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Dietary Inflammatory Potential during Pregnancy Is Associated with Lower Fetal Growth and Breastfeeding Failure: Results from Project Viva[1–3]

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Abstract

Background: Inflammation during pregnancy has been linked to adverse maternal and infant outcomes. There is limited information available on the contribution of maternal diet to systemic inflammation and pregnancy health.

Objective: The objective of this study was to examine associations of maternal prenatal dietary inflammatory index (DII), a composite measure of the inflammatory potential of diet, with markers of maternal systemic inflammation and pregnancy outcomes.

Methods: We studied 1808 mother-child pairs from Project Viva, a pre–birth cohort study in Massachusetts. We calculated the DII from first- and second-trimester food-frequency questionnaires by standardizing the dietary intakes of participants to global means, which were multiplied by the inflammatory effect score and summed. We examined associations of DII with maternal plasma C-reactive protein and white blood cell count in the second trimester and the following perinatal outcomes: gestational diabetes, preeclampsia, length of gestation, fetal growth, mode of delivery, and duration of breastfeeding. We used multivariable linear and logistic regression models to analyze the strength of these associations.

Results: Maternal age was (mean ± SD) 32.2 ± 5.0 y, prepregnancy body mass index (BMI; in kg/m^2) was 24.9 ± 5.2, and DII was −2.56 ± 1.42 units with a range of −5.4 to 3.7. DII was positively correlated with prepregnancy BMI (Pearson's r = 0.13, $P < 0.0001$). Higher DII scores, reflecting more proinflammatory dietary potential, were associated with higher second-trimester plasma CRP (β: 0.08 mg/L per 1-unit increase in maternal DII; 95% CI: 0.02, 0.14) and lower birth weight for gestational age z score in infants born to obese mothers (β: −0.10 z score per 1-unit increase in maternal DII; 95% CI: −0.18, −0.02). Higher DII scores were associated with lower odds of breastfeeding for at least 1 mo (OR = 0.85; 95% CI: 0.74, 0.98).

Conclusion: A proinflammatory diet during pregnancy is associated with maternal systemic inflammation and may be associated with impaired fetal growth and breastfeeding failure. *J Nutr* 2016;146:728–36.

Keywords: obesity, inflammation, pregnancy, diet, breastfeeding, fetal growth

Introduction

Excessive inflammation and oxidative stress during pregnancy, mainly studied in women with infections or diabetes, has been linked to adverse pregnancy outcomes such as early pregnancy loss, prematurity, congenital malformations, fetal growth restriction, and preeclampsia (1–3). Two studies have investigated the specific link between maternal systemic inflammation and pregnancy outcomes in healthy pregnancies. Scholl et al. (4) found, in an urban US population, that higher C-reactive protein (CRP)[9]

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[3] Supplemental Figures 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.

[9] Abbreviations used: CRP, C-reactive protein; DII, dietary inflammatory index; GCT, glucose challenge test; GDM, gestational diabetes mellitus; OGTT, oral glucose tolerance test; SGA, small for gestational age.

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was associated with a greater risk of early preterm delivery and pregnancy-induced hypertension in lean women only but not overweight or obese women. Khoury et al. (5) randomized Norwegian women in the second trimester of pregnancy to a control diet or an "anti-inflammatory" diet high in fish, low-fat meats and dairy products, vegetable and nut oils, whole grains, fruits, vegetables, and legumes. This intervention resulted in a lower rate of preterm delivery, but there was no effect of the intervention on maternal inflammatory markers.

Diet may play a central role in the regulation of chronic inflammation in nonpregnant adults (6, 7). The so-called Western diet, which is characterized by a high intake of red meat, high-fat dairy products, refined grains, and simple carbohydrates, has been associated with higher concentrations of CRP and IL-6 (8). On the other hand, the Mediterranean and many non-Western diets, which are high in whole grains, fish, fruit, and green vegetables, low in red meat and butter consumption, and associated with moderate alcohol and olive oil intake have been associated with lower levels of inflammation (9). Diets high in fruit and vegetables have also been associated with lower concentrations of CRP (10). Specific nutrients such as n–3 FAs (11), fiber (12) vitamin E (13), vitamin C (14), β-carotene (15), and magnesium (16) also have consistently been shown to be associated with lower levels of inflammation, obesity, and cardiovascular disease. However, we are not aware of any studies investigating the links among maternal diet during pregnancy, inflammation, and pregnancy outcomes.

We investigated the role of the inflammatory potential of diet during pregnancy on maternal systemic inflammation and pregnancy outcomes in a pre–birth cohort in Massachusetts by using the dietary inflammatory index (DII). The DII is a literature-derived dietary index developed by Shivappa et al. (17) to determine the inflammatory potential of an individual's diet. We hypothesized that proinflammatory diet during pregnancy would positively correlate with *1*) markers of maternal inflammation and *2*) adverse pregnancy outcomes. In addition, we hypothesized that associations would be particularly strong in mothers who were obese entering pregnancy, because dietary patterns tend to be more proinflammatory and baseline levels of inflammation are higher in obese individuals (18).

Methods

Subjects

We analyzed data from participants in Project Viva, a prospective, observational, longitudinal cohort of 2128 mother and child pairs enrolled from 1999 to 2002 at the mothers' initial prenatal visits (median 9.9 wk of gestation) at 8 locations of Atrius Health, a multispecialty group practice in urban and suburban eastern Massachusetts. Study procedures for this cohort have been described previously (19). For the current analysis, we included 1808 women with a prepregnancy BMI (in kg/m^2) ≥18.5 without preexisting type 1 or 2 diabetes mellitus who completed first- and/or second-trimester FFQs (n = 1692 first-trimester FFQ, 1584 second-trimester FFQ, and 1808 first- or second-trimester FFQ) (**Supplemental Figure 1**). The Institutional Review Board of Harvard Pilgrim Health Care approved the study. All mothers provided written informed consent.

