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Prenatal Micronutrient Supplementation Is Not Associated with Intellectual Development of Young School-Aged Children[1–3]

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Abstract

Background: Micronutrient supplementation is often prescribed during pregnancy. The effects of prenatal iron and multimicronutrient supplementation on intellectual development in young school-aged children are less than clear.

Objective: The aim of this study was to examine the long-term effects of prenatal iron plus folic acid or multiple micronutrient (including iron and folic acid) supplementation vs. folic acid supplementation on the intellectual development of young school-aged children in rural China.

Methods: Young school-aged children (aged 7−10 y, n = 1744) of women who had participated in a trial of prenatal supplementation with various combinations of micronutrients and remained residents in 2 rural counties in China were followed. We measured their intellectual development by Wechsler Intelligence Scale for Children Fourth Edition (WISC-IV). The WISC-IV generated the Full-Scale Intelligence Quotient (FSIQ), Verbal Comprehension Index (VCI), Working Memory Index (WMI), Perceptual Reasoning Index (PRI), and Processing Speed Index (PSI). Multilevel analyses were used to assess the effect of prenatal micronutrient supplementation on the intellectual development of children.

Results: The mean differences in FSIQ, VCI, WMI, PRI, and PSI, respectively, were not significant between prenatal folic acid supplementation and either iron plus folic acid [−0.34 (P = 0.65), −0.06 (P = 0.95), −0.22 (P = 0.76), −0.01 (P = 0.99), and −1.26 (P = 0.11)] or multimicronutrient [−0.39 (P = 0.60), −0.64 (P = 0.48), 0.11 (P = 0.87), −0.43 (P = 0.59), and −0.34; (P = 0.65)] supplementation after adjusting for confounders.

Conclusions: No evidence suggests different effects on intellectual development between prenatal iron plus folic acid, multimicronutrient supplementation, and prenatal folic acid supplementation in children aged 7−10 y. This trial was registered at www.isrctn.com as ISRCTN08850194. *J Nutr* doi: 10.3945/jn.114.207795.

Keywords: prenatal micronutrient supplementation, young school-aged children, intellectual development, longitudinal study, rural China

Introduction

Most governments and health professionals have recommended that pregnant women take prenatal formulas that contain various micronutrients to ensure a healthy pregnancy and healthy baby. However, the effects of micronutrient supplementation and the presence of a long-term impact on the children's mental development are still being debated and investigated (1).

The results of 2 intervention studies were inconsistent (2, 3) regarding the effect of prenatal iron supplementation. One intervention trial showed a positive effect of prenatal iron plus folic acid supplementation on intellectual and motor function in 7- to 9-y-old children in Nepal, where iron deficiency is prevalent (2). However, another controlled trial in Australia showed that prenatal iron supplementation (20 mg/d) had no effect on intelligence quotient (IQ)[8] test performance in 4-y-old children (3). Many studies have reported that prenatal multimicronutrient supplementation increases birth weight and decreases early infant

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[8] Abbreviations used: FSIQ, Full-Scale Intelligence Quotient; IQ, intelligence quotient; PRI, Perceptual Reasoning Index; PSI, Processing Speed Index; VCI, Verbal Comprehension Index; WISC-IV, Wechsler Intelligence Scale for Children Fourth Edition; WMI, Working Memory Index.

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mortality rates (4–6). However, no conclusive evidence indicates that prenatal multimicronutrient supplementation is associated with mental development in children (7).

Childhood intellectual development is important to an individual's potential for success in life (8) and is inversely associated with several somatic health outcomes ascertained in middle to later life (9, 10). Therefore, the aim of this study was to assess intellectual function in a cohort of rural Chinese children aged 7–10 y in 2012–2013 whose mothers received daily prenatal micronutrient supplements in a controlled, cluster-randomized, double-blind trial conducted between 2002 and 2006. This trial was registered at www.isrctn.com as ISRCTN08850194.

