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Journal
Journal of Nutrition, 151(4)

ISSN
0022-3166

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Publication Date
2021-04-01

DOI
10.1093/jn/nxaa395

Peer reviewed

The Journal of Nutrition
Nutritional Epidemiology

Associations Between Maternal Nutrition in Pregnancy and Child Blood Pressure at 4–6 Years: A Prospective Study in a Community-Based Pregnancy Cohort

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ABSTRACT

Background: The intrauterine environment may influence offspring blood pressure, with effects possibly extending into adulthood. The associations between prenatal nutrition and offspring blood pressure, alone or in combination with other sociodemographic or behavioral factors, are unclear.

Objectives: To investigate the associations of maternal dietary patterns and plasma folate concentrations with blood pressure in children aged 4–6 years, and assess the potential effect modifications by child sex, maternal race, pre-pregnancy overweight or obesity, maternal smoking, and breastfeeding.

Methods: Participants were 846 mother-child dyads from the Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) study. Maternal nutrition was characterized by the Healthy Eating Index 2010 (HEI) scores and plasma folate concentrations in pregnancy. We calculated the systolic blood pressure (SBP) and diastolic blood pressure percentiles, incorporating sex, age, and height, and categorized children as either having high blood pressure (HBP; ≥90th percentile) or normal blood pressure. Linear regressions were performed to quantify the associations between maternal nutrition and continuous blood pressure percentiles, and Poisson regressions were used to estimate the incidence rate ratio (IRR) of binary HBP. We examined the effect modifications using interaction models.

Results: Mean HEI scores and folate concentrations were 60.0 (SD, 11.3) and 23.1 ng/mL (SD, 11.1), respectively. Based on measurements at 1 visit, 29.6% of the children were defined as having HBP. Maternal HEI scores and plasma folate concentrations were not associated with child blood pressure percentiles or HBP in the full cohort. Among mothers self-identified as white, there was an inverse relationship between maternal HEI score and child SBP percentile (β, −0.40; 95%CI: −0.75 to −0.06). A maternal HEI score above 59 was associated with a reduced risk of HBP in girls (IRR, 0.53; 95% CI: 0.32–0.88). No modified associations by pre-pregnancy overweight or obesity, maternal smoking, or breastfeeding were indicated.

Conclusions: We found little evidence for effects of maternal nutrition during pregnancy on childhood blood pressure, but detected sex- and race-specific associations. The study contributes to the evolving scientific inquiry regarding developmental origins of disease. *J Nutr* 2021;151:949–961.

Keywords: Healthy Eating Index, plasma folate, maternal nutrition, blood pressure, child health

Manuscript received August 11, 2020. Initial review completed September 30, 2020. Revision accepted November 16, 2020.
First published online February 9, 2021; doi: https://doi.org/10.1093/jn/nxaa395.

Introduction

High blood pressure (HBP) is a major risk factor for heart disease and stroke, 2 leading causes of death in the United States (1). Large cohort studies show that elevated blood pressure can track from childhood to adulthood (2, 3). Untreated pediatric HBP is also directly associated with target organ damage (4–6). It is increasingly recognized that adverse early-life experiences, including in-utero exposure to poor maternal nutrition, may predispose children to future cardiometabolic abnormalities (7, 8).

The evidence supporting this hypothesis is circumstantial. Animal experiments in rodents and sheep have suggested associations between nutritional deprivation during pregnancy and vascular resistance, and studies from diet-induced obese dams have shown endothelial dysfunction and elevated blood pressure in offspring (9–12). In humans, earlier cohort studies focusing on maternal famine or malnutrition during pregnancy have reported long-lasting effects on offspring cardiovascular impairments, even in middle and old age (13–17). Due to the obesity epidemic, pregnancy overnutrition and suboptimal nutrition have been of great concern in the past decades. Studies of single food or nutrient intakes in pregnancy have reported inconsistent associations with child blood pressure (18–24). Clinical trials and their follow-up studies, mainly of supplement intakes, have uniformly yielded null results, except for fish oil supplementation (25–32). As nutrients are not consumed in isolation, dietary pattern analysis has been used increasingly to assess the effects of maternal overall food intake on several offspring outcomes, but little is known about child blood pressure (33–35). We are aware of only 3 studies that have evaluated this exposure-outcome association: 2 using Mediterranean Diet scores and 1 using dietary patterns defined by a data-driven approach (36–38). Among these, only the 1 conducted in pooled Greek and US cohorts using Mediterranean Diet scores detected weak, inverse relationships with both systolic blood pressure (SBP) and diastolic blood pressure (DBP) (38).

In addition to dietary patterns, there is a growing interest in the utilization of biomarkers in nutrition studies, particularly for micronutrients. Folate is an essential B vitamin involved in nucleic acid synthesis, DNA methylation, and cellular division. The preventative effect of sufficient folate intake on fetal neural tube defects is well established, and folate's benefits on cardiovascular health have been suggested by previous research (39–41). Although daily folic acid supplementation is universally advised for women who are planning pregnancy or currently pregnant in the United States, approximately one-quarter of this population do not follow this recommendation (42). A mechanism by which maternal sufficient folate intake may protect against elevated blood pressure in children by improving endothelial functions has been proposed (43). Yet to the best of our knowledge, only 3 studies have estimated the effects of maternal folate concentration on child blood pressure using biomarkers in pregnancy (44–46). Of these, only the study by Wang et al. (46) in Boston has found notably reduced odds of child elevated blood pressure with higher folate levels, restricted to the subset of mothers with cardiometabolic conditions. The need for more evidence is acknowledged.

We investigated the associations of maternal prenatal dietary patterns and plasma folate concentrations with blood pressure in children aged 4–6 years, using data from a community-based pregnancy cohort in the American South. It was hypothesized that children would have lower blood pressure percentiles and reduced risks of high blood pressure if their mothers had better adherence to the 2010 Dietary Guidelines for Americans and/or had higher concentrations of plasma folate during pregnancy. Moreover, nutrition status is related to socioeconomic status (SES) and health literacy, and obstacles to improving diet may co-occur with other behaviors that may impact child health, such as smoking or formula feeding (47–50). Over- or suboptimal nutrition is directly linked with being overweight and obese (51). There is also evidence for sex-specific differences and racial disparities in nutrition status and cardiovascular disease programming (52, 53). As such, we examined whether the associations of interest would be modified by child sex, maternal race, pre-pregnancy overweight or obesity, maternal smoking, and breastfeeding practice.

Subjects

The Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) study is a socio-demographically diverse pregnancy cohort in Memphis, Tennessee, originally established to identify risk factors that impact child neurodevelopment and learning. Participants were pregnant women residing in Shelby County aged 16–40 years. All were at 16–27 weeks of gestation with a singleton, had a low-risk pregnancy, planned to deliver at a participating study hospital, and were able to speak and understand English. From 2006 to 2011, 1503 participants were recruited from prenatal care clinics and the community. More details of the sampling, recruitment, and data collection have been described elsewhere (54). We included 846 mother-child dyads with a primary exposure metric [either the Food Frequency Questionnaire (FFQ) taken in the second trimester or plasma folate measured in mid- to late pregnancy] and a valid measure of child blood pressure at age 4–6 years.

