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Original Research Article

School-based supplementation with iron-folic acid or multiple micronutrient tablets to address anemia among adolescents in Burkina Faso: a cluster-randomized trial

Ilana R. Cliffer [1,*,†], Ourohiré Millogo [2,3,†], Yllassa Barry [2], Idrissa Kouanda [2], Guillaume Compaore [2], Dongqing Wang [4], Ali Sie [2], Wafaie Fawzi [1,5,6]

[1] *Department of Global Health and Population, Harvard T.H. Chan School of Public Health, Harvard University, Boston, MA, United States;* [2] *Nouna Health Research Center (CRSN), Nouna, Burkina Faso;* [3] *Institut de Recherche en Sciences de la Santé (IRSS), Centre National de Recherche Scientifique et Technologique (CNRST), Ouagadougou, Burkina Faso;* [4] *Department of Global and Community Health, College of Public Health, George Mason University, Fairfax, VA, United States;* [5] *Department of Nutrition, Harvard T.H. Chan School of Public Health, Harvard University, Boston, MA, United States;* [6] *Department of Epidemiology, Harvard T.H. Chan School of Public Health, Harvard University, Boston, MA, United States*

A B S T R A C T

Background: Iron-deficiency anemia is a leading cause of morbidity among adolescents (aged 10–19 y), especially in low- and middle-income settings. Few policies and programs have targeted adolescent health.

Objectives: This study aimed to evaluate the effectiveness of school-based supplementation with iron-folic acid (IFA) or multiple micronutrient supplements (MMSs) in addressing anemia among adolescents in Burkina Faso.

Methods: In this cluster-randomized trial, 3123 secondary school students aged 10 to 18 y in Burkina Faso were either supplemented with weekly IFA, daily MMSs, or received standard nutrition education as controls. Supplementation occurred between April 2021 and April 2022 over 2 supplementation periods (10 wk, then 16 wk) separated by a gap of 20 wk without supplementation. Hemoglobin was evaluated 4 times: at baseline prior to each supplementation period and at the end of each period. Anemia was categorized by the World Health Organization hemoglobin level cutoffs as none, mild, moderate, or severe. Associations between treatment arm and anemia or continuous hemoglobin (g/dL) were assessed using multilevel mixed effects generalized linear models with schools as a random effect, controlling for baseline hemoglobin or anemia status.

Results: Baseline anemia prevalence was similar across study arms, with 32.7% in IFA, 31.2% in MMS, and 29.5% in the control arm. Over the full study period, adolescents provided IFA had hemoglobin levels higher than those in the control arm (adjusted β: 0.32; 95% CI: 0.02, 0.62). No significant associations were observed for MMS or for anemia outcomes; however, the direction and magnitude of nonsignificant associations indicate potential protective effects of IFA and MMSs on anemia.

Conclusions: The results do not provide strong evidence that weekly IFA or daily MMS alone is effective, but supplementation may play a role in addressing adolescent anemia if combined with cointerventions. Additional research is required to determine the best strategy to address anemia.
This trial was registered at clinicaltrials.gov as NCT04657640.

Keywords: iron deficiency, anemia, multiple micronutrient supplements, adolescents

Introduction

Iron-deficiency anemia is one of the leading causes of morbidity and disability among adolescents in low- and middle- income countries (LMICs) [1]. It is associated with long-term health problems, cognitive impairment, and poor school performance, which all carry lasting economic consequences [2,3]. Historically, the period of adolescence, when people are between 10 and 19 y of age, has been overlooked by public health policy and programs. Despite the importance of the period for physical and cognitive development, during which people gain an estimated 20% to 40% of their adult height and weight [4,5], there are no global nutrition targets for older children or adolescents

Abbreviations: aβ, adjusted β; CI, confidence interval; HDDS, Household Diet Diversity Score; HFIAS, Household Food Insecurity Access Scale; ICC, intracluster correlation coefficient; IFA, iron and folic acid; LMIC, low- and middle- income country; MCA, multiple correspondence analysis; MMS, multiple micronutrient supplement.

* Corresponding author.
E-mail address: icliffer@hsph.harvard.edu (I.R. Cliffer).

† IRC and OM contributed equally to this work.

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[5]. As a result, micronutrient deficiency levels remain high among this age group, who make up 23% of the overall world population [6,7]. In Sub-Saharan Africa, where over half the population is under the age of 18 [8], diet quality is low, food insecurity and infectious disease burden are high, and early pregnancy is common; hence, addressing micronutrient deficiencies, including iron-deficiency anemia among adolescents, is especially important to reducing inequities and promoting population health [9–12].

Given that interventions have not been focused on adolescents in the past, there is little evidence to support decision making about optimal programming and policy to reduce iron-deficiency anemia and other micronutrient deficiencies among this age group [13]. School-based supplementation with iron and folic acid (IFA) has been effective in reducing anemia among adolescent females [14], and World Health Organization guidelines recommend intermittent IFA supplementation for adolescents in regions where anemia prevalence is high [15–17]. However, these guidelines have not been put into practice, or evaluated beyond small pilot programs. Further, since multiple micronutrient deficiencies are likely to coexist in areas with a high anemia burden, and having multiple deficiencies at once may limit effectiveness of iron supplementation in increasing hemoglobin levels [18], supplementation with more than just IFA may carry additional benefits to adolescent health. Although multiple micronutrient supplements (MMSs) have been evaluated and deemed more effective at addressing micronutrient deficiencies than IFA among pregnant women in LMICs [19,20], similar comparative studies have yet to be conducted in an adolescent population of both males and females.

To advance understanding of the types of interventions that will have the most impact in tackling the burden of anemia and other micronutrient deficiencies among adolescents in LMICs, we implemented a school-based distribution program providing either IFA plus standard nutrition and health education, MMSs plus standard nutrition and health education, or standard of care (only nutrition and health education) to adolescents in the Center West province of Burkina Faso. The study, called "School-based assessment of micronutrient interventions in adolescents," aims to determine the optimal supplementation scheme to improve adolescent nutrition, health, and education. This work directly supports the Ministry of Health in Burkina Faso in its efforts to tackle anemia among adolescents. The government of Burkina Faso has laid out a nutrition action plan [21] that includes supplementation efforts in the adolescent population; thus, the present study helps inform national scale-up of the most effective supplementation strategy in the context of Burkina Faso, as well as decision making across similar LMIC environments.

Methods

Study setting

The study was conducted in the Centre West region of the landlocked country of Burkina Faso, in the province of Bulkiemdé. Secondary schools were selected from the periurban areas surrounding Koudougou, the capital city of the region, situated 100 km from the capital of Burkina Faso. The Centre West region is slightly above the national average in terms of post primary school enrollment rate (60.5% in Centre West compared with 47.3% national average) and below the national average for prevalence of undernourishment (224 kcal/person/d deficit in Centre West compared with 212 kcal/person/d national average deficit), and sanitation facilities (50% with improved sanitation in Centre West compared with 58.8% national average).

Study design

We conducted a 3-arm cluster-randomized controlled trial to evaluate the effects of different supplementation strategies on anemia prevalence among school-going adolescents aged 10 to 18 y. We compared individuals in a control group who received standard nutrition and health education to either weekly supplementation with IFA tablets (60 mg iron + 2800 μg folic acid, supplied by UNICEF) or daily supplementation with MMSs provided by Kirk Humanitarian. The MMS contains the 15 micronutrients in the United National International Multiple Micronutrient Preparation: 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), and iodine (150 μg).

