby's sex in the fully adjusted analysis. Birthweight data were summarised at monthly intervals, generating 24 cross-sectional summaries of mean birthweight within each study arm to investigate temporal trends in birthweight changes between the intervention groups. For the primary analysis, the mean birthweight of participants was summarised based on their randomised treatment allocation, irrespective of intervention uptake (ie, intention-to-treat analysis). A mixed-effects generalised linear model assuming a Gaussian distribution of the outcome variable, incorporating cluster-level random effects, was employed to estimate the overall mean difference in birthweight over the evaluation period. This comparison was conducted between the MMS and IFA clusters, with treatment effects presented as mean differences in birthweight with 95% CIs. Statistical analysis was conducted using Stata MP version 17.

Preplanned subgroup analyses investigated the effect of the intervention on birthweight of babies of women who: (1) initiated the intervention within the first 24 weeks of gestation (reflecting women who still had sufficient time to consume supplements for at least the recommended 90 days); and (2) self-reported consuming at least 90 supplement tablets during pregnancy.[18]

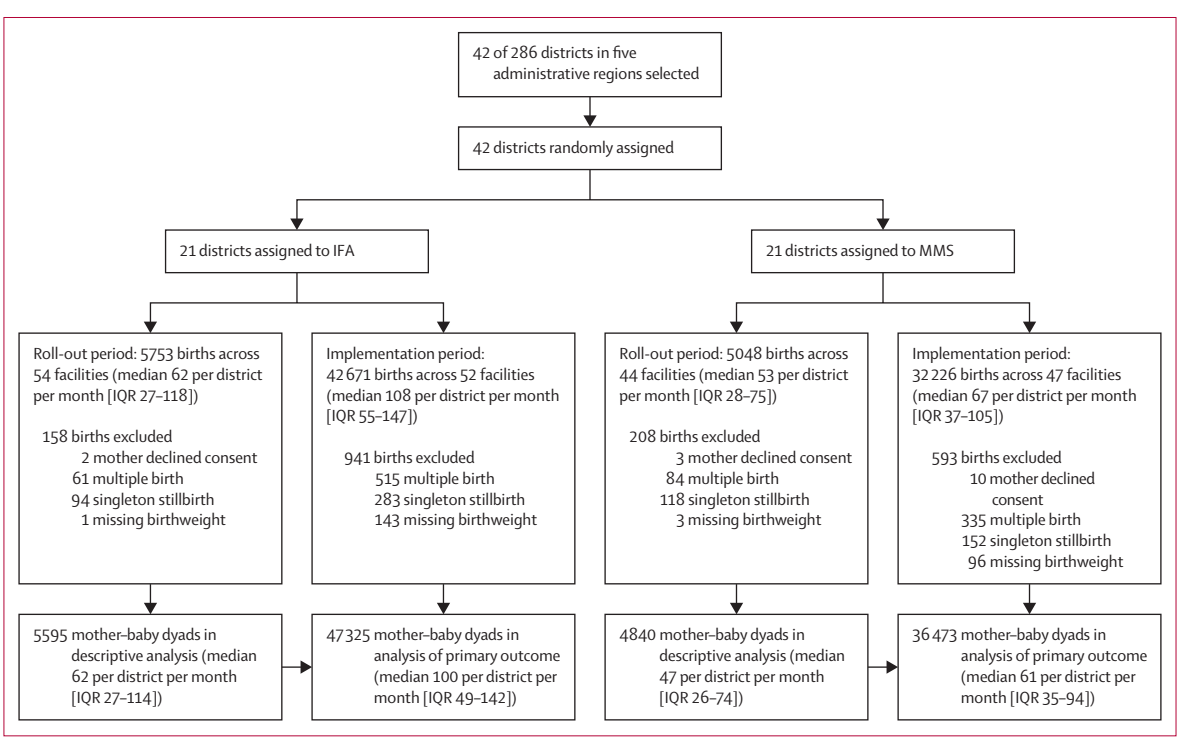


***Figure 1:*** **Trial profile**
No districts were excluded in full. IFA=iron–folic acid supplementation. MMS=multiple micronutrient supplementation.

