Proinflammatory Diets during Pregnancy and Neonatal Adiposity in the Healthy Start Study

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Objective To evaluate the association between dietary inflammatory index (DII) scores during pregnancy and neonatal adiposity.

Study design The analysis included 1078 mother–neonate pairs in Healthy Start, a prospective prebirth cohort. Diet was assessed using repeated 24-hour dietary recalls. DII scores were obtained by summing nutrient intakes, which were standardized to global means and multiplied by inflammatory effect scores. Air displacement plethysmography measured fat mass and fat-free mass within 72 hours of birth. Linear and logistic models evaluated the associations of DII scores with birth weight, fat mass, fat-free mass, and percent fat mass, and with categorical outcomes of small- and large-for-gestational age. We tested for interactions with prepregnancy BMI and gestational weight gain.

Results The interaction between prepregnancy BMI and DII was statistically significant for birth weight, neonatal fat mass, and neonatal percent fat mass. Among neonates born to obese women, each 1-unit increase in DII was associated with increased birth weight (53 g; 95% CI, 20, 87), fat mass (20 g; 95% CI, 7-33), and percent fat mass (0.5%; 95% CI, 0.2-0.8). No interaction was detected for small- and large-for-gestational age. Each 1-unit increase in DII score was associated a 40% increase in odds of a large-for-gestational age neonate (1.4; 95% CI, 1.0-2.0; $P = .04$), but not a small-for-gestational age neonate (1.0; 95% CI, 0.8-1.2; $P = .80$). There was no evidence of an interaction with gestational weight gain.

Conclusions Our findings support the hypothesis that an increased inflammatory milieu during pregnancy may be a risk factor for neonatal adiposity. *(J Pediatr 2017;■■:■■-■■).*

Trial Registration Clinicaltrials.gov NCT02273297

See editorial, p ••• and related article, p •••

Future risk for obesity may manifest as early as 2 months of age,[1] which suggests that intrauterine exposures may predispose offspring to obesity.[2] An inflammatory milieu during pregnancy can result in fetal overgrowth.[3-6] In both human and animal pregnancies, exposure to inflammatory cytokines is associated with increased adiposity in offspring.[5,6]

Prepregnancy obesity is an important contributing factor to neonatal adiposity and maternal subclinical inflammation may be a key mechanism.[7-10] Obesity is characterized by chronic, low-grade inflammation that is further exacerbated by metabolic changes during pregnancy.[11,12] Fetuses from obese women are exposed to a proinflammatory environment during development,[4,12-15] which may be associated with increased adiposity at birth.[16] Excessive gestational weight gain may also contribute to inflammation via maternal fat accumulation.[17]

A proinflammatory diet during pregnancy may alter the risk for neonatal adiposity, especially in the context of preexistent maternal obesity or excessive gestational weight gain. The dietary inflammatory index (DII) is an indicator of the overall inflammatory potential of an individual's diet.[18] The DII ranges from −9 (most anti-inflammatory) to +8 (most proinflammatory),[18] where higher DII scores

ASA24	Automated Self-Administered 24-hour Dietary Recall
BMI	Body mass index
CRP-hs	High-sensitivity C-reactive protein
DII	Dietary inflammatory index
IL	Interleukin

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are associated with increased circulation of inflammatory markers.[19-21] Higher DII scores may indicate a diet high in the consumption of processed meat and sugar-sweetened beverages, whereas lower DII scores may indicate a diet with ample servings of fruit, vegetables, whole grains, fish, and eggs.[20] Sen et al demonstrated that higher DII scores among women who were obese entering pregnancy is associated with an increase in odds of a small-for-gestational age neonate.[20] However, the impact of DII scores on neonatal adiposity is unknown.

Our goal was to evaluate the association between DII scores during pregnancy and neonatal adiposity, incorporating a direct measure of body composition. We hypothesized that a higher DII score would be associated with greater adiposity at birth, particularly among neonates born to obese mothers or mothers with excessive gestational weight gain.

Methods

The Healthy Start study recruited 1410 pregnant women aged ≥16 years with singleton pregnancies enrolled before 24 weeks of gestation from the obstetrics clinics at the University of Colorado Hospital from 2009 through 2014. Participants completed research visits in early pregnancy (median 17 weeks of gestation), mid-pregnancy (median 27 weeks of gestation), and at delivery (median 1 day after delivery). Additional inclusion criteria for this study included completion of ≥1 dietary recall, neonates born ≥32 weeks of gestation, those with complete body composition measures at birth, and those born to women with a prepregnancy body mass index (BMI) of ≥18.5 kg/m^2. The Healthy Start study protocol was approved by the Colorado Multiple Institutional Review Board. All women provided written informed consent before the first study visit. The Healthy Start study was registered as an observational study at clinicaltrials.gov as NCT02273297.

