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Maternal Dietary Nutrient Intake and Risk of Preterm Delivery

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Abstract

Objective—To examine maternal dietary intake and preterm delivery.

Study Design—Data included 5738 deliveries from the National Birth Defects Prevention Study. Odds ratios (ORs) reflected risks of delivery at <32, 32–34, or 35–36 versus ≥37 weeks for maternal intake in the lowest or highest quartile of nutrient intake compared with the middle two.

Results—Among deliveries < 32 weeks, many ORs were ≥1.5 or ≤0.7, but few confidence intervals excluded one. ORs were 1.5 for lowest quartiles of protein, thiamin, riboflavin, choline, vitamin A, α-carotene, β-carotene, vitamin E, iron, copper, and zinc and for highest quartiles of carbohydrate, glycemic index, and Mediterranean Diet Score. ORs were ≤0.7 for lowest quartiles of glycemic index and betaine and for highest quartiles of protein, alanine, methionine, vitamin B_6, betaine, and calcium. Few ORs met these criteria for later preterm deliveries.

Conclusions—Results suggested an association of nutrient intake with earlier preterm deliveries.

Keywords

nutrition; pregnancy; preterm delivery

Etiologies for spontaneous preterm delivery are largely unknown. Several factors have been associated with the increased risk of preterm delivery. These include racial disparities, infection, stress, and genetics.[1] Many nutrients have been investigated for their contributions to the etiologies of preterm delivery, for example iron, folate, zinc, carotenoids, calcium, and magnesium.[2,3] Nutrients contribute to a variety of mechanisms that are potentially important to preterm delivery, such as infection, inflammation, oxidative stress, and muscle contractility.[2]

Although many studies have suggested associations of various nutrients with preterm delivery, the body of literature for any particular nutrient has inconsistencies. Variability in study design (e.g., trials versus observational studies, retrospective versus prospective

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studies) and approach to exposure assessment (e.g., serum biomarkers versus intake from foods or supplements) may contribute to discrepancies.

In addition, differences in definitions of preterm delivery (e.g., whether spontaneous or medically indicated, or <37 weeks versus earlier) may contribute. Third, variability in baseline characteristics of the study populations, such as the baseline prevalence of overt deficiency or the baseline risk of preterm delivery, may result in different findings. Thus, inconsistencies likely stem at least in part from the inherent complexity of the question, although they may also be indicative of truly no association or only weak association.

Many studies of nutrition and preterm delivery have focused on serum biomarkers or supplementation trials. Understanding the association of dietary intake of nutrients is also important, given that many women do not take supplements. In addition, most studies have focused on one or at most a few nutrients at a time, but understanding the association of preterm delivery with a broader spectrum of nutrients is also important. Nutrients co-occur in foods and interact in vivo, and multiple nutrients contribute to many of the mechanisms proposed to contribute to preterm delivery.[4] For example, folate has been proposed to contribute to preterm delivery,[5] but multiple nutrients are involved in folate-related metabolism. Investigations that extend beyond just folate could provide evidence for coherence regarding this proposed pathway. Analytic approaches that attempt to account for these inherent interactions may also contribute to our understanding; one such approach is to characterize the overall diet quality.

The objective of the current study was to examine the association of dietary intake of a broad spectrum of nutrients, as well as general diet quality, with risk of preterm delivery. Data are from mothers who delivered nonmalformed infants and participated in the National Birth Defects Prevention Study (NBDPS), a multicenter population-based case-control study.

Methods

This analysis included data on deliveries that were part of the NBDPS. The NBDPS is an approved activity of the Institutional Review Boards of the participating study centers, and informed consent was obtained from study subjects. Detailed study methods have been published.[6] Each center randomly selected around 150 nonmalformed, live-born controls per study year from birth certificates (Arkansas 2000 to 2005, Georgia 2001 to 2005, Iowa, Massachusetts, North Carolina, New Jersey, Utah) or from birth hospitals (Arkansas 1997 to 1999, California, Georgia 1997 to 2000, New York, Texas) to represent the population from which the cases were derived. Infants selected as controls for the multicenter effort served as the base study population for this analysis.

We included deliveries that had estimated due dates from September 1998 through December 2005. Although deliveries from an earlier time period were available, we restricted to the 1998 period onward to coincide with the timing of U.S. fortification of the food supply with folic acid. Thus, included deliveries were all potentially exposed to a folate-fortified food supply during their entire pregnancy.