Ethics

Written informed consent was obtained from all enrolled women. All CANDLE research activities were approved by the Institutional Review Board of the University of Tennessee Health Sciences Center, and this secondary analysis was approved by the University of Washington Human Subjects Division.

This research is supported by the Environmental Influences on Child Health Outcomes (ECHO) Prenatal and Early Childhood Pathways To Health: An Integrated Model of Chemical and Social Exposures, Biological Mechanisms, and Sex-Specific Effects on Neurodevelopment and Respiratory Outcomes (PATHWAYS) consortium (NIH 1UG3OD023271-01 and 4UH3OD023271-03). The Conditions Affecting Neurocognitive Development and Learning in Early Childhood (CANDLE) Study is funded by the Urban Child Institute and NIH (1R01HL109977).

Author disclosures: YN, AS, CL, FT, MK, NRB, KZL, SS, DAE, RD, ALF, JS, QZ, and CJK, no conflicts of interest.

Supplemental Tables 1–3 and Supplemental Figures 1–6 are available from the "Supplementary data" link in the online posting of the article and from the same link in the table of contents at http://academic.oup.com/jn.

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Abbreviations used: CANDLE, Conditions Affecting Neurocognitive Development and Learning in Early Childhood; DBP, diastolic blood pressure; GAM, Generalized Additive Model; HBP, high blood pressure; HEI, Healthy Eating Index 2010; IRR, incidence relative rate; SBP, systolic blood pressure; SES, socioeconomic status; TPRS, thin-plate regression splines.

Methods

Maternal nutrition assessment

Maternal dietary patterns were assessed using the Block (2005) FFQ in the second trimester, in which mothers reported intake of 111 food and beverage groups over the past 3 months (55). Healthy Eating Index 2010 (HEI) scores and total energy intakes were calculated based on their responses. The HEI uses a scoring system to evaluate a set of foods aligning with key dietary recommendations from the 2010 US Dietary Guidelines for Americans (56). It comprises 12 nutrient density–adjusted components that sum to a total score ranging from 0 to 100, 9 of which reflect intake adequacy of foods including fruits, vegetables, and protein, and 3 of which reflect intake moderation of foods including refined grains, sodium, and empty calories.

Maternal blood samples were collected in the second and third trimesters. Plasma was separated by centrifuging at 1250–1300 × *g* for 10 min with a centrifugation temperature from −2 to −8°C. Folate concentrations were assessed using the 96-well plate adaptation of the lactobacillus casei microbiological assay, with a minimum detection limit of 3 ng/mL (57). The intra-assay and the inter-assay variability were 4.8–5.9% and 5.5–6.5%, respectively. All measurements were performed within 3 months of sample collection. Measurements from both trimesters were averaged. We further defined an HEI score below 59 as representing poor adherence to the dietary guidelines according to a grading system recently proposed by Krebs-Smith et al. (58), and grouped maternal folate concentrations into 2 categories (first quartile vs. second–fourth quartiles).

Blood pressure assessment

Child blood pressure assessments were conducted by study nurses according to a standardized protocol at the 4–6-year-old visit. We first conducted an assessment of the child's arm circumference to estimate the correct cuff size. After a rest period of at least 2 minutes, blood pressure measurements were taken twice in the right arm at heart level using a BpTRU Medical Devices blood pressure monitor, Model BPM-100. Up to 4 measurements were taken if there was a discrepancy greater than 5 mmHg. Final blood pressure values were calculated by averaging the measurements within a 5-mmHg difference. We calculated sex-, age-, and height-specific blood pressure percentiles using the American Academy of Pediatrics 2017 Clinical Practice Guideline, based on the US pediatric population with normal weight (59). An SBP and/or DBP measurement at the 90th percentile and above was defined as HBP.

Effect modifiers

We evaluated several potential effect modifiers. Child sex (female vs. male) was obtained from birth records. Maternal race (black vs. white vs. others) and breastfeeding practice (ever vs. none) were self-reported. We identified prenatal smokers as those who reported smoking at enrollment and/or had a positive urinary cotinine test (≥200 ng/mL) in the third trimester (60). Pre-pregnancy overweight or obesity was defined as a BMI 25.0 kg/m^2 and above based on clinical measurements (61).

Covariates

We included a number of maternal, child, and other characteristics in this study. Maternal characteristics included age at delivery, education level, marital status, insurance coverage, income adjusted by household size (62), parity, maternal psychopathology as measured by the Global Severity Index (63), hypertensive disorders of pregnancy, alcohol consumption, and weight gained during pregnancy. Child characteristics included height; age; BMI *z*-score at the 4–6-year-old visit; being small for gestational age, defined based on an updated US-based, sex-specific birth weight for gestational age reference (64); sleep quality as measured by the Children's Sleep Habits Questionnaire (65); physical activity level; and medication use that potentially increased blood pressure (e.g., albuterol or methylphenidate). We calculated the average child HEI score, total energy intake, and nutrition density–adjusted folate measurement from 24-hour food recalls by parental reports at the age 2- and age 3-year-old visits (66). Neighborhood-level SES was measured using 2 domains of the Childhood Opportunity Index: the educational and economic opportunity domains (67). We also included recruitment site (safety-net clinics vs. general recruitments) as an indicator for enrollment patterns and SES.

Statistical analysis

We conducted descriptive analyses to summarize the characteristics of the analytic sample overall and by maternal nutrition levels, and to estimate the distributions of exposures and outcomes. Based on complete data, linear regressions with robust standard errors were performed to quantify the associations of maternal HEI scores and plasma folate concentrations with continuous blood pressure percentiles, and Poisson regressions with robust standard errors were used to estimate the incidence rate ratio (IRR) of binary HBP. Based on existing literature regarding risk factors for pediatric HBP, as well as Directed Acyclic Graphs, we identified confounders, precision variables, and potential mediators, and developed a hierarchical adjustment approach of 4 models. Model 1 was minimally adjusted for child sex, child height, age at 4–6-year-old visit, and recruitment site. Model 2 was considered the full model and was extensively controlled for maternal age at delivery, maternal race, education, marital status, insurance coverage, income adjusted by household size, pre-pregnancy BMI, breastfeeding practice, smoking and alcohol consumption during pregnancy, parity, Global Severity Index score, child sleep quality, child physical activity level, child use of medications that potentially increased blood pressure, and Childhood Opportunity Index scores. We further included total energy intake, truncated at 750 and 5000 kcal/d (72 outliers excluded), in the models with maternal HEI scores to address potential residual confounding. In Model 3, an exploratory analysis, we additionally controlled for child HEI score and total energy intake in analyses of maternal HEI scores and child nutrient density–adjusted folate measurements in analyses of maternal plasma folate concentrations. Model 4 was an extended model for Model 2, including 4 potential confounders that might also be in the causal pathway: hypertensive disorders of pregnancy, weight gained during pregnancy, the child being small for gestational age, and child BMI *z*-score.