Exposure

Mothers completed self-administered FFQs at the first (median 9.9 wk of gestation) and second (median 27.9 wk of gestation) study visits in pregnancy (20). The FFQs assessed diet intake since the last menstrual period (the first-trimester FFQs) or during the previous 3 mo (second-trimester FFQs). Research assistants gave participants the FFQs at in-person visits, answered any questions, and also provided them with written instructions regarding how to complete these questionnaires. This FFQ has been validated in pregnancy (20). Supplement intake was assessed with an interview in the first trimester and was included in the FFQs in the second trimester. To obtain estimates of nutrients, we used the Harvard nutrient composition database, which is based primarily on USDA publications and is continually supplemented by other published sources and personal communications from laboratories and manufacturers, as previously described (21, 22).

Resultant dietary data were used to calculate DII scores for each mother. The DII was developed to provide an aggregate assessment of dietary inflammation in adults. The DII has been previously validated with various inflammatory markers, including CRP (23), TNF-α, and IL-6 in nonpregnant adults (24–26). A complete description of the DII is available elsewhere, but a flowchart overview of the DII method is depicted in **Supplemental Figure 2** (17). Briefly, to calculate the DII, the dietary data were first linked to a world database that provided a robust estimate of a mean and SD for each food parameter included in the DII. A z score was created by subtracting the "standard global mean" from the amount reported and dividing this value by the SD. To minimize the effect of "right skewing," this value was then converted to a centered percentile score. The centered percentile score for each food parameter was then multiplied by the respective food parameter effect score (derived from reviewing and scoring 1943 research articles examining the relation between the food parameters and inflammation) to obtain a food parameter–specific DII score, which were all summed to create the overall DII score for each participant. DII = b1 · n1 + b2 · n2 . . . b28 · n28, where b refers to the literature-derived inflammatory effects score for each evaluable food parameter, and n refers to the food parameter–specific centered percentiles, which were derived from the dietary data. A higher DII score indicates a more proinflammatory diet. The DII minimum/maximum in nonpregnant populations is −8.87 to +7.98 (17). The 28 dietary parameters used for DII calculation are energy, carbohydrate, protein, fat, alcohol, fiber, cholesterol, SFAs, MUFAs, PUFAs, n–3 and n–6 FAs, *trans*-fat, niacin, thiamin, riboflavin, vitamin B-12, vitamin B-6, iron, magnesium, zinc, selenium, vitamin A, vitamin C, vitamin D, vitamin E, folic acid, and β-carotene. In Project Viva, first- and second-trimester DII scores were strongly correlated (Pearson's r = 0.61, $P < 0.0001$). A higher (i.e., more positive) DII score indicates a more proinflammatory diet, whereas a more negative score represents a more anti-inflammatory diet. We analyzed data with first- and second-trimester CRP separately and the mean of first- and second-trimester CRP, with the same results. Thus, the mean of first- and second-trimester DII was used for this analysis.

Outcomes

Our primary outcomes were markers of inflammation and pregnancy outcomes.

Markers of inflammation. Second-trimester blood samples were collected at the time of the glucose challenge test, between 22 and 31 wk of gestation, and processed within 24 h and stored at −80°C until analyses. Plasma CRP was assayed by using a multiplex method (n = 853) (Luminex Corporation) (27). White blood cell count was measured by the clinical laboratory, and results were abstracted from the clinical record by the research staff (n = 1611). We analyzed both markers as continuous outcomes.

Pregnancy outcomes.

Glucose testing. At the end of the second trimester of gestation, participating women completed routine clinical screening for gestational diabetes mellitus (GDM) (28). Given a combination of the glucose challenge test (GCT) and the oral glucose tolerance test (OGTT) results, we formed 3 categories of glucose intolerance by defining *1*) GDM as failing the GCT followed by ≥2 high values on the OGTT (29), *2*) impaired glucose tolerance as failing the GCT followed by one high value on the OGTT, and *3*) isolated hyperglycemia as failing the GCT followed by a normal OGTT. Women who passed the GCT were categorized as normal.

Preeclampsia. Research staff obtained data on maternal blood pressure by chart review. We classified women as having chronic hypertension if they were taking antihypertensive medication or if they had 2 elevated clinically measured blood pressure values (systolic >140 mm Hg or diastolic >90 mm Hg) before 20 wk of gestation. We defined preeclampsia and gestational hypertension according to the recommendations of the National High Blood Pressure Education Program (30). We categorized a woman as having gestational hypertension if she did not have chronic hypertension and developed elevated systolic or diastolic blood pressure on ≥2 occasions after 20 wk of gestation. We categorized a woman as having preeclampsia if she did not have chronic hypertension but developed increased blood pressure and proteinuria (dipstick value of 1+ on ≥2 occasions or ≥2+ once) for >4 h but ≤7 d apart, or if she had chronic hypertension and developed proteinuria after 20 wk of gestation.

Length of gestation. We calculated gestation length from the last menstrual period. Among women for whom the prenatal ultrasound estimate differed from the last menstrual period estimate by >10 d, we calculated gestation length by using the ultrasound results. We defined preterm births as <37 wk of gestation.

Fetal growth. We obtained infant birth weight from hospital medical records. We calculated sex-specific percentiles of birth weight for gestational age by using US national reference data (31). We defined small for gestational age (SGA) as birth weight for gestational age and sex below the 10th percentile and large for gestational age as above the 90th percentile. We compared both SGA and large-for-gestational-age with appropriate-for-gestational-age infants.

Weight gain. We calculated total gestational weight gain as the difference between the last recorded clinical weight before delivery and self-reported prepregnancy weight reported at the first study visit. We previously reported the validity of self-reported prepregnancy weight in our cohort (28). We categorized women as having gained inadequate, adequate, or excessive weight according to the 2009 Institute of Medicine guidelines (32).

Mode of delivery. We obtained delivery route information (cesarean or vaginal delivery) from hospital medical records.

Breastfeeding. Breastfeeding duration information was obtained by structured maternal interview at an in-person visit at 6 mo postpartum. We chose to analyze breastfeeding success as a dichotomous outcome of ≥1 or ≤1 mo of breastfeeding among participants who initiated breastfeeding, given that breastfeeding beyond 1 mo may be influenced by nonphysiologic (social and economic) factors (33).