Maternal interviews were conducted using a standardized, computer-based questionnaire, primarily by telephone, in English or Spanish, no earlier than 6 weeks after the infant's estimated date of delivery, and no later than 24 months after delivery. Exposures to a variety of factors were assessed, relative to a woman's estimated date of conception, using telephone interviews. Date of conception and gestational age at delivery were derived primarily from mother's self-reported due date and the baby's date of birth. Participation in the interview was 68% among studied control mothers. Interviews were conducted with 5952 mothers who had singleton pregnancies and were completed within an average of 9 months from date of delivery. We limited analyses to 5912 women without type I (*n* ¼ 18) or type II (*n* ¼ 22) diabetes.

A shortened version of the food frequency questionnaire from the Nurse's Health Study was used to assess frequency of intake of 58 food items during the year before pregnancy.[7] Separate, more detailed questions were used to assess intakes of breakfast cereals and sodas during the 3 months before pregnancy. The U.S. Department of Agriculture (USDA) nutrient database (version 20) was the source of values used to compute dietary intake of the specific nutrients that we investigated.[8] The overall dietary glycemic index was calculated by multiplying each food item's glycemic index value by its number of servings and grams of carbohydrate per serving, summing these products across all food items, and then dividing the sum by the total reported carbohydrate. Data on dietary constituents were available (not missing) for 5738 of the 5912 eligible study subjects.

We also examined two diet quality indices that were modeled after the Mediterranean Diet Score (MDS)[9,10] and the Diet Quality Index for Pregnancy (DQI),[11] which focus on overall diet quality from the perspective of the Mediterranean diet and the USDA Food Guide Pyramid, respectively. Details are provided elsewhere.[12] In brief, the MDS is a summary of intake of six positively scored components (legumes, grains, fruits and nuts, vegetables, fish, and the ratio of monounsaturated to saturated fatty acid intake) and three negatively scored components (dairy, meat, and sweets). The DQI is the summary score of six positively scored components (grains, vegetables, fruits, folate, iron, and calcium) and two negatively scored components (percent of calories from fat and sweets).

Logistic regression analyses were conducted to estimate odds ratios (ORs) and 95% confidence intervals (CIs) reflecting the association of preterm delivery with intake of each nutritional factor of interest. We examined risk of delivery at <32 weeks, 32 to 34 weeks, and 35 to 36 weeks, relative to delivery at ≥37 weeks. Dietary intake variables were categorized into quartiles based on the distribution among nonpreterm deliveries. The middle two quartiles served as the reference group. We also assessed each nutritional factor as a continuous variable. All analyses were adjusted for energy intake as a continuous variable. Intake of vitamin/mineral supplements was assessed as any versus no intake of folic acid-containing supplements (which are largely multivitamin/mineral formulations in this study) from 1 month before delivery through the date of delivery.[13] The following covariates were selected a priori for consideration as potential confounders: maternal race/ethnicity (non-Hispanic white, U.S.-born Hispanic, foreign-born Hispanic, African-American, other); education (less than, equal to, or greater than high school); number of previous live births (0, 1, 2, >2); age (years); prepregnancy body mass index (kg/m^2);

gestational diabetes; and any versus no smoking, alcohol intake, or fertility treatments or procedures that occurred from 1 month before delivery through the date of delivery. Given that most women took vitamin/mineral supplements, we examined whether results were markedly different after excluding women who did not take supplements.

Results

Approximately 8.2% of infants were born preterm (<37 weeks), with 1.0% *n* = 58) born at <32 weeks gestation, 2.1% (*n* ¼ 120) at 33 to 34 weeks, and 5.1% (*n* = 293) at 35 to 36 weeks. Mothers of the most preterm infants (<32 weeks) were significantly ($p < 0.05$) more likely to be black and less likely to drink (**Table 1**). Differences based on the other covariates were not statistically significant ($p > 0.05$).

We investigated 27 dietary constituents and two dietary quality indices. From these analyses (**Table 2**), very few ORs based on the quartile comparisons had CIs that excluded 1.0. Low intakes of β-carotene and zinc were associated with increased risk of deliveries before 32 weeks. Low intake of α-carotene was associated with increased risk of deliveries at 35 to 36 weeks. Using a criterion of ORs ≥1.5 or ≤0.7 several other potential associations are notable. Among deliveries < 32 weeks, many ORs were ≥1.5 or ≤0.7. The OR was ≥1.5 for the lowest quartile of protein, thiamin, riboflavin, choline, vitamin A, α-carotene, β-carotene, vitamin E, iron, copper, zinc, and the MDS and for the highest quartile of carbohydrate and glycemic index. The OR was ≤0.7 for the lowest quartile of glycemic index and betaine and for the highest quartile of protein, alanine, methionine, vitamin B_6, betaine, and calcium. Among deliveries at 32 to 34 weeks, the OR was ≥1.5 for the lowest quartile of vitamin C, iron, and the MDS, and for high glycemic index and choline intake; and it was ≤0.7 for the highest quartile of niacin, β-carotene, calcium, zinc and the DQI. Among deliveries at 35 to 36 weeks, only one OR was ≤1.5 or ≥0.7; the OR for high quartile intake of iron was 0.7. Thus, many associations met the magnitude criterion in the <32-week group, whereas only a few met it in the groupings of deliveries that were more frequent but less preterm.