Students in both treatment arms were supplemented for 2 periods of approximately 12 wk, following the school calendar, and as recommended by the WHO in settings where continuous supplementation is not possible. Although the aim was to supplement for 12 wk at a time, constraints of the school, vacation, and testing timeline allowed for a first 10-wk period followed by a second 16-wk period, separated by 20 wk in which there was no supplementation. The first 10-wk period was between April and June 2021, and the second between November 2021 and February 2022. For the initial intervention period, students in the MMS arm received a loading dose of IFA for the first 4 wk of supplementation. This was an institutional review board-approved departure from the original study design that did not include the loading dose, after a miscommunication led to students in the MMS arm also receiving IFA for a brief period. Given the high prevalence of anemia in this setting, and the hypothesis that larger doses (60 mg) of IFA than the standard 30 mg in MMS may be beneficial in preventing and treating anemia [22], the study design of a loading dose is justified.

Sample size determination

We calculated our target sample size based on the minimum sample size needed to detect an expected relative risk of 0.65, established using results from a recent systematic review investigating the effects of intermittent iron supplementation on anemia reduction [23]. To account for the cluster-randomized study design effect, we assumed an average cluster (school class) size of 50 students, and calculated the design effect as:

$$\textit{Design effect} = 1 + (n-1)\rho = 1+(49)(0.05) = 3.45$$

where n is the average cluster size (50) and ρ is the intracluster correlation coefficient (ICC) for the outcome of anemia. The ICC was set based on prior studies [24]. Anemia prevalence in Burkina Faso was determined using the most recent Demographic and Health Survey data as 50.7% [25]. Thus, at an alpha level of 0.05 and 80% power, and an expected attrition rate of 10%, we determined that we would need 14 schools per treatment arm, with at least 50 students enrolled per school, for a target sample size of 2100, including controls.

Participant selection, randomization, and masking

Schools were selected using a sampling frame consisting of all secondary schools within the province of Bulkiemdé and their key characteristics, obtained from the Ministry of Education. At study inception in 2020, the province of Bulkiemdé had 251 secondary schools (117 public and 134 private), consisting of post primary education students in 4 grades, grades 6th (youngest) through 3rd (oldest). Schools were then matched on the number of students, school ranking profile, and distance to city council, using coarsened exact matching (*cem* command) in Stata 16 [26] (StataCorp LLC), and subsequently

randomized to either IFA, MMS, or control arms using a list randomizer (https://www.random.org/lists) [27]. Once randomized, entire classes were selected from each of the 42 schools (14 per study arm). The largest class was selected first at each school, followed by the second largest, until the minimum number of students per school was reached. Due to obvious differences in the supplements' appearance, we were unable to blind participants and researchers to group assignment.

Parents from all 42 selected schools were invited to meetings to learn about the study protocol and given the opportunity to provide informed consent for their adolescent children to participate. If participants were 18 y of age, they did not require parental consent to participate; however, consent was obtained from all parents regardless of the age of their children as this was done prior to enrollment.

Inclusion and exclusion criteria

Adolescents whose parents had provided consent were then asked if they provided their assent to participate and were enrolled if they agreed. Participants who self-reported pregnancies or were over 18 at the time of enrollment were excluded. Other than that, all students in the chosen schools and classes, selected as described above, were included in the study.

Data collection

Participants were recruited and data were collected between April 2021 and April 2022. Focal points (directors of academic life) at each intervention school were trained to distribute the supplements to the students either daily (MMS) or weekly (IFA) and keep track of their attendance and compliance (whether they consumed the supplement) using forms provided and collected by the study team. Students were always given the supplement at school to consume in the presence of the school focal point. Data from the forms were then collected by study enumerators and entered into SurveyCTO using electronic tablets, and the data were uploaded to a central server.

An initial baseline survey (baseline 1) was conducted prior to supplementation to collect data on hemoglobin status, malaria status, demographics, socioeconomic status and wealth, physical activity, hygiene and sanitation, menstruation, dietary factors, mental health and social development, and anthropometry. Hemoglobin was assessed with a finger-prick, using HemoCue hemoglobinometers (model Hb 201+) and anthropometric measurements were recorded as the average of duplicate-measures using Seca 874 scales for weight and Shorr-Board Infant/Child measuring boards for height. Malaria status was assessed using a finger-prick and a rapid diagnostic test (SD Bioline Malaria Ag P.f/Pan, Abbott). Food security was assessed using the Household Hunger Scale (FAO), and diet was assessed using a food frequency questionnaire. The same survey used for baseline data collection was then administered at the end of the first 10-wk supplementation period (endline 1), prior to the second supplementation period (baseline 2), and at the end of the second 16-wk supplementation period (endline 2).

Variable specification

Covariates

We examined the balance of several potential covariates across treatment arms and adjusted for those that were not well balanced. A wealth status indicator was derived using multiple correspondence analysis (MCA), using 17 individual items including possession of electricity, radio, television, cell phone, refrigerator, washing machine, computer, camera, DVD/CD player, bed or mattress, table, chair, cupboard, bicycle, motorcycle or scooter, car or truck, solar panel, and type of fuel used for cooking. The MCA resulted in a continuous score that was then categorized into quintiles.

Food security was assessed using the 3-question version of the Household Food Insecurity Access Scale (HFIAS), developed by the Food and Nutrition Technical Assistance Project [28]. The last 3 questions of the HFIAS, which ask how often in the past 30 d the respondent has experienced having no food in the home due to lack of resources, going to bed hungry, and going a whole day and night without eating due to lack of food were each coded into 2 frequency categories for rarely/sometimes and often. Scores were then totaled to obtain a continuous Household Hunger Score between 0 and 3, which was coded into a binary variable for "no hunger" (0) or "any hunger" (1–3) [29].

A Household Diet Diversity Score (HDDS) was constructed consisting of 12 categories determined by the FAO: cereals; roots and tubers; vegetables; fruits; meat and poultry; eggs; fish and seafood; pulses; legumes and nuts; milk and milk products; oils and fats; sweets; and spices, condiments, and beverages [30]. Food frequency data from surveys asking how often individual preidentified foods were consumed in the previous 30 d were converted into indicators approximating daily consumption of each food. Weekly frequencies were first obtained using the midpoint of the food frequency categories as follows: 0 for "never" or "1–3 times per month"; 1 for "once a week"; 3 for "2–4 times per week"; 5.5 for "5–6 times per week"; and 7 for "6 or more times per day". Total daily frequencies for each of the 12 food categories were then calculated by dividing weekly frequencies by 7 to get daily frequencies for each food and then adding up daily frequencies of all the foods in a category. Finally, the food group category was coded as "yes" if the total daily frequency for that category was at least one, and "no" if not. The overall HDDS variable was made by summing each of the 12 binary indicators for daily food group consumption to get a score between 0 and 12, which was then categorized into 3 categories (0–3 food groups, 4–5 food groups, >5 food groups).

Anthropometric measurements taken in duplicate were averaged, and indices were calculated with the Stata macro who2007.ado, which creates z-scores using the 2007 WHO growth standards [31]. z-scores were then categorized by WHO guidelines. Sex-specific BMI-for-age z-scores were categorized as underweight for z-scores <-2 SD, normal weight for z-scores -2 SD to <1 SD, overweight for z-scores 1 SD to <2 SD, and obese for z-scores $\geq$ 2 SD. Stunting was categorized as sex-specific height-for-age z-scores <-2 SD.