Methods

Study design and participants. The participants in the present study were from a large trial that aimed to determine the effect of micronutrient supplementation during pregnancy on birth weight. The details of the double-blind, cluster-randomized, controlled trial of prenatal supplementation with various combinations of micronutrients were described elsewhere (4). Briefly, this trial was conducted in 2 rural counties in Shaanxi Province of Northwest China from 2002 to 2006. We allocated the same treatment to all pregnant women in the same village, and the randomization of villages was stratified according to county and township to ensure geographic balance. The enrolled pregnant women in the same village were randomly assigned to 3 supplementation groups (daily folic acid, folic acid plus iron, or multimicronutrients). The intervention groups were folic acid (400 μg/d), folic acid plus iron (60 mg/d), and 15 minerals or vitamins as follows: 30 mg/d iron, 400 μg/d folate, 15.0 mg/d zinc, 2.0 mg/d copper, 65.0 μg/d selenium, 150.0 μg/d iodine, 800.0 μg/d vitamin A, 1.4 mg/d thiamine, 1.4 mg/d riboflavin,1.9 mg/d vitamin B-6, 2.6 μg/d vitamin B-12, 5.0 μg/d vitamin D, 70.0 mg/d vitamin C, 10.0 mg/d vitamin E, and 18.0 mg/d niacin. A total of 5828 pregnant women from 531 villages were enrolled in the study, and there were 4604 single live births.

From October 2012 to September 2013, a follow-up study was conducted, and children of women who had participated in the trial of prenatal micronutrient supplementation and remained residents in the study area were eligible for follow-up. We excluded migrations in the present study because it was not possible to trace them. More importantly, the migrations were not representative of rural China, and many potential confounders that may be associated with mental development of children could not be well estimated in migrations. Households with eligible children were invited to participate in the present follow-up study. Parents' interviews were conducted to collect information about household demographic characteristics and socioeconomic status. The children's type of school and number of completed and repeated years of schooling were collected. In addition, we also collected information about morbidity of respiratory tract infection or diarrhea in study children in the previous 2 wk. The purpose of the study was explained, and parental written consent and child assent were obtained. We estimated a minimum of 426 children (142 children in each group) would be needed to detect a minimum difference of 5 Full-Scale Intelligence Quotient (FSIQ) points (33.3% of SD) between groups with 80% power and type I error ($\alpha = 0.05$). A 5-IQ point difference was considered clinically significant because it is of the order of magnitude associated with IQ differences in children who were fed breast milk rather than formula as infants (11) or were exposed to high lead concentrations (12). Finally, we followed 1744 children in the present study, and this sample size was able to detect the difference of 2.5 FSIQ points(16.7% of SD) between groups with 80% power and type I error ($\alpha = 0.05$). The study was approved by the Human Research Ethics Committee of the Xi'an Jiaotong University Health Science Center.

Psychological testing. Five postgraduate students in psychology were rigorously trained and overseen by LC who served as psychometrician and qualified to administer the latest version of Wechsler Intelligence Scale for Children Fourth Edition (WISC-IV). The students were trained by methods introduced in the Chinese version of the WISC-IV technical manual. When each student performed a fully accurate test administration and scoring, they were certified to collect data. WISC-IV is a standardized test, with the same order of administered subsets, and the same scoring method and criteria. The psychological tests were conducted in the primary school or local hospital where the school or hospital was asked to provide 5 quiet rooms to ensure the children would not be interrupted. All the answers of each subset were recorded, and scoring accuracy of each child was reviewed by the psychometrician after field work was completed each day.

WISC-IV included 10 core subtests (Block Design, Similarities, Digit Span, Picture Concepts, Coding, Vocabulary, Letter-Number, Matrix Reasoning, Comprehension, and Symbol Search) and 4 supplement subtests (Picture Completion, Cancellation, Information, and Arithmetic) for children between the ages of 6 and 16 y. A total of 5 composite scores can be derived with the WISC-IV. The WISC-IV generates a FSIQ which represents overall cognitive ability and 4 other composite scores. The 4 other composite scores are Verbal Comprehension Index (VCI), Working Memory Index (WMI), Perceptual Reasoning Index (PRI), and Processing Speed Index (PSI).