Several ORs for the analysis of each nutritional factor as a continuous variable had CIs that excluded 1.0. Specifically, the results suggested that higher glycemic index was associated with increased risk of delivery <32 weeks; higher intakes of α-carotene and magnesium were associated with decreased risk of delivery at 32 to 34 weeks, but higher intake of vitamin B_{12} was associated with increased risk; and higher intakes of vitamin E and iron were associated with decreased risk of delivery at 35 to 36 weeks.

Adjustment for race-ethnicity and alcohol intake (the two potential covariates that were significantly associated with the gestational age groupings; **Table 1**) did not substantially change this pattern of results (data not shown). Removing women who did not take folic acid-containing vitamin/mineral supplements during the month before pregnancy or during pregnancy also did not substantially affect the pattern (data not shown).

Discussion

We explored a broad spectrum of nutrients for their potential association with preterm delivery. Dietary intake of most of the studied nutrients was not associated with risk of preterm delivery, based on the observation that confidence intervals for most of the comparisons included one. However, based on magnitude of effect (e.g., an odds ratio of >1.5 for low intake rather than statistical precision criteria), intake of many of the nutrients was associated with delivery at <32 weeks' gestation. Most of these associations were in the expected direction, which for many nutrients was that higher intake would be associated with reduced odds of early delivery. Fewer nutrients were associated with later preterm delivery. Thus, the results suggest that dietary nutrient intake may be more important for the very early deliveries than for the later preterm deliveries.

The literature on the association of nutrient status and preterm birth is highly variable, with no firm consensus on any particular nutrient. Some of the more commonly investigated nutrients include iron, zinc, vitamins C and E, folate, and calcium. Studies suggest that anemia is associated with increased risk and iron supplementation may be protective, although this is still debatable.[4,14,15] Dietary iron has not been studied. Dietary zinc was investigated by one study of low-income women and found to be protective especially against very preterm birth[16]; a review of numerous supplementation trials concluded that zinc was modestly protective.[17] Trials of vitamin C and E supplementation have not shown protective effects,[18–20] but only a few have been conducted, primarily among high-risk women. One trial reported that combined supplementation with vitamins C and E was protective against preterm premature rupture of membranes (PPROM) at <32 weeks' gestation but not later PPROM,[18] and another study reported that dietary vitamin C was protective against PPROM at <37 weeks' gestation,[21] whereas vitamin C was not protective against other preterm subtypes. Another recent study reported that higher maternal serum levels of various carotenoids at 24 to 26 weeks' gestation were associated with reduced risk of preterm delivery, regardless of preterm subtype (i.e., preceded by labor or premature rupture of membranes) or gestational age.[3] Vitamins C and E and carotenoids all have antioxidant properties and thus may contribute to a common biological pathway. Many studies have examined folate, in serum, supplements, or diet, but results are inconsistent.[22] Many trials have examined supplemental calcium but do not show an overall protective effect.[23] Associations with these nutrients were observed in the current study (albeit most not statistically significant), with the exception of folate. Although this synopsis is not exhaustive, it illustrates the general perspective of the literature and how limited our knowledge is regarding most specific nutrients. In particular, few studies have investigated dietary intake of most nutrients, and thus our study contributes to that aspect of our understanding.

As far as we know, our study represents the first investigation of some of the studied nutritional factors in relation to preterm delivery. For example, dietary glycemic index has been associated with birth outcomes such as growth retardation,[24] but we are unaware of any previous studies of its association with preterm delivery, except for one small trial of a low glycemic load diet among overweight and obese women.[25] Its investigation is plausible, however, given that increasing glucose levels, within ranges below levels that are diagnostic of diabetes, have been associated with preterm delivery,[26] and dietary glycemic index correlates with glycemic control in pregnant women.[27] As noted, several studies have examined the association of folate with preterm delivery, but other nutrients involved in one-carbon metabolism (e.g., other B vitamins, methionine) have not to our knowledge been investigated.