### Role of the funding source
The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

## Results
The intervention was rolled out between Jan 1 and May 31, 2023 (roll-out period), and fully implemented between June 1, 2023 and Dec 31, 2024 (implementation period), across 21 IFA districts and 21 MMS districts. Between Jan 1, 2023, and Dec 31, 2024, the total number of births in the IFA districts was 48 424, of which 47 325 (98%) were included; the total number of births in the MMS districts was 37 274, of which 36 473 (98%) were included. During the roll-out period, 5753 births in the IFA districts and 5048 in the MMS districts were assessed and contributed to the descriptive baseline (roll-out period) analysis, and 5595 births in the IFA districts and 4840 in the MMS districts contributed to the analysis of the primary outcome. During the implementation period, there were 42 671 births in the IFA districts and 32 226 in the MMS districts, with 41 730 births in the IFA districts and 31 633 in the MMS districts contributing to the crude analysis of the primary outcome after exclusions (figure 1).

Maternal and birth characteristics were similar between the IFA and MMS districts in the roll-out phase (table 1). Mean age of mothers was 26·2 years (SD 5·3) and on average they had had two births before the current pregnancy (median parity of 2 [IQR 2–4]). The number of antenatal visits and gestational age at first antenatal visit and at birth were also similar across the groups, as were the sex distribution of babies born, modes of birth, and mean birthweights.

As expected, the proportion of mothers reporting receiving the supplements assigned to their group increased over the roll-out period and throughout the implementation period, settling at 85% at the end of the implementation period (figure 2).

The distribution of birthweights is presented in appendix 1 (p 6). A gradual and sustained trend of higher mean birthweights among babies in the MMS arm compared with the IFA arm was observed over the 24 months of the evaluation (figure 3). The mean birthweight of babies born in the IFA districts was 3229·9 g (SE 20·9) and that of babies in the MMS districts was 3274·9 g (17·9), a crude difference of 60·6 g (95% CI 43·4–77·9, p<0·0001) when accounting for trial design factors (time and geographical region stratification; table 2). When adjusted for gestational age, sex of baby, and parity, the effect of the intervention on birthweight was 37·7 g (95% CI 20·1–55·3, p<0·0001).

There was evidence of a duration-dependent effect of the intervention: among babies of mothers who reported taking supplements for less than 90 days, the adjusted mean difference in birthweight between those in the MMS arm compared with the IFA arm was –2·7 g (95% CI –26·8 to 21·4), whereas the adjusted mean difference in birthweight among babies whose mothers reported taking 90 days or more of supplementation was 58·3 g (37·8 to 78·9; interaction p<0·0001; table 2, figure 4). Further exploratory analysis to examine shorter intervals of duration of use was consistent with an optimal duration of supplementation of at least 90 days (appendix 1 p 7).