In the secondary analysis of effect modification, we included cross-product terms of each exposure and effect modifiers of interest (child sex, etc.) and estimated interaction *P* values and stratum-specific associations using the fully adjusted Model 2. In an additional, secondary analysis, we replaced the continuous maternal HEI scores and plasma folate concentrations with their binary forms and repeated the primary analyses and effect modification analyses. We performed 4 sensitivity analyses. To estimate the nonlinear associations of continuous maternal HEI scores and plasma folate concentrations with outcomes of interest, Generalized Additive Models (GAM) with fitted smooth curves were performed. As GAM analyses can be sensitive to the presence of extreme predictors, the curves for plasma folate concentrations were truncated at 60 ng/mL. To explore whether confounding by child nutrition would be nonlinear, we categorized child HEI scores and folate measurements into quartiles and substituted the continuous measurements in Model 3. To compare the influence of 2 potentially interchangeable factors that may be in the causal pathway of our associations, which both serve as proxies for intrauterine growth restriction, we replaced being small for gestational age with birthweight in Model 4. To evaluate whether the percentiles accurately expressed a child's raw blood pressure in the reference population, child age and height at the blood pressure assessment were modeled flexibly using 2-dimensional, unpenalized, thin-plate regression splines (TPRS) in the full models. TPRS were generated from the MGCV package with varied degrees of freedom from 5 to 12. All analyses were conducted in R 3.6.2 (R Cord Team).

Results

Characteristics of the study population

The retention of participants in the CANDLE study from enrollment to the 4–6-year-old visit, as well as the sample sizes for primary analyses of each maternal nutrition variable,

TABLE 1 Characteristics of Conditions Affecting Neurocognitive Development and Learning in Early Childhood participants in the overall analytic sample and by maternal nutrition levels

	Analytic sample $n = 846$	HEI ≤59 $n = 352$	HEI >59 $n = 394$	First folate quartile $n = 225$	Second–fourth folate quartile $n = 621$
Child characteristics					
Gestational age at birth, wk	38.8 (1.8)	38.6 (2.0)	38.9 (1.7)	38.8 (2.0)	38.8 (1.7)
Delivery at <37 wks, *n* [%]	76 [9.0]	40 [11.4]	26 [6.6]	24 [10.7]	52 [8.4]
Birth weight, kg	3.2 (0.6)	3.2 (0.6)	3.3 (0.5)	3.1 (0.5)	3.3 (0.6)
Low birth weight, <2500g, *n* [%]	59 [7.0]	37 [10.6]	18 [4.6]	24 [10.7]	35 [5.7]
Small for gestational age, *n* [%]	77 [9.2]	39 [11.2]	27 [6.9]	26 [11.6]	51 [8.3]
Sex, *n* [%]					
Male	421 [49.8]	177 [50.3]	200 [50.8]	116 [51.6]	305 [49.1]
Female	425 [50.2]	175 [49.7]	194 [49.2]	109 [48.4]	316 [50.9]
Age at visit, y	4.4 (0.6)	4.5 (0.7)	4.3 (0.5)	4.5 (0.7)	4.4 (0.6)
Height at visit, cm	106 (6.1)	106 (6.3)	106 (5.7)	107.2 (6.7)	106.1 (5.8)
Sleep scores	46.8 (7.3)	47.6 (7.3)	45.9 (7.0)	48.3 (7.1)	46.3 (7.2)
Dietary measurements					
HEI	52.4 (10.4)	50.2 (10.7)	54.8 (9.9)	50.8 (9.6)	52.9 (10.6)
Total energy intake, kcal/d	1481 (851.8)	1517 (596.2)	1473 (1068)	1606 (823.2)	1440 (857.8)
Nutrient density–adjusted folate	209 (92.2)	199 (86.1)	215 (91.0)	199 (91.2)	212 (92.4)
Medication use potentially leading to hypertension, *n* [%]	67 [7.9]	36 [10.2]	26 [6.6]	18 [8.0]	49 [7.9]
Vigorous activity frequency, *n* [%]					
Never or occasionally	121 [14.5]	60 [17.3]	33 [8.5]	42 [19.1]	79 [12.9]
Once or twice per week	90 [10.8]	42 [12.1]	36 [9.2]	29 [13.2]	61 [9.9]
3 or more times per week	623 [74.7]	244 [70.5]	321 [82.3]	149 [67.7]	474 [77.2]
BMI class at visit,[1] *n* [%]					
Underweight	21 [2.5]	11 [3.1]	10 [2.5]	5 [2.2]	16 [2.6]
Normal weight	571 [67.6]	239 [68.1]	267 [67.8]	150 [66.7]	421 [67.9]
Overweight	125 [14.8]	48 [13.7]	58 [14.7]	32 [14.2]	93 [15.0]
Obesity	128 [15.2]	53 [15.1]	59 [15]	38 [16.9]	90 [14.5]
Maternal characteristics					
Age at delivery, y	26.1 (5.5)	24.4 (4.9)	28 (5.4)	24.5 (4.7)	26.6 (5.7)
Total energy intake, kcal/d	2396 (965.4)	2674 (995.0)	2179 (844.0)	2789 (1028)	2280 (915.2)
Income adjusted by household size, thousand	17.0 (16.6)	11.0 (12.4)	24.1 (17.5)	8.8 (10.0)	20.0 (17.5)
Total weight gained during pregnancy, kg	14.5 (7.2)	14.2 (7.5)	14.7 (6.8)	12.9 (7.9)	15.0 (6.8)
Global Severity Index	46.7 (10.8)	46.7 (11.3)	46.2 (10.1)	47.1 (11.5)	46.5 (10.6)
Race, *n* [%]					
Black	563 [66.6]	274 [77.8]	211 [53.6]	202 [89.8]	361 [58.1]
White	229 [27.1]	56 [15.9]	159 [40.4]	12 [5.3]	217 [34.9]
Other	54 [6.4]	22 [6.3]	24 [6.1]	11 [4.9]	43 [6.9]
Education, *n* [%]					
<High school	114 [13.5]	66 [18.8]	26 [6.6]	55 [24.4]	59 [9.5]
High school/GED	403 [47.7]	207 [58.8]	147 [37.3]	131 [58.2]	272 [43.9]
Technical school	85 [10.1]	30 [8.5]	42 [10.7]	18 [8.0]	67 [10.8]
College degree	150 [17.8]	32 [9.1]	108 [27.4]	16 [7.1]	134 [21.6]
Grad/professional degree	93 [11]	17 [4.8]	71 [18]	5 [2.2]	88 [14.2]
Marital status at enrollment, *n* [%]					
Married	296 [35.0]	78 [22.2]	199 [50.5]	30 [13.3]	266 [42.9]
Widowed/divorced/separated/never married	398 [47.1]	191 [54.3]	140 [35.5]	136 [60.4]	262 [42.3]
Living with partner	151 [17.9]	83 [23.6]	55 [14]	59 [26.2]	92 [14.8]
Insurance status, *n* [%]					
No insurance	2 [0.2]	0 [0]	2 [0.5]	0 [0]	2 [0.3]
Medicaid or Medicare only	510 [60.3]	259 [73.6]	170 [43.2]	192 [85.3]	318 [51.2]
Medicaid/Medicare and private insurance	28 [3.3]	17 [4.8]	10 [2.5]	8 [3.6]	20 [3.2]
Private insurance only	306 [36.2]	76 [21.6]	212 [53.8]	25 [11.1]	281 [45.3]
Baseline household income, *n* [%]					
$0–$24,999	372 [48.3]	198 [64.7]	114 [29.8]	133 [70.0]	239 [41.2]
$25,000–$54,999	196 [25.5]	70 [22.9]	116 [30.4]	42 [22.1]	154 [26.6]