Another unique feature of our current analysis is its examination of many dietary components in a single study population. Most previous studies of nutrition and preterm birth have focused on supplements or biomarkers rather than dietary intake. Most have also focused on one or two nutrients at a time. Given the breadth of contributions that various nutrients make to various potential underlying mechanisms (e.g., oxidative stress, iron status) of preterm delivery, we believed it prudent to cast a broad net. Accordingly, we examined a variety of nutrients, and we also examined general diet quality. We did not apply complex multivariable modeling to the nutrients, however, largely due to the limited number of very preterm deliveries. We are aware of two previous studies that attempted to characterize overall diet quality, based on how closely women's diets followed a Mediterranean dietary pattern, which typically emphasizes fruits and vegetables, whole grains, and unsaturated fats. One study was positive and one was negative.[28,29] The impetus to conduct these observational studies was a trial that found that assignment to a diet emphasizing this type of dietary pattern was protective against preterm delivery among low-risk women.[30] Diet quality indices were not consistently associated with preterm delivery in our study. We acknowledge that there are many other approaches to characterizing diet quality, and it is possible that others would better capture underlying interactions between nutrients and foods, but their pursuit was beyond the scope of the present analysis.

A continued challenge facing studies of preterm delivery is the most appropriate way to consider the preterm pheno-types. Our study split deliveries based on gestational age; further information about preceding events (e.g., labor, premature rupture of membranes, or medical indication) was not available. Most studies of preterm delivery and nutrition have limited their investigation to risks among deliveries at <37 weeks versus later. A few exceptions do exist,[3,18,21,24] but at this point it is difficult to reach conclusions regarding how best to parse specific phenotypes for etiologic inquiries.

Strengths of the current analysis include its population-based design, its investigation of multiple nutrients and varied gestational age cutoffs, and its exclusion of infants born with major birth defects (which are more likely to be delivered preterm and may also be related to maternal nutritional status). Important limitations are the relatively small number of very early deliveries, the inability to analyze subtypes of preterm delivery (e.g., those preceded by spontaneous onset of labor), and the fact that gestational age was self-reported. We could not rule out chance as an alternative explanation for most of our results, due in part to limited sample size. In addition, we did not adjust results for multiple comparisons but instead have focused on the pattern and magnitude of odds ratios. Another limitation is that we relied on maternal recall of prepregnancy diet, using a food frequency questionnaire. The instrument we used has been validated previously in other populations indicating reasonable estimates of usual dietary intake for diets consumed even in the distant past.[7,31] It enabled assessment of a variety of nutrients, although some nutrients of interest were either not available or not particularly suitable to assessment by food frequency questionnaire (e.g., vitamin D). Our study examined diet during the year before pregnancy. This timing is likely to represent the mother's dietary habits during the first weeks of pregnancy, before she knew she was pregnant and/ or before major symptoms like nausea and vomiting ensued, which could result in substantial changes in dietary intake. Although the critical time window of exposure for the potential prevention of preterm delivery is uncertain, evidence is accumulating that exposures during very early pregnancy may contribute to the timing of delivery.[4]

In conclusion, results suggested an association of dietary intake of several nutrients with risk of very early preterm delivery, but no apparent association with later preterm delivery. The relatively small number of very early deliveries, and the novelty of many of our inquiries, indicate that our results should be interpreted with caution until they can be verified in other study populations. Current findings coupled with the general perspective from the literature that a variety of nutrients is associated with preterm delivery support current recommendations regarding diet during pregnancy. That is, pregnant women should consume a well-balanced diet rich in a variety of macro- and micronutrients.[32] The etiologies of preterm delivery remain elusive. It would appear that further investigations are necessary to elucidate the specifics of any particular nutrient-preterm association, but such knowledge would likely improve our eventual understanding of what causes preterm delivery and how to prevent it.

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Table 1

Descriptive characteristics of mothers of infants who were or were not delivered preterm

	Percent of subjects[a]				*p* Value[b]
	<32 wk (*n* = 58)	32–34 wk (*n* = 120)	35–36 wk (*n* = 293)	≥37 wk (*n* = 5267)	
Maternal race/ethnicity					
Non-Hispanic white	46.6	52.5	57.3	59.6	<0.01
Non-Hispanic black	29.3	15.8	11.9	10.7	
US-born Hispanic	8.6	11.7	12.6	10.2	
Foreign-born Hispanic	10.3	10.8	9.9	12.5	
Other	3.4	9.2	7.5	36.4	
Education					
<High school	19.0	15.0	17.4	16.8	0.47
=High school	31.0	31.7	25.9	24.5	
>High school	48.3	53.3	55.6	58.2	
Parity					
0	46.6	41.7	40.3	39.8	0.76
1	36.2	30.8	29.7	33.4	
2	10.3	16.7	18.4	17.4	
>2	6.9	10.8	11.3	49.4	
Vitamin/mineral supplement intake[c]					
No	6.9	4.2	5.8	4.8	0.73
Yes	89.7	94.2	93.2	94.1	
Smoking[c]					
No	84.5	74.2	77.5	80.9	0.12
Yes	15.5	25.8	22.2	18.9	
Alcohol intake[c]					
No	75.9	62.5	66.2	59.5	0.01
Yes	24.1	36.7	33.4	40.0	
Gestational diabetes					
No	91.4	92.5	92.5	93.6	0.40
Yes	6.9	5.0	5.1	4.0	
Fertility treatments or procedures[c]					
No	93.1	96.7	93.9	95.9	0.48
Yes	5.2	3.3	5.8	4.1	
Maternal age at delivery (y), mean (SD)	26.21 (6.61)	27.23 (6.40)	27.74 (6.42)	27.55 (6.07)	0.33
Prepregnancy body mass index (kg/m^2), mean (SD)	25.31 (5.53)	24.92 (6.82)	24.72 (5.58)	24.96 (5.66)	0.86

Abbreviation: SD, standard deviation.