Covariates. In questionnaires and interviews, mothers reported information about their age, education, household income, race/ethnicity, parity, and smoking status. We calculated maternal prepregnancy BMI from self-reported height and prepregnancy weight. Lean was defined as a prepregnancy BMI 18.5 to <25, overweight as BMI 25 to <30, and obese as BMI ≥30.

Statistical analysis. We first examined distributions of participant characteristics and outcomes by DII quartiles. Next, using Pearson's correlations, we examined bivariate associations of the DII with nutrient intake, as well as participant characteristics. We then conducted multivariable logistic and linear regression analyses for categorical and continuous outcomes, respectively. We constructed models to adjust for the following covariates: maternal prepregnancy BMI, education, age, parity, race/ethnicity, smoking, and household income. Additional adjustment for total caloric intake did not affect the strength or direction of associations, so data are presented without this additional adjustment. For CRP and white blood cell outcomes, we adjusted for gestational age at blood draw. For pregnancy weight gain and fetal growth, we also adjusted for gestation length. Given the independent impact of maternal obesity on systemic inflammation and adverse pregnancy outcomes, we conducted all analyses with all subjects and then stratified by maternal BMI category, with adjustment for continuous maternal BMI within each BMI category. We examined distributions of food groups across quartiles of the DII, with quartile 1 as the lowest DII and quartile 4 as the highest DII. We considered effects to be significant if the 95% CI excluded the null. Values in the text are means ± SDs unless otherwise indicated. Missing data were not included in the analysis. We conducted all analyses with the use of SAS version 9.3 software (SAS Institute).

Results

Overall, the DII in the study cohort was −2.56 ± 1.42 units with a range of −5.4 to 3.7 (**Table 1**). Higher maternal BMI (r = 0.13) and smoking (r = 0.09) were associated with a more proinflammatory (i.e., higher) DII score, and maternal education (r = −0.26) and household income (r = −0.15) were associated with a more anti-inflammatory (i.e., lower) DII score; $P \leq 0.0001$).

In our cohort, intake of vitamin A, β-carotene, fiber, and magnesium had the strongest negative association with the DII score (r = −0.58, −0.57, −0.56, and −0.56, respectively; P < 0.001), and intake of *trans*-fat, SFAs, MUFAs, and caffeine had the strongest positive association with the DII score (r = 0.44, 0.35, 0.22, and 0.21, respectively; P < 0.001). The associations were similar within DII quartiles, suggesting linear relations (**Table 2**).

The distribution of 7 food groups across DII quartiles is shown in **Table 3**. Servings of fruit, vegetables, whole grains, fish, and whole eggs decreased significantly from quartile 1 to quartile 4, whereas servings of sugar-sweetened soda increased (P < 0.0001).

DII and markers of inflammation

The plasma CRP in the cohort was 1.5 ± 1.3 mg/L with a range of 0.01–7.8 mg/L. Maternal DII scores were directly associated with CRP in the second trimester (β: 0.08-mg/L increase in CRP per 1-unit increase in DII; 95% CI: 0.02, 0.14; **Table 4**) after adjustment for gestational age at blood draw, prepregnancy BMI, education, household income, maternal age, parity, race/ethnicity, and smoking. Associations of DII with CRP did not differ by BMI category (P-interaction = 0.61). When the association with CRP was analyzed by quartile of DII, the highest DII quartile had the strongest association with plasma CRP. Maternal DII scores were not associated with second-trimester white blood cell count (Table 4).

Individual nutrients had modest correlations with systemic inflammation. In particular, vitamin A, β-carotene, fiber, magnesium, folate, vitamin D, and zinc were modestly negatively associated with CRP [Pearson's r (P) = −0.08 (0.02), −0.08 (0.02), −0.10 (0.005), −0.11 (0.001), −0.08 (0.03), −0.11 (0.001), and −0.10 (0.003), respectively]. By contrast, intake of *trans*-fats; SFAs, MUFAs, n–3 and n–6 PUFAs; and cholesterol were all nonsignificantly associated with CRP [Pearson's r (P) = 0.05 (0.13), 0.03 (0.40), 0.04 (0.31), 0.07 (0.06), 0.07 (0.05), 0.07 (0.05), and 0.01 (0.86), respectively].

DII and clinical pregnancy outcomes

Glucose testing. The DII was not associated with rates of isolated hyperglycemia or impaired glucose tolerance in any BMI group (**Table 5**). We did observe that a more proinflammatory diet was associated with a lower likelihood of diagnosis of GDM (adjusted OR = 0.78; 95% CI: 0.65, 0.95) in all participants. This association was particularly strong in overweight (compared with normal-weight or obese) women (adjusted OR = 0.57; 95% CI: 0.36, 0.91).

Preeclampsia. The DII was not associated with the development of chronic hypertension, gestational hypertension, or preeclampsia in any BMI group after adjustment (Table 5).

Pregnancy weight gain. There was no association between the DII and inadequate or excessive weight gained during pregnancy, with an adjusted OR of 0.97 (95% CI: 0.86, 1.09) for inadequate weight gain and 0.95 (95% CI: 0.87, 1.03) for excessive weight gain (Table 5).