| | IFA arm | MMS arm | Overall |
|---|---|---|---|
| Number of districts | 21 | 21 | 42 |
| Number of mother–baby dyads | 5595 | 4840 | 10 435 |
| Maternal characteristics | | | |
| Age, years | 26·4 (5·3) | 25·9 (5·3) | 26·2 (5·3) |
| Parity | 2 (2–4) | 2 (2–4) | 2 (2–4) |
| Number of antenatal clinic visits if at least one visit reported | | | |
| n | 3799 | 3371 | 7170 |
| Median (IQR) | 3 (1–4) | 2 (1–4) | 2 (1–4) |
| Gestational age at first antenatal clinic visit, weeks | | | |
| n | 2430 | 2344 | 4791 |
| Median (IQR) | 21 (16–28) | 22 (16–28) | 22 (16–28) |
| Exposure to supplements | | | |
| Supplement given at any antenatal clinic visit | | | |
| IFA | 4261 (76·2%) | 629 (13·0%) | 4890 (46·9%) |
| MMS | 165 (3·0%) | 2933 (60·6%) | 3098 (29·7%) |
| Both IFA and MMS | 131 (2·3%) | 671 (13·9%) | 802 (7·7%) |
| Neither IFA nor MMS | 1038 (18·6%) | 607 (12·6%) | 1645 (15·8%) |
| Number of days IFA taken | | | |
| n | 4880 | 4631 | 9549 |
| Median (IQR) | 60 (0–90) | 0 (0–0) | 0 (0–60) |
| Number of days MMS taken | 0 (0–0) | 90 (90–130) | 0 (0–83) |
| Supplement taken for ≥90 days | | | |
| n | 3677 | 3604 | 7281 |
| Median (IQR) | 1896 (51·6) | 2433 (67·5) | 4329 (59·5) |
| Birth outcomes | | | |
| Gestational age, weeks | | | |
| n | 4561 | 4448 | 9009 |
| Median (IQR) | 38 (38–39) | 38 (38–39) | 38 (38–39) |
| Sex of baby | | | |
| Female | 2792 (49·9%) | 2367 (48·9%) | 5159 (49·4%) |
| Male | 2803 (50·1%) | 2473 (51·1%) | 5276 (50·6%) |
| Mode of birth | | | |
| Spontaneous vaginal | 4545 (81·2%) | 4249 (87·8%) | 8794 (84·3%) |
| Episiotomy | 766 (13·7%) | 381 (7·9%) | 1147 (11·0%) |
| Vacuum-assisted | 73 (1·3%) | 32 (0·7%) | 105 (1·0%) |
| Caesarean | 211 (3·8%) | 178 (3·7%) | 389 (3·7%) |
| Birthweight, g | 3233·0 (460·4) | 3214·9 (453·7) | 3224·6 (457·3) |

Data are mean (SD), median (IQR), or n (%), unless indicated otherwise. n is reported for a characteristic when it differed from the group denominator. IFA=iron–folic acid supplementation. MMS=multiple micronutrient supplementation.

***Table 1:*** **Characteristics of participants surveyed during the roll-out period**

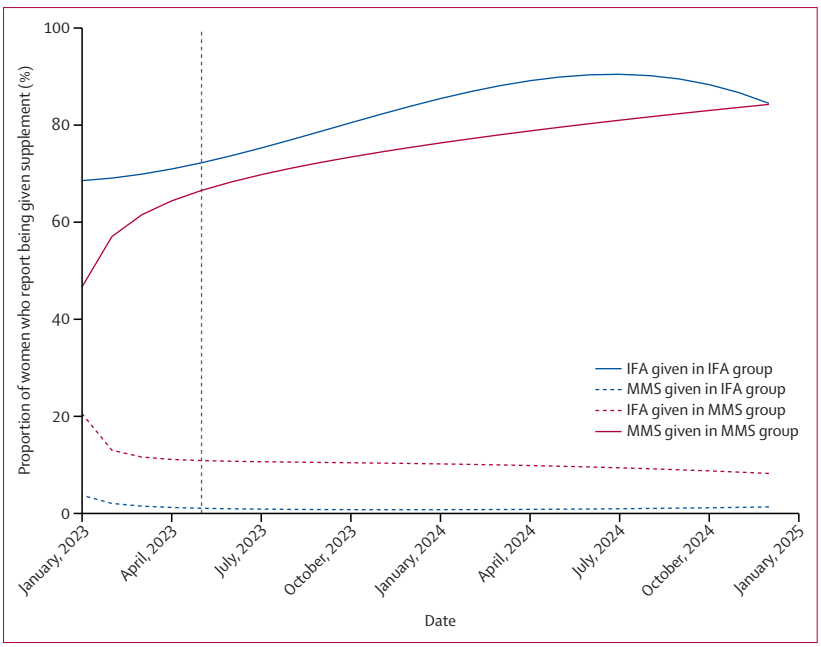


***Figure 2:*** **Proportion of women who report being given IFA and MMS over the 24 months of the evaluation**
IFA=iron–folic acid supplementation. MMS=multiple micronutrient supplementation.