Currently, the WISC-IV is commercialized in China and is established as the Chinese standard to determine the following scores: FSIQ, VCI, WMI, PRI, and PSI. These scales are translated into Chinese and are locally standardized to become culturally appropriate. The reliability and validity of these measures were tested and shown to be satisfactory (13).

Statistical analysis. Data were analyzed on an intention-to-treat basis. Baseline characteristics of subjects were compared across treatment groups by using ANOVA or chi-square tests. A wealth index was constructed from an inventory of 16 household assets or facilities with a principal component analysis method (14), and this index was categorized into thirds as an indicator for the poorest, middle income, and richest households. Values in the text and tables are means ± SDs or *n* (%). Because of the multilevel hierarchical structure of the data and original randomized design, the multilevel model approach, which is a good method for analyzing data with a hierarchical structure, can be applied in cluster sampling investigations (15). Finally, a 3-level analysis was developed to adjust for the effect of randomization by villages and to compare the FSIQ, VCI, WMI, PRI, and PSI with township to level 3, village to level 2, and individual to level 1. In addition, because the FSIQ represents overall cognitive ability, 4-factor scoring solution examines its validity (13). Therefore, we did not account for correlation among the 4 composite scores in the analysis.

Estimations of the mean difference and 95% CIs were calculated according to the categories of prenatal micronutrient supplementation. Variables that were unbalanced between the treatment groups and associated with outcomes were controlled for in the adjusted analyses. Age, sex, schooling, household wealth index, and history of anemia were strongly associated with child mental development (2, 16, 17). In addition, father's educational level, mother's occupation classification, gestational age at birth, birth weight, and morbidity of respiratory infection in the previous 2 wk differed among prenatal micronutrient supplement groups, so we ran models that adjusted for these variables as confounders in addition to the number of supplement tablets consumed to assess FSIQ, VCI, WMI, PRI, and PSI differences among prenatal micronutrient supplementation groups. All reported *P* values were 2-tailed, and values of $\alpha < 0.05$ were considered statistically significant. Data were analyzed with STATA software version 12.0 (Stata Corporation).

Results

The profile of this trial is shown in **Figure 1**. In the present study, we excluded the children (37.8%) who had moved out of the study area and those who died; of the remaining children, those who remained residents in the study area were eligible for inclusion in this analysis. After excluding death and migration, participants and those who did not take part in the study did not differ in any enrollment measure (**Table 1**).