Length of gestation. There was no association between the DII and rates of preterm (<34 wk) or late preterm (34–37 wk)

TABLE 1 Characteristics of participants during pregnancy by dietary inflammatory index quartile[1]

			DII quartile (first and second trimesters)			
	n	Total (*n* = 1808)	Q1 (*n* = 452)	Q2 (*n* = 452)	Q3 (*n* = 452)	Q4 (*n* = 452)
First-trimester DII	1692	−2.28 ± 1.67	−3.96 ± 0.49	−2.99 ± 0.53	−2.16 ± 0.59	−0.11 ± 1.45
Second-trimester DII	1584	−2.91 ± 1.36	−4.20 ± 0.42	−3.37 ± 0.50	−2.58 ± 0.61	−1.32 ± 1.54
DII (first and second trimesters)	1808	−2.56 ± 1.42	−4.09 ± 0.36	−3.18 ± 0.22	−2.36 ± 0.26	−0.62 ± 1.17
DII range	1808	−5.4, 3.7	−5.4, −3.6	−3.6, −2.9	−2.8, −1.9	−1.9, 3.7
Age at enrollment, y	1808	32.2 ± 5.0	33.4 ± 4.4	32.9 ± 4.6	32.2 ± 4.7	30.4 ± 5.5
Prepregnancy BMI, kg/m^2	1808	24.9 ± 5.2	24.1 ± 4.6	24.6 ± 4.9	25.1 ± 5.1	25.8 ± 5.8
Prepregnancy BMI category, kg/m^2	1808					
18.5 to <25		1141 (63.1)	313 (69.2)	301 (66.6)	272 (60.2)	255 (56.4)
25 to <30		406 (22.5)	85 (18.8)	97 (21.5)	111 (24.6)	113 (25.0)
≥30		261 (14.4)	54 (11.9)	54 (11.9)	69 (15.3)	84 (18.6)
Education (graduated college)	1804	1237 (68.6)	374 (82.9)	314 (69.6)	315 (70.0)	234 (51.8)
Household income ≤$70,000	1670	609 (36.5)	139 (32.2)	119 (28.4)	153 (36.4)	198 (49.6)
Race/ethnicity	1804					
Black		250 (13.9)	52 (11.5)	40 (8.9)	61 (13.6)	97 (21.5)
Hispanic		122 (6.8)	24 (5.3)	22 (4.9)	24 (5.3)	52 (11.5)
Asian		91 (5.0)	33 (7.3)	15 (3.3)	21 (4.7)	22 (4.9)
White		1273 (70.6)	327 (72.5)	363 (80.5)	329 (73.1)	254 (56.2)
Other		68 (3.8)	15 (3.3)	11 (2.4)	15 (3.3)	27 (6.0)
Smoking status	1799					
Never		1219 (67.8)	325 (72.5)	309 (68.7)	296 (65.6)	289 (64.2)
Former		378 (21.0)	99 (22.1)	100 (22.2)	93 (20.6)	86 (19.1)
During pregnancy		202 (11.2)	24 (5.4)	41 (9.1)	62 (13.7)	75 (16.7)
Nulliparous	1808	879 (48.6)	253 (56.0)	229 (50.7)	206 (45.6)	191 (42.3)
Second-trimester plasma CRP, mg/L	853	1.5 ± 1.3	1.4 ± 1.2	1.6 ± 1.3	1.6 ± 1.2	1.7 ± 1.4
Second-trimester WBC count, ×10^9/L	1611	9.7 ± 2.1	9.7 ± 2.3	9.7 ± 2.1	9.7 ± 2.1	9.6 ± 2.0
GCT plasma glucose, mg/dL	1772	114 ± 26.9	114 ± 27.4	115 ± 27.7	116 ± 28.1	113 ± 24.4
Glucose testing	1779					
Normoglycemic		1465 (82.3)	361 (81.3)	362 (81.3)	361 (81.1)	381(85.6)
Isolated hyperglycemia		160 (9.0)	46 (10.4)	36 (8.1)	41 (9.2)	37 (8.3)
Impaired glucose tolerance		58 (3.3)	12 (2.7)	17 (3.8)	16 (3.6)	13 (2.9)
Gestational diabetes mellitus		96 (5.4)	25 (5.6)	30 (6.7)	27 (6.1)	14 (3.1)
Pregnancy weight gain, kg	1775	15.6 ± 5.6	15.6 ± 5.0	16.2 ± 5.9	15.6 ± 5.5	15.1 ± 6.0
Preeclampsia status	1772					
Normal		1563 (88.2)	396 (89.6)	386 (87.1)	389 (86.8)	392 (89.3)
Chronic hypertension		25 (1.4)	5 (1.1)	9 (2.0)	6 (1.3)	5 (1.1)
Gestational hypertension		122 (6.9)	29 (6.6)	32 (7.2)	36 (8.0)	25 (5.7)
Preeclampsia		62 (3.5)	12 (2.7)	16 (3.6)	17 (3.8)	17 (3.9)
Cesarean delivery	1792	428 (23.9)	105 (23.5)	112 (25.1)	119 (26.5)	92 (20.4)
Gestation length, wk	1808	39.5 ± 1.9	39.5 ± 1.8	39.5 ± 1.8	39.5 ± 2.0	39.2 ± 2.2
GA category, wk	1808					
<34		37 (2.0)	9 (2.0)	8 (1.8)	8 (1.8)	12 (2.7)
34 to <37		98 (5.4)	21 (4.6)	22 (4.9)	24 (5.3)	31 (6.9)
≥37		1673 (92.5)	422 (93.4)	422 (93.4)	420 (92.9)	409 (90.5)
BW, g	1807	3475 ± 586	3465 ± 561	3525 ± 552	3537 ± 611	3373 ± 604
BW/GA *z* score	1807	0.20 ± 0.96	0.17 ± 0.96	0.26 ± 0.94	0.30 ± 0.99	0.05 ± 0.95
BW/GA category, %	1807					
SGA <10		104 (5.8)	27 (6.0)	18 (4.0)	26 (5.8)	33 (7.3)
AGA 10–90		1453 (80.4)	365 (80.9)	366 (81.0)	352 (77.9)	370 (81.9)
LGA >90		250 (13.8)	59 (13.1)	68 (15.0)	74 (16.4)	49 (10.8)
Breastfeeding duration, mo	1464	5.9 ± 4.6	7.6 ± 4.4	6.1 ± 4.5	5.6 ± 4.5	4.5 ± 4.3
Breastfeeding >1 mo (among initiated)	1265	1124 (88.9)	318 (95.5)	284 (87.7)	285 (88.2)	237 (83.2)
Female infant	1808	883 (48.8)	239 (52.9)	212 (46.9)	193 (42.7)	239 (52.9)

[1] Data presented are means ± SDs or *n* (%). AGA, appropriate for gestational age; BW, birth weight; CRP, C-reactive protein; DII, dietary inflammatory index; GA, gestational age; GCT, glucose challenge test; LGA, large for gestational age; Q, quartile; SGA, small for gestational age; WBC, white blood cell.

delivery, with an adjusted OR of 1.06 (95% CI: 0.83, 1.36) and 1.10 (95% CI: 0.95, 1.28), respectively, compared with term delivery (>37 wk) (Table 5).