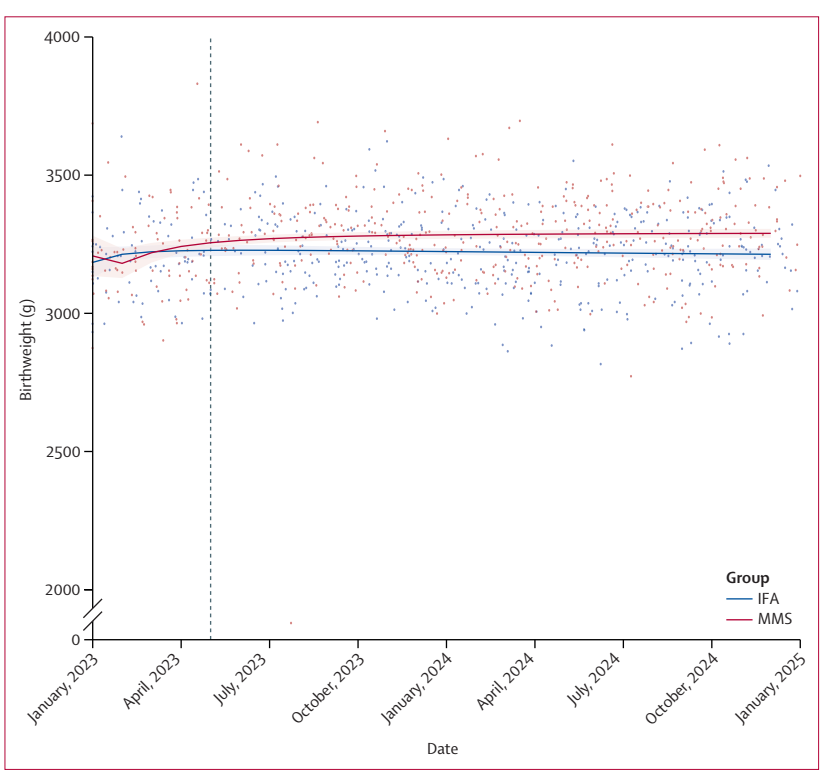


***Figure 3:*** **Birthweights of babies born over the 24 months of the evaluation**
The grey dashed line shows the end of the roll-out period and start of the implementation period. IFA=iron–folic acid supplementation. MMS=multiple micronutrient supplementation.

There was no evidence of a difference in effect between babies of mothers whose first antenatal care visit was before 24 weeks gestation versus those who first attended after 24 weeks (figure 4). This finding was supported by additional exploratory analysis on the timing of first antenatal care (appendix 1 p 8). The difference between overall adjusted effects and stratum-specific effects according to timing of antenatal care visit suggested that timing of antenatal care was independently associated with the outcome, with mothers whose antenatal visits were earlier having higher birthweight babies. Further adjustment of the intervention effect for timing of antenatal care visit in addition to adjustment for trial design factors (time and geographical region stratification), gestational age (including quadratic term), sex of baby, and parity resulted in an estimated difference in mean birthweight of 56·6 g (95% CI 31·4–81·8, p<0·0001) in the MMS arm compared with the IFA arm.

