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Original Contribution

Association of Periconceptional Multivitamin Use and Risk of Preterm or Small-for-Gestational-Age Births

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The authors' objective was to determine the relation between periconceptional multivitamin use and the risk of small-for-gestational-age (SGA: <5th percentile; 5th–<10th percentiles) or preterm (<34 weeks; 34–<37 weeks) births. Women in the Pregnancy Exposures and Preeclampsia Prevention Study (1997–2001) reported at enrollment their regular multivitamin use in the past 6 months ($n = 1,823$). Women were classified as users or nonusers in multinomial logistic models. After adjustment for race, age, education, enrollment gestational age, and household density, periconceptional multivitamin use was associated with a reduced risk of preterm births (<34 weeks) (odds ratio (OR) = 0.29, 95% confidence interval (CI): 0.13, 0.64) and spontaneous preterm births (<34 weeks) (OR = 0.40, 95% CI: 0.16, 0.99). Risk of SGA (<5th percentile) was marginally lower (OR = 0.64, 95% CI: 0.40, 1.03) after adjustment for smoking, education, parity, enrollment gestational age, and body mass index. Prepregnancy body mass index modified this relation. Nonobese users had a reduction (OR = 0.54, 95% CI: 0.32, 0.91) in risk of SGA (<5th percentile); there was no effect among obese women. There was no effect of multivitamin use on risk of preterm births (34–<37 weeks) or SGA (5th–<10th percentiles). Sensitivity analysis for unmeasured confounding by folate intake supported these findings. Study results indicate lower rates of severe preterm births and extreme SGA in women who report periconceptional vitamin use, although these should be considered cautiously until replicated.

body mass index; dietary supplements; infant, small for gestational age; premature birth

Abbreviations: CI, confidence interval; OR, odds ratio; SGA, small for gestational age.

Preterm birth and fetal growth restriction are dominant determinants of neonatal morbidity and mortality, affecting 5–25 percent of births worldwide (1). Infants born very preterm or very much smaller than their growth potential have the highest risks of death and disability (2). Although preterm birth and fetal growth restriction are thought to have distinct pathogeneses, risk factors overlap. Black race (3–5), maternal smoking (5–7), nulliparity (5, 8), and lean maternal body mass index (8, 9) are risk factors for both preterm birth and growth restriction. Women with a first pregnancy complicated by preterm birth or growth restriction are more likely to have other complications in subsequent pregnancies, such as stillbirth (10). Interestingly, preterm infants are more prone to differential fetal growth compared with term infants, such that spontaneous preterm births before 34 weeks' gestation have from two- to threefold increased risk of growth restriction compared with spontaneous term births (11).

Nutrition is believed to play a role in the pathogenesis of adverse pregnancy outcomes, including preterm birth and

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growth restriction as measured by small for gestational age (SGA). Several studies have reported a relation between prenatal vitamin and mineral supplementation and risk of SGA (12–15) or preterm (15–17) birth, but the few studies relating periconceptional vitamin use to either outcome report conflicting results or the estimates have been imprecise (18–22). We hypothesized that periconceptional multivitamin use would be associated with a reduced risk of both preterm birth and SGA and that the effects would be stronger for the more severe subtypes, as these may likely involve placental pathogeneses.

The objective of this study was to determine the relation between periconceptional multivitamin use and the risk for delivery of a singleton SGA infant (<5th percentile; 5th–10th percentiles) or preterm infant (<34 weeks; 34–<37 weeks).

MATERIALS AND METHODS

The Pregnancy Exposures and Preeclampsia Prevention Study is a prospective study of women enrolled at less than 16 weeks and followed through the postpartum visit. Women were recruited from clinics and private practices from 1997 to 2001. The study was approved by the institutional review board, and all participants provided written informed consent. We performed a secondary analysis utilizing this cohort. Of the 2,211 women enrolled in the study, we excluded those with preexisting hypertension or diabetes ($n = 46$), multiple gestation ($n = 38$), or a positive toxicology screen at delivery ($n = 46$). Women with incomplete diagnostic information ($n = 109$) were also excluded, as were 141 observations that represented second or third pregnancies from the same women in the cohort. The final study population was 1,823 women.