Water, sanitation, and hygiene indicators were each examined as separate variables. The indicators collected included: main drinking water source, treating water, toilet type, sharing sanitation facilities, tooth brushing frequency, dentist visits, handwashing before eating or after using toilets, and handwashing technique.

Outcomes

Outcomes were evaluated at the individual participant level. Cutoffs for anemia were established based on the sex- and age- specific WHO cutoffs for hemoglobin levels in adolescents (Table 1) [32]. Anemia was thus categorized into none, mild, moderate, and severe; however, few participants had severe anemia (12 people), so the categories for moderate and severe were ultimately combined. The 2 primary outcome measures were binary indicators for any anemia and moderate/severe anemia. We used no anemia as the reference for both outcomes. For the outcome of moderate/severe anemia, we removed those with mild anemia from the analysis to compare only the extremes. In addition, hemoglobin levels were investigated as a continuous measure (g/L).

TABLE 1
World Health Organization (WHO) hemoglobin cutoffs (g/L) to diagnose anemia and anemia prevalence in sample of adolescent students in Burkina Faso, 2021–2022

	No anemia	Anemia		
		Mild	Moderate	Severe
Children 10–11 y	≥115	110–114	80–109	<80
Children 12–14 y	≥120	110–119	80–109	<80
Nonpregnant females >15 y	≥120	110–119	80–109	<80
Males >15 y	≥130	110–129	80–109	<80
Prevalence of anemia in sample ($N = 3123$)	63.80%	24.20%	11.60%	0.40%

Statistical analysis

Balance of key characteristics among the study arms was assessed using chi-square tests. Associations between treatment arm and the outcomes of anemia (yes/no or no/moderate or severe) and continuous hemoglobin (g/dL) were assessed using multilevel mixed effects generalized linear models with schools as a random effect to quantify the difference in anemia prevalence and mean hemoglobin associated with each treatment arm. Models with dichotomous outcomes for anemia were specified with a Poisson distribution and a log-link function with robust standard errors, given the high prevalence of anemia in our sample. Continuous hemoglobin was modeled with a Gaussian distribution and robust standard errors. To control for effects of time trends, we adjusted each model for baseline anemia (baseline 1) or hemoglobin status, depending on the outcome being estimated. Fully adjusted models were then controlled for covariates that showed significant lack of balance among the study arms ($P < 0.05$ from chi-square tests) and changed the crude coefficients by at least 10%. Separate models were estimated for the overall study period (baseline 1 to endline 2), and each round of supplementation (baseline 1 to endline 1; baseline 2 to endline 2). Model fit was tested using likelihood ratio tests, and assumptions of normality and homogeneity of variance were tested by examining residual plots.

We explored effect modification by compliance level, interacting binary variables for compliance with treatment arm. Compliers for the models over the entire study period were those who received at least 50% of the intended distributions, whether or not the student was present at school. For the models covering each of the separate supplementation periods, compliers were considered those who received 80% of the intended distributions during that period. We descriptively examined a second form of compliance, defined as taking the supplement program when present at school. We also examined effect modification by sex.

Lastly, we investigated malaria as an outcome of treatment arm using mixed effects logistic regression models, to explore the relationship between the supplements and malaria infection, given the history of iron supplementation in malaria endemic zones [33].

Analyses were conducted using Stata 17 (StataCorp LLC) [34].

Ethics

This study was approved by the Ethics Committee for Health Research (deliberation N° 2020-8-148) of Burkina Faso and by the Institutional Review Board of the Harvard TH Chan School of Public Health (IRB20-1108). Written informed consent was obtained from parents and verbal assent from students prior to participation in the trial. The trial was registered on clinicaltrials.gov under identifier NCT04657640 on December 8, 2020.

Results

Participant characteristics

In total, 3123 students were included in the study at the first baseline survey, 3059 were at the first endline survey (after 10 wk of supplementation), and 2057 were present for the final endline survey (after the second 16 wk of supplementation). Figure 1 shows the full study flowchart. Investigation of the characteristics of those who completed the study compared with those who were not present for the second endline revealed that attritors were significantly older, had lower diet diversity, more siblings, and were more likely to have experienced menarche and be underweight (based on BMI-for-age z-scores). Overall, participant characteristics were relatively balanced across all 3 study arms (Table 2). There were slight differences in the sex breakdown (more males in the MMS arm), more participants with many siblings (>9) in the control arm, more people in the lowest wealth quintile in the control arm, a higher percentage of people with recent cough symptoms in the MMS arm, and greater diet diversity in the MMS arm. Compliance was slightly higher among adolescents in the IFA arm (47.7%) compared with the MMS arm (43.9%) (Table 3). No adverse events or side effects were noted throughout the trial.

Anemia status

Baseline anemia status in the overall sample was 31.2% and was similar across study arms, with 32.7% in IFA, 31.2% in MMS, and 29.5% in the control arm (Table 3). Most cases of anemia were classified as mild (19.8% of the population) and fewer as moderate or severe (11.4% of the population). Although the prevalence of mild anemia increased between 4 and 8 percentage points in all study arms between the first baseline to the last endline survey, the prevalence of moderate or severe anemia decreased in the IFA and MMS arms by about 2 percentage points and increased slightly (by less than 1 percentage point) in the control arm. Males had a higher prevalence of mild anemia than females, whereas females had a higher prevalence of moderate or severe anemia, and hemoglobin levels were higher among males than females overall. Trends in anemia status over time by study arm are visualized in Figure 2. Anemia levels decreased within each supplementation period; however, the second supplementation period started at a higher anemia prevalence than both the baseline and the first endline. Improvements in anemia level after the first supplementation period were not sustained.

Associations between supplementation group and anemia

We observed few significant associations between supplementation group and anemia or hemoglobin status. Rather, the most significant predictor of endline anemia status was baseline anemia status (Table 4). No significant relationships were seen in either of the 2 supplementation subperiods; however, over the full study period (between initial baseline and final endline), those in the IFA arm had hemoglobin levels 0.32 g/dL higher than those in the control arm (adjusted β [aβ]: 0.32; 95% confidence interval [CI]: 0.02, 0.62). Though this was the only relationship that was statistically significant, the general direction of the relationship between study arm and anemia or hemoglobin status was consistent; those in the IFA or MMS arm had lower risk of anemia and higher hemoglobin than those in the control arm in the adjusted model. Effects of larger magnitude were observed when the outcome was moderate or severe anemia compared with no anemia than the effects of treatment on any anemia.