Post-hoc analysis showed that the prevalence of low birthweight (<2500 g) was similar in both arms during the roll-out period (4·4% [95% CI 3·2–6·0] in the IFA arm *vs* 4·2% [3·1–5·6] in the MMS arm) but higher in the IFA arm during the implementation period (4·0% [3·1–5·2] in the IFA arm *vs* 2·8% [1·8–4·3] in the MMS arm; appendix 1 p 9), corresponding to a further adjusted odds ratio of 0·73 (95% CI 0·52–1·01, p=0·059). Post-hoc subgroup analysis by sex of baby found no evidence of a difference in intervention effect by sex (interaction p=0·35). Sensitivity analyses limited to data from the implementation period only (ie, with no baseline adjustment using data from the roll-out period) led to similar conclusions compared with the analyses using all data (appendix p 10).

Safety analysis focused on prevalence of stillbirth. The risk of stillbirth was 7·5 per 1000 births in the IFA arm and 6·9 per 1000 births in the MMS arm.

## Discussion

This study of 85 698 mother–baby dyads across 42 districts in Ethiopia demonstrated that babies born in districts providing MMS exhibited a mean birthweight that was 38 g higher (95% CI 20–55) compared with those in IFA districts, after adjusting for gestational age, sex, and parity. The difference in birthweight between the MMS and IFA groups was 58 g (38–79) among subgroups of women who reported taking either IFA or MMS for at least 90 days. During the study period, supplement coverage was high (85% in both groups by December, 2024). Our study was conducted within routine antenatal care settings across a large geographical area evaluating the effectiveness of MMS compared with routine IFA in a real-world setting. The results not only corroborate previous efficacy trials[12] but also extend them by demonstrating the potential for improved birthweight outcomes when MMS is integrated into existing maternal health programmes at scale.

Birthweight is widely recognised as a determinant of short-term and long-term health trajectories, serving as a powerful predictor of health outcomes.[3] Observational studies have shown an inverse association between

| | IFA arm | MMS arm | Crude difference (95% CI) | Adjusted difference (95% CI) |
|---|---|---|---|---|
| Number of districts | 21 | 21 | .. | .. |
| Number of mother–baby dyads | 47 325 | 36 473 | .. | .. |
| Overall mean birthweight, g | 3229·9 (20·9) | 3274·9 (17·9) | 60·6 (43·4 to 77·9) | 37·7 (20·1 to 55·3) |
| p value | .. | .. | p<0·0001 | p<0·0001 |
| Duration of supplementation | | | | |
| <90 days | 3214·6 (22·9) | 3214·2 (24·0) | 16·0 (–7·9 to 39·8) | –2·7 (–26·8 to 21·4) |
| ≥90 days | 3249·4 (23·2) | 3313·3 (18·0) | 73·7 (53·7 to 93·8) | 58·3 (37·6 to 78·9) |
| Timing of first antenatal care visit, weeks of gestation | | | | |
| ≥24 weeks | 3237·5 (28·8) | 3299·7 (20·7) | 58·6 (30·9 to 86·3) | 61·6 (34·0 to 89·2) |
| <24 weeks | 3236·6 (20·3) | 3299·2 (18·0) | 59·5 (34·0 to 85·0) | 54·4 (28·8 to 80·1) |

Data are mean (SE). Data are from both the roll-out period and implementation period, with roll-out period data used for baseline adjustment. Crude difference is adjusted for time and geographical region stratification factor. Adjusted difference is adjusted for time, geographical region stratification factor, gestational age, sex of baby, and parity. IFA=iron–folic acid supplementation. MMS=multiple micronutrient supplementation.

