

Maternal Energy Stores and Diet Composition During Pregnancy Program Adolescent Blood Pressure

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Background—Fetal undernutrition is hypothesized to program blood pressure (BP) later in life. Human epidemiological studies that use birth weight as a proxy for fetal malnutrition fail to identify specific aspects of maternal nutrition responsible for programming.

Methods and Results—We examined how maternal nutrition during pregnancy and infant birth weight relate to systolic and diastolic BP (SBP and DBP) in 2026 Filipino adolescents. Data were collected prospectively during the Cebu (Philippines) Longitudinal Health and Nutrition Survey. Women were assessed at \approx 30 weeks gestation, and children were followed from birth through adolescence. Regression models were used to examine how the mothers' total energy intake, percentage of energy from protein and fat, triceps skinfold thickness during pregnancy, and infant birth weight relate to adolescent BP, controlling for current age, height, and body mass index and other potential confounders. Maternal triceps skinfold thickness was significantly inversely related to SBP among boys and to DBP in boys and girls. Maternal nutrition variables attenuated but did not eliminate an inverse birth weight–SBP relationship in boys. SBP was significantly inversely related to the mothers' percent of dietary energy from protein in boys. Among girls, SBP and DBP were inversely related to the mothers' percentage of calories from fat. There was no evidence of confounding of these relationships by current diet, maturation status, physical activity, or socioeconomic status.

Conclusions—Maternal diet composition and energy stores in the form of subcutaneous fat have long-term effects on offspring BP in adolescence. (*Circulation*. 2001;104:1034-1039.)

Key Words: blood pressure ■ adolescents ■ pregnancy ■ nutrition

There is considerable evidence for an inverse relationship between birth weight and blood pressure (BP) later in life.¹ Because fetal growth is largely a reflection of nutrient and oxygen supply to the fetus, it is widely assumed that prenatal nutrition is the most important programming stimulus.² The fetal programming hypothesis has led to the hope that the risk of hypertension and other chronic diseases in future generations might be reduced through improvements in maternal nutrition during pregnancy.³ Birth weight is the most commonly used measure of the quality of the prenatal environment, but it is widely recognized as an imperfect proxy for fetal nutrition. It is at best a sensitive but nonspecific indicator of fetal growth reflective of a range of genetic, hormonal, and nutritional factors. At present, the best evidence that nutrition is an important programming stimulus comes from studies of rats, showing that maternal protein restriction during pregnancy leads to reduced birth weight and elevated BP in offspring.^{4,5}

Despite promising leads in animal models, few studies have directly tested the fetal nutrition hypothesis in humans by assessing the role of maternal nutritional status or dietary intake during pregnancy. Several studies used maternal an-

thropometry to indicate nutritional status during pregnancy. Clark and colleagues⁶ found that maternal weight gain between 18 and 28 weeks gestation was inversely related to offspring BP among women with below-median triceps skinfold thickness at 18 weeks gestation. Godfrey et al⁷ similarly found an inverse relation between maternal skinfold thickness during pregnancy and offspring BP in Jamaican children. In contrast, the study by Laor and colleagues⁸ of BP in Jewish military conscripts found no evidence for an association between BP and birth weight, maternal body mass index (BMI) before pregnancy, or weight gain during pregnancy.

Several studies have used the "natural experiment" of famine to test the hypothesis, but results have generally been contrary to expectations. Prenatal exposure to the Leningrad Siege was found not to relate to adult BP.⁹ In the Dutch Famine Study, individuals exposed to famine in utero did not have elevated BP as adults, but their adult BP related inversely to birth weight.^{10,11} A recent study from this cohort found an inverse association between BP and the ratio of protein to carbohydrates in the mother's diet during the third, but not the first or second trimester, as reflected in ration

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records collected during the war.¹² There was no association between offspring BP and maternal intake of total calories, protein, carbohydrate, or fat, suggesting that diet composition may be more important than total intake. Thus, the few studies that include measures of maternal nutritional stress or nutritional status during pregnancy provide mixed support for the hypothesis that maternal nutrition is key to programming in humans.

