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Multiple Micronutrient Supplementation Reduces Anemia and Anxiety in Rural China's Elementary School Children[1–4]

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Abstract

Despite growing wealth and a strengthening government commitment to improve livelihoods and welfare, many students across rural China have inadequate access to micronutrient-rich diets. Poor diets can lead to nutritional problems, such as iron-deficiency anemia, that can adversely affect health, attention, learning, and mental health. The overall goal of this paper is to assess the impact of multiple micronutrient supplementation (MMS) on anemia and anxiety among students in poor areas of rural China. To achieve this goal, we conducted a randomized controlled trial in 54 randomly chosen elementary schools in 8 of the poorest counties in Shaanxi Province in Northwest China. Study participants were 2730 fourth-grade students, mostly aged 10–12 y. Schools were randomly assigned to 1 of 2 groups: a control group that received no intervention and an intervention group that received a daily MMS with 5 mg of iron (ferrous sulfate) for 5 mo. Our primary outcome measures were hemoglobin (Hb) concentrations (assessed by HemoCue 201+ technology), anemia prevalence (defined as Hb) concentrations ≤120 g/L), and anxiety (using a written mental health test). The results showed that 42.4% of students were anemic at baseline. The Hb concentration was 121.7 ± 10.7 g/L in the treatment group and 123.4 ± 11.4 g/L in the control group. MMS increased Hb concentrations by 1.7 g/L ± 0.15 and reduced anemia rates by 7.0 percentage points ($P < 0.05$). Anxiety was reduced by 0.30 SDs ($P < 0.01$). MMS reduced both anemia and anxiety. Our results should encourage further research on the linkages between nutrition and mental health in a development context. J. Nutr. 143: 640–647, 2013.

Introduction

An emerging international literature suggests that investment into the overall well-being of students in developing countries plays an important role in raising their educational performance (1,2). This focus on health has been previously limited to physical health (3), but there is evidence that psychological health can be just as important (4). Indeed, in a meta-analysis encompassing more than 150 studies, anxiety was shown to be negatively correlated with academic performance (5,6).

In many developing countries with competitive education systems and limited resources, including China, these psychological stressors are particularly intense and can affect students from a young age (7–13). In China a nationwide school consolidation policy has forced many children, often at young ages, to live far from home in poor-quality boarding facilities with little supervision and inadequate meals (10,14). These stressors have all been correlated with poor academic achievement in our sample population and in others (5,14).

There are more signs, also in China, that rural students are at high risk of poor mental health (15,16). Rural students have worse mental health than their urban peers, as well as lower educational performance and attainment (17). In addition to these documented pressures and the resulting psychological problems, there may be other causes of anxiety that have received less attention yet which may ultimately be easier to address. In rural China, a large proportion of students eat some

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[3] The trial was registered with the International Standard Randomized Controlled Trial Number database as ISRCTN42055081.
[4] A copy of the Mental Health Test used to collect mental health data from study participants, Supplemental Figure 1, and Supplemental Tables 1 and 2 are available from the ''Online Supporting Material'' link in the online posting of the article and from the same link in the online table of contents at http://jn.nutrition.org.
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or all of their meals at school; school-provided meals consist almost entirely of inexpensive starches (14). Consequently, micronutrient deficiencies, including iron deficiency, are prevalent (18–20). Moreover, a large body of research links anemia and iron deficiency with cognitive impairment and altered brain function (20–23). Other researchers have found a significant correlation between zinc concentrations and mental health outcomes in children, including anxiety and depression (24).

Childhood anemia is also negatively correlated with educational outcomes such as grades, attendance, and test scores (3,25–31). In a competitive school system such as China's, this lack of ability to perform may itself be a source of anxiety, creating a cycle of poor achievement and worsening mental health. Indeed, Chinese policymakers recognize this problem and are focused on reducing anxiety at all levels of schooling (16).

The overall goal of this paper is to test whether multiple micronutrient supplementation (MMS)[10] can improve students' mental health. First, we seek to document the pervasiveness of undernutrition as well as measure mental health levels (especially anxiety) among school children in poor areas of China. Second, we seek to investigate the relationship between MMS and anxiety. Finally, we will test the effect of MMS on subscales of the anxiety scale to assess what aspect of anxiety is most affected by the MMS intervention.