Fetal growth. The DII was not associated with fetal growth category in normal-weight or overweight subjects based on prepregnancy BMI (Table 5 and **Figure 1**). In obese subjects, the

TABLE 2 Correlation between daily intake of individual nutrients and the DII and CRP, as well as mean of individual nutrients within quartiles of DII, among pregnant participants[1]

	Correlation with DII		DII quartile (first and second trimesters)					Correlation with CRP	
	Pearson's *r*	*P* value	Total (*n* = 1808)	Q1 (*n* = 452)	Q2 (*n* = 452)	Q3 (*n* = 452)	Q4 (*n* = 452)	Pearson's *r*	*P* value
Mean DII			−2.56 ± 1.42	−4.09 ± 0.36	−3.18 ± 0.22	−2.36 ± 0.26	−0.62 ± 1.17		
Carbohydrates, g/d	−0.15	<0.0001	276 ± 33.1	287 ± 30.8	275 ± 31.2	270 ± 31.8	270 ± 35.5	0.00	0.99
Protein, g/d	−0.21	<0.0001	87.5 ± 13.4	89.7 ± 13.4	89.0 ± 12.4	87.6 ± 13.1	83.4 ± 14.0	−0.02	0.53
Fats, g/d									
Trans-fat	0.44	<0.0001	2.17 ± 0.65	1.75 ± 0.53	2.12 ± 0.50	2.26 ± 0.58	2.53 ± 0.71	0.05	0.13
SFAs	0.35	<0.0001	23.9 ± 5.2	20.8 ± 4.3	23.7 ± 4.2	24.9 ± 4.7	26.2 ± 5.80	0.03	0.40
MUFAs	0.22	<0.0001	24.2 ± 5.10	22.2 ± 4.80	24.0 ± 4.90	25.0 ± 4.80	25.6 ± 5.10	0.04	0.31
n–3 FAs	0.05	0.03	1.14 ± 0.40	1.12 ± 0.41	1.11 ± 0.35	1.16 ± 0.44	1.19 ± 0.41	0.07	0.06
n–6 FAs	0.03	0.18	12.0 ± 2.90	11.9 ± 2.90	11.8 ± 2.60	12.2 ± 3.00	12.2 ± 3.00	0.07	0.05
PUFAs	0.02	0.32	13.7 ± 3.20	13.6 ± 3.30	13.4 ± 3.00	13.8 ± 3.30	13.9 ± 3.30	0.07	0.05
Fiber, g/d	−0.56	<0.0001	19.7 ± 5.6	24.6 ± 5.2	20.4 ± 4.5	17.8 ± 3.9	15.9 ± 4.5	−0.10	0.005
Caffeine, mg/d	0.21	<0.0001	73.7 ± 81.1	54.8 ± 63.8	67.8 ± 69.8	74.0 ± 71.6	98.2 ± 106	0.04	0.25
Cholesterol, mg/d	0.15	<0.0001	267 ± 76.0	243 ± 69.1	266 ± 72.3	280 ± 76.6	280 ± 79.9	0.01	0.86
Vitamins									
Vitamin A, IU/d	−0.58	<0.0001	13,500 ± 5450	17,900 ± 5940	14,400 ± 4400	12,300 ± 3770	9520 ± 3520	−0.08	0.02
β-Carotene, μg/d	−0.57	<0.0001	4720 ± 2300	6720 ± 2630	4990 ± 1670	4050 ± 1500	3130 ± 1470	−0.08	0.02
Magnesium, mg/d	−0.56	<0.0001	336 ± 61.9	383 ± 60.5	346 ± 45.4	322 ± 53.4	291 ± 47.1	−0.11	0.001
Folate, μg/d	−0.48	<0.0001	1090 ± 420	1260 ± 296	1200 ± 527	1100 ± 303	814 ± 364	−0.08	0.03
Niacin, mg/d	−0.48	<0.0001	40.5 ± 10.3	44.4 ± 11.3	42.8 ± 9.0	41.1 ± 8.6	33.5 ± 8.4	−0.06	0.07
Vitamin D, IU/d	−0.47	<0.0001	540 ± 177	602 ± 154	581 ± 159	554 ± 157	421 ± 178	−0.11	0.001
Vitamin C, mg/d	−0.30	<0.0001	278 ± 177	342 ± 282	289 ± 132	267 ± 109	214 ± 91.9	−0.02	0.53
Vitamin B-6, mg/d	−0.19	<0.0001	5.11 ± 5.30	6.14 ± 7.15	5.46 ± 4.54	5.06 ± 5.03	3.77 ± 3.55	−0.05	0.16
Vitamin E, mg/d	−0.15	<0.0001	28.4 ± 57.5	39.5 ± 93.2	28.8 ± 35.3	28.7 ± 48.8	16.7 ± 25.6	−0.03	0.35
Vitamin B-12, μg/d	−0.12	<0.0001	11.1 ± 17.1	13.2 ± 31.2	11.0 ± 5.5	11.2 ± 11.4	8.80 ± 4.50	−0.02	0.59
Minerals									
Zinc, mg/d	−0.45	<0.0001	29.8 ± 9.7	33.1 ± 8.6	32.1 ± 8.9	30.3 ± 9.0	23.6 ± 9.5	−0.10	0.003
Iron, mg/d	−0.31	<0.0001	41.0 ± 17.9	45.5 ± 15.5	44.5 ± 17.5	40.6 ± 16.5	33.4 ± 19.1	−0.07	0.05
Selenium, μg/d	−0.13	<0.0001	1.39 ± 5.28	2.37 ± 8.92	1.43 ± 3.62	1.30 ± 3.81	0.46 ± 1.56	−0.01	0.87

[1] Data presented are means ± SDs of individual nutrients within each mean DII quartile. *P* and *r* values from Pearson's correlations with continuous nutrients as the exposures and continuous mean DII or CRP as the outcome. CRP, C-reactive protein; DII, dietary inflammatory index; Q, quartile.