Our study examines the relationship of size at birth to BP in Filipino adolescents, with and without considering indicators of maternal nutritional status and dietary intake during pregnancy. Our detailed longitudinal data also allow us to test for potentially confounding variables such as current lifestyle factors. Finally, we assess the contribution of current maternal BP.

Survey Design and Sample

Data come from the Cebu Longitudinal Health and Nutrition Survey (CLHNS). This ongoing community-based survey follows a cohort of 3080 infants born in 1983 to 1984. The study area is Metro Cebu, the second largest metropolitan area of the Philippines. The 33 communities randomly selected for the survey include densely populated urban and periurban neighborhoods and more isolated rural villages in the mountains or nearby islands.

All pregnant women in the selected communities were initially invited to participate and were included in the longitudinal study if they gave birth between May 1, 1983, and April 30, 1984 ($n=3327$). Initial refusal rates were very low ($<3\%$), but no data are available on those who declined participation. Women were measured and completed a single 24-hour dietary recall during a baseline survey at a mean of 30 ± 4 weeks gestation. Although numerous follow-up surveys compose the CLHNS, the present analysis focuses on data from the baseline, birth, and 1998 to 2000 follow-up survey when adolescents were 14 to 16 years of age.

As indicators of the mother's nutritional status during pregnancy, we used triceps skinfold thickness and dietary intakes of protein, fat, and total energy at 30 weeks gestation. Infant length was measured within 6 days of birth by trained project staff using custom length boards. For hospital births, birth weight was measured with hospital scales. Infants born at home were measured by birth attendants provided with Salter hanging-type scales and trained in their use. Gestational age was estimated from the mothers' reports of last menstrual period date. If this was unknown, if pregnancy complications occurred, or if the infant weighed <2.5 kg at birth, gestational age was determined by the Ballard method.¹³ BMI was calculated as a measure of relative weight.

Anthropometric assessments in adolescents included weight; height; arm, waist, and hip circumferences; and triceps and subscapular skinfolds. Dietary intakes were measured with two 24-hour recalls on consecutive days, and the mean was used in analyses. Energy and nutrient intakes were calculated from Philippines Food Composition Tables produced by the Food and Nutrition Research Institute of the Philippines. We included total energy and protein intakes in our models. Physical activity was measured by Caltrac accelerometer. Activity levels were categorized into high,

average, and low, representing thirds of the distribution of 24-hour Caltrac accelerometer counts. Adolescents were asked about their smoking history and current smoking. BP was measured in triplicate with a mercury sphygmomanometer after a 10-minute seated rest, and the mean was used in analyses. The same interviewer measured the adolescent's and the mother's BP. The mother's BP during her pregnancy with the index child was not measured. Household socioeconomic status is represented by total household income and possession of a television. We expect socioeconomic variables to affect BP primarily through more proximate determinants, such as nutritional status and diet, but we include them in analyses to account for other unmeasured determinants of BP (such as stress levels).

From the original sample of 3080 single live births, 2089 adolescents were located and included in the 1998 follow-up survey. Of these, 2026 had birth and current measurements, and they form the main analysis sample. Slightly fewer subjects ($n=1881$) had maternal BP data. Birth weight and length and BP in adolescence were not significantly different in those with and without missing data. When data were collected for the 1998 to 2000 survey, girls were completely surveyed before boys. Consequently, boys are ≈ 1 year older than girls. All analyses are stratified by sex.

Analysis Methods

Systolic and diastolic BP (SBP and DBP) were analyzed as continuous variables by ordinary least-squares regression. We first examined the relationship of birth characteristics to adolescent BP, controlling for current age, height, and BMI. We sequentially added maternal nutritional and BP variables. We tested for confounding by current diet, activity, and socioeconomic status of the adolescents, but because none of these variables were shown to be confounders, we excluded them from the final models.