Periconceptional multivitamin use

Women enrolled in the Pregnancy Exposures and Preeclampsia Prevention Study underwent a structured interview at their first prenatal visit that occurred, on average, at 9.9 weeks' gestation (standard deviation: 3.9 weeks) and were asked the question, ''In the past 6 months, have you taken multivitamins or prenatal vitamins regularly, at least once per week?'' Interviewers were instructed not to include supplements that participants began using after pregnancy was detected; however, this assessment included vitamin use prior to conception, at the time of conception, and immediately after conception and therefore was categorized as periconceptional. Women who responded that they took a multivitamin regularly in the past 6 months were asked to report their usual use as 1–3 times/week, 4–6 times/week, or daily. Data on dose or brand of supplement were not collected. Because 88 percent of regular supplement users reported daily use (751 of 852 total users), we classified women as users or nonusers of periconceptional multivitamins.

SGA and preterm birth

Small-for-gestational-age infants were those below the fifth percentile and those between the fifth and below the 10th percentiles of weight according to nomograms based on race, gender, and gestational age from a reference population of over 10,000 infants delivered at Magee-Womens Hospital in Pittsburgh, Pennsylvania. Gestational age was assessed upon delivery on the basis of early pregnancy ultrasound examinations, and preterm births were characterized as those less than 34 weeks and those between 34 and less than 37 weeks to describe severity of preterm birth status. Term births were 37 or more weeks' gestation. We further categorized spontaneous preterm births as those occurring after spontaneous onset of preterm labor with intact membranes or following preterm spontaneous premature rupture of the fetal membranes.

Covariates

Covariates considered were maternal age at delivery; education (less than high school for women older than 19 years who did not complete high school, high school, or some college); smoking during pregnancy (none, 1–10 cigarettes per day, ≥11 cigarettes per day); marital status; and race. Because of the small number of women who reported their race as other than Black or White ($n = 4$), results are reported for Black women vs. White and other women. Measured height and reported prepregnancy weight at the intake visit were used to calculate prepregnancy body mass index (kg/m^2), and women were classified as obese (body mass index: ≥30) or nonobese (body mass index: <30) (23). Family history of hypertension, preeclampsia, or transient hypertension was also self-reported. Preeclampsia during the study pregnancy was considered as de novo systolic blood pressure of greater than 140 mmHg and/or diastolic blood pressure of greater than 90 mmHg on at least two occasions, accompanied by proteinuria. Transient hypertension was defined as the same blood pressure elevations without proteinuria. Household density was categorized as living alone, living with 2–4 in the household, or living with five or more in the household. Moderate or vigorous physical activity in the year before becoming pregnant was self-reported, as were hours of television watching per week as a proxy for sedentary lifestyle.

Analysis

Characteristics of periconceptional vitamin users and nonusers were compared by chi-squared or t tests. Multinomial logistic regression models were used to separately estimate the independent effect of regular periconceptional multivitamin use on the risk of SGA (<5th percentile; 5th–<10th percentiles) and preterm (<34 weeks; 34–<37 weeks) births. Covariates were considered confounders if they changed the beta coefficient of regular multivitamin use related to either the moderate or severe categories of SGA or preterm birth by more than 10 percent; all covariates in the data set were considered. There were 17 infants that were both SGA and preterm. These were included in each separate model and then excluded to ensure that the results were unchanged. Similarly, in order to estimate the unbiased, total effect of vitamin use on the risk of preterm birth and SGA, including that which may be mediated by an

effect on preeclampsia, cases of preeclampsia were included in the analysis. We subsequently limited analysis to spontaneous preterm births. For models evaluating SGA risk, preeclampsia cases were excluded to explore if the results were changed. We also evaluated the effects of daily multivitamin use ($n = 751$) compared with nonuse ($n = 971$).

Effect modification by race, smoking, and prepregnancy body mass index was evaluated using the likelihood ratio test ($\alpha = 0.10$). To account for the possibility of residual confounding, we then sequentially forced into the parsimonious models the remaining socioeconomic variables, lifestyle variables, and pregnancy characteristics that were available in our data set to ensure that the estimates associated with periconceptional multivitamin use remained unchanged.

As with any observational study, unmeasured confounders may have biased our effect estimate. For instance, poor maternal folate intake is more common among nonusers of supplements than regular users (24) and is associated with an increased risk of SGA and preterm birth (16, 25). Thus, it may confound the relation between multivitamin use and SGA and preterm birth. Unfortunately, our study did not collect dietary intake data to quantify folate intake. Therefore, we conducted a sensitivity analysis for unmeasured confounding by low folate intake that was adapted from the work of Lash and Fink (26), as previously described (27). To quantify the degree of unmeasured confounding by folate intake, we parameterized the relative risk due to confounding using a trapezoidal distribution. The limit of the relative risk due to confounding was calculated according to the methods of Flanders and Khoury (28). We compared the odds ratio and 95 percent confidence interval from the conventional multinomial logistic regression model with the estimates obtained after sensitivity analysis iterations and a bootstrapping procedure. These estimates accounted for both systematic and random error.