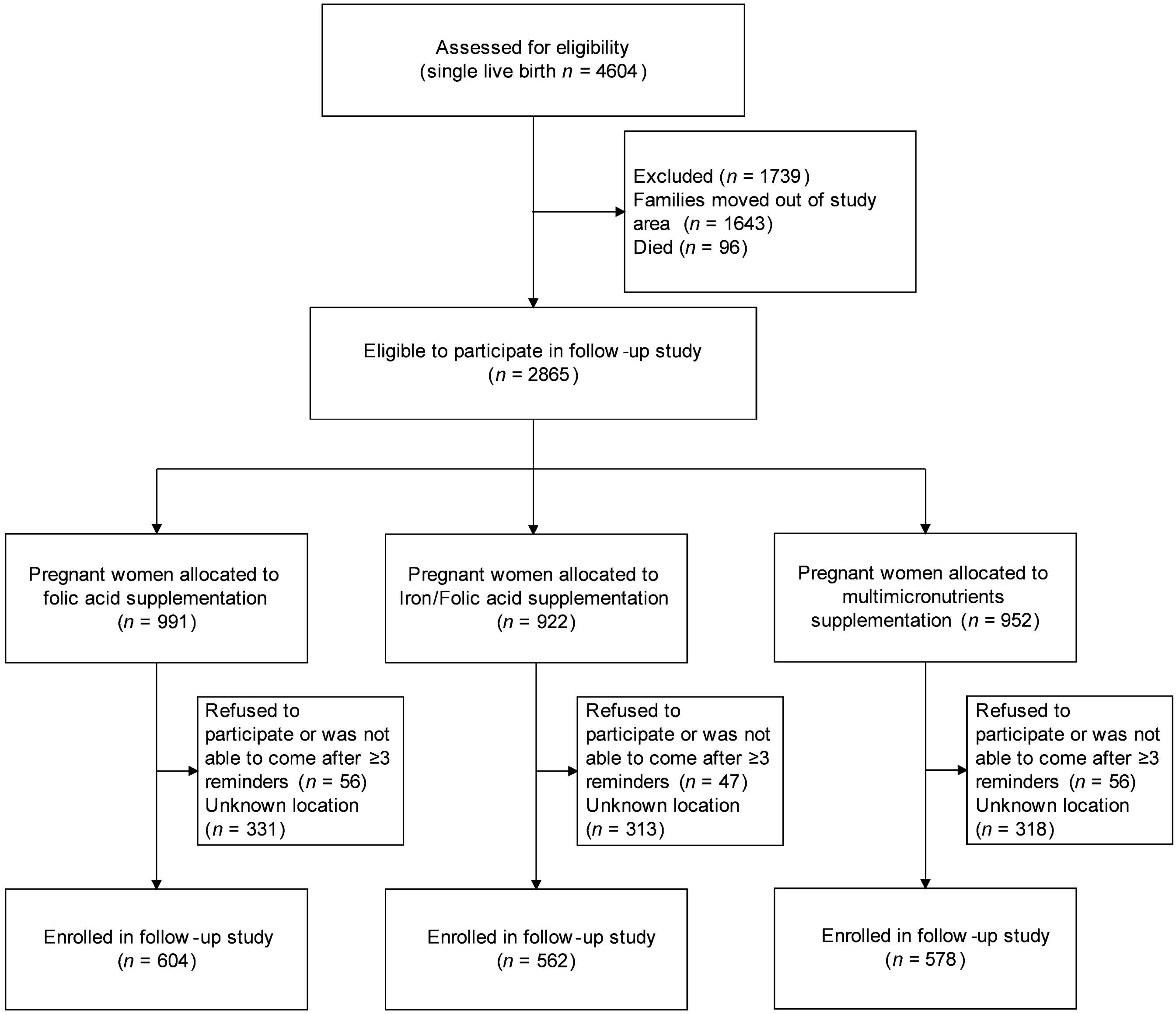

FIGURE 1 Study participation by treatment group.

The baseline characteristics of children and households across treatment groups are shown (**Table 2**). The mean age of children at follow-up was 8.8 ± 0.83 y. The majority of children (75.6%) attended township or village schools, which differed by treatment group (P = 0.024). Treatment groups differed for school type, percentage of reporting symptoms of lower respiratory tract infection in the previous 2 wk, father's education, and mother's occupation. The proportions of the educational level of mother (P = 0.11) and occupational classification of father (P = 0.08), sex of the newborn (P = 0.61), socioeconomic status (P = 0.42), and history of anemia (P = 0.51) did not differ by treatment group. The mean age of children (P = 0.65) and the mean birth weight (P = 0.26) were not significantly different among treatment groups.

No relevant differences were found in FSIQ, VCI, WMI, PRI, and PSI between the folic acid, folic acid plus iron, and multimicronutrient groups. Adjusting for age, sex, schooling, household wealth index, gestational age at birth, father's educational level, mother's occupation classification, number of supplement tablets consumed, birth weight, and lower respiratory tract infection in the previous 2 wk did not change the results of the univariate analysis. The mean differences in FSIQ, VCI, WMI, PRI, and PSI, respectively, were not significant between prenatal folic acid supplementation and either the iron plus folic acid (P = 0.65, P = 0.95, P = 0.76, P = 0.99, and P = 0.11) or multimicronutrient (P = 0.60, P = 0.48, P = 0.87, P = 0.59, and P = 0.65) supplementation after adjusting for confounders (**Table 3**).

In addition, we found socioeconomic factors (household economic status, sex of children, children's schooling, parents' educational level, and maternal occupation) were strongly associated with the intellectual development of children (**Supplemental Table 1** and **2**).

Discussion

The major finding in this study is that no effects of prenatal iron plus folic acid or multimicronutrients (including iron and folic acid) vs. folic acid were found on the intellectual development of young school-aged children (mean age: 8.7 y) in rural China.