DII (as a continuous variable) was associated with a higher likelihood of delivering an SGA infant (adjusted OR = 1.68; 95% CI: 1.09, 2.60) but did not affect likelihood of delivering an LGA infant (adjusted OR = 0.81; 95% CI: 0.62, 1.06), after adjustment for maternal age, prepregnancy BMI, education, household income, race/ethnicity, smoking, parity, and length of gestation. Similarly, in obese women, DII was associated with lower birth weight/gestational age *z* score (β: −0.10, lower birth weight/gestational age *z* score for every unit increase in DII; 95% CI: −0.18, −0.02) after adjustment for the above covariates (Figure 1). When the association between DII and fetal growth was analyzed with DII as a categorical variable by quartile, there was no association with fetal growth category, likely due to inadequate power.

Mode of delivery. Maternal dietary inflammation was not associated with rate of cesarean delivery in the participants

TABLE 3 Distribution of servings of food groups across quartiles of DII among pregnant participants[1]

	Correlation with DII		DII quartile (first and second trimesters)					Correlation with CRP	
	Pearson's *r*	*P* value	Total (*n* = 1808)	Q1 (*n* = 452)	Q2 (*n* = 452)	Q3 (*n* = 452)	Q4 (*n* = 452)	Pearson's *r*	*P* value
DII			−2.6 ± 1.4	−4.1 ± 0.36	−3.2 ± 0.22	−2.4 ± 0.26	−0.62 ± 1.2		
Food groups, servings/wk									
Vegetables	−0.61	<0.0001	201 ± 12	32 ± 13	22 ± 8.4	16 ± 6.7	12 ± 6.2	−0.06	0.10
Fruit	−0.50	<0.0001	12 ± 8.3	19 ± 9.5	13 ± 7.4	9.6 ± 5.3	7.1 ± 4.6	−0.05	0.13
Whole-grain foods	−0.45	<0.0001	8.5 ± 7.3	14 ± 8.5	9.3 ± 6.5	7.0 ± 6.1	4.4 ± 4.3	−0.07	0.03
Fish/seafood	−0.26	<0.0001	1.7 ± 1.5	2.3 ± 2.0	1.6 ± 1.2	1.5 ± 1.1	1.2 ± 1.3	−0.04	0.29
Whole eggs	−0.14	<0.0001	2.1 ± 1.8	2.4 ± 2.0	2.1 ± 1.7	2.1 ± 1.9	1.7 ± 1.6	−0.07	0.06
Red or processed meat	0.01	0.83	3.9 ± 2.9	3.6 ± 3.4	4.2 ± 2.9	4.1 ± 2.9	3.7 ± 2.5	0.08	0.02
Sugar-sweetened soda	0.17	<0.0001	2.3 ± 3.8	1.6 ± 2.8	2.0 ± 3.1	2.5 ± 4.1	3.3 ± 4.7	0.14	<0.0001

[1] Data presented are mean ± SD servings of each food group within each mean DII quartile. *P* and *r* values from Pearson's correlations. CRP, C-reactive protein; DII, dietary inflammatory index; Q, quartile.

TABLE 4 Associations of maternal DII (per unit) with markers of inflammation in the second trimester of pregnancy[1]

Outcome and exposure	*n*	Model 1	Model 2	Model 3	Model 4
Plasma CRP, mg/L					
DII continuous	853	0.09 (0.03, 0.15)	0.07 (0.01, 0.12)	0.08 (0.02, 0.13)	0.08 (0.02, 0.14)
DII quartile					
Q1	201	0.0 (reference)	0.0 (reference)	0.0 (reference)	0.0 (reference)
Q2	223	0.21 (−0.03, 0.45)	0.18 (−0.05, 0.40)	0.19 (−0.04, 0.43)	0.17 (−0.07, 0.41)
Q3	219	0.21 (−0.03, 0.45)	0.15 (−0.07, 0.38)	0.16 (−0.07, 0.40)	0.17 (−0.07, 0.41)
Q4	210	0.32 (0.08, 0.57)	0.23 (0.00, 0.45)	0.25 (0.00, 0.49)	0.25 (−0.01, 0.50)
WBC count, $\times 10^9$/L					
DII continuous	1611	−0.03 (−0.10, 0.05)	−0.05 (−0.12, 0.03)	−0.05 (−0.13, 0.03)	−0.03 (−0.11, 0.05)
DII quartile					
Q1	408	0.0 (reference)	0.0 (reference)	0.0 (reference)	0.0 (reference)
Q2	404	−0.01 (−0.30, 0.29)	−0.03 (−0.33, 0.26)	−0.12 (−0.42, 0.18)	−0.18 (−0.47, 0.11)
Q3	399	0.03 (−0.26, 0.33)	−0.01 (−0.30, 0.29)	−0.02 (−0.32, 0.28)	−0.02 (−0.31, 0.28)
Q4	400	−0.07 (−0.37, 0.22)	−0.14 (−0.44, 0.15)	−0.19 (−0.50, 0.12)	−0.14 (−0.45, 0.17)

[1] Data presented are β (95% CI). Model 1: adjusted for gestational age at blood draw; model 2: model 1 + prepregnancy BMI; model 3: model 2 + education and income; and model 4: model 3 + age, parity, race/ethnicity, and smoking. CRP, C-reactive protein; DII, dietary inflammatory index; Q, quartile; WBC, white blood cell.

overall, before or after adjustment for maternal age, prepregnancy BMI, race/ethnicity, education, parity, smoking, household income, and child sex (OR = 0.97; 95% CI: 0.89, 1.05) (Table 5).