RESULTS

A total of 47 percent of women reported regular periconceptional multivitamin use. Regular users were more likely than nonusers to be older, better educated, married, of normal body mass index, and to have participated in moderate or vigorous physical activity in the year before becoming pregnant (table 1). Regular users were also less likely to be of Black race/ethnicity, to live alone or with five or more individuals, to report more than 30 hours per week of television viewing, and to smoke during pregnancy. Infants born to mothers who reported regular periconceptional multivitamin use were less likely to be less than 34 weeks preterm, had higher birth weights, on average, and were somewhat less likely to be born SGA (<5th percentile).

Periconceptional multivitamin use and SGA

After adjustment for smoking, education, parity, gestational age at the baseline interview, and prepregnancy body mass index, regular vitamin users had a marginally reduced risk of SGA (<5th percentile) (odds ratio (OR) = 0.64, 95 percent confidence interval (CI): 0.40, 1.03) (table 2). Periconceptional multivitamin use, however, had no effect on the risk of SGA (5th–<10th percentiles). Additional adjustment for other covariates did not meaningfully alter the results, and results remained unchanged when the 17 infants born both preterm and SGA were excluded. In addition, estimates were consistent when limited to women with daily multivitamin use versus none (OR = 0.53, 95 percent CI: 0.31, 0.91) and when cases of preeclampsia were excluded (OR = 0.58, 95 percent CI: 0.35, 0.97).

Sensitivity analysis revealed that unmeasured confounding by low folate intake slightly biased the results away from the null, but the results were consistent with those from the conventional analysis. For example, the adjusted odds ratio of 0.64 associated with SGA (<5th percentile) obtained from the conventional analysis in the total population was attenuated to 0.67 (95 percent simulation interval: 0.41, 1.09) after accounting for systematic and random error.

Prepregnancy obesity modified the relation between periconceptional multivitamin use and the risk of SGA ($p = 0.07$). After adjustment for confounders, nonobese women who used multivitamins had about half the risk of SGA (<5th percentile) compared with nonobese women who did not use multivitamins (OR = 0.54, 95 percent CI: 0.32, 0.91). The risk of SGA (<5th percentile) was not altered by multivitamin use among obese women (OR = 0.87, 95 percent CI: 0.38, 2.01) compared with the same referent. We did not observe further effect modification on the multiplicative scale by race or smoking status.

Periconceptional multivitamin use and preterm birth

After adjustment for confounders that met our a priori criteria (race/ethnicity, age, education, gestational age at interview, and household density), periconceptional multivitamin use was associated with a reduced risk of preterm birth (<34 weeks) (OR = 0.29, 95 percent CI: 0.13, 0.64) (table 3). There was no effect of periconceptional multivitamin use on the risk of preterm birth (34–<37 weeks' gestation). Estimates were unaffected by additional adjustment for maternal, lifestyle, or pregnancy characteristics or by exclusion of infants that were both SGA and preterm. Similarly, sensitivity analysis that accounted for unmeasured confounding by low folate intake did not notably alter the magnitude of the estimates. In addition, results were similar when limited to the 32 cases of spontaneous preterm birth (<34 weeks) (OR = 0.40, 95 percent CI: 0.16, 0.99) and when limited to women who reported daily multivitamin use compared with none (OR = 0.26, 95 percent CI: 0.11, 0.61). There was no evidence of effect measure modification by obesity, body mass index, race, or smoking.