Compliance with the supplementation program was not an important effect modifier of the relationship between study arm and anemia

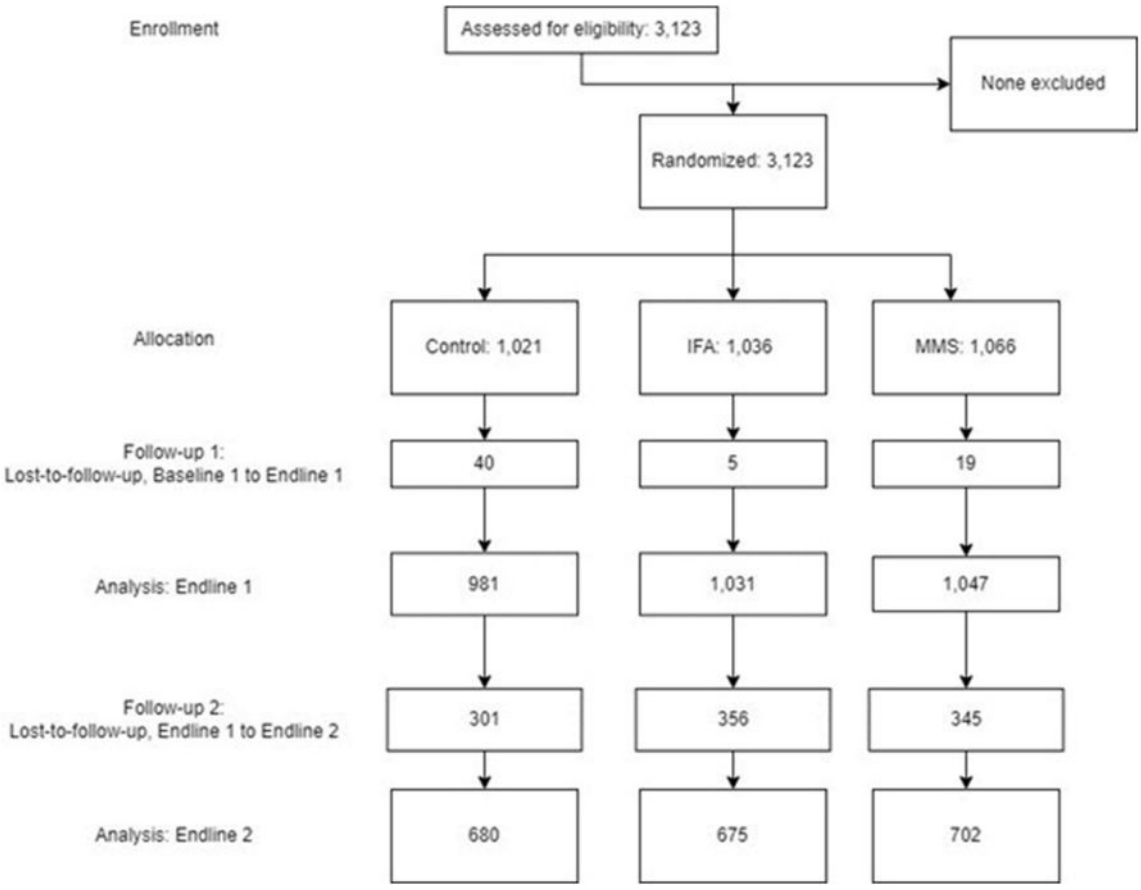

FIGURE 1. Study flowchart for "School-based assessment of micronutrient interventions in adolescents" (SAMIA) trial, Burkina Faso, 2021–2022. IFA, iron + folic acid; MMS, multiple micronutrient supplements.

outcomes (*P* value for Wald test = 0.49) (Table 5). When stratified by compliance level, the only statistically significant relationship is that IFA noncompliers had hemoglobin levels 0.35 g/dL (aβ: 0.35; 95% CI: 0.05, 0.65) higher than those in the control group over the full study period. Some contrast was observed between treatment effects among compliers and noncompliers when considering each subperiod separately, with protective effects of both IFA and MMSs against moderate or severe anemia among compliers, though these were not statistically significant.

Sex was a significant effect modifier (*P* value for Wald test = 0.0138) (Table 6). Over the entire study period, IFA was associated with 0.43 g/dL significantly higher hemoglobin in males (aβ =0.43; 95% CI: 0.14, 0.73), and MMSs were associated with 0.36 g/dL significantly higher hemoglobin also only among males (aβ: 0.36; 95% CI: 0.07, 0.66). Similar relationships are seen in each subperiod. Additionally, MMSs were associated with a 68% lower risk of moderate or severe anemia among males (adjusted risk ratio: 0.32; 95% CI: 0.11, 0.98), with no significant differences found among females.

Lastly, investigation of associations between malaria prevalence and treatment group (Supplementary Table 1) revealed no significant effects of either IFA or MMSs on malaria status.

Discussion

In one of the few studies to compare MMSs to IFA among an adolescent population, and to our knowledge the first to do so among both boys and girls using a school-based supplementation program, we found higher hemoglobin among students supplemented with IFA compared with those who received no supplementation, with larger effects on males than females, and higher hemoglobin after MMS supplementation only in males. We observe a dose-response relationship in which larger magnitudes of effect (though not significant) are seen when the outcome is moderate or severe anemia versus no anemia. Thus, despite the general lack of statistically significant effects on anemia, the direction and magnitude of the associations between either IFA or MMSs and anemia suggests that either treatment could potentially be useful in addressing anemia among school-going adolescents under the right conditions. However, since results from our study do not provide conclusive or strong evidence that weekly IFA or daily MMS supplementation alone are effective ways of addressing anemia among adolescents, additional research will be required to continue to determine the best delivery platform and supplementation strategy.

We find no comparable trials comprised of both adolescent boys and girls comparing IFA and MMSs with which to relate our results; thus, we interpret our findings in relation to prior studies in populations mostly of adolescent girls. Our finding that IFA improves hemoglobin status is supported by previous work summarized in a recent meta-analysis of randomized controlled trials of intermittent IFA supplementation among adolescents. The magnitude of effects of IFA on hemoglobin in our study are similar to those observed in this meta-analysis, which found a mean 0.52 g/dL increase in hemoglobin after supplementation [23]. In addition, a study with a similar school-based delivery method to ours found that school-based weekly supplementation with IFA among adolescent schoolgirls in Ghana increased

TABLE 2
Characteristics of adolescents participating in school-based micronutrient supplementation program, Burkina Faso, 2021–2022