(*Continued*)

TABLE 1 (*Continued*)

	Analytic sample $n = 846$	HEI ≤59 $n = 352$	HEI >59 $n = 394$	First folate quartile $n = 225$	Second–fourth folate quartile $n = 621$
$55,000–$74,999	83 [10.8]	19 [6.2]	61 [16.0]	7 [3.7]	76 [13.1]
$75,000 or over	119 [15.5]	19 [6.2]	91 [23.8]	8 [4.2]	111 [19.1]
Smoking, from urinary cotinine + self report, *n* [%]	115 [13.6]	58 [16.5]	38 [9.7]	45 [20.1]	70 [11.3]
Alcohol consumption, *n* [%]	76 [9.0]	33 [9.4]	40 [10.2]	14 [6.2]	62 [10.0]
Supplement intake of vitamins, *n* [%]	780 [94.0]	316 [92.9]	378 [96.7]	190 [87.6]	590 [96.3]
Pre-pregnancy BMI class,[2] *n* [%]					
Underweight	41 [4.9]	18 [5.1]	17 [4.3]	12 [5.4]	29 [4.7]
Normal	340 [40.3]	142 [40.6]	165 [42.0]	72 [32.1]	268 [43.3]
Overweight	186 [22.1]	83 [23.7]	75 [19.1]	46 [20.5]	140 [22.6]
Obese	276 [32.7]	107 [30.6]	136 [34.6]	94 [42.0]	182 [29.4]
Pregnancy hypertensive disorder, *n* [%]	49 [5.8]	17 [4.8]	27 [6.9]	10 [4.4]	39 [6.3]
Breastfeeding, *n* [%]					
No	312 [37.5]	180 [52.3]	84 [21.7]	118 [53.4]	194 [31.8]
Yes, 6 months or less	305 [36.7]	116 [33.7]	157 [40.6]	63 [28.5]	242 [39.7]
Yes, above 6 months	214 [25.8]	48 [14.0]	146 [37.7]	40 [18.1]	174 [28.5]
Parity, *n* [%]					
No prior births	512 [60.5]	232 [65.9]	221 [56.1]	177 [78.7]	335 [54.0]
At least 1 prior birth	334 [39.5]	120 [34.1]	173 [43.9]	48 [21.3]	286 [46.1]
Other characteristics					
Childhood Opportunity Index					
Postnatal Educational Index	−0.03 (0.5)	−0.14 (0.4)	0.11 (0.6)	−0.26 (0.3)	0.05 (0.6)
Postnatal Economics Index	−0.10 (0.6)	−0.19 (0.6)	0.03 (0.6)	−0.35 (0.6)	−0.01 (0.6)
Site, *n* [%]					
General recruitment	650 [76.8]	252 [71.6]	371 [94.2]	137 [60.9]	513 [82.6]
Safety net hospitals	196 [23.2]	100 [28.4]	23 [5.8]	88 [39.1]	108 [17.4]

For continuous variables, values are means (SDs); for categorical variables, values are frequency [percentage]. Abbreviations: GED, General Education Development; HEI, Healthy Eating Index.

[1] Child obesity was defined as a BMI at or above the 95th percentile for children of the same age and sex; overweight was defined as a BMI from the 85th to less than the 95th percentile; normal weight was defined as a BMI from the 5th to less than the 85th percentile; and underweight was defined as a BMI less than the 5th percentile.

[2] Maternal pre-pregnancy obesity was defined as a BMI 30.0 kg/m^2 or higher; overweight was defined as a BMI 25.0 kg/m^2 to less than 30.0 kg/m^2; normal weight was defined as a BMI 18.5 kg/m^2 to less than 25.0 kg/m^2; and underweight was defined as a BMI less than 18.5 kg/m^2.

are illustrated in **Supplemental Figure 1**. The analytic samples were 746 and 846 for maternal HEI scores and plasma folate concentrations, respectively. Two-thirds of mothers included in this analysis self-identified as black and approximately one-quarter self-identified as white (**Table 1**). Many (61%) of the mothers had a high school education or less, and 48% of the participating families reported a household income of less than $25,000 per year. More than half of the mothers were classified as overweight or obese before pregnancy. Based on self-reports and/or urinary cotinine analyses, 14% of the mothers were defined as smokers during pregnancy. About two-thirds breastfed their newborns, but less than half of them breastfed more than 6 months. Children had an equal sex distribution, with a mean age of 4.4 years old (SD, 0.6) at the time of blood pressure measurement. At the 4–6-year-old visit, 15% of children were categorized as overweight and another 15% were categorized as obese. The results from the 24-hour food recalls showed the average child HEI score as 52.4 (SD, 10.4), total energy intake as 1481 kcal (SD, 851.8), and nutrient density–adjusted folate intake as 209 μg/1000 kcal (SD, 92.2).

Compared with mothers with an HEI score greater than 59, mothers with an HEI score of 59 or below were more likely to be younger at delivery, self-identify as black, have a lower annual household income, have a lower education level, smoke during pregnancy, and feed their newborn with formula (Table 1). Their children were more likely to be small for gestational age, take medication that potentially increased blood pressure, be less physically active, have poorer dietary quality, and have lower folate intake. Similarly, higher maternal plasma folate concentrations were related to a higher SES and more health-promoting behaviors. We did not observe meaningful differences in baseline characteristics when comparing the CANDLE population at enrollment and the 2 analytic samples available for maternal HEI scores and plasma folate concentrations, except that a larger portion of mothers from the general recruitment cohort than from the safety-net hospital recruitment cohort had available FFQ data (**Supplemental Table 1**).

Child blood pressure

The average SBP was 92.3 mmHg (SD, 9.9) for the raw measurement and 48.6 (SD, 25.5) for the percentile, and the average raw DBP and DBP percentile were 61.1 mmHg (SD, 9.1) and 75.7 (SD, 19.3), respectively. The data of both raw blood pressure measurements and of the SBP percentile were normally distributed, while the DBP percentile was left skewed (**Supplemental Figure 2**). We classified 250 children (29.6%) with an SBP or DBP at the 90th percentile or above as having HBP, largely driven by isolated elevations in DBP.