DISCUSSION

Our findings suggest that women who reported periconceptional multivitamin use had a reduced risk of preterm birth before 34 weeks and a reduced risk of SGA (<5th percentile). Report of multivitamin use had no effect on the risk for less severe cases of preterm birth or SGA. While we cannot rule out the possibility that our findings are

TABLE 1. Maternal characteristics by periconceptional multivitamin use, Pregnancy Exposures and Preeclampsia Prevention Study, 1997–2001

	Periconceptional multivitamin users ($n = 852$)	Nonusers ($n = 971$)	p value*
Demographics			
Maternal age (years) (mean (SD†))	27.0 (6)	23.5 (5)	<0.01
Black race ethnicity (no. (%))	193 (22.7)	436 (44.9)	<0.01
Education (no. (%))			<0.01
Less than high school (aged ≥19 years)	46 (5.4)	151 (15.6)	
High school	263 (30.9)	505 (52.0)	
Some college	543 (63.7)	315 (32.4)	
Married or marriage like (no. (%))	397 (46.7)	128 (13.2)	<0.01
Household (no. (%))			
Lives alone	62 (7.3)	85 (8.8)	0.02
2–4 in household	693 (81.6)	734 (76.3)	
≥5 in household	94 (11.1)	143 (14.9)	
Prepregnancy moderate or vigorous physical activity (no. (%))	323 (38.0)	213 (22.0)	<0.01
Prepregnancy usual television watching of >30 hours/week (no. (%))	103 (12.1)	215 (22.2)	<0.01
Prepregnancy body mass index (kg/m^2) (mean (SD))	24.8 (5.9)	25.8 (6.8)	<0.01
<18.5 (no. (%))	57 (6.7)	60 (6.2)	0.03
18.5–24.9 (no. (%))	479 (56.3)	483 (50.0)	
25.0–29.9 (no. (%))	172 (20.2)	221 (22.9)	
≥30 (no. (%))	143 (16.8)	202 (20.9)	
Pregnancy			
Nulliparous (no. (%))	530 (62.2)	594 (61.2)	0.65
Gestational age at baseline interview (weeks) (mean (SD))	10.2 (3.7)	9.7 (4.1)	<0.01
Family history of preeclampsia or hypertension during pregnancy (no. (%))	62 (7.3)	90 (9.3)	0.12
Transient hypertension (no. (%))	48 (5.6)	76 (7.8)	0.09
Smoking (no. (%))			
None	644 (75.6)	608 (62.6)	<0.01
1–10 cigarettes/day	157 (18.4)	293 (30.2)	
≥11 cigarettes/day	51 (6.0)	70 (7.2)	
Gestational age at delivery (weeks) (mean (SD))	38.9 (1.8)	38.7 (2.3)	0.04
Birth weight (g) (mean (SD))	3,349 (562)	3,191 (607)	<0.01
Preterm birth (no. (%))			
34–<37 weeks	52 (6.1)	56 (5.8)	<0.01
<34 weeks	10 (1.2)	34 (3.5)	
Birth weight centile (mean (SD))	54.8 (29.6)	49.5 (29.5)	<0.01
Small for gestational age (no. (%))			
5th–10th percentiles	45 (4.8)	48 (4.9)	0.08
<5th percentile	31 (3.6)	57 (5.9)	

* Chi-squared or t test.
† SD, standard deviation.

TABLE 2. Association between periconceptional multivitamin use and the risk of small for gestational age, Pregnancy Exposures and Preeclampsia Prevention Study, 1997–2001

	5th–<10th percentile			<5th percentile		
	Unadjusted prevalence (%)	Adjusted odds ratio	95% confidence interval	Unadjusted prevalence (%)	Adjusted odds ratio	95% confidence interval
No periconceptional multivitamin use	4.9	1.00		5.9	1.00	
Periconceptional multivitamin use*	4.8	1.13	0.69, 1.77	3.6	0.64	0.40, 1.03
Adjustment for additional confounders						
Maternal characteristics†		1.06	0.65, 1.72		0.68	0.41, 1.12
Health and lifestyle behaviors‡		1.11	0.70, 1.76		0.63	0.39, 1.02
Pregnancy characteristics§		1.12	0.70, 1.79		0.64	0.40, 1.03
Sensitivity analysis: unmeasured confounding by low folate intake¶						
Systematic error and random error						
Point estimate (95% bootstrapped sensitivity analysis interval)		1.07	0.67, 1.72		0.67	0.41, 1.09

* Main model adjusted for smoking, education, parity, gestational age at interview, and body mass index.
† Maternal age, race, marital status, and household density were added to the main model.
‡ Moderate or vigorous physical activity and greater than 30 hours of television watching per week were added to the main model.
§ Gestational age at delivery, transient hypertension, and family history of preeclampsia were added to the main model.
¶ Sensitivity analysis was performed on the main model adjusted for smoking, education, parity, gestational age at interview, and body mass index.

confounded by unmeasured diet and lifestyle factors, our estimates were independent of a variety of sociodemographic, lifestyle, and pregnancy characteristics. In addition, our results did not appear to be confounded by dietary folate intake, an unmeasured variable in our data set. Interestingly, our findings also suggest that periconceptional multivitamin use interacts with body size and may reduce risk of SGA (<5th percentile) only among nonobese women.