	Overall ($N = 3123$)	Intervention			P
		IFA ($n = 1036$)	MMS ($n = 1066$)	Control ($n = 1021$)	
Male sex	1392 (44.6)	431 (41.6)	514 (48.2)	447 (43.8)	0.008
Age, y					0.050
<12	134 (4.3)	41 (4.0)	37 (3.5)	56 (5.5)	
12–14	1161 (37.2)	366 (35.3)	398 (37.3)	397 (38.9)	
>14	1828 (58.5)	629 (60.7)	631 (59.2)	568 (55.6)	
Number of siblings					<0.001
0–4	1130 (36.2)	380 (36.7)	380 (35.7)	370 (36.2)	
5–9	1469 (47.0)	505 (48.8)	544 (51.0)	420 (41.1)	
>9	524 (16.8)	151 (14.6)	142 (13.3)	231 (22.6)	
Lives with mother	2831 (96.0)	950 (97.0)	973 (94.3)	908 (96.7)	0.003
Lives with father	2686 (91.1)	903 (92.2)	923 (89.4)	860 (91.6)	0.070
Father occupation					
Farmer	2484 (84.2)	827 (84.5)	852 (82.6)	805 (85.7)	0.150
Livestock keeper	365 (12.4)	95 (9.7)	142 (13.8)	128 (13.6)	0.008
Merchant	222 (7.5)	88 (9.0)	59 (5.7)	75 (8.0)	0.017
Teacher	49 (1.7)	16 (1.6)	17 (1.7)	16 (1.7)	0.992
Government official	97 (3.3)	37 (3.8)	39 (3.8)	21 (2.2)	0.091
Unemployed	11 (0.4)	5 (0.5)	4 (0.4)	2 (0.2)	0.562
Mother occupation					
Farmer	1801 (61.1)	582 (59.5)	610 (59.1)	609 (64.9)	0.015
Livestock keeper	59 (2.0)	9 (0.9)	33 (3.2)	17 (1.8)	0.001
Merchant	297 (10.1)	100 (10.2)	88 (8.5)	109 (11.6)	0.075
Teacher	48 (1.6)	19 (1.9)	18 (1.7)	11 (1.2)	0.385
Government official	20 (0.7)	10 (1.0)	7 (0.7)	3 (0.3)	0.173
Homemaker	1767 (59.9)	640 (65.4)	611 (59.2)	516 (55.0)	<0.001
Unemployed	4 (0.1)	2 (0.2)	1 (0.1)	1 (0.1)	0.773
Father has some education	458 (18.6)	152 (19.1)	152 (17.8)	154 (18.9)	0.779
Mother has some education	303 (11.9)	110 (13.5)	96 (10.8)	97 (11.7)	0.214
Wealth quintile					<0.001
1	678 (23.0)	217 (22.2)	200 (19.4)	261 (27.8)	
2	621 (21.1)	165 (16.9)	219 (21.2)	237 (25.2)	
3	599 (20.3)	194 (19.8)	210 (20.4)	195 (20.8)	
4	506 (17.2)	193 (19.7)	199 (19.3)	114 (12.1)	
5	546 (18.5)	210 (21.5)	204 (19.8)	132 (14.1)	
Experienced menarche	1080 (67.9)	389 (68.9)	372 (70.2)	319 (64.4)	0.121
Home garden available	124 (4.2)	29 (3.0)	47 (4.6)	48 (5.2)	0.046
Cough in past month	630 (21.4)	196 (20.0)	274 (26.6)	160 (17.0)	<0.001
Malaria diagnosis in past month	187 (6.3)	63 (6.4)	69 (6.7)	55 (5.9)	0.744
BMI-for-age z-score category					0.537
Normal	2508 (85.4)	840 (86.1)	884 (86.0)	784 (83.9)	
Thin	301 (10.3)	96 (9.8)	104 (10.1)	101 (10.8)	
Overweight/obese	129 (4.4)	40 (4.1)	40 (3.9)	49 (5.3)	
Stunted	514 (17.4)	165 (16.9)	193 (18.7)	156 (16.6)	0.403
Dietary diversity					<0.001
0–3 food groups consumed	1184 (37.9)	415 (40.1)	346 (32.5)	423 (41.4)	
4–5 food groups consumed	896 (28.7)	297 (28.7)	299 (28.1)	300 (29.4)	
>5 food groups consumed	1043 (33.4)	324 (31.3)	421 (39.5)	298 (29.2)	
Food security (no hunger)	2343 (79.6)	754 (77.1)	805 (78.4)	784 (83.7)	0.001
Household water source					<0.001
Piped into house or bottled	304 (10.3)	107 (10.9)	90 (8.7)	107 (11.4)	
Piped into neighborhood	1762 (59.7)	535 (54.7)	608 (58.9)	619 (65.9)	
Well or surface water	884 (30.0)	337 (34.4)	334 (32.4)	213 (22.7)	

All data are shown as n (%). P values derived from chi-square tests. BMI, body mass index; IFA, iron + folic acid; MMS, multiple micronutrient supplements. Thin, sex-specific BMI-for-age z-score <-2 standard deviations (SD); normal weight, z-scores -2 SD to < 1 SD; overweight, z-scores 1 to < 2 SD; obese, z-scores ≥ 2 SD. Stunted defined as height-for-age z-score < -2. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

hemoglobin by 0.17 g/dL among those who consumed 27 to 33 tablets (higher compliance) but did not increase hemoglobin among those who consumed 0 to 20 tablets [14].

Although IFA improved continuous hemoglobin, we did not find differences in anemia status with either IFA or MMS supplementation. This is a divergence from previous studies that have found more definitive effects of IFA on anemia. A review conducted in 2017 found that weekly IFA supplementation among adolescent girls reduced anemia by 27% [35], and in a separate review conducted in 2016, school-based delivery of IFA or IFA in combination with other micronutrient supplements significantly reduced anemia by 33% among adolescents (mostly girls, though some studies included boys as well) [36]. However, another supplementation study conducted in a similar setting in Burkina Faso testing the effects of IFA compared with folic acid alone found that the supplements did not improve iron status or reduce anemia among adolescent girls [37].

TABLE 3
Anemia status of adolescents participating in school-based micronutrient supplementation program, Burkina Faso, 2021–2022

	Overall ($N = 3123$)	Intervention		
		IFA ($n = 1036$)	MMS ($n = 1066$)	Control ($n = 1021$)
Compliance				
Expected number of doses	NA	24	120	0
Average number of doses	NA	11.4 ± 3.7	52.7 ± 18.9	NA
% compliance when present	NA	96.7 ± 12.8	94.7 ± 17.8	NA
% compliance overall	NA	47.7 ± 15.4	43.9 ± 15.8	NA
Hemoglobin level at baseline (g/dL), males	12.7 ± 1.5	12.7 ± 1.5	12.8 ± 1.5	12.6 ± 1.4
Hemoglobin level at baseline (g/dL), females	12.4 ± 1.4	12.3 ± 1.4	12.4 ± 1.4	12.5 ± 1.4
Anemia at initial baseline (January–March 2021)				
None, all students	2150 (68.8)	697 (67.3)	733 (68.8)	720 (70.5)
Mild, all students	618 (19.8)	209 (20.2)	213 (20.0)	196 (19.2)
Moderate/severe, all students	355 (11.4)	130 (12.6)	120 (11.3)	105 (10.3)
None, males	951 (68.3)	295 (68.5)	350 (68.1)	306 (68.5)
Mild, males	312 (22.4)	92 (21.4)	118 (23.0)	102 (22.8)
Moderate/severe, males	129 (9.3)	44 (10.2)	46 (9.0)	39 (8.7)
None, females	1199 (69.3)	402 (66.5)	383 (69.4)	414 (72.1)
Mild, females	306 (17.7)	117 (19.3)	95 (17.2)	94 (16.4)
Moderate/Severe, females	226 (13.1)	86 (14.2)	74 (13.4)	66 (11.5)
Anemia at last endline (March–April 2022)				
None, all students	1322 (64.3)	440 (65.3)	440 (62.8)	442 (65.0)
Mild, all students	521 (25.4)	161 (23.9)	196 (28.0)	164 (24.1)
Moderate/severe, all students	212 (10.3)	73 (10.8)	65 (9.3)	74 (10.9)
None, males	550 (61.5)	178 (63.8)	194 (58.6)	178 (62.7)
Mild, males	269 (30.1)	72 (25.8)	116 (35.1)	81 (28.5)
Moderate/severe, males	75 (8.4)	29 (10.4)	21 (6.3)	25 (8.8)
None, females	772 (66.5)	262 (66.3)	246 (66.5)	264 (66.7)
Mild, females	252 (21.7)	89 (22.5)	80 (21.6)	83 (21.0)
Moderate/severe, females	137 (11.8)	44 (11.1)	44 (11.9)	49 (12.4)
Difference in anemia prevalence from baseline to endline (%)				
Mild	5.6	3.7	8	4.9
Moderate/severe	-1.1	-1.8	-2	0.6

IFA, iron + folic acid; MMS, multiple micronutrient supplements; NA, not applicable.