TABLE 1 Baseline characteristics of study participants in follow-up and lost to follow-up[1]

	Follow-up	Lost to follow-up	*P*
Children's characteristics			
n	1744	1121	
Age, y	8.8 ± 0.83	8.8 ± 0.78	0.14
Birth weight, kg	3.2 ± 0.43	3.2 ± 0.42	0.71
Sex			0.10
Boy	1045 (59.9)	637 (56.8)	
Girl	699 (40.1)	484 (43.2)	
Gestational age at birth, wk	39.9 ± 1.68	39.8 ± 1.73	0.40
Women's characteristics			
Age, y	34.0 ± 4.51	34.1 ± 4.37	0.59
Women's education			0.44
<3 y	121 (7.0)	65 (5.8)	
Primary	512 (29.4)	314 (28.1)	
Secondary	909 (52.2)	614 (54.9)	
≥High school	198 (11.4)	125 (11.2)	
History of anemia			0.40
Yes	341 (19.6)	223 (19.9)	
No	1403 (80.4)	898 (80.1)	
Women's occupation at enrollment			0.72
Farmer	1517 (87.4)	969 (87.0)	
Other	218 (12.6)	145 (13.0)	
BMI at enrollment, kg/m^2	20.9 ± 2.21	20.9 ± 2.32	0.41
Other characteristics			
Father's education			0.39
<3 y	28 (1.6)	17 (1.5)	
Primary	260 (15.0)	142 (12.7)	
Secondary	1096 (63.0)	725 (64.7)	
≥High school	355 (20.4)	236 (21.1)	
Father's occupation at enrollment			0.19
Farmer	1408 (80.9)	884 (78.9)	
Other	332 (19.1)	236 (21.1)	
Household wealth index at enrollment			0.67
Poorest	620 (35.6)	411 (36.6)	
Middle	621 (35.6)	381 (34.0)	
Richest	503 (28.8)	329 (29.4)	

[1] Values are *n* (%) or means ± SDs.

Evidence suggests that various micronutrients play a role in children's mental development. Iron and iodine deficiency anemia were 2 key risk factors for child mental development (17). Many studies found that infants with iron deficiency anemia showed lower pretreatment mental scores and lower motor scores than infants without such anemia (18, 19). In addition, iodine deficiency is associated with poor development, and iodine deficiency during pregnancy has negative effects on the developing fetus and mental development of the offspring. However, universal salt iodization has been implemented in all counties in China since 1995, individual iodine nutrition has improved, and the current iodine nutrition status of the population is adequate (20). Conversely, studies have demonstrated that there was no effect of zinc supplementation alone, at daily doses of 25 mg and 30 mg, on children's mental development (21, 22). Similarly, weekly supplementation with vitamin A in addition to iron during gestation was found to have no effect on mental development (23).

We previously reported that the prenatal iron plus folic acid supplementation did not show additional benefits in infant mental development, compared with folic acid supplementation alone (24). In the present study, we also found no benefit of prenatal iron plus folic acid supplementation on child intellectual development. This result was consistent with another long-term follow-up study of a randomized, controlled trial from Australia (3). That study also failed to demonstrate any relevant benefits in the intelligence quotient and behavior of children at 4 y of age, compared with placebo treatment (3). Conversely, the positive effect of prenatal iron supplementation during pregnancy on child intellectual development was found in Nepal (2). However, iron deficiency anemia was prevalent in Nepal (~64% iron deficiency anemia was reported in a previous study) (25). Australia is an industrialized country with well-nourished populations in whom the incidence of iron deficiency anemia at the end of pregnancy is only 11% (3). Anemia in China is more common than in Australia, but it is not as prevalent as in Nepal. The prevalence rate of iron deficiency anemia was ~45% in the third trimester of pregnancy in rural western China (26). The results of the study provide reference for future intervention studies of iron supplementation in other similar areas. Although no significant differences in FSIQ, VCI, WMI, PRI, and PSI were found between prenatal 60 mg/d iron plus folic acid supplementation and folic acid supplementation (P = 0.11–0.99), the effect of prenatal iron supplementation alone on childhood intellectual development cannot be determined.