TABLE 3. Association between periconceptional multivitamin use and the risk of moderate and early preterm delivery, Pregnancy Exposures and Preeclampsia Prevention Study, 1997–2001

	Preterm birth (34–<37 weeks)			Preterm birth (<34 weeks)		
	Unadjusted prevalence (%)	Adjusted odds ratio	95% confidence interval	Unadjusted prevalence (%)	Adjusted odds ratio	95% confidence interval
No periconceptional multivitamin use	5.8	1.00		3.5	1.00	
Periconceptional multivitamin use*	6.1	1.13	0.74, 1.73	1.2	0.29	0.13, 0.64
Adjustment for additional confounders						
Maternal characteristics†		1.07	0.69, 1.65		0.28	0.12, 0.64
Health and lifestyle behaviors‡		1.08	0.70, 1.66		0.32	0.14, 0.70
Pregnancy characteristics§		1.17	0.77, 1.79		0.29	0.13, 0.64
Sensitivity analysis: unmeasured confounding by low folate intake¶						
Systematic error and random error						
Point estimate (95% bootstrapped sensitivity analysis interval)		1.07	0.70, 1.65		0.31	0.14, 0.67

* Main model adjusted for race, age, education, gestational age at interview, and household density.
† Marital status and body mass index were added to the main model.
‡ Smoking, moderate physical activity, and greater than 30 hours of television watching per week were added to the main model.
§ Parity, preeclampsia, transient hypertension, and family history of preeclampsia were added to the main model.
¶ Sensitivity analysis was performed on the main model adjusted for race, education, gestational age at interview, and household density.

It is well documented that multivitamin users are better educated, have higher incomes, practice more health-promoting behaviors, and are less likely to be of minority ethnicity compared with nonusers (29–32). These are factors also associated with reduced risk of adverse pregnancy outcomes. In addition, randomized trials of vitamin supplementation to reduce the risk of chronic disease and adverse pregnancy outcomes, justified by promising observational findings, have been disappointing (33, 34). Taken together, these factors suggest that our findings should be interpreted cautiously. In addition, while the magnitude of our finding regarding the relation between periconceptional multivitamin use and risk of preterm birth (<34 weeks) was particularly surprising, it was also quite imprecise. However, the periconceptional period may provide a critical opportunity to reduce the risk of the most severe pregnancy complications. Given the current recommendations that women contemplating pregnancy consume supplemental folate, it is unlikely that a randomized trial of periconceptional vitamin use would be feasible. Therefore, cautious and methodologically rigorous observational studies may be the best we will have to investigate this important possibility.

Prenatal multivitamin use during pregnancy and the concentrations of folate, zinc, and vitamins C and E during pregnancy have been related to preterm birth risk (15–17, 21, 35). Periconceptional multivitamin use, however, has been studied less frequently. One case-control study related preconception sufficiency of vitamins B_6 and B_{12} in maternal serum to a 50–60 percent reduced risk for preterm birth (19), a magnitude of effect consistent with our results for spontaneous preterm birth. Another study demonstrated that women who reported multivitamin use throughout the periconceptional period (1 month before through 3 months after conception) had a 60 percent reduction in risk for preterm birth (<37 weeks), but these results were not independent of race/ethnicity and cigarette smoking (18). Our adjusted results suggested an independent protective effect of periconceptional multivitamin use related to preterm birth (<34 weeks only); there was no effect when all preterm births at less than 37 weeks were grouped. Our results are generally consistent with those from another study that suggested that preconception multivitamin use reduced the risk of preterm birth (20). In that study, combining preconception use and prenatal use into one variable masked the protective effect of preconception use. Similarly, when we combined multivitamin use in the last 3 months of pregnancy with periconceptional use in our analysis, there was no longer a significant association with preterm birth (<34 weeks) (data not shown).