***Table 2:*** **Effect of the intervention on birthweight**

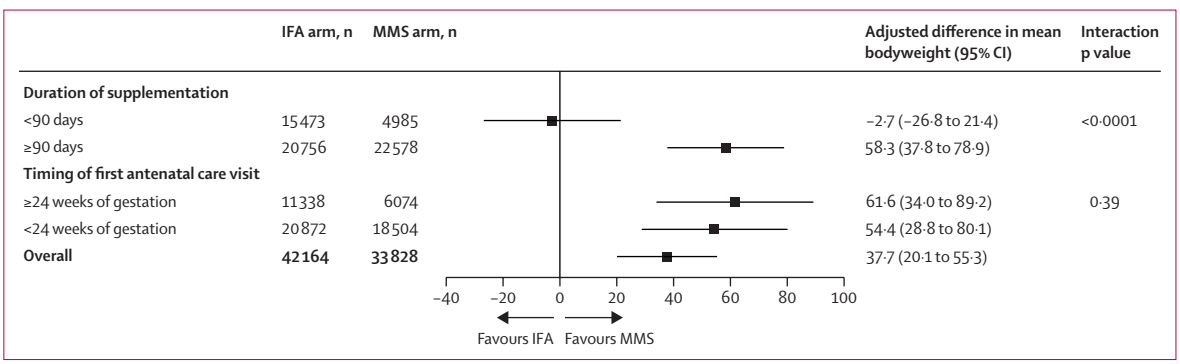


***Figure 4:*** **Subgroup analysis of the effect of the intervention on birthweight**
n represents the number of mother-baby dyads. Differences in n between the crude and adjusted analysis are due to listwise deletion of observations with missing covariates. IFA=iron–folic acid supplementation. MMS=multiple micronutrient supplementation.

birthweight and neonatal mortality.[2,3,19] Beyond immediate survival, low birthweight—an umbrella term that captures small vulnerable babies born preterm or small for gestational age—is intricately linked to a spectrum of adverse developmental and health sequelae throughout the lifespan.[19] A previous meta-analysis reported that the greatest magnitude of effects observed from prenatal MMS compared with IFA were for small vulnerable babies, including those born with low birthweight.[20] Although this trial was not designed or powered to evaluate low birthweight as an outcome, when dichotomising birthweight to low (<2500 g) or normal (≥2500 g) in a post-hoc analysis we observed evidence of a reduction in low birthweight in the MMS group. This finding suggests that the observed improvement in mean birthweight in the MMS arm might also have translated into a reduction in the incidence of low birthweight. Achieving the global target of a 30% reduction in low birthweight by 2030 appears difficult for many LMICs; in Ethiopia, the prevalence of low birthweight has been estimated to be 13%,[21] and has shown little change since 2016. The potential of MMS within routine antenatal care to improve birthweight and reduce low birthweight offers a promising pathway to accelerate progress towards this global goal.

The Ministry of Health antenatal care implementation plan in these 42 districts of Ethiopia was designed to enhance programme delivery and coverage by prioritising the consistent availability of both MMS and IFA within the antenatal care system.[14] This included strengthening supply chain management to prevent stockouts and ensure timely distribution. Additionally, efforts were made to promote adherence to supplements by fostering community engagement and building the capacity of health workers to administer supplements and provide comprehensive counselling. Adherence to micronutrient supplementation is a complex issue shaped by both demand and supply factors that can limit programme success.[22–24] Adherence measurement lacks a universally recognised gold standard, and self-reported adherence measures are known to have suboptimal validity.[25,26] Nonetheless, there is no reason to expect a differential bias in self-reported adherence between MMS and IFA arms and in this study, women adhering to at least 90 MMS tablets showed an even more pronounced increase in mean birthweight compared with those adhering to at least 90 IFA tablets. Consistent with the meta-analysis by Smith and colleagues,[27] our analysis indicated a potential dose–response relationship,

highlighting the importance of adherence for optimal impact. Evidence has shown that low adherence to supplements is associated with poor outcomes and lower quality of life.[25] Although previous recommendations for IFA adherence have often cited a minimum of 90 days,[22,28] these recommendations were not consistently linked to health outcomes.[23] Our study directly links adherence to MMS with birthweight outcome, suggesting a minimum effective duration of supplementation, with particular relevance for LMICs facing widespread maternal undernutrition and micronutrient deficiencies.[10]