Maternal nutrition

Distributions of maternal HEI scores and plasma folate concentrations are shown in **Supplemental Figure 3**. Maternal

TABLE 2 Estimated effects of maternal Healthy Eating Index 2010 scores and plasma folate concentrations on blood pressure percentiles and high blood pressure

Model[1]	n	Maternal HEI	n	Plasma folate
SBP percentile, β (95% CI)				
Model 1	746	− 0.14 (−0.31 to 0.03)	846	− 0.02 (−0.19 to 0.14)
Model 2	597	− 0.16 (−0.37 to 0.05)	752	− 0.02 (−0.20 to 0.17)
Model 3	492	− 0.18 (−0.42 to 0.05)	611	− 0.004 (−0.21 to 0.20)
Model 4	556	− 0.13 (−0.35 to 0.09)	693	− 0.01 (−0.21 to 0.18)
DBP percentile, β (95% CI)				
Model 1	746	− 0.09 (−0.21 to 0.04)	846	− 0.01 (−0.12 to 0.11)
Model 2	597	− 0.08 (−0.25 to 0.08)	752	0.003 (−0.13 to 0.14)
Model 3	492	− 0.11 (−0.30 to 0.07)	611	− 0.02 (−0.17 to 0.13)
Model 4	556	− 0.06 (−0.23 to 0.11)	693	− 0.02 (−0.16 to 0.12)
HBP, IRR (95% CI)				
Model 1	746	1.00 (0.98–1.01)	846	1.00 (0.99–1.01)
Model 2	597	1.00 (0.98–1.01)	752	1.00 (0.99–1.01)
Model 3	492	0.99 (0.98–1.01)	611	1.00 (0.99–1.01)
Model 4	556	1.00 (0.99–1.02)	693	1.00 (0.98–1.01)

Data are from the study population of the CANDLE cohort. Abbreviations: CANDLE, Conditions Affecting Neurocognitive Development and Learning in Early Childhood; DBP, diastolic blood pressure; HBP, high blood pressure; HEI, Healthy Eating Index 2010; IRR, incidence rate ratio; SBP, systolic blood pressure.

[1] Linear regressions with robust standard errors were used for blood pressure percentiles, and Poisson regressions with robust standard errors were used for HBP. Model 1 was adjusted for child sex, child height, age at the 4–6-year-old visit, and recruitment site. Model 2 was further controlled for maternal age at delivery, maternal race, education, marital status, insurance coverage, income adjusted by household size, pre-pregnancy BMI, breastfeeding practice, smoking and alcohol consumption during pregnancy, parity, Global Severity Index score, child sleep quality, child physical activity level, child use of medication that potentially increased blood pressure, and Childhood Opportunity Index score. Maternal total energy intake was further included in models with HEI scores. Model 3 was additionally adjusted for child HEI scores and total energy intake in analyses of maternal HEI scores and child nutrient density–adjusted folate measurements in analyses of maternal plasma folate concentrations. Model 4 included hypertensive disorders of pregnancy, weight gained during pregnancy, being small for gestational age, and child BMI *z*-score, based on Model 2.

HEI scores ranged from 26.2 to 88.4, with a mean of 60.0 (SD, 11.3), and more than three-quarters of the scores were under 70. The average maternal total energy intake was 2396 kcal (SD, 965.4). Plasma folate concentrations ranged from 2.6 ng/mL to 80.5 ng/mL, with a mean of 23.1 ng/mL (SD, 11.1), and the maximum folate concentration in the first quartile was 15.7 ng/mL. Although universally accepted cut-offs to define folate deficiency using plasma samples in pregnancy are uncertain, the folate concentrations within the second–fourth quartiles were considered as adequate according to a report from the WHO Technical Consultation and a population-based randomized trial in China (68, 69). The pairwise correlations of maternal HEI scores and plasma folate concentrations (r, 0.30), maternal and child HEI scores (r, 0.27), and maternal plasma folate and child folate intakes (r, 0.11) were moderate.

Associations between maternal nutrition and child blood pressure

The Directed Acyclic Graph showing the exposure-outcome associations is presented in **Supplemental Figure 4**. Overall, we found no evidence of association of maternal HEI scores and plasma folate concentrations with child blood pressure percentiles and HBP from multivariate linear and Poisson regressions (Table 2). We investigated 5 potential effect modifiers for the associations of maternal nutrition in pregnancy with offspring cardiometabolic traits: child sex, maternal race, maternal pre-pregnancy weight status, smoking during pregnancy, and breastfeeding (Figure 1). In mothers self-identified as white, we observed an inverse association between maternal HEI score and child SBP percentile. Each 1-unit increase of maternal HEI score was associated with a 0.40 lower SBP percentile in offspring (β, −0.40; 95% CI: −0.75 to −0.06). This association was null in mothers who self-identified as black (β, −0.03; 95% CI: −0.29 to 0.23) or other race (β, −0.29; 95% CI: −0.94 to 0.37), and the interaction term between maternal race and HEI score was insignificant (P-interaction = 0.22).

Results from the analyses with binary maternal HEI scores indicated that an index score greater than 59 was associated with a 4.79 lower child DBP percentile (β, −4.79; 95% CI: −8.89 to −0.68) when child HEI score, total energy intake, and other confounders were taken into account (Model 3; Table 3). In agreement with the results from the effect modification assessment with continuous form, in those who were white, the child SBP percentile was 8.97 lower (β, −8.97; 95% CI: −17.5 to −0.40) when comparing mothers with an HEI score above 59 to those with an HEI score 59 and below (Figure 2). We also found a significant interactive effect between child sex and maternal HEI score on the risk of a child having HBP (P-interaction = 0.01): maternal HEI scores above 59 were associated with a 47% reduction in the risk of HBP in girls but no reduction in boys [girls: IRR, 0.53 (95% CI: 0.32–0.88); boys: IRR, 1.13 (95% CI: 0.78–1.66)]. No modified associations by pre-pregnancy overweight or obesity, smoking during pregnancy, or breastfeeding were indicated. When dichotomized at the first quartile, the plasma folate measurement was not related to any outcome in the overall sample or any stratum.

In the sensitivity analyses, the smooth effect curves generated from GAMs (**Supplemental Figure 5**) indicated no significant departures from the overall conclusions of the primary analyses,