[a]Percentages may not equal 100 due to missing data or rounding.

[b]For categorical variables, chi-square tests were applied except for gestational diabetes. Fisher exact test was used for gestational diabetes due to 25% of the cells having expected counts less than 5. F test was used for continuous variables.

[c]Refers to the period 1 month before through end of pregnancy.

Table 2

Association of dietary nutrient intakes with risk of preterm delivery

Nutrients and quartile ranges[b]	No. of subjects				Odds ratios (95% confidence intervals)[a]		
	<32 wk	32–34 wk	35–36 wk	≥ 37	<32 wk	32–34 wk	35–36 wk
Carbohydrate (g)							
<150.7	12	36	68	1316	0.8 (0.4, 1.8)	1.2 (0.7, 2.0)	1.0 (0.7, 1.4)
150.7–278.9	26	56	144	2634	Reference	Reference	Reference
≥279.0	20	28	81	1317	1.9 (0.8, 4.4)	1.1 (0.6, 2.2)	1.1 (0.7, 1.6)
Continuous (128.3-unit change)	58	120	293	5267	1.56 (0.69, 3.54)	1.12 (0.60, 2.10)	0.96 (0.66, 1. 41)
Protein (g)							
<50.1	17	32	70	1317	1.6 (0.8, 3.1)	1.0 (0.6, 1.6)	1.0 (0.7, 1.4)
50.1–84.4	27	63	149	2634	Reference	Reference	Reference
≥84.5	14	25	74	1316	0.7 (0.3, 1.5)	0.9 (0.5, 1.5)	0.9 (0.6, 1.2)
Continuous (34.4-unit change)	58	120	293	5267	0.84 (0.49, 1.44)	0.72 (0.47, 1.09)	0.93 (0.72, 1.20)
Alanine (g)							
<2.3 (g)	16	32	71	1316	1.4 (0.7, 2.6)	1.0 (0.6, 1.6)	1.0 (0.8, 1.4)
2.3–3.8	28	64	148	2634	Reference	Reference	Reference
≥3.9	14	24	74	1317	0.7 (0.3, 1.6)	0.8 (0.4, 1.4)	0.9 (0.6, 1.2)
Continuous (1.6-unit change)	58	120	293	5267	0.99 (0.63, 1.56)	0.82 (0.57, 1.17)	0.99 (0.80, 1.22)
Methionine (g)							
<1.1	16	30	63	1317	1.3 (0.7, 2.6)	0.9 (0.5, 1.4)	0.8 (0.6, 1.2)
1.1–1.8	29	66	160	2633	Reference	Reference	Reference
≥1.9	13	24	70	1317	0.6 (0.3, 1.4)	0.8 (0.4, 1.4)	0.8 (0.5, 1.1)
Continuous (0.8-unit change)	58	120	293	5267	0.92 (0.57, 1.47)	0.82 (0.57, 1.18)	1.01 (0.81, 1.25)
Cysteine (g)							
<0.7	16	39	80	1316	1.4 (0.7, 2.7)	1.4 (0.9, 2.2)	1.3 (0.9, 1.7)
0.7–1.1	26	53	135	2635	Reference	Reference	Reference
≥1.2	16	28	78	1316	1.0 (0.5, 2.1)	1.1 (0.6, 1.9)	1.0 (0.7, 1.4)
Continuous (0.5-unit change)	58	120	293	5267	0.94 (0.61, 1.45)	0.81 (0.58, 1.14)	1.02 (0.83, 1.24)
Fat (g)							
<33.9	15	30	71	1317	1.3 (0.6, 2.5)	0.9 (0.5, 1.4)	1.1 (0.8, 1.4)
33.9–60.6	28	61	151	2634	Reference	Reference	Reference
≥60.7	15	29	71	1316	0.8 (0.3, 1.8)	1.2 (0.7, 2.2)	0.8 (0.5, 1.1)
Continuous (26.8-unit change)	58	120	293	5267	0.70 (0.40, 1.23)	1.10 (0.72, 1.69)	1.07 (0.83, 1.39)
Glycemic index							
<49.2	8	29	62	1316	0.6 (0.3, 1.3)	1.1 (0.7, 1.8)	0.9 (0.6, 1.2)
49.2–55.6	28	52	145	2634	Reference	Reference	Reference
≥55.7	22	39	86	1317	1.6 (0.9, 2.7)	1.5 (1.0, 2.3)	1.2 (0.9, 1.6)
Continuous (6.5-unit change)	58	120	293	5267	1.74 (1.21, 2.51)	1.28 (0.99, 1.65)	1.12 (0.95, 1.32)