To reach these objectives, we report on the results of an intervention administered as part of a cluster, randomized, controlled trial in which we provided MMS to elementary school students in 54 schools in China's poor northwest region. To our knowledge, this is one of the first appropriately powered, randomized, controlled trials investigating the link between MMS and anxiety in school-aged children.

Methods

Setting and participants

In total, 2730 fourth-grade students in 54 sample schools participated in the study. Sample schools were randomly chosen from a larger sampling frame of elementary schools from 8 of the poorest counties in Shaanxi Province in China's poor northwest region.

In choosing our sample, we first obtained a list of all counties in the province. Each of the counties on the list was then given a poverty ranking based on a poverty map of Shaanxi (32). The village-specific poverty indicators from the poverty map were aggregated to produce county-level indicators of poverty. Once each county was assigned a poverty indicator, the research team chose the 8 poorest counties in Shaanxi. Based on estimates from pilot studies, we used Optimal Design software (33) to calculate that we required 50 individuals/school and 24 schools/experimental group to detect a standardized effect size for the outcome variables of 0.2 SDs with 80% power at a 5% significance level (2-tail test). We assumed an intra-cluster correlation of 0.15, a pre- and postintervention correlation of 0.6, and a 10% loss to follow-up. The assumptions for the power calculations were based on the published international and Chinese literature on nutritional interventions (13,29,31,34,35) as well as on independent consultations with a regional psychologist and nutritionist.

The next step was to choose the sample elementary schools. To do so, the research team conducted a canvass survey by visiting each county's bureau of education. In each bureau, we obtained a list of all elementary schools that had at least 200 students. We also required that at least 50 students lived in the school dormitory and ate most of their meals (5 d of 7) at school. These criteria were used because China's government is currently consolidating existing rural schools into new ones with these characteristics (36). A total of 116 schools fit these criteria. From this list, the research team randomly chose 54 schools (the number needed to achieve the 80% statistical power target). The sample is representative of students in larger elementary schools with boarding facilities in Shaanxi Province's poorest counties, an area that contains about 10 million people. These areas, however, are not too different from the rest of China's poor areas. Luo et al. (18) reported the list of sample counties and number of schools and students per county.

Differences between treatment and control groups at baseline were insignificant on several key observable characteristics as well as on the primary outcome variables: hemoglobin (Hb) concentrations, anemia rates, and Mental Health Test (MHT) scores (**Table 1**). At the time of the baseline survey, neither study participants nor enumerators knew whether their school would ultimately be assigned to the treatment or control arm of the study.

Of the 3203 students enrolled in the study at baseline, we were able to obtain endline data for 2730 (85%). Attrition was almost entirely due to students not being present at the time of the endline survey; the refusal rate was <1%. Attrition did not differ between the control and treatment arms (results not shown).

The study received ethical approval from the Stanford University Institutional Review Board (IRB). All necessary permissions were obtained from the Chinese government as well. Oral assent was obtained from all participating children and oral consent was obtained from the school principals, who serve as the children's legal guardians while they are in school. Principals in control schools were told only that their students were invited to participate in a study of child nutrition and that the research team would be administering a written test and a test of nutritional status. Principals in intervention schools were additionally told that their students would receive a daily multivitamin. All study participants were cognizant of the minimal risks involved and understood that their participation was purely voluntary. The final IRB approval did not allow the research team to give placebos to students in the control schools.

Study outcomes and data collection

Primary outcomes. The study included 3 primary outcomes. The first was change in altitude-adjusted Hb concentration measured in g/L. Our second primary outcome was anemia status after the intervention. We used anemia as a hallmark indicator of micronutrient deficiencies in general. The WHO recommends an anemia cutoff of 115 g/L for children aged 5–11 y and 120 g/L for those aged 12–14 y (37). Given that a large proportion of our sample falls in the 12–14 y age range and that Hb concentrations borderline for anemia have also been shown to affect cognitive functioning, we used the 120-g/L cutoff for our analysis of anemia (25). Iron deficiency and other nutrient indicators were not assessed, because this would have required venous blood and necessitated significantly increased costs.

Our third primary outcome was anxiety, as measured by a psychological test of well-being, the MHT. The MHT was developed by Professor Zhou Bucheng of East China Normal University, who adapted it from the General Anxiety Test developed by Kiyoshi Suzuki in Japan (38). These tests are variations of the Children's Manifest Anxiety Scale, which is an internationally standardized test for anxiety in children that has been widely used in the United States and other developed countries (39). The MHT contains 100 yes/no questions, has a reliability of 0.84–0.88, and a retest reliability of 0.78–0.86. This high retest reliability shows that the MHT measures an aspect of mental health that is stable over time.