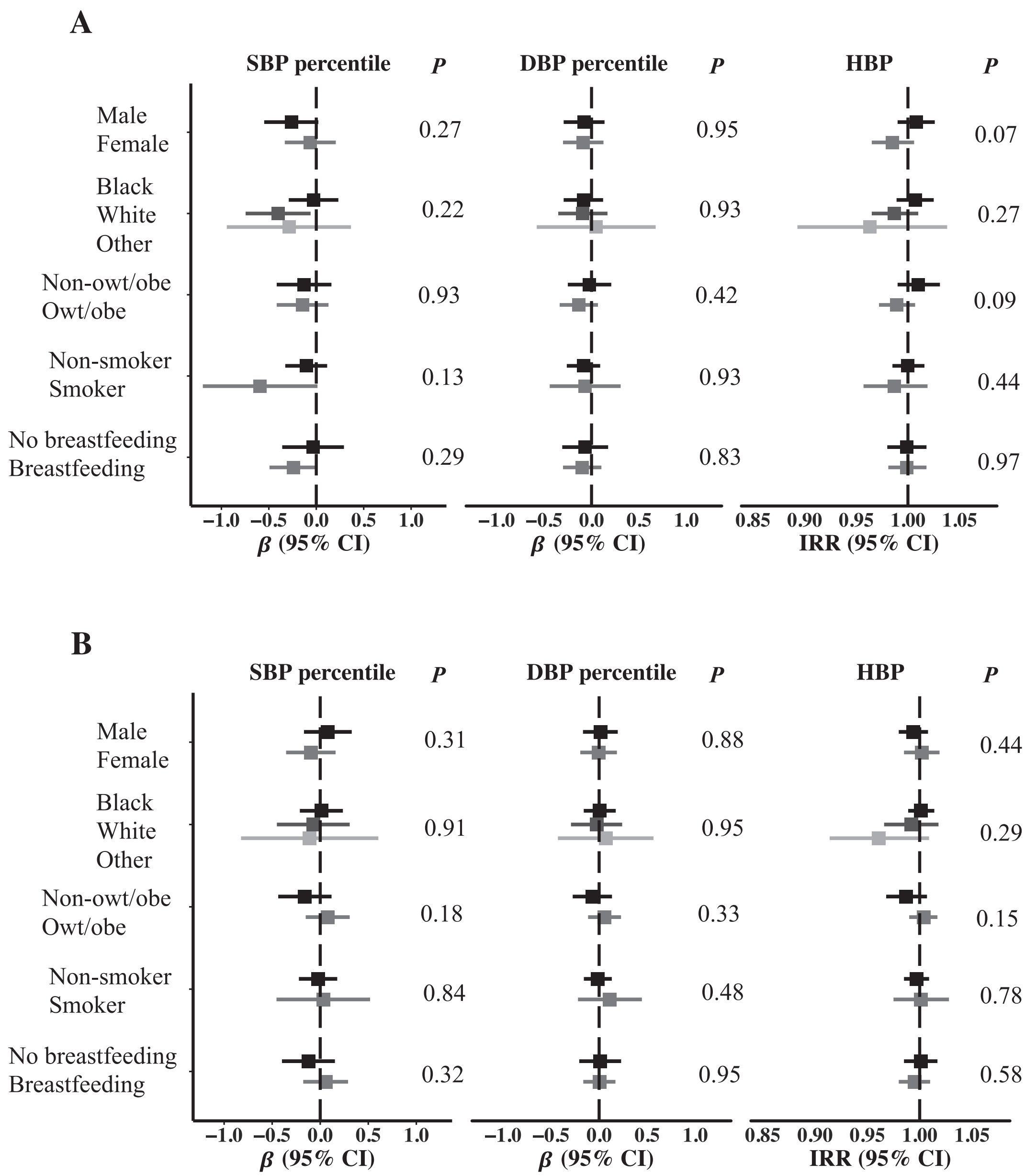

FIGURE 1 Estimated associations of continuous maternal (A) Healthy Eating Index 2010 scores and (B) plasma folate concentrations during pregnancy with child blood pressure (DBP and SBP percentiles and risk of HBP) by child sex (female vs. male), maternal race (black vs. white vs. other), maternal overweight/obesity before pregnancy (overweight/obese vs. nonoverweight/nonobese), maternal smoking during pregnancy (smoker vs. nonsmoker), and breastfeeding practice (breastfeeding vs. no breastfeeding) in the study population of the CANDLE cohort. The analytic samples of Model 2 for maternal Healthy Eating Index 2010 scores and plasma folate concentrations were 597 and 752, respectively. Linear regressions with adjustments in Model 2 were performed for continuous blood pressure percentiles, and Poisson regressions with robust standard errors were used to estimate IRRs. A cross-product term of each exposure and effect modifier of interest were included in the model, and interaction *P* values were reported in the graph. Squares represent the effect estimates, error bars are 95% CIs, and dotted lines show null values. Abbreviations: CANDLE, Conditions Affecting Neurocognitive Development and Learning in Early Childhood; DBP, diastolic blood pressure; HBP, high blood pressure; IRR, incidence rate ratio; Owt/obe, overweight/obese; SBP, systolic blood pressure.

except that we observed a W-shaped pattern for the association between maternal plasma folate concentrations and child SBP percentile from Model 3 ($P = 0.04$). For maternal folate concentrations below 15 ng/mL and between 30–40 ng/mL, there was an inverse association with child SBP percentile independent of child nutrient density–adjusted folate measurements; however, the associations were positive for maternal folate concentrations between 20–30 ng/mL or above 40 ng/mL. Nonetheless, this finding might be driven by the right tail and could be spurious. Replacing continuous child HEI scores and folate measurements with their quartiles did not produce meaningful changes in effect estimates and precision (**Supplemental Table 2**). No appreciable difference was found when being small for gestational age was substituted by birthweight in Model 4 (**Supplemental Table 3**). We also obtained similar results with the primary analysis of blood pressure percentile when controlling for child age and height at the 4–6-year-old visit using TPRS with a degree of freedom varying from 5 to 12 (**Supplemental Figure 6**).

TABLE 3 Estimated effects of binary maternal Healthy Eating Index 2010 scores and plasma folate measurements on blood pressure percentiles and high blood pressure

Model[1]	n	Maternal HEI ($\leq$59 vs. $>$59)	n	Plasma folate (first quartile vs. second–fourth quartiles)
SBP percentile, β (95% CI)				
Model 1	746	− 3.22 (−6.93 to 0.50)	846	− 1.41 (−5.38 to 2.55)
Model 2	597	− 3.32 (−7.93 to 1.29)	752	− 0.15 (−4.83 to 4.54)
Model 3	492	− 4.69 (−9.97 to 0.59)	611	− 0.27 (−5.63 to 5.10)
Model 4	556	− 3.37 (−8.02 to 1.29)	693	− 0.55 (−5.45 to 4.36)
DBP percentile, β (95% CI)				
Model 1	746	− 2.57 (−5.29 to 0.16)	846	0.26 (−2.55 to 3.07)
Model 2	597	− 2.74 (−6.34 to 0.85)	752	0.75 (−2.70 to 4.20)
Model 3	492	− 4.79 (−8.89 to -0.68)	611	0.84 (−3.08 to 4.76)
Model 4	556	− 2.65 (−6.24 to 0.94)	693	0.22 (−3.39 to 3.83)
HBP, IRR (95% CI)				
Model 1	746	0.83 (0.65–1.05)	846	0.96 (0.76–1.21)
Model 2	597	0.84 (0.61–1.16)	752	0.99 (0.75–1.31)
Model 3	492	0.74 (0.52–1.04)	611	1.01 (0.75–1.37)
Model 4	556	0.84 (0.61–1.18)	693	0.89 (0.68–1.18)

Data are from the study population of the CANDLE cohort. Abbreviations: CANDLE, Conditions Affecting Neurocognitive Development and Learning in Early Childhood; DBP, diastolic blood pressure; HBP, high blood pressure; HEI, Healthy Eating Index 2010; IRR, incidence rate ratio; SBP, systolic blood pressure.

[1] Linear regressions with robust standard errors were used for blood pressure percentiles, and Poisson regressions with robust standard errors were used for HBP. Model 1 was adjusted for child sex, child height, age at 4–6-year-old visit, and recruitment site. Model 2 was extensively controlled for maternal age at delivery, maternal race, education, marital status, insurance coverage, income adjusted by household size, pre-pregnancy BMI, breastfeeding practice, smoking and alcohol consumption during pregnancy, parity, Global Severity Index score, child sleep quality, child physical activity level, child use of medication that potentially increased blood pressure, and Childhood Opportunity Index score. Maternal total energy intake was further included in models with HEI scores. Model 3 was additionally adjusted for child HEI scores and total energy intake in analyses of maternal HEI scores and child nutrient density–adjusted folate measurements in analyses of maternal plasma folate concentrations. Model 4 included hypertensive disorders of pregnancy, weight gained during pregnancy, being small for gestational age, and child BMI z-score, based on Model 2.