Nutrients and quartile ranges[b]	No. of subjects				Odds ratios (95% confidence intervals)[a]		
	<32 wk	32–34 wk	35–36 wk	≥ 37	<32 wk	32–34 wk	35–36 wk
Folate (μg DFE)							
<339.4	15	38	77	1317	1.2 (0.6, 2.4)	1.3 (0.9, 2.1)	1.1 (0.8, 1.5)
339.4–718.0	26	56	146	2633	Reference	Reference	Reference
≥718.1	17	26	70	1317	1.2 (0.6, 2.3)	1.0 (0.6, 1.6)	0.8 (0.6, 1.2)
Continuous (378.7-unit change)	58	120	293	5267	1.12 (0.88, 1.42)	0.94 (0.74, 1.19)	0.89 (0.76, 1.04)
Thiamin (mg)							
<0.9	18	35	78	1316	1.8 (0.9, 3.5)	1.2 (0.7, 1.8)	1.2 (0.9, 1.6)
0.9–1.6	22	59	145	2635	Reference	Reference	Reference
≥1.7	18	26	70	1316	1.4 (0.7, 2.9)	0.9 (0.5, 1.6)	0.8 (0.6, 1.1)
Continuous (0.8-unit change)	58	120	293	5267	1.25 (0.89, 1.77)	0.94 (0.68, 1.29)	0.86 (0.71, 1.06)
Riboflavin (mg)							
<1.4	17	35	78	1316	1.5 (0.8, 2.9)	1.2 (0.7, 1.8)	1.2 (0.9, 1.6)
1.4–2.5	26	59	137	2635	Reference	Reference	Reference
≥2.6	15	26	78	1316	0.9 (0.4, 1.9)	0.9 (0.5, 1.6)	1.0 (0.7, 1.4)
Continuous (1.2-unit change)	58	120	293	5267	0.91 (0.60, 1.40)	1.13 (0.83, 1.53)	0.94 (0.78, 1.15)
Niacin (mg)							
<13.4	12	32	79	1317	0.9 (0.4, 1.8)	1.0 (0.6, 1.5)	1.2 (0.9, 1.7)
13.4–23.5	27	65	138	2633	Reference	Reference	Reference
≥23.6	19	23	76	1317	1.4 (0.7, 2.8)	0.7 (0.4, 1.3)	1.0 (0.7, 1.4)
Continuous (10.2-unit change)	58	120	293	5267	1.33 (0.97, 1.82)	0.88 (0.64, 1.21)	0.90 (0.74, 1.09)
Vitamin B_6 (mg)							
<1.4	16	32	72	1316	1.4 (0.7, 2.7)	1.0 (0.6, 1.6)	1.0 (0.8, 1.4)
1.4–2.6	28	63	152	2634	Reference	Reference	Reference
≥2.7	14	25	69	1317	0.7 (0.3, 1.6)	0.8 (0.5, 1.5)	0.8 (0.5, 1.1)
Continuous (1.3-unit change)	58	120	293	5267	1.10 (0.75, 1.61)	0.84 (0.59, 1.18)	0.88 (0.72, 1.09)
Vitamin B_{12} (μg)							
<3.5	16	33	69	1317	1.4 (0.7, 2.7)	1.1 (0.7, 1.7)	1.0 (0.7, 1.3)
3.5–7.3	25	59	155	2634	Reference	Reference	Reference
≥7.4	17	28	69	1316	1.2 (0.6, 2.4)	1.0 (0.6, 1.7)	0.8 (0.6, 1.1)
Continuous (3.9-unit change)	58	120	293	5267	0.96 (0.75, 1.23)	1.13 (1.01, 1.25)	1.04 (0.96, 1.14)
Choline (mg)							
<191.6	18	33	80	1317	1.8 (0.9, 3.5)	1.0 (0.7, 1.7)	1.3 (0.9, 1.7)
191.6–342.8	23	55	138	2633	Reference	Reference	Reference
≥342.9	17	32	75	1317	1.1 (0.5, 2.5)	1.5 (0.9, 2.6)	0.9 (0.6, 1.3)
Continuous (151.3-unit change)	58	120	293	5267	1.15 (0.75, 1.76)	1.26 (0.92, 1.74)	0.98 (0.79, 1.21)
Betaine (mg)							
<46.6	8	34	72	1316	0.5 (0.2, 1.0)	1.1 (0.7, 1.7)	1.0 (0.7, 1.3)
46.6–123.5	36	61	149	2634	Reference	Reference	Reference