The test is scored out of 90 points, where a lower score corresponds to lower anxiety. The test results can be broken down into 8 subcategories, each of which represents a specific aspect of anxiety: school performance, social relationships, loneliness, self-punishment, sensitivity, physical symptoms, fear, and impulsiveness. A score of >8 on any subpart is considered clinically high and indicates a need for treatment. The test has been extensively used by researchers across China to measure the mental health of grade school children (17,31). The MHT was administered and proctored by our survey team in the classroom. Students had 10 min to complete the test. Of the 100 test questions, 10 are used

[10] Abbreviations used: Hb, hemoglobin; IRB, Institutional Review Board; MHT, Mental Health Test; MMS, multiple micronutrient supplementation.

TABLE 1 Participant characteristics of control and MMS schools at baseline[1]

	Total sample	Control	MMS treatment	Difference between control and MMS treatment[2]
Characteristic				
Female, *n (%)*	1218 (44)	660 (46)	558 (43)	−3.1
Lives in boarding school, *n (%)*	1014 (37)	499 (35)	515 (39)	4.3
Both parents present at home, *n (%)*	1383 (51)	726 (51)	657 (50)	−0.7
Outcome variables				
Hb concentration, *g/L*	122.6 ± 11.1	123.4 ± 11.4	121.7 ± 10.7	−1.71
Anemia rate, *%*	42.4	39.8	45.2	5.4
MHT score, *points*	39.1 ± 12.5	38.8 ± 12.4	39.5 ± 12.8	0.81
Invalid MHT, *%*	4.7	5.3	4.5	0.8

[1] Values are frequency and percentages or means ± SDs. Hb, hemoglobin; MHT, Mental Health Test; MMS, multiple micronutrient supplementation.
[2] The difference between control and MMS treatment schools was calculated by subtracting the control schools' value from the MMS treatment schools' value. Differences for key characteristics are percentages. The key characteristics and outcome variables of control and MMS treatment schools did not differ at baseline.

to detect whether the student is lying in his or her responses. If the student answers yes to >7 of these, questions the test is considered invalid. Only students with valid tests for both the baseline and endline surveys were included. This exclusion criterion resulted in dropping 260 observations (<9% of the total sample (**Fig. 1**). Invalid test scores did not correlate with anemia and were nearly equally distributed between treatment and control groups (Table 1). The interested reader can view a copy of the MHT in the Supplemental Material in either Chinese or English.

Primary school surveys. Basic demographic data on the students (including student gender and boarding status, as well as parental migration status) and principal- and teacher-reported school data were collected by survey enumerators. Demographic information was provided by students' parents, each of whom filled out a survey form that was sent home by the teacher.

Hb concentrations and anxiety were measured once at baseline and again at the end of the study. Two trained nurses from Jiaotong University's School of Medicine in Xi'an assessed Hb concentrations onsite using the HemoCue Hb 201+ system. These portable instruments are known to provide rapid, in-the-field measurements of Hb concentrations with high degrees of accuracy.

Figure 1 depicts the flow of participants through each stage of the study as well as the project timeline.

Randomization and interventions

Following the baseline survey, our research team used Stata 10 to randomly assign schools to 1 of 2 experimental arms: 24 schools to an intervention group that received MMS and 30 schools to a control group that received neither treatment nor a placebo. The number of schools was unbalanced, because in the larger experiment (29) there also was a third set of schools in a second experimental arm (which gave nutritional information to parents to see if this had an effect on their levels of anemia). These schools are not included in this study, because we did not give those students MHT. Because we were interested in using a single control group in 2 separate experiments, statistical power considerations required that the number of schools in the control arm be larger than the number of schools in each of the 2 individual experimental arms.

The sampling was stratified at the school level; all schools that met the inclusion criteria were randomly sampled and all of the fourth-grade students within a selected school were included in the study. The randomization procedure was repeated until achieving balance in Hb concentration across the 2 arms (with 95% confidence). Neither study participants nor survey enumerators were informed of study arm allocation.