The present research had several strengths. First, it was a large-scale randomised study conducted in a real-world setting, adhering to WHO recommendations, and involving over 85 000 women across 42 districts of Ethiopia. Second, the direct comparative evaluation of MMS relative to IFA within the context of routine antenatal care offers pertinent insights for programmatic decision making. Third, the 24-month study duration captures potential seasonal fluctuations that might influence birthweight. Lastly, the collection of data on both adherence and birth outcomes permitted a like-for-like sub-analysis of birthweight by differential levels of adherence. Nonetheless, measurement limitations warrant consideration. MMS has demonstrated a good safety profile in multiple controlled trials.[12] In this study, we used routine registers to monitor the frequency of stillbirths in enrolled facilities, finding no difference between the two study arms, although stillbirths were likely under-reported.[29] Although evidence from efficacy trials suggests that MMS is associated with multiple small improvements in health outcomes at the population level, this study only measured the outcome of birthweight, an outcome that was feasible to measure accurately in this context and at this scale. The study did not attempt to analyse gestational age at birth as an outcome due to concerns regarding data accuracy in this context where midwives rely on the estimated date of last menstruation for pregnancy dating. Measuring birthweight using digital scales necessitated a facility-based study that almost certainly resulted in recruitment of a population with better health-seeking behaviour than the general population. Further, a small number of birthweights were not recorded and we hypothesise that these could have been cases of especially low birthweight neonates or mothers who needed urgent health care. The low prevalence of low birthweight almost certainly reflects these limitations and could also have been exacerbated by some heaping in the birthweight distribution (where certain values cluster disproportionately at round numbers or preferred digits, often due to rounding or digit preference; appendix 1 p 6). Additionally, the study's reliance on self-reported measures of adherence introduced the potential for recall inaccuracies and response biases, which could affect the precision of adherence estimates.[25] These measurement limitations were a consequence of a large-scale study conducted in a real-world setting but there is no evidence to suggest any differential bias between study arms. Finally, as a real-world study, the evaluation team had no influence over implementation plans, including the transition phase from IFA to MMS in the 21 MMS districts, meaning that a true pre-MMS baseline was not possible.

See Online for appendix 2

In conclusion, this large-scale, cluster-randomised study, following WHO guidelines, has shown a small but clear relative increase in mean birthweight in MMS districts compared with IFA districts in Ethiopia, which might have translated into a lower incidence of low birthweight. Subgroup analysis further emphasises the importance of adherence. The findings, consistent with previous efficacy trials, suggest that scaling up the MMS programme nationally could improve birthweight in Ethiopia, provided programme sustainability is considered. The results of the present study possess considerable public health implications, notably for LMICs, wherein the widespread adoption of MMS at a national level could have a profound impact on population-wide birthweight outcomes.

#### Contributors

TM and MT designed the intervention, study materials, and evaluation with input from CO, JS, L-ÅP, GT, and AD. TM and MT wrote the manuscript with input from CO and JS. CO conducted the trial design, sample size calculations, and statistical analyses, and drafted the results. AKD, AD, and AT coordinated the field trial. BT conducted trial data management with input from CO, who is the trial statistician. All authors had access to the data, verified data and results, and take final responsibility for the decision to submit for publication.

#### Equitable partnership declaration

The authors of this paper have submitted an equitable partnership declaration (appendix 2). This statement allows researchers to describe how their work engages with researchers, communities, and environments in the countries of study. This statement is part of The Lancet Group's broader goal to decolonise global health.

#### Declaration of interests

We declare no competing interests.

#### Data sharing

Upon publication of our findings, the final databases—including variable names and definitions and de-identified individual participant information—will be archived at the Ethiopian National Data Management Center at the Ethiopian Public Health Institute, accessible via https://ndmc.ephi.gov.et/. The meta-dataset is currently available at the same institution (https://doi.org/10.7910/DVN/XIXNMV). Access to these datasets will be granted to scientists from other institutions upon written request to the corresponding author. This request must outline the objectives of their analyses, specify the variables requested, and detail any plans for collaboration with the core research team.

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