The idea of using MMSs to address anemia instead of solely IFA is supported by research that has found that the coexistence of multiple micronutrient deficiencies in the same person may limit the effectiveness of IFA supplementation in increasing hemoglobin on its own [18]. Such coexistence of multiple deficiencies is common in LMICs, including among adolescents [38,39]. However, despite promising findings that MMSs are more effective than IFA at preventing adverse birth outcomes among pregnant women [20] and pregnant adolescents [39], we observed no differences in the prevalence of anemia among adolescents randomized to receive MMSs versus IFA. Even with a loading dose of IFA for the first 4 wk, we find that while MMSs improve hemoglobin levels among males, there was no effect on

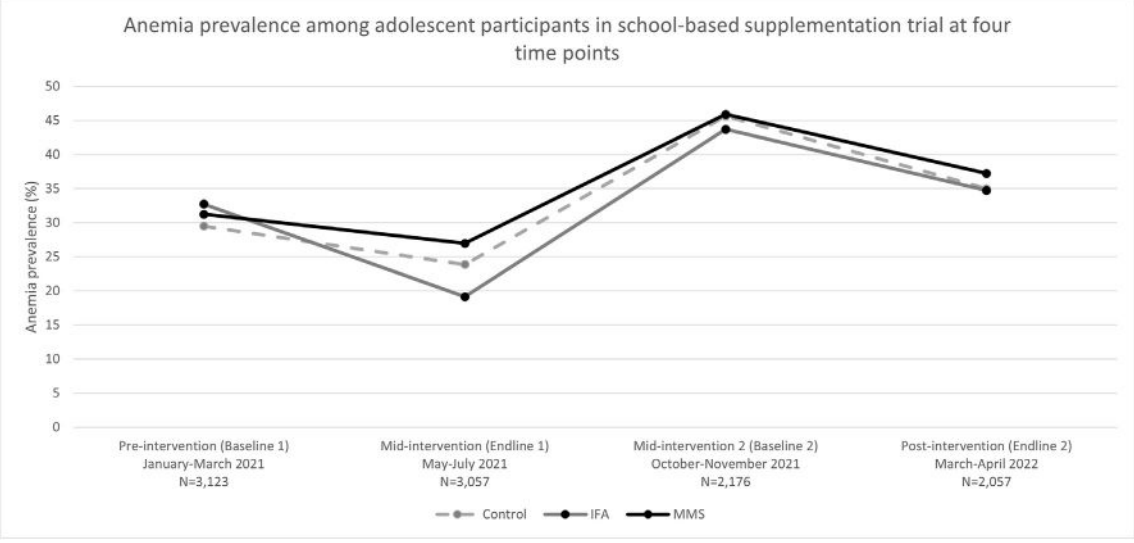

FIGURE 2. Anemia prevalence among adolescent males and females ages 10–18 y participating in the "School-based assessment of micronutrient interventions in adolescents" (SAMIA) trial, Burkina Faso, 2021–2022. IFA, iron + folic acid; MMS, multiple micronutrient supplement.

TABLE 4
Associations between treatment group and anemia or hemoglobin. Results from generalized linear mixed effects models with school (cluster) as random intercept

Full study period	Anemia yes/no		No anemia vs. moderate/severe anemia		Hemoglobin (g/dL)	
	Crude RR (95% CI)	Adjusted RR (95% CI)	Crude RR (95% CI)	Adjusted RR (95% CI)	Crude β (95% CI)	Adjusted β (95% CI)
	$N = 1962$	$N = 1540$	$N = 1177$	$N = 919$	$N = 1963$	$N = 1541$
Treatment (Ref=control)						
IFA	0.98 (0.78, 1.24)	0.83 (0.62, 1.11)	0.99 (0.55, 1.78)	0.78 (0.34, 1.80)	0.13 (-0.19, 0.45)	0.32* (0.02, 0.62)
MMS	1.08 (0.86, 1.34)	0.95 (0.72, 1.24)	0.84 (0.40, 1.78)	0.35 (0.11, 1.06)	0.09 (-0.23, 0.41)	0.17 (-0.14, 0.48)
Baseline anemia status[1] (Ref=no anemia)	1.62*** (1.34, 1.96)	1.60*** (1.31, 1.97)	5.80*** (3.33, 10.10)	6.18*** (2.29, 16.68)	NA	NA
Baseline hemoglobin	NA	NA	NA	NA	0.37*** (0.37, 0.38)	0.37*** (0.30, 0.44)
Baseline 1 to endline 1	$N = 2894$	$N = 1499$	$N = 1953$	$N = 1264$	$N = 2084$	$N = 1542$
Treatment (Ref=control)						
IFA	0.80 (0.55, 1.15)	0.74 (0.54, 1.01)	0.84 (0.44, 1.61)	0.86 (0.42, 1.77)	0.24 (-0.11, 0.59)	0.24 (-0.09, 0.57)
MMS	1.16 (0.83, 1.62)	0.91 (0.69, 1.21)	0.95 (0.47, 1.93)	0.78 (0.37, 1.65)	0.14 (-0.20, 0.49)	0.21 (-0.12, 0.54)
Baseline anemia status[1] (Ref=no anemia)	1.86*** (1.39, 2.49)	2.07*** (1.59, 2.69)	6.26*** (3.36, 11.67)	6.38*** (3.67, 11.10)	NA	NA
Baseline hemoglobin	NA	NA	NA	NA	0.41*** (0.41, 0.42)	0.41*** (0.40, 0.42)
Baseline 2 to endline 2	$N = 1903$	$N = 1502$	$N = 1041$	$N = 1036$	$N = 1924$	$N = 1912$
Treatment (Ref=control)						
IFA	1.01 (0.82, 1.25)	0.87 (0.65, 1.15)	0.94 (0.40, 2.20)	0.75 (0.29, 1.91)	0.06 (-0.21, 0.33)	0.11 (-0.14, 0.36)
MMS	1.07 (0.88, 1.30)	0.96 (0.74, 1.24)	0.51 (0.15, 1.69)	0.39 (0.11, 1.40)	0.09 (-0.18, 0.35)	0.11 (-0.13, 0.36)
Baseline anemia status[1] (Ref=no anemia)	1.96*** (1.68, 2.28)	1.86*** (1.59, 2.17)	5.49*** (3.10, 9.72)	5.84*** (3.17, 10.76)	NA	NA
Baseline hemoglobin	NA	NA	NA	NA	0.45*** (0.44, 0.46)	0.43*** (0.42, 0.44)

Estimates are risk ratios (RRs) and 95% confidence intervals (CIs) or β coefficients derived from modified mixed effects Poisson regression models for binary outcomes and linear regressions for continuous hemoglobin. IFA, iron + folic acid; MMS, multiple micronutrient supplements; NA, not applicable; Ref, reference.