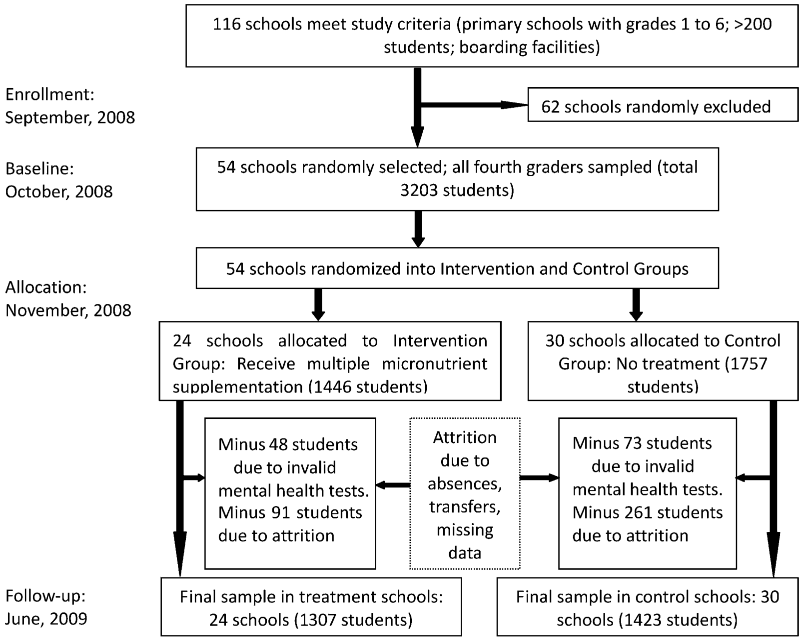

FIGURE 1 Flow of participants through each stage of the study and the project timeline.

Schools in the intervention group received shipments of MMS every 6 wk for 36 wk. The research team gave the MMS directly to the teacher responsible for the fourth-grade students in each school (the homeroom teacher). During the homeroom period (typically after lunch), homeroom teachers handed out the MMS. On Friday afternoons, students were given 2 MMSs to take home for the weekend. During winter break (a 3.5-wk period between January 23 and February 13), no MMS was dispensed. The homeroom teachers were paid 100 yuan/mo (equivalent to 2 days' pay) for their services during the project. Based on periodic unannounced visits by the research team, there was nearly 100% compliance to the study protocol.

The MMS included 5 mg of iron per tablet (ferrous sulfate) in addition to 20 other vitamins and mineral supplements (**Supplemental Table 1**). The MMS is available over the counter in most large cities in China but are not available in any of the study counties (most likely due to lack of demand).

To minimize Hawthorne Effects (40), during each visit to the MMS schools for MMS delivery, the research teams also visited the control schools, checking in on the principal and observing classroom activities. Principals, teachers, and students in control schools had no knowledge that other schools were receiving the MMS, so there was no unmet expectation in control schools. We were careful to prevent accidental transfer of this information across schools by including only 1 school/district. In treatment schools, neither educators nor students were told of any link between the supplements and anxiety or between nutrition and anxiety. Because the MMS is not widely available or even understood in these rural areas, there is little reason for children, parents, or educators to put much hope in them.

Statistical analysis

Our primary outcome variables were Hb concentrations, anemia rates, and MHT scores. We used an intent-to-treat analysis that controlled for county-specific effects. This type of analysis first takes the differences between the treatment and control students in each county, and then a weighted mean of the differences in each county is used to calculate the measure of the effect of the intervention.

In addition to the intent-to-treat analysis, we also used adjusted analyses to estimate how Hb concentrations and MHT scores changed in the MMS schools relative to control schools. The adjusted analysis examined the effect of the treatment on the outcome variables while controlling for a set of demographic factors. Our adjusted model controlled for student boarding status, student gender, and parental migration status as well as interaction terms for each. We used the adjusted analysis model to improve estimation efficiency and control for any observable differences that existed between the control and treatment schools at baseline. This approach allows for a more accurate estimate of the impact of our intervention even if the treatment and control schools were prebalanced at baseline (41). Such an approach is standard practice in the analysis of randomized controlled trials, including in the field of nutrition (42,43). We included these particular controls, because these subpopulations of students might be more susceptible to anxiety and by controlling for them in a regression, we are able to estimate the impact of the intervention as if these variables were constant, allowing for greater efficiency. Regressions 1–3 in Tables 3 and 4 control for increasing amounts of observable, preexisting differences in the 2 groups. Such control variables have been used by others in studies of health and nutrition in China (18,19,29). Standard errors are corrected for clustering at the school level throughout.