Discussion

In this analysis of prospective data from a US urban pregnancy cohort with high socio-demographic diversity, we found no association in the overall cohort between maternal nutrition in pregnancy, measured by the HEI score and plasma folate concentrations, and child blood pressure at age 4–6 years. This conclusion remained the same after including factors that may serve as confounders and also potentially acted in the causal pathway in the extended models and in several sensitivity analyses. Potential race- and sex-specific relationships were suggested. White mothers with better adherence to the 2010 Dietary Guidelines for Americans in early pregnancy had offspring with lower SBP percentiles. Relatively better maternal dietary quality (HEI score $>$59) was associated with a reduced risk of HBP in girls. However, these findings should be interpreted with caution owing to the multiple comparisons in the effect modifier analysis. The results also suggested that child nutrition may confound the nonlinear maternal nutrition–child blood pressure relationships.

We did not detect associations between maternal HEI scores and child blood pressure at age 4–6 years. The findings are in agreement with the 2 European studies with maternal dietary quality. The Infancia y Medio Ambiente study in Spain reported null relationships between maternal Mediterranean diet scores and child cardiometabolic risk at age 4 (36). The Generation R study in the Netherlands used a data-driven approach to define maternal posteriori dietary patterns, and found no association with child blood pressure at age 6 (37). However, a similar study based on pooled data from 2 birth cohorts, 1 in Greece and 1 in the United States, observed lower offspring SBP and DBP in mid-childhood if mothers had better adherence to the Mediterranean diet (38). Other observational studies also have estimated the effects of single food or nutrient intakes in pregnancy on child blood pressure, such as carbohydrate, protein, or fat, or the effects of maternal dietary patterns on health conditions that are closely relevant to child blood pressure, such as fetal growth or obesity, but the results are inconclusive (18–23, 70–72). There may be several explanations for the null results in our study with maternal HEI score. First, as the study by Chatzi et al. (38) has shown, the effects of prenatal nutrition exposure might not appear until age 6. Second, the FFQ was administered in the second trimester, which was more likely to reflect the nutrition status in early pregnancy. Although the first trimester is critical for programming the lipid profile, the second and third trimesters are the windows when nephron development, adipogenesis, and fat accumulation mostly occur (73–76). Third, despite more than 75% of the mothers in the CANDLE cohort having a poor pregnancy diet, they were relatively young with low–medical risk pregnancies, and extreme under- or overnutrition was not observed. Associations might be more detectable when studying extreme exposures with greater contrasts. Some stratum-specific associations of maternal HEI score were evident. National representative data have indicated sexual and racial differences in cardiovascular disease programming (53). Mothers who self-identified as white in the CANDLE cohort had higher HEI scores, but there is also the potential for misclassification of exposures that may lead to null associations in the other race groups, when some foods and nutrients consumed are underrepresented by the Dietary Guidelines. Data on sex-specific associations between pregnancy nutrition and child blood pressure are limited: only 2 Danish randomized trials have reported higher blood pressure