The multimicronutrient supplementation in our study was composed of 5 minerals and 10 vitamins. Many studies have found small changes in cognitive outcomes with this intervention but mostly in infants or young children (2). In a stratified analysis, infants of mothers with low BMI who received multiple micronutrients had small but relevant increments in motor scores and activity ratings than infants whose mothers received iron plus folic acid in Bangladesh (27). We also previously reported that multimicronutrient supplementation was associated with increases in mental development raw scores of 1.00 and 1.22 points with folic acid and folic acid plus iron supplementation, respectively, but not in psychomotor scores at 1 y of age (24). In the present study, we found no effect of prenatal multimicronutrient supplementation on the intellectual development of children at age 7–10 y. The result was consistent with the trial in Nepal which also found that the outcomes in the multiple micronutrient supplement group were not different from the control (vitamin A alone) in children at age 7–9 y (2). Our results provide evidence that there was no long-term effect of prenatal multimicronutrient supplementation on intellectual function of 7- to 10-y-old children.

Many studies have revealed the strong influence of childhood socioeconomic background on intellectual development (28, 29). A study revealed that the general environment today is much more complex and stimulating and includes pictures on the wall, movies, television, video games, and computers. Each item can stimulate the cognitive development of children (30). Therefore, children may be exposed to more items and ideas if they have higher socioeconomic status (which includes parents' educational level, household economic status, and children's school). Sex differences in test scores may be related to the emphasis on proficiency in household chores and taking care of younger siblings among girls, which does not allow them sufficient time for schoolwork and study. Schoolwork proficiency may itself be valued differently by sex (2).

Our study has several limitations and strengths. As with any study of this nature, a limitation was our inability to follow all children in the original cohort. This factor was mostly because of rapid development of China, with mass migration out of the area in which the original study took place, making it impossible to trace the participants. After excluding death and migration,

TABLE 2 Baseline characteristics of study participates by maternal supplementation group[1]

	Folic acid	Folic acid + iron	Multimicronutrients	*P*
Children's characteristics				
n	604	562	578	
Age, y	8.8 ± 0.84	8.8 ± 0.82	8.8 ± 0.82	0.65
Sex				0.61
Boy	355 (58.8)	346 (61.6)	344 (59.5)	
Girl	249 (41.2)	216 (38.4)	234 (40.5)	
School				0.024
Village	211 (34.9)	175 (31.1)	210 (36.3)	
Township	234 (38.8)	264 (47.0)	223 (38.6)	
County	159 (26.3)	123 (21.9)	145 (25.1)	
Birth weight, kg	3.2 ± 0.44	3.2 ± 0.41	3.2 ± 0.44	0.26
Gestational age at birth, wk	39.7 ± 1.72	39.9 ± 1.63	39.9 ± 1.67	0.051
Respiratory tract infection				0.032
Yes	413 (70.0)	343 (63.3)	397 (69.3)	
No	177 (30.0)	199 (36.7)	176 (30.7)	
Women's characteristics				
Educational level				0.11
Primary	224 (37.2)	208 (37.1)	201 (34.8)	
Secondary	300 (49.8)	304 (54.3)	305 (52.8)	
≥High school	78 (13.0)	48 (8.6)	72 (12.4)	
Occupational class				0.047
Farmer	386 (65.3)	390 (71.4)	374 (65.5)	
Others	205 (34.7)	156 (28.6)	197 (34.5)	
BMI at enrollment, kg/m^2	20.8 ± 2.16	20.8 ± 2.22	21.0 ± 2.24	0.83
History of anemia				0.51
Yes	126 (20.9)	102 (18.2)	113 (19.5)	
No	478 (79.1)	460 (81.9)	465 (80.5)	
Other characteristics				
Father's occupational class				0.08
Farmer	224 (37.8)	220 (40.4)	195 (34.0)	
Others	368 (62.2)	324 (59.6)	378 (66.0)	
Household wealth index				0.42
Poorest	186 (30.8)	181 (32.2)	206 (35.6)	
Middle	204 (33.8)	196 (34.9)	184 (31.8)	
Richest	214 (35.4)	185 (32.9)	188 (32.5)	