Nutrients and quartile ranges[b]	No. of subjects				Odds ratios (95% confidence intervals)[a]		
	<32 wk	32–34 wk	35–36 wk	≥ 37	<32 wk	32–34 wk	35–36 wk
≥123.6	14	25	72	1317	0.7 (0.4, 1.4)	0.8 (0.5, 1.4)	0.9 (0.7, 1.3)
Continuous (77-unit change)	58	120	293	5267	1.09 (0.93, 1.27)	0.93 (0.79, 1.10)	1.01 (0.92, 1.10)
Vitamin A (μg RAE)							
<391.5	19	35	84	1317	1.8 (0.9, 3.3)	1.1 (0.7, 1.7)	1.4 (1.0, 1.8)
391.5–854.4	24	61	129	2634	Reference	Reference	Reference
≥854.5	15	24	80	1316	1.0 (0.5, 2.1)	0.8 (0.5, 1.4)	1.1 (0.8, 1.6)
Continuous (463-unit change)	58	120	293	5267	1.01 (0.81, 1.25)	1.06 (0.91, 1.23)	1.05 (0.96, 1.15)
Alpha-carotene (μg)							
<158.6	20	41	89	1317	1.6 (0.9, 2.8)	1.4 (1.0, 2.2)	1.4 (1.1, 1.9)
158.6–843.4	26	57	125	2633	Reference	Reference	Reference
≥843.5	12	22	79	1317	0.9 (0.4, 1.7)	0.8 (0.5, 1.3)	1.2 (0.9, 1.6)
Continuous (684.9-unit change)	58	120	293	5267	1.02 (0.86, 1.22)	0.75 (0.58, 0.96)	1.02 (0.93, 1.11)
Beta-carotene (μg)							
<1072.2	22	36	86	1317	1.9 (1.1, 3.5)	1.1 (0.7, 1.7)	1.3 (1.0, 1.7)
1072.2–3591.2	24	64	135	2633	Reference	Reference	Reference
≥3591.3	12	20	72	1317	0.9 (0.4, 1.8)	0.6 (0.4, 1.1)	1.0 (0.8, 1.4)
Continuous (2519.1-unit change)	58	120	293	5267	1.05 (0.86, 1.28)	0.82 (0.65, 1.04)	0.99 (0.89, 1.10)
Lutein (μg)							
<762.3	16	33	74	1316	1.2 (0.6, 2.2)	1.1 (0.7, 1.7)	1.1 (0.8, 1.4)
762.3–2212.2	29	58	145	2634	Reference	Reference	Reference
≥2212.3	13	29	74	1317	0.8 (0.4, 1.6)	1.0 (0.7, 1.6)	1.0 (0.7, 1.3)
Continuous (1450-unit change)	58	120	293	5267	1.02 (0.86, 1.22)	0.98 (0.85, 1.14)	1.00 (0.91, 1.09)
Vitamin C (mg)							
<60.0	15	41	81	1316	1.2 (0.6, 2.3)	1.6 (1.0, 2.4)	1.2 (0.9, 1.6)
60.0–154.7	26	52	140	2635	Reference	Reference	Reference
≥154.8	17	27	72	1316	1.2 (0.6, 2.3)	1.1 (0.6, 1.8)	0.9 (0.7, 1.3)
Continuous (94.8-unit change)	58	120	293	5267	1.03 (0.77, 1.37)	0.97 (0.77, 1.22)	0.93 (0.80, 1.07)
Vitamin E (mg)							
<2.9	19	32	78	1316	1.9 (1.0, 3.6)	1.0 (0.6, 1.5)	1.2 (0.9, 1.6)
2.9–6.1	23	64	145	2634	Reference	Reference	Reference
≥6.2	16	24	70	1317	1.1 (0.5, 2.3)	0.8 (0.5, 1.3)	0.8 (0.6, 1.2)
Continuous (3.3-unit change)	58	120	293	5267	0.79 (0.55, 1.15)	0.97 (0.78, 1.21)	0.85 (0.72, 0.99)
Iron (mg)							
<8.7	19	39	78	1316	1.9 (1.0, 3.7)	1.5 (0.9, 2.3)	1.2 (0.9, 1.6)
8.7–17.6	23	50	150	2634	Reference	Reference	Reference
≥17.7	16	31	65	1317	1.1 (0.5, 2.3)	1.3 (0.8, 2.2)	0.7 (0.5, 1.0)
Continuous (9-unit change)	58	120	293	5267	1.11 (0.84, 1.46)	1.04 (0.83, 1.31)	0.83 (0.70, 0.99)
Calcium (mg)							