Results

Hb concentrations and anemia. At baseline, the mean Hb concentration was slightly higher in control schools than in treatment schools and the anemia rate was slightly lower (**Table 2**). Hb concentrations in both the treatment and control schools were normally distributed.

The mean change in the Hb concentrations between baseline and endline was higher for students in the treatment schools than for students in the control schools ($P < 0.01$).

Anemia rates fell more in treatment schools than in control schools during the study period ($P < 0.01$). Given baseline levels of anemia, the change in treatment schools represents a 15% decrease in anemia.

When we included county fixed effects, the results were unchanged: the change in Hb concentrations was still larger in the treatment schools ($P < 0.01$). This change corresponded to a decline in anemia of 5.5 percentage points ($P < 0.05$). This means that MMS reduced anemia by ~13% when controlling for county effects.

The adjusted analyses supported the above findings (**Table 3**). As described above, we conducted 3 versions of the adjusted analysis model: one that controlled for baseline Hb concentrations (column 1), one that added controls for student-specific control variables (column 2), and one that added family-specific control/interaction variables (column 3). Table 3 shows that the results were robust to model specification. The adjusted Hb concentration effects were only slightly smaller than the effects in the intent-to-treat analyses. The impacts on anemia using the adjusted models were similar to the impact in the intent-to-treat analysis (results not shown).

MHT scores. The mean MHT score of students in the treatment schools at baseline was slightly higher than the mean MHT score of

TABLE 2 Difference between baseline and endline, and intent-to-treat analysis of MMS treatment[1]

	Baseline survey (October 2008)	Endline survey (June 2009)	Difference between baseline and endline surveys[2]	Intent-to-treat analysis of MMS treatment[3]	*P* value of intent-to-treat analysis
Hb concentration, *g/L*					
MMS treatment	121.7 ± 10.7	125.0 ± 11.3	3.2	1.3	0.002
Control	123.4 ± 11.4	124.9 ± 11.0	1.5		
Anemia rate, *%*					
MMS treatment	45.2	32.9	−12.3	−5.5	0.01
Control	39.8	34.5	−5.3		
MHT score, *points*					
MMS treatment	39.5 ± 12.8	37.7 ± 14.2	−1.8	−2.4	0.04
Control	38.8 ± 12.4	38.6 ± 13.8	−0.2		

[1] Values are means ± SDs or percentages in the baseline and evaluation surveys. Hb, hemoglobin; MHT, Mental Health Test; MMS, multiple micronutrient supplementation.
[2] The difference between baseline and endline survey was calculated by subtracting the baseline survey value from endline survey value.
[3] Adjusted for county effects.

TABLE 3 Effect of the MMS treatment on the change of Hb concentrations between October 2008 and June 2009[1]

Independent variable	Dependent variable: the difference in Hb concentration before and after interventions,[2] g/L					
	1[3]		2		3	
	Coefficient	t[4]	Coefficient	t	Coefficient	t
MMS treatment[5]	1.29	2.28**	1.25	1.85*	1.18	1.75*
Boarding status[6]	−0.08	0.12	−0.07	0.10	−1.15	1.50
MMS treatment × boarding status[7]	0.13	0.15	0.12	0.14	0.16	0.17
Gender[8]			−0.31	0.53	−0.34	0.59
MMS treatment × gender[7]			0.08	0.10	0.19	0.22
Parent migration status[9]					−0.88	1.63
Parent migration status × boarding status[7]					2.1	2.37**
Adjusted for county effects	Yes		Yes		Yes	
Constant	3.22	4.24***	3.36	4.16***	3.82	4.59**
Observations	2730		2730		2730	
R^2	0.17		0.17		0.17	

[1] Hb, hemoglobin; MMS, multiple micronutrient supplementation.
[2] The difference in Hb concentrations before and after interventions were calculated by subtracting the baseline survey Hb concentrations from endline survey Hb concentrations.
[3] Regressions 1–3 include an increasing number of independent variables.
[4] T-statistics adjusted for clustering within schools. Different from zero: $*P \leq 0.10$, $**P \leq 0.05$, $***P \leq 0.01$.
[5] 1 indicates student in MMS treatment schools and 0 indicates student not in MMS treatment schools.
[6] 1 indicates boarding student and 0 indicates nonboarding student.
[7] Interaction of 2 variables.
[8] 1 indicates female student and 0 indicates male student.
[9] 1 indicates student with both parents at home and 0 indicates student with one or both parents absent.

students in the control schools (Table 2). At the endline survey, the mean MHT score was lower in treatment than in control schools (Table 2). The mean MHT score fell by 1.6 points more in the treatment schools than in the control schools; however, when county effects were taken into account, the decrease in the mean MHT score in the treatment schools compared with control schools became greater ($P < 0.05$).