[1] Baseline anemia status was a binary variable for anemia or no anemia. Adjusted models control for: compliance, month (only controlled for in full study period models), and endline sex, malaria (yes/no), number of siblings (continuous), lives with mother (yes/no), father is a livestock owner (yes/no), mother is a farmer (yes/no), mother is a livestock owner (yes/no), mother is a homemaker (yes/no), wealth quintile, cough (yes/no), diet diversity (0–12), food security (yes/no), and household water source (piped into house/bottled, piped into neighborhood, well, or surface). Compliers for the entire study period are those that consumed at least 50% of expected doses, and compliers for each subperiod are those that consumed at least 80% of expected doses throughout the subperiod. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$. Intraclass correlation coefficients: anemia yes/no = 0.07; anemia moderate/severe = 0.30; hemoglobin = 0.10.

hemoglobin in females. Similarly, a study that compared a 12-wk period of twice weekly supplementation with MMSs or IFA among adolescent girls in Bangladesh observed no differences in mean hemoglobin or serum ferritin concentrations between the 2 groups. However, in that study, both IFA and multiple micronutrient supplementation groups had significantly lower prevalence of anemia after the intervention [40]. Subsequent follow-up on the same population with longer supplementation periods showed similar results, with no significant increases in hemoglobin concentration among the MMS group compared with IFA supplements but significant reductions in anemia in both study arms [41].

A possible explanation for the overall lack of definitive effects of supplementation on anemia status among our overall sample is that the cause of anemia among adolescents in this setting may not be primarily iron deficiency but rather factors related to inflammation, infection, or iron losses that would not be remedied solely by supplementation with iron or other micronutrients [42]. Our findings on effect modification by sex, which showed that the supplements have larger effects on adolescent males than females, offer insight. It is possible that the supplement is sufficient to raise hemoglobin levels among males, but not among females who experience menstrual losses in addition to the dietary and inflammatory causes of low hemoglobin [36]. This also helps explain why we see effects only on continuous hemoglobin but not on risk of anemia in our sample. Since females have lower overall hemoglobin than males and had higher levels of moderate or severe anemia than males in our sample, the supplements likely are not enough to put our population of adolescents over the threshold from anemia to no anemia but rather just to increase hemoglobin among males who do not experience iron losses.

In terms of other causes of low hemoglobin besides the dietary factors that would be remedied by supplementation, Burkina Faso is considered a hyperendemic zone for malaria [43] and has high levels of other parasitic infections and inflammation [44]. According to evidence from the Biomarkers Reflecting Inflammation and Nutritional Determinants of Anemia project, the proportion of anemia attributable to iron deficiency is lower (~35%) in countries with a high infection burden compared with those with a lower infection burden (65%–71%) [45]. Additional evidence has shown that in malaria hyperendemic regions such as Burkina Faso, anemia is less responsive to intervention with iron supplementation. Although iron supplementation did not increase risk of malaria in our study, or in the aforementioned Gies et al. [37] study conducted in Burkina Faso, in children under 6 y of age, it was estimated that 40% to 60% of baseline anemia was responsive to intervention with iron supplementation, compared with a

TABLE 5
Anemia prevalence and mean hemoglobin associated with treatment group, considering compliance. Results from generalized linear mixed effects models with school (cluster) as random intercept

Full study period	Anemia yes/no	Anemia none vs. moderate/severe	Hemoglobin (g/dL)
	$N = 1\,540$	$N = 919$	$N = 1951$
P value for treatment–compliance interaction	$P = 0.49$	$P = 0.06$	$P = 0.05$
	Adjusted RR (95% CI)	Adjusted RR (95% CI)	Adjusted β (95% CI)
Treatment (Ref=control)			
IFA compliers	0.85 (0.63, 1.16)	0.89 (0.38, 2.09)	0.14 (-0.15, 0.44)
IFA noncompliers	0.70 (0.44, 1.11)	0.96 (0.36, 2.56)	0.35* (0.05, 0.65)
MMS compliers	0.94 (0.72, 1.23)	0.32 (0.10, 1.00)	0.13 (-0.16, 0.42)
MMS noncompliers	0.95 (0.68, 1.31)	0.91 (0.26, 3.20)	0.07 (-0.23, 0.36)
Baseline anemia status[1] (Ref=no anemia)	1.60*** (1.31, 1.96)	6.18*** (2.29, 16.68)	NA
Baseline hemoglobin	NA	NA	0.37*** (0.36, 0.37)
Baseline 1 to endline 1	$N = 1499$	$N = 932$	$N = 1542$
P value for treatment–compliance interaction	$P = 0.28$	$P = 0.03$	$P < 0.001$
	Adjusted RR (95% CI)	Adjusted RR (95% CI)	Adjusted β (95% CI)
Treatment (Ref=control)			
IFA compliers	0.73 (0.52, 1.03)	0.85 (0.33, 2.15)	0.26 (-0.08, 0.59)
IFA noncompliers	0.78 (0.53, 1.14)	2.33 (0.47, 11.69)	0.16 (-0.20, 0.51)
MMS compliers	0.97 (0.74, 1.29)	0.72 (0.33, 1.58)	0.19 (-0.14, 0.53)
MMS noncompliers	0.79 (0.49, 1.26)	1.05 (0.44, 2.46)	0.25 (-0.09, 0.59)
Baseline anemia status[1] (Ref=no anemia)	2.07*** (1.59, 2.69)	7.94*** (4.36, 14.5)	NA
Baseline hemoglobin	NA	NA	0.41*** (0.40, 0.42)
Baseline 2 to endline 2	$N = 1502$	$N = 823$	$N = 1912$
P value for treatment–compliance interaction	$P = 0.83$	$P = 0.55$	$P = 0.02$
	Adjusted RR (95% CI)	Adjusted RR (95% CI)	Adjusted β (95% CI)
Treatment (Ref=control)			
IFA compliers	0.89 (0.67, 1.18)	0.99 (0.38, 2.55)	0.10 (-0.15, 0.35)
IFA noncompliers	0.78 (0.50, 1.21)	1.13 (0.34, 3.76)	0.10 (-0.16, 0.37)
MMS compliers	0.95 (0.74, 1.22)	0.37 (0.09, 1.49)	0.13 (-0.12, 0.38)
MMS noncompliers	1.02 (0.73, 1.42)	1.21 (0.28, 5.26)	0.04 (-0.21, 0.28)
Baseline anemia status[1] (Ref=no anemia)	1.86*** (1.60, 2.18)	5.75*** (2.66, 12.44)	NA
Baseline hemoglobin	NA	NA	0.43*** (0.42, 0.44)

Estimates are risk ratios (RRs) and 95% confidence intervals (CIs) or β coefficients derived from modified mixed effects Poisson regression models for binary outcomes and linear regressions for continuous hemoglobin. IFA, iron + folic acid; MMS, multiple micronutrient supplements; NA, not applicable; Ref, reference.

[1] Baseline anemia status was a binary variable for anemia or no anemia. Adjusted models control for: compliance, month (only controlled for in full study period models), and endline sex, malaria (yes/no), number of siblings (continuous), lives with mother (yes/no), father is a livestock owner (yes/no), mother is a farmer (yes/no), mother is a livestock owner (yes/no), mother is a homemaker (yes/no), wealth quintile, cough (yes/no), diet diversity (0–12), food security (yes/no), and household water source (piped into house/bottled, piped into neighborhood, well, or surface). P values displayed are from Wald Tests for interaction of treatment arm with compliance level, where compliers for the entire study period are those that consumed at least 50% of expected doses, and compliers for each subperiod are those that consumed at least 80% of expected doses throughout the subperiod. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

range of 6% to 30% responsiveness in malaria hyperendemic regions [46]. In our own baseline analyses from the present study, presented in detail elsewhere [47], we found that the factors associated with anemia in our sample of adolescent boys and girls were mainly hygienic factors, which we hypothesize to be related to inflammatory responses. This supports the idea that in order to properly address anemia in this (and similar) populations, infection and inflammation and their associated factors must also be addressed.