Breastfeeding. A more proinflammatory diet (using DII as a continuous variable) was associated with a decreased likelihood of breastfeeding for >1 mo (compared with ≤1 mo) (OR = 0.85; 95% CI: 0.74, 0.98) in participants who initiated breastfeeding in both unadjusted models and after adjustment for maternal BMI, education, income, age, parity, and race/ethnicity (Table 5). When analyzed by BMI subgroup, this effect was observed in the lean (OR = 0.79; 95% CI: 0.66, 0.95) but not overweight

TABLE 5 Associations of the dietary inflammatory index (per unit) with pregnancy outcomes[1]

		BMI, kg/m^2		
	Total (*n* = 1808)	18.5 to <25 (*n* = 1141)	25 to <30 (*n* = 406)	≥30 (*n* = 261)
Glucose status				
Normal	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Isolated hyperglycemia	0.94 (0.82, 1.07)	0.89 (0.74, 1.08)	0.92 (0.69, 1.23)	1.08 (0.82, 1.41)
Impaired glucose tolerance	0.88 (0.71, 1.09)	0.94 (0.70, 1.27)	0.88 (0.59, 1.31)	0.70 (0.43, 1.16)
Gestational diabetes mellitus	0.78 (0.65, 0.95)	0.87 (0.66, 1.16)	0.57 (0.36, 0.91)	0.80 (0.57, 1.12)
IOM pregnancy weight gain				
Inadequate	0.97 (0.86, 1.09)	0.93 (0.80, 1.08)	0.96 (0.66, 1.40)	1.07 (0.78, 1.47)
Adequate	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Excessive	0.95 (0.87, 1.03)	0.91 (0.82, 1.01)	1.03 (0.85, 1.27)	1.00 (0.77, 1.29)
Preeclampsia status				
Normal	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
Chronic hypertension	0.91 (0.65, 1.28)	0.89 (0.42, 1.86)	0.81 (0.41, 1.60)	0.93 (0.54, 1.62)
Gestational hypertension	0.97 (0.83, 1.14)	0.93 (0.73, 1.19)	1.11 (0.82, 1.51)	0.97 (0.72, 1.30)
Preeclampsia	1.04 (0.85, 1.26)	0.81 (0.57, 1.16)	1.12 (0.79, 1.59)	1.18 (0.85, 1.63)
GA category, wk				
<34	1.06 (0.83, 1.36)	1.18 (0.86, 1.63)	0.98 (0.51, 1.89)	0.85 (0.51, 1.43)
34 to <37	1.10 (0.95, 1.28)	1.13 (0.92, 1.37)	1.04 (0.76, 1.43)	1.04 (0.71, 1.51)
≥37	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
BW/GA category, %				
SGA <10	1.04 (0.89, 1.22)	0.91 (0.74, 1.13)	1.19 (0.81, 1.75)	1.68 (1.09, 2.60)
AGA 10–90	1.0 (reference)	1.0 (reference)	1.0 (reference)	1.0 (reference)
LGA >90	0.95 (0.85, 1.07)	1.07 (0.92, 1.25)	0.90 (0.71, 1.13)	0.81 (0.62, 1.06)
Cesarean delivery (yes vs. no)	0.97 (0.89, 1.05)	1.00 (0.89, 1.13)	0.80 (0.66, 0.97)	1.08 (0.89, 1.30)
BF >1 mo (vs. ≤1 mo)	0.85 (0.74, 0.98)	0.79 (0.66, 0.95)	0.94 (0.70, 1.25)	1.17 (0.77, 1.79)

[1] Values are presented as ORs (95% CIs). Adjusted for maternal prepregnancy BMI, education, age, parity, race/ethnicity, smoking during pregnancy, and household income. IOM pregnancy weight gain and BW/GA category models also adjusted for length of gestation. AGA, appropriate for gestational age; BF, breastfeeding; BW, birth weight; DII, dietary inflammatory index; GA, gestational age; IOM, Institute of Medicine; LGA, large for gestational age; SGA, small for gestational age.

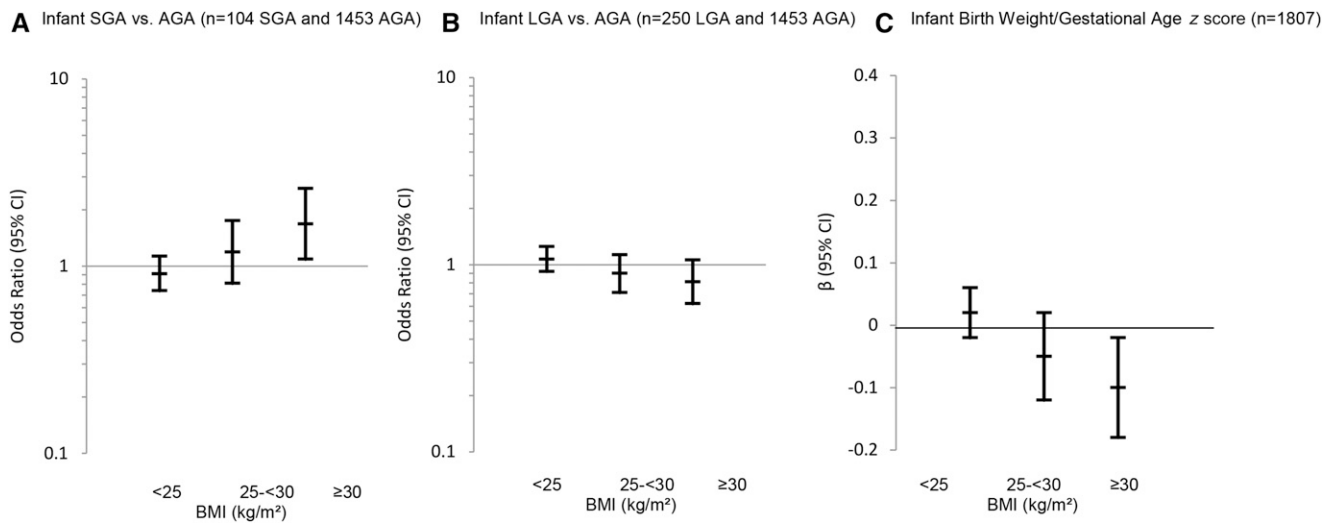

FIGURE 1 Associations of maternal dietary inflammatory index (per unit) with fetal growth within maternal BMI (in kg/m^2) categories. In women with a prepregnancy BMI ≥30, a proinflammatory diet was associated with higher odds of delivering an SGA (compared with an AGA) infant (A), as well as with lower birth weight/gestational age *z* score (C). There was no effect on odds of delivering an LGA infant (B). Data shown were adjusted for maternal prepregnancy BMI, education, age, parity, race/ethnicity, smoking during pregnancy, household income, and length of gestation. AGA, appropriate for gestational age; LGA, large for gestational age; SGA, small for gestational age.