The essence of the intent-to-treat analysis can also be seen graphically in **Supplemental Figure 1**, which presents the distributions of baseline and endline MHT scores for control students in the upper panel and for treatment students in the lower panel. The effect of the MMS on MHT scores is apparent in the greater shift in the distribution of MHT scores of students in the treatment schools relative to that of students in the control schools.

The results of the multivariate analysis using the adjusted model supported the results of the intent-to-treat analysis and were robust across the different specifications (**Table 4**). When we controlled for other characteristics, the estimated impact of the MMS treatment on MHT scores rose (in absolute value terms). The coefficients on the MMS treatment variable were all larger than those in the intent-to-treat analyses ($P < 0.01$). The coefficient for the intervention from the most complete model (which should provide the most efficient estimate) corresponded to a 0.3-SD reduction in the MHT score.

When we tested the effect of MMS on subscales of the anxiety scale, we found that the effect on overall MHT scores was mostly due to reductions in personal and body anxiety (Supplemental Table 2). When we compared the mean MHT scores from the baseline with those from the endline for learning anxiety, loneliness anxiety, self-blaming tendency, sensitivity tendency, phobia anxiety, and impulsive tendency, we found no significant differences; what differences did exist were mostly small in magnitude.

Discussion

We found that a 5-mo MMS program administered to fourth-grade students in rural Chinese boarding schools increased Hb concentrations and reduced anemia. Most importantly, the MMS reduced MHT scores, a general measure of anxiety, by as much as 0.3 SDs, where lower scores represent better psychological health.

Are these large effects? According to Cohen (44), this effect size is between a small (0.2 SD) and medium (0.5 SD) effect size. Hence, from this perspective, the impact is on the smaller side. However, compared with other types of interventions (and their relative costs), we think the measured effect sizes are important for policy. For example, previous interventions for psychological health in China have focused primarily on training teachers and working with individual students with mental disorders. In 2007, a personal treatment and counseling intervention involving 600 Tianjin students showed a 0.3-SD reduction in MHT scores after 2 y (31). The effect size in our study must be considered of interest to policymakers, because the per capita cost of MMS is certainly lower than that of interventions such as one-on-one counseling and therapy. Ideally, both should be included in school health programs.

These findings are in line with our hypothesis that MMS may improve the symptoms of anxiety. One of the largest effects was on how students felt about their bodies, offering support for the idea that the treatment of anemia and other micronutrient deficiencies can alleviate psychological anxiety (45). Indeed, 2 subcomponents of the MHT, body anxiety and personal anxiety, were responsible for most of the significant impact of the MMS on the MHT scores and were large and significant in the intent-to-treat analysis.

Interestingly, we did not observe a significant change in the impulsive tendency. Previous research (46) in children has shown

TABLE 4 Effect of the MMS treatment on the change of MHT scores between October 2008 and June 2009 [1]

	Dependent variable: the difference in MHT scores before and after interventions[2], points					
	1[3]		2		3	
Independent variable	Coefficient	t[4]	Coefficient	t	Coefficient	t
MMS treatment[5]	−2.85	3.32***	−3.78	3.48***	−3.74	3.58***
Boarding status[6]	−0.39	0.46	−0.43	0.52	0.08	0.06
MMS treatment × boarding status[7]	1.21	0.6	1.24	0.64	1.23	0.64
Gender[8]			0.87	1.35	0.93	1.43
MMS treatment × gender[7]			2.26	1.52	2.21	1.57
Parent migration status[9]					−0.44	0.79
Parent migration status × boarding status[7]					−1.01	0.57
Adjusted for county effects	Yes		Yes		Yes	
Constant	2.16	1.76*	1.74	1.38	1.87	1.49
Observations	2730		2730		2730	
R^2	0.02		0.03		0.03	