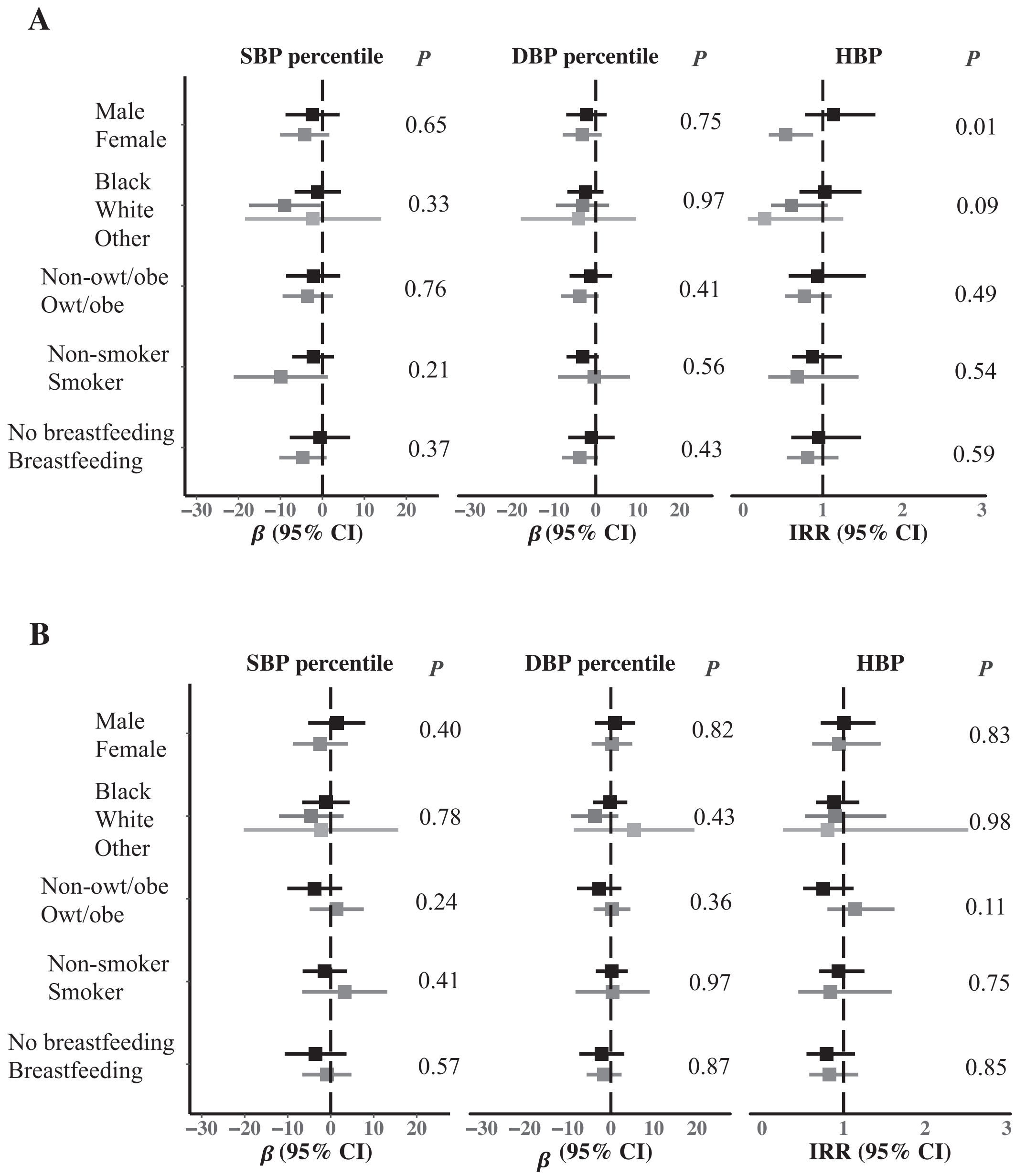

FIGURE 2 Estimated associations of binary maternal (A) Healthy Eating Index 2010 scores (≤59 vs. >59) and (B) plasma folate measurements (first quartile vs. second–fourth quartiles) during pregnancy with child blood pressure (DBP and SBP percentiles and risk of HBP) by child sex (female vs. male), maternal race (black vs. white vs. other), maternal overweight/obesity before pregnancy (overweight/obese vs. nonoverweight/nonobese), maternal smoking during pregnancy (smoker vs. nonsmoker), and breastfeeding practice (breastfeeding vs. no breastfeeding) in study population of the CANDLE cohort. The analytic samples of Model 2 for maternal Healthy Eating Index 2010 scores and plasma folate levels were 597 and 752, respectively. Linear regressions with adjustments in Model 2 were performed for continuous blood pressure percentiles, and Poisson regressions with robust standard errors were used to estimate IRRs. A cross-product term of each exposure and effect modifier of interest were included in the model, and interaction *P* values were reported in the graph. Squares represent the effect estimates, error bars are 95% CIs, and dotted lines show null values. Abbreviations: CANDLE, Conditions Affecting Neurocognitive Development and Learning in Early Childhood; DBP, diastolic blood pressure; HBP, high blood pressure; IRR, incidence rate ratio; Owt/obe, overweight/obese; SBP, systolic blood pressure.

associated with fish supplementation in boys (28, 31). Animal studies have shown that the response to poor maternal diet triggers sex-specific epigenetic alternations in offspring, together with sexually dimorphic deregulation of certain genes, further resulting in sexual disparities in the uptake and metabolism of amino acids, glucose, and fats (77, 78).

We detected little evidence of associations between maternal plasma folate concentrations and child blood pressure. The findings are consistent with the 2 micronutrient supplement trials in rural Nepal and Bangladesh and with the 2 observational studies addressing this research topic in the Netherlands (26, 44, 45, 79). The study based on the Boston Birth Cohort reported 40% reduced odds of child elevated blood pressure when comparing mothers with plasma folate concentrations above median to below median, in the subset of mothers with cardiometabolic conditions (46). We did not observe any association in the stratum of mothers with pre-pregnancy overweight or obesity. The disparity in results between our study and the study in Boston may be attributed to the differences in selective criteria for subgroups and the cut-offs of folate concentrations. Another study by Wang et al. (80) in Boston has reported an L-shaped association between maternal plasma folate concentrations and child overweight or obesity. In line with this study, our results suggested a weak, nonlinear relationship between maternal plasma folate concentrations and child SBP percentiles, independent of child nutrient density–adjusted folate measurements, but the GAM curve indicated a W-shaped pattern of the associations. Adequate maternal folate levels may protect against offspring elevated blood pressure by reducing plasma homocysteine concentrations and increasing NO synthesis in endothelial cells, scavenging superoxide anions, and subsequently counteracting oxidative stress and promoting resilience of vessels (81–84). However, the plausible biological mechanism explaining this W-shaped relationship needs future exploration. Even though our study had relatively higher maternal folate concentrations compared with the studies aforementioned and the national representative data of women of childbearing age (85), most of the studies, including ours, have obtained similar null results. It could be due to the fact that the associations between maternal folate concentrations and child cardiovascular health are likely to be nonlinear, and the ability to detect potential associations may vary by the utilization of study-specific plasma folate thresholds.

Our study has several strengths. To our knowledge, this is the first study to use the HEI as a measurement for diet quality in pregnant women to predict offspring blood pressure. Although other diet quality scores, such as Mediterranean Diet Score or Dietary Approaches to Stop Hypertension, are also designed to evaluate adherence to specific dietary recommendations, the food compositions, weights assigned to each food group, and cut-offs of intake of nutrients vary widely, suggesting that identification of suitable measurements for intended populations and health outcomes is influential (86, 87). We elected to use the HEI because the Dietary Guidelines aim to help the general American population to make healthy choices about food and beverages in their daily lives, and systematic reviews and large meta-analyses have convincingly demonstrated that higher diet quality, as described with the use of the HEI, is associated with lower risks of cardiovascular disease mobility and mortality (88, 89). Another strength of our study is the application of nutrient biomarker data. Folate measurements determined from self-reported data could overestimate the intake from diet and supplemental folic acid, particularly when folate is consumed from multiple sources, as 1 source may reduce the absorption and bioavailability of the others (90). Utilization of plasma folate concentrations, which directly reflect physiological responses to overall intakes after absorptive and metabolic processes (91), is more likely to reveal the true exposure-outcome associations. In addition, contributory evidence from observational nutrition studies is commonly subject to residual confounding. A predisposition to cardiometabolic disorder may be attributable to postnatal nutrition as much as prenatal nutrition. Besides child nutrtion measurements, we were also able to adjust rigorously for individual- and neighborhood-level SES in the current analysis. Furthermore, previous studies have suggested adverse health effects from both under- and overnutrition, and nonlinear associations were frequently assessed by using tertiles or quartiles, the arbitrary cut-offs of which limit the external generalizability to other populations. Here, we adopted 2 approaches to assess the nonlinear associations: curve fitting and an analysis of cut-offs with public health meaning. Finally, child blood pressure measurements were standardized using the 2017 guidelines with the normal-weight pediatric population as the reference, which performed better than the 2004 guidelines in identifying children with adverse cardiometabolic profiles (92).

Our study has some limitations. One is the self-reported nature of maternal HEI components and child nutrition. Even though these measurements were adjusted for nutrient density, potential measurement error may still exist. In addition, child nutrition was not measured contemporaneously with the outcome assessment. As plasma folate is an indicator for short-term exposure, it is an imperfect measure of chronic deficiency in pregnancy (93). It is also difficult to pinpoint the food source with folate biomarkers and, therefore, to inform dietary interventions. Furthermore, we cannot rule out the misclassification of HBP. Although blood pressure was measured repeatedly during an assessment, the examination was performed on a single occasion. As such, the definition of HBP in our analysis does not meet the clinical definition (94, 95). Moreover, although we did not observe meaningful differences in baseline characteristics between the families at enrollment and the analytic samples for each nutritional measurement, selection bias remains a concern. Finally, due to the skewed socio-demographic features and other health characteristics in our study sample, the findings of this study may not be generalized to the other populations.

Despite the limitations, our study shows that pregnancy nutrition, characterized by HEI scores and plasma folate concentrations, is not associated with child blood pressure in a community-based cohort in the United States. It contributes to the evolving science regarding the developmental origins of disease. Continuing investigations are needed to verify our hypotheses in other well-characterized populations.

Acknowledgments

The authors' responsibilities were as follows—YN, AS, CL, FT, MK, ALF, JS, and CJK: designed the study; YN and AS: analyzed the data; YN, AS, CL, and CJK: wrote the manuscript; FT, MK, NRB, KZL, SS, DAE, RD, ALF, JS, and QZ: provided instructions for the result interpretations and comments for the writing; YN: had primary responsibility for the final content; and all authors: read and approved the final manuscript.

Data availability

Data described in this manuscript can be requested from the CANDLE study website (https://candlestudy.uthsc.edu/research/guidelines-collaboration), and will be made available after approval. The data codebook can be downloaded from the same webpage. The computing code in R can be obtained from the corresponding author via email request.

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