[1] Values are *n* (%) or means ± SDs.

participants and those who did not take part in the study did not differ in any enrollment measure. Although excluding migrations limited the ability to generalize to the population in other areas, these data are still rare, meaningful, and representative of rural China. Another limitation is that we did not include all possible confounders (such as diet of children and smoking) in our analysis, mainly because of similar same dietary habits and small number of smokers among children and their mothers. The main strength of this study is that the information about maternal pregnancy and infants at birth, such as the type of

TABLE 3 Differences in WISC-IV test scores by maternal supplementation group relative to folic acid group among children aged 7–10 y[1]

	Folic acid + iron				Multimicronutrients			
	Unadjusted analysis		Adjusted analysis[2]		Unadjusted analysis		Adjusted analysis[2]	
	MD (95% CI)	*P*	MD (95% CI)	*P*	MD (95% CI)	*P*	MD (95% CI)	*P*
FSIQ	−0.67 (−2.21, 0.87)	0.39	−0.34 (−1.83, 1.14)	0.65	−0.38 (−1.91, 1.15)	0.63	−0.39 (−1.84, 1.05)	0.60
VCI	−0.49 (−2.32, 1.34)	0.60	−0.06 (−1.85, 1.74)	0.95	−0.72 (−2.54, 1.09)	0.44	−0.64 (−2.38, 1.11)	0.48
WMI	−0.26 (−1.66, 1.15)	0.72	−0.22 (−1.62, 1.19)	0.76	0.29 (−1.10, 1.68)	0.68	0.11 (−1.26, 1.48)	0.87
PRI	−0.05 (−1.57, 1.68)	0.95	−0.01 (−1.61 ,1.60)	0.99	−0.02 (−1.59, 1.64)	0.98	−0.43 (−2.00, 1.13)	0.59
PSI	−1.25 (−2.77, 0.27)	0.11	−1.26 (−2.79, 0.27)	0.11	−0.36 (−1.87, 1.15)	0.64	−0.34 (−1.83, 1.15)	0.65

[1] Multilevel models were used to adjust for the effect of randomization by villages, with township to level 3, village to level 2, and individual to level 1. FSIQ, Full-Scale Intelligence Quotient; MD, mean difference; PRI, Perceptual Reasoning Index; PSI, Processing Speed Index; VCI, Verbal Comprehension Index; WISC-IV, Wechsler Intelligence Scale for Children Fourth Edition; WMI, Working Memory Index.
[2] *P* value adjusted for the age of children, household wealth index, fathers' educational level, maternal occupation, child school level, number of supplement tablets consumed, birth weight, history of anemia, gestational weeks, and respiratory tract infection in the past 2 wk.

prenatal micronutrient supplementation or birth weight, was collected during the time of pregnancy or at birth, ensuring that this study does not experience the potential biases that may be introduced in using recalled information. In addition, we revealed the long-term effect of prenatal micronutrient supplementation on intellectual development of children because of the original randomized study design and relatively large sample size. We used well-known, standardized intelligence scales for use in various cultures and settings and the latest version of WISC-IV to test the intellectual development of 7- to 10-y-old children. Although we found no long-term effect of prenatal iron plus folic acid and multimicronutrient supplementation on the intellectual development of children compared with prenatal folic acid supplementation, these results are still valuable for further studies.

In conclusion, there is no evidence to suggest a different effect on intellectual development between prenatal iron plus folic acid and multimicronutrient supplementation and prenatal folic acid supplementation in children aged 7–10 y. Further research is required to clearly delineate the population in other areas that may benefit from micronutrient supplementation in pregnancy.

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CL designed the research, analyzed the data, and wrote the first draft of the paper; LZ designed the research and analyzed the data; DW, WY, SD, and JZ analyzed the data; HY was the principal investigator, designed the research, analyzed the data, edited the paper, and is the guarantor. All authors read and approved the final manuscript.

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