Fetal growth has a well-established relation with maternal nutrition (36), but studies designed to relate periconceptional micronutrients and SGA risk are sparse. Ronnenberg et al. (19) reported a modest, nonsignificant reduction in risk of delivering an SGA infant among women with high preconception folate concentrations. It is noteworthy that this study aggregated SGA (<10th percentile), as our results approached significance only when limited to infants (<5th percentile). This threshold may better distinguish growth-restricted from constitutionally small infants. Indirect evidence from a large, randomized preeclampsia prevention trial among high-risk women indicated that pregnant women who were taking multivitamins prior to randomization at 18 weeks' gestation, a reasonable proxy for periconceptional exposure, had the highest serum concentrations of vitamin C and had fewer SGA infants (<5th percentile) (OR = 0.42, 95 percent CI: 0.26, 0.67) (34). A systematic review of prenatal nutritional interventions in developed countries to prevent or treat impaired fetal growth produced equivocal results (37). Indeed, this review indicated that one understudied area was the role of periconceptional supplementation, a primary aim of these analyses.

Although mechanisms that may link periconceptional multivitamin use to preterm birth or SGA are not understood, placentation is one possibility. Abnormal placentation with failed remodeling of maternal vessels perfusing the placenta has been associated with both spontaneous preterm birth (38–41) and growth restriction without preeclampsia (42, 43). Our group has previously reported that regular multivitamin use in the periconceptional period may reduce the risk of preeclampsia, a pregnancy complication with a well-established relation with poor placentation (27). Placentation is characterized by vascular remodeling, oxidative stress, inflammation, and rapid cell division, all of which may be affected by nutritional status. In fact, nearly all nutrients found in typical prenatal/multivitamins may be hypothesized to aid in the process of normal placentation. Folate and vitamin B_{12} have already been linked to defects in the placental vascular bed (44), but other nutrients such as vitamin C, vitamin E, vitamin D, iron, and zinc may be equally as important. (45) It is likely that some of the effect of periconceptional multivitamin use on the risk of preterm birth and SGA may be mediated by the effect on preeclampsia risk, perhaps by impacting placentation. However, a protective effect persisted in our data when results were limited to spontaneous preterm births that removed all but two cases of preeclampsia from the preterm births before 34 weeks. Similarly, the effect of periconceptional use on SGA (<5th percentile) was detectable when cases of preeclampsia were removed.

Our finding that periconceptional vitamin supplementation is associated with preterm birth (<34 weeks) has been reported by others (15). Given the strong association between intrauterine infection and early preterm birth (46), it is possible that micronutrient supplementation leading to improved nutritional status at the time of implantation may play a key role in this pathway. Evidence from other disease processes involving inflammatory pathogeneses supports this possibility (47–50). We were unable to assess the presence of infection or inflammation early in pregnancy related to periconceptional multivitamin use, but this warrants further study.

Our results suggest the intriguing possibility that periconceptional multivitamin use may reduce the risk of only SGA (<5th percentile) among nonobese women. Although we had limited power to definitively test this hypothesis, our results are consistent with previous evidence that high body mass index reduces or eliminates the protective effect that multivitamins or single supplements have on preeclampsia (27), birth weight (14), preterm birth (14), and neural tube defects (51). In addition, our results are consistent with the evidence that underweight is a risk factor for fetal growth

restriction (8), as low body mass index may identify a nutritionally high-risk population amenable to supplementation benefits. Our study did not have adequate numbers of underweight women to explore this hypothesis specifically.

Our results should be considered in light of several important limitations. We attempted to account for factors that might be related to periconceptional multivitamin use, preterm birth, and growth restriction, including folate intake (an unmeasured confounder). However, we cannot rule out the possibility that our results are due to misclassification of the confounders we measured and/or confounding by additional unmeasured factors, such as other dietary exposures, lifestyle factors, maternal genetic variation, access to health care, or additional socioeconomic factors. We also relied on self-reported multivitamin use, which may have been prone to misclassification. However, it is noteworthy that our assessment of multivitamin use occurred, on average, before 10 weeks' gestation, thus limiting the possibility of confounding by multivitamin use initiated after the start of pregnancy. Because our study did not assess the brand or dose of supplements and did not more finely classify the duration or frequency of supplement use, we were unable to evaluate which micronutrients may have contributed most to this effect. We also could not determine when in the periconceptional period multivitamin use may be most related to risk for adverse pregnancy outcomes.

Our results indicate that nutritional status before conception or very early in pregnancy may play a critical role in the delivery of an appropriately grown, term infant. Our findings appear robust, as they were independent of a variety of maternal, lifestyle, and pregnancy characteristics, and they did not appear to be confounded by folate intake. However, the relation between vitamin use, lifestyle, and adverse pregnancy outcomes requires further investigation.

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