(OR = 0.94; 95% CI: 0.70, 1.25) or obese (OR = 1.17; 95% CI: 0.77, 1.79) women. When the association between DII and breastfeeding success was analyzed with DII as a categorical variable by quartile, there was no association with breastfeeding success, likely due to inadequate power.

Discussion

Dietary inflammation has been shown to contribute to a variety of disease states through the life cycle, but to our knowledge, the impact on pregnancy health has not been studied. Here we describe the association of dietary inflammation with pregnancy outcomes. Our results suggest that the DII is associated with CRP, a marker of systemic inflammation during pregnancy. Dietary inflammation may also be linked to infant birth weight and breastfeeding success.

In line with our finding that the DII was directly associated with second-trimester CRP, a previous study in an urban US population of pregnant women found that higher maternal intakes of calories, protein, and cholesterol were positively associated with maternal CRP, but dietary assessment was limited to a single 24-h recall of macronutrients known to be related to cardiovascular risk (34). Given the thorough dietary recall and assessment methods used in this study, we were able to identify a broader panel of foods and nutrients that may contribute to a pro- or anti-inflammatory diet and systemic inflammation in pregnancy. Khoury et al. (5) performed a targeted dietary intervention with Norwegian pregnant women randomly allocated to a standard diet or to a high-protein, low-fat diet and found a decrease in rates of preterm birth. However, in our study, dietary inflammation was not associated with length of gestation.

A proinflammatory diet in our cohort was associated with a lower likelihood of breastfeeding past 1 mo of age, specifically in lean women. Interestingly, this association was not seen in overweight and obese women, possibly because of low rates of breastfeeding initiation in this population. Hennigar et al. (35) recently found in a mouse model that maternal systemic inflammation was associated with breastfeeding failure, associated histologically with premature mammary involution and autophagy. To our knowledge, our study is the first to link inflammation from any source to breastfeeding failure in humans.

We found that a more proinflammatory diet was associated with a lower likelihood of GDM diagnosis, particularly among overweight women. In the Project Viva cohort, we previously found that higher animal fat and cholesterol intake was associated with the development of GDM, but there was no association between carbohydrate intake and the development of GDM (36). In the current analysis, carbohydrate intake was modestly ($r = -0.15$, $P < 0.0001$) associated with a negative (anti-inflammatory) DII. In overweight women, who have a predisposition for GDM, a higher intake of carbohydrates could have contributed to this counterintuitive correlation between the DII and GDM.

In obese women, there was an inverse relation between the DII and fetal growth in our cohort. Existing literature suggests that inflammation and oxidative stress, particularly in excess, influence fetal growth. Markers of oxidative stress found in placenta, cord blood, maternal serum, and urine, including malondialdehyde, xanthine oxidase, and 8-oxo-7,8-dihydro-2′-deoxyguanosine, have been found to be higher in pregnancies with growth-restricted fetuses compared with controls (37, 38), and maternal inflammatory markers, including IL-6, TNF-α, CRP, and thrombopoietin, have been negatively correlated with birth weight (39). In the Generation R study, Ernst et al. (40) found that early pregnancy CRP was negatively associated with birth weight and positively associated with the likelihood of an SGA fetus. Oxidative stress or inflammation has been linked to shallow placental invasion and abnormal vascular development, which could lead to higher resistance and lower flow placental circulation. This mechanism may be particularly relevant to obese women, because obesity before and during pregnancy is characterized by high baseline inflammation and oxidative stress. This study sets the foundation for future translational studies that could delineate this mechanism at the placental level.

Our study is limited by maternal CRP measurement at only one time point in the second trimester. CRP is a nonspecific measure of inflammation that cannot aid in distinguishing the source of inflammation. In addition, most of our subjects had

low plasma CRP concentrations compared with the normal ranges in healthy pregnancy seen in the literature (41). Having dietary assessment in postpartum women would have provided more relevant dietary influences on breastfeeding. The DII, as previously mentioned, is a literature-based assessment of dietary inflammatory potential. Inference is limited by the paucity of studies examining the nutritional influences in pregnancy, with much of the background literature extrapolated from studies of nonpregnant adults. Currently, there are no widely accepted cutoff points for the DII, but a more positive score indicates a more proinflammatory diet. In addition, our cohort was relatively well educated and drawn from a single practice in Massachusetts, which may limit the applicability of our findings to other populations.

This study provides an assessment of dietary inflammation and systemic inflammation in relation to pregnancy outcomes. We have used the DII in a pregnant population for the first time, to our knowledge, and found a strong correlation with maternal CRP during pregnancy, suggesting that the DII may be a valuable tool in assessment of dietary inflammation in pregnancy. We also found that maternal dietary inflammation may contribute to breastfeeding failure and lower birth weight. Future studies may seek to understand the mechanisms linking inflammation with these outcomes as well as attempt to limit these deleterious effects through intervention studies.

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SS, SLR-S, and EO designed the research, analyzed the data or performed the statistical analysis, and wrote the article; SS, SLR-S, NS, MDW, JRH, and EO conducted the research; DRG and MWG provided essential data for research; SS had primary responsibility for the final content. All authors read and approved the manuscript.

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