Lastly, our study contributes to understanding the utility of schools as a platform for supplement or other intervention delivery. Our results support the potential effectiveness of school-based supplementation, though more definitive evidence is needed. Schools have the advantage of being a place where adolescents are comfortable receiving care, as demonstrated by the relatively high levels of participation in our program, as opposed to healthcare facilities, which may not have adequate or dedicated services for adolescents [13]. Education programs are also implemented by default in schools and could easily be added to supplementation interventions. However, the school schedule does not allow for continuous supplementation, which may also have impacted the effectiveness of IFA and MMSs in addressing anemia. We observe, for example, that hemoglobin levels increase after each supplementation period but decrease again after a break from supplementation. This indicates that the effects of the supplements may be short-lived, and for more sustainable effects, supplementation programs may need platforms that provide the opportunity for longer or more consistent periods of supplementation. In addition, using schools as the platform for distribution may have contributed to the nondetection of significant differences in anemia status in the supplementation groups. Given the relatively low school enrollment rates in Burkina Faso, it is likely that those able to attend school are economically advantaged and may have fewer risk factors for anemia overall.

TABLE 6
Anemia prevalence and mean hemoglobin associated with treatment group, considering sex. Results from generalized linear mixed effects models with school (cluster) as random intercept

Full study period	Anemia yes/no	Anemia none vs. moderate/severe	Hemoglobin (g/dL)
	$N = 1540$	$N = 919$	$N = 1951$
P value for treatment–sex interaction	$P = 0.01$	$P = 0.54$	$P < 0.001$
	Adjusted RR (95% CI)	Adjusted RR (95% CI)	Adjusted β (95% CI)
Treatment (Ref=control)			
IFA females	0.81 (0.61, 1.07)	0.76 (0.30, 1.89)	0.01 (-0.29, 0.30)
IFA males	0.87 (0.61, 1.23)	0.82 (0.35, 1.94)	0.43** (0.14, 0.73)
MMS females	0.83 (0.62, 1.11)	0.36 (0.11, 1.16)	-0.05 (-0.35, 0.24)
MMS males	1.11 (0.84, 1.47)	0.32* (0.11, 0.98)	0.36* (0.07, 0.66)
Baseline anemia status[1] (Ref=no anemia)	1.60*** (1.30, 1.97)	6.18*** (2.26, 16.9)	NA
Baseline hemoglobin	NA	NA	0.36*** (0.36, 0.37)
Baseline 1 to endline 1	$N = 1499$	$N = 932$	$N = 1542$
P value for treatment–sex interaction	$P = 0.02$	$P = 0.99$	$P < 0.001$
	Adjusted RR (95% CI)	Adjusted RR (95% CI)	Adjusted β (95% CI)
Treatment (Ref=control)			
IFA females	0.67* (0.47, 0.95)	Model did not converge	0.15 (-0.18, 0.48)
IFA males	0.84 (0.57, 1.24)		0.38* (0.05, 0.72)
MMS females	0.82 (0.61, 1.10)		0.11 (-0.22, 0.44)
MMS males	1.04 (0.77, 1.42)		0.36* (0.03, 0.69)
Baseline anemia status[1] (Ref=no anemia)	2.07*** (1.59, 2.69)		NA
Baseline hemoglobin	NA	NA	0.41*** (0.40, 0.42)
Baseline 2 to endline 2	$N = 1502$	$N = 823$	$N = 1912$
P value for treatment–sex interaction	$P = 0.01$	$P = 0.77$	$P < 0.001$
	Adjusted RR (95% CI)	Adjusted RR (95% CI)	Adjusted β (95% CI)
Treatment (Ref=control)			
IFA females	0.84 (0.63, 1.12)	0.79 (0.28, 2.21)	-0.04 (-0.29, 0.22)
IFA males	0.90 (0.64, 1.25)	1.08 (0.41, 2.85)	0.31* (0.05, 0.56)
MMS females	0.84 (0.64, 1.10)	0.38 (0.10, 1.40)	-0.02 (-0.28, 0.23)
MMS males	1.11 (0.85, 1.44)	0.51 (0.11, 2.39)	0.31* (0.05, 0.56)
Baseline anemia status[1] (Ref=no anemia)	1.86*** (1.59, 2.17)	5.59*** (2.52, 12.37)	NA
Baseline hemoglobin	NA	NA	0.43*** (0.42, 0.44)

Estimates are risk ratios (RRs) and 95% confidence intervals (CIs) or β coefficients derived from modified mixed effects Poisson regression models for binary outcomes and linear regressions for continuous hemoglobin. IFA, iron + folic acid; MMS, multiple micronutrient supplements; NA, not applicable; Ref, reference.

[1] Baseline anemia status was a binary variable for anemia or no anemia. Adjusted models control for: compliance, month (only controlled for in full study period models), and endline sex, malaria (yes/no), number of siblings (continuous), lives with mother (yes/no), father is a livestock owner (yes/no), mother is a farmer (yes/no), mother is a livestock owner (yes/no), mother is a homemaker (yes/no), wealth quintile, cough (yes/no), diet diversity (0–12), food security (yes/no), and household water source (piped into house/bottled, piped into neighborhood, well, or surface). P values displayed are from Wald Tests for interaction of treatment arm with sex. *$P < 0.05$; **$P < 0.01$; ***$P < 0.001$.

Limitations of our study design include the inability to randomize at the individual level and that we were unable to blind the participants and researchers to the intervention. However, we account for cluster randomization in analyses, and we do not believe that information bias was introduced through lack of blinding, as all statistical analyses were done with neutrality and will be made available upon request, for transparency. In addition, due to the school calendar, supplementation was not consistent, and interruptions may have attenuated potential effects of the supplements on anemia status. Loss to follow-up was also quite high (~35%) due to students abandoning school or being excluded from school for not passing exams. This may also have reduced the power to detect any effect.

However, as one of the only studies to investigate and compare IFA and MMSs in a population of both male and female adolescents using a school-based setting, our results add critical evidence to the literature to support decision making about nutrition interventions targeted to the often-neglected population of adolescents.

In conclusion, given that we find minimal effects of both weekly IFA and daily MMSs on our population of adolescent males and females and no material differences between the IFA and MMS interventions in addressing anemia, our recommendation based on these results alone are that any school-based supplementation program aimed at addressing anemia among adolescents be accompanied by a larger intervention strategy that includes deworming, malaria prophylaxis, and reinforcement of positive hygiene practices. Before either IFA or MMS supplementation is to be scaled up, more evidence is needed on effects when administered as part of a more comprehensive intervention strategy. In addition, future studies could investigate whether

extending the intervention period using supplements may be more effective than using the relatively short supplementation periods we were able to implement in our study.

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Author contributions

The authors' responsibilities were as follows—IRC: conducted the analyses and drafted the manuscript; OM, YB, GC, IK: supervised field data collection; IK: managed the database; WF: designed the study, obtained funding, and provided regular monitoring; OM, YB, IK, GC, DW, AS, DW, WF: critically reviewed the manuscript; IRC, OM, IK: directly accessed and verified the underlying data reported in the manuscript; IRC, OM, WF: are responsible for the final content; and all authors: read and approved the final manuscript.

Conflict of interest

The authors report no conflicts of interest.

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Data availability

All deidentified participant data and statistical code will be made available upon request with publication. The full study protocol will also be made available upon request. A version of the protocol is also published as a manuscript [48].

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ajcnut.2023.09.004.

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