Fat mass and fat-free mass were measured using air displacement plethysmography (PEA POD, COSMED, Rome Italy) within approximately 72 hours of delivery. The PEA POD device measures body mass and volume, calculates body density, and estimates fat mass (g), fat-free mass (g), and percent fat mass. Each neonate was measured twice by trained research personnel, with a third measurement taken when percent fat mass differed by >2.0%. The average of the 2 closest readings was used for analysis.

We calculated sex-specific percentiles of birth weight for gestational age by using United States national reference data.[22] Neonatal size was defined as follows: small-for-gestational age (birth weight <10th percentile for age and sex), appropriate-for-gestational age (birth weight ≥10th percentile, and ≤90th percentile for age and sex), and large-for-gestational age (birth weight >90th percentile for age and sex). For this analysis, appropriate-for-gestational age served as the reference category.

Maternal diet was measured throughout pregnancy using the Automated Self-Administered 24-hour Dietary Recall (ASA24), an online platform developed and hosted by the National Cancer Institute (ASA24-Beta and ASA24-2011, Bethesda, Maryland). Healthy Start participants were asked to complete 1 dietary recall per month, beginning at the first study visit. Approximately 76% of the participants completed ≥2 dietary recalls over the pregnancy period (range, 1-8; median, 3). Trained, bilingual study staff members administered recalls in-person for Spanish-speaking participants (n = 60) at study visits and over the phone between research visits. Data from the ASA24 were collected and processed by the Diet, Physical Activity and Body Composition Core of the Nutrition Obesity Research Center at the University of North Carolina at Chapel Hill. Individual nutrients were derived from the recalls using the US Department of Agriculture Food and Nutrient Database for Dietary Studies, versions 1.0 and 4.1.

The DII scores were based on 28 nutrients obtained from the 24-hour dietary recalls[18]: energy, total fat, saturated fat, monounsaturated fat, polyunsaturated fat, omega-3 polyunsaturated fatty acids, omega-6 fatty acids, trans-fat, carbohydrates, fiber, protein, cholesterol, iron, vitamin A, vitamin C, vitamin D, vitamin E, niacin, thiamin, riboflavin, vitamin B_6, vitamin B_{12}, folic acid, magnesium, zinc, selenium, alcohol, and caffeine. Inflammatory effect scores were computed for each of the 28 nutrients based on approximately 6500 peer-reviewed articles (**Figure 1**; available at www.jpeds.com). Inflammatory effect scores were derived by first assigning "+1" to anti-inflammatory nutrients and "-1" to proinflammatory nutrients and then adjusting the scores by the total number of articles that cited its proinflammatory or anti-inflammatory effects. The inflammatory effect scores indicate the relative contribution of each nutrient to the final DII score, where fiber is the most anti-inflammatory nutrient and saturated fat is the most proinflammatory nutrient.

The DII score for each dietary recall was obtained by standardizing the nutrient intakes to global means, multiplying by the appropriate inflammatory effect scores, and taking the sum of the 28 nutrients.[18] For women with >1 dietary recall, the DII scores were averaged across the entire pregnancy.

Maternal height was measured using a stadiometer at the first research visit by research personnel. Prepregnancy weight was obtained from medical records (91%) or from questionnaires completed at the early pregnancy research visit (9%). Previous studies have reported strong agreement between self-reported prepregnancy weight and prepregnancy weights obtained from medical records or study data.[23,24] Prepregnancy BMI was calculated as prepregnancy weight (kg) divided by height (m) squared. Prepregnancy BMI categories were defined as follows: lean (BMI of >18.5 kg/m^2 and <25 kg/m^2), overweight (BMI of ≥25 kg/m^2 and <30 kg/m^2), and obese (BMI of ≥30 kg/m^2).[25]

Gestational weight gain was calculated as the difference between the last available weight measurement during pregnancy (measured by research staff or medical personnel) and the prepregnancy weight (as described). Gestational weight gain was categorized as less than recommended, within the recommended range, and greater than recommended as based on the 2009 Institute of Medicine guidelines.[26]

In a subset of the Healthy Start cohort, inflammatory markers interleukin (IL)-6 and high-sensitivity C-reactive protein (CRP-hs) were measured in maternal blood samples, collected at a median gestational age of 27 weeks. IL-6 was measured using

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