[1] MHT, Mental Health Test; MMS, multiple micronutrient supplementation.
[2] The difference in MHT scores before and after interventions was calculated by subtracting the baseline survey MHT scores from evaluation survey MHT scores.
[3] Regressions 1–3 include an increasing number of independent variables.
[4] T-statistics adjusted for clustering within schools. Different from zero: $^*P \leq 0.10$, $^{**}P \leq 0.05$, $^{***}P \leq 0.01$.
[5] 1 indicates student in MMS treatment schools and 0 indicates student not in MMS treatment schools.
[6] 1 indicates boarding student and 0 indicates nonboarding student.
[7] Interaction of 2 variables.
[8] 1 indicates female student and 0 indicates male student.
[9] 1 indicates student with both parents at home and 0 indicates student with one or both parents absent.

that iron deficiency might actually underlie some of the impulsive behavior seen in children with attention disorders. It is possible that impulsive tendencies were expressed in more subtle ways in our sample or that this reflects a cultural difference between American and Chinese elementary school students.

Why did Hb concentrations rise in the control group? Although we do not know for certain, this increase may reflect seasonality (47). The baseline was conducted in the late summer, before the time most farmers in the study area had harvested and marketed their crops (48,49); the endline survey was conducted in the spring after the harvest/marking season. This change in the Hb concentrations of students in the control schools reinforces the need for a randomized controlled trial to dissociate the effects of external influences from those attributable to the intervention.

A key limitation of our study is that the supplement provided contained many micronutrients that may affect mental health besides iron, including zinc and others. For example, increased zinc concentrations have been associated with decreased anxiety levels in school-aged children (24), and zinc, magnesium, iodine, and vitamin B-12 deficiencies have all been associated with depression. Supplementation with these nutrients has in some but not all studies been shown to produce improvements in mental health, including reduced anxiety (24,50,51).

Although we show that our intervention was biologically efficacious in improving anemia and mental health scores, due to cost constraints we did not include measurement of other biomarkers, including measures of iron status (such as ferritin) or other nutrient deficiencies. Thus, we have no information on whether iron status or the status of other micronutrients was improved; further, we cannot claim that the effect on mental health was due to the iron in the supplements, although it remains a plausible explanation. The dose provided 5 mg of ferrous sulfate daily for 5 mo and was consumed in the context of a cereal-based diet. Without detailed dietary intake information, it is difficult to specify how much of the iron provided was absorbed. However, 5 mg probably represents an important amount relative to the estimated requirement for children 9–13 y (~5.8 mg) or the RDA (8 mg) specified by the Institute of Medicine (52). Our findings support the work of other researchers who have found that low and regular doses of iron supplementation are effective at boosting iron stores (53).

Another limitation of the study was the lack of a placebo in the control schools due to fears (raised by the IRB) of nutritional substitution in an already malnourished population. The absence of a placebo means that we have to carefully interpret our findings to exclude a Hawthorne effect (i.e., students become less anxious because they are getting attention by outsiders). Likewise, we need to consider the possibility that the impact of the supplementation might be a combination of true and placebo effects. There are at least 2 reasons to think that the findings are not explained by the lack of a placebo group. First, the length of time between baseline and endline was more than 9 mo. Given this length of time, transient effects of excitement or anticipation about receiving daily supplements should be dissipated. Second, because students, teachers, and principals were not informed about the hypothesized link among the supplements, Hb concentrations, and psychological health and because all participants were generally unfamiliar with nutritional supplements, it is unlikely that the MHT scores were influenced by an expectation placed on the MMS. Therefore, the influence of the placebo effect should be minimal.

Our study has several strengths. Most previous research into the links between nutritional supplementation and mental health consists of small, observational studies. To our knowledge, ours is the first randomized controlled trial with a large enough sample to have adequate power to detect an effect size as small as

0.2 SDs. Furthermore, we use a set of internationally standardized measures and procedures.

The main conclusion of our study is that when we gave school-based MMS, we observed reductions in both anemia and measures of mental health. We think these results are generalizable to other vulnerable populations in poor rural regions in western China. These findings have important policy implications given the emphasis that the current government in China is placing on developing human capital (54) and the fact that so many Chinese children reside in government-run boarding schools like the ones studied in this project.

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L.Z., R.L., Y.S., R.M., and S.R. designed research; R.L., L.Z., and Y.S. conducted research; R.L., M.K.-W., and S.R. analyzed data; and M.K.-W., R.M., A.M., and S.R. wrote the paper. All authors read and approved the final manuscript.

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