Nutrients and quartile ranges[b]	No. of subjects				Odds ratios (95% confidence intervals)[a]		
	<32 wk	32–34 wk	35–36 wk	≥ 37	<32 wk	32–34 wk	35–36 wk
<495.2	14	34	75	1317	1.0 (0.5, 2.0)	1.1 (0.7, 1.7)	1.1 (0.8, 1.5)
495.2–1036.6	31	63	141	2634	Reference	Reference	Reference
≥1036.7	13	23	77	1316	0.7 (0.3, 1.4)	0.7 (0.4, 1.3)	1.0 (0.7, 1.4)
Continuous (541.5-unit change)	58	120	293	5267	0.66 (0.43, 1.02)	0.91 (0.67, 1.22)	0.94 (0.78, 1.12)
Copper (mg)							
<0.7	17	35	75	1317	1.6 (0.8, 3.3)	1.2 (0.7, 1.9)	1.2 (0.8, 1.6)
0.7–1.2	23	54	138	2634	Reference	Reference	Reference
≥1.3	18	31	80	1316	1.3 (0.6, 2.8)	1.4 (0.8, 2.3)	1.0 (0.7, 1.5)
Continuous (0.6-unit change)	58	120	293	5267	0.92 (0.70, 1.21)	1.09 (0.98, 1.21)	1.03 (0.95, 1.12)
Magnesium (mg)							
<173.5	16	38	75	1317	1.4 (0.7, 2.8)	1.4 (0.9, 2.2)	1.1 (0.8, 1.6)
173.5–306.1	27	55	146	2634	Reference	Reference	Reference
≥306.2	15	27	72	1316	0.8 (0.3, 1.8)	1.0 (0.6, 1.8)	0.8 (0.5, 1.2)
Continuous (132.7-unit change)	58	120	293	5267	0.72 (0.43, 1.22)	0.65 (0.43, 0.97)	0.79 (0.62, 1.00)
Selenium (μg)							
<54.0	15	35	68	1317	1.3 (0.6, 2.5)	1.2 (0.7, 1.8)	1.0 (0.7, 1.3)
54.0–92.6	26	58	146	2634	Reference	Reference	Reference
≥92.7	17	27	79	1316	1.1 (0.5, 2.4)	1.0 (0.6, 1.8)	1.0 (0.7, 1.4)
Continuous (38.7-unit change)	58	120	293	5267	1.31 (0.85, 2.01)	0.77 (0.53, 1.11)	0.98 (0.79, 1.21)
Zinc (mg)							
<8.0	20	37	72	1316	2.3 (1.2, 4.5)	1.3 (0.8, 2.0)	1.1 (0.8, 1.5)
8.0–14.2	20	61	141	2635	Reference	Reference	Reference
≥14.3	18	22	80	1316	1.4 (0.6, 3.1)	0.7 (0.4, 1.2)	1.1 (0.7, 1.5)
Continuous (6.3-unit change)	58	120	293	5267	0.91 (0.59, 1.41)	0.84 (0.60, 1.18)	0.89 (0.73, 1.09)
Diet Quality Index							
<9	16	40	90	1485	1.1 (0.6, 2.0)	1.2 (0.8, 1.8)	1.2 (0.9, 1.6)
9–16	29	60	140	2591	Reference	Reference	Reference
≥17	13	20	63	1191	0.8 (0.4, 1.7)	0.7 (0.4, 1.3)	0.9 (0.6, 1.2)
Continuous (8-unit change)	58	120	293	5267	0.92 (0.56, 1.50)	0.78 (0.55, 1.10)	0.83 (0.66, 1.03)
Mediterranean Diet Score							
<11	16	37	82	1228	1.5 (0.8, 2.8)	1.5 (1.0, 2.4)	1.3 (0.9, 1.7)
11–15	23	50	137	2570	Reference	Reference	Reference
≥16	19	33	74	1469	1.4 (0.8, 2.6)	1.2 (0.8, 1.9)	0.9 (0.7, 1.2)
Continuous (5-unit change)	58	120	293	5267	0.96 (0.68, 1.36)	0.92 (0.72, 1.18)	0.88 (0.75, 1.03)

Abbreviations: DFE, dietary folate equivalents; RAE, retinol activity equivalents.

[a]Odds ratios were adjusted for total energy intake.

[b]Odds ratios reflect a comparison of the lowest quartile and highest quartile of intake with intake in the middle two quartiles as reference, based on the distribution among the controls. Odds ratios based on continuous specification of each nutrient reflect the unit difference between the 25th and 75th percentiles of the distribution of the nutrient among the controls.