Results

Characteristics of study participants are given in Table 1. Cebu adolescents are relatively short and thin compared with US adolescents. Compared with the new National Center for Health Statistics reference,¹⁴ mean height z scores were -1.92 ($SD=0.81$) for boys and -1.97 ($SD=0.86$) for girls; 85.6% of boys and 70.7% of girls had a BMI below the age- and sex-specific median; 40.8% of boys and 22.0% of girls had a BMI below the 10th percentile. This BMI distribution reflects delayed maturation relative to the US populations and a higher prevalence of undernutrition. Median age at menarche was 13.1 years.¹⁵ No girls reported currently smoking, but 5.5% of boys reported currently smoking regularly. Low birth weight (<2.5 kg) occurred in 10.0% of the analysis sample, and 20.4% were small for gestational age (birth weight for gestational age below the 10th percentile of a commonly used reference population). We have no data on prepregnancy BMI. On the basis of weight 2 months after giving birth, $\approx 15\%$ of women had a BMI suggestive of chronic energy deficiency ($BMI<18.5$).

There was no significant crude relationship of birth weight, length, or gestational age to SBP or DBP in boys or girls. Gestational age had no significant main effect, nor did it

TABLE 1. Characteristics of the Participants

	Boys (n=967)	Girls (n=1059)
Adolescents		
Age	16.08±0.33	15.04±0.34
Height, cm	158.4±6.8	149.1±5.6
Weight, kg	46.79±8.40	41.93±6.41
BMI, kg/m ²	18.55±2.54	18.83±2.42
Birth weight, g	3.02±0.42	2.98±0.41
Birth length, cm	49.34±2.02	48.91±1.99
SBP, mm Hg	105.6±10.8	97.2±8.9
DBP, mm Hg	69.4±9.0	66.0±7.4
Mothers of index children (all)		
During pregnancy		
Height, cm	150.6±5.0	
Triceps skinfold thickness in 3rd trimester, mm	12.8±3.92	
BMI 2 months postpartum, kg/m ²	20.9±2.4	
Current		
BMI, kg/m ²	23.7±4.1	
SBP, mm Hg	113±19	
DBP, mm Hg	77±12	

modify the effects of birth weight or length, so it was dropped from subsequent models. The adolescent's current diet, activity, maturation status, household socioeconomic status, and household socioeconomic status during the mother's pregnancy were not consistently associated with BP, nor did they substantially alter the relationship of birth or maternal characteristics to BP. Accordingly, we focus on results from 4 models. Model 1 includes birth weight and length and current

age, height, and BMI. Model 2 adds maternal anthropometry during pregnancy, model 3 adds maternal diet during pregnancy, and model 4 adds current maternal BP. Results for SBP and DBP are shown in Tables 2 and 3, respectively.

Systolic BP

In boys, there was a significant inverse relationship of birth weight to SBP only after control for current height, age, and BMI (Table 2, model 1). As expected, SBP was highly related to current age, height, and BMI in both boys and girls.

Maternal height and triceps skinfold thickness during pregnancy were significantly inversely related to SBP in boys. Addition of maternal pregnancy variables in model 2 attenuated but did not eliminate the birth weight–SBP relationship. Birth size and maternal anthropometric variables were unrelated to SBP in girls. The relationship of maternal diet variables during pregnancy differed in boys and girls (model 3). In boys, percent of dietary energy from protein was inversely related to SBP, whereas in girls, a higher percentage of calories from fat was significantly associated with lower SBP. The relationship of the mothers' height and skinfold thickness during pregnancy to SBP remained virtually unchanged when birth weight and length were omitted (not shown). The mother's SBP was significantly related to SBP in boys and girls (model 4), suggesting either a genetic effect or an unmeasured effect of a shared environment.

As judged by the R^2 values, birth and maternal nutritional characteristics played a minor role. Birth weight, however, is significantly positively related to height and BMI in adolescence and thus may have direct and indirect effects on BP.

Diastolic BP

Among girls, birth length was inversely related to DBP after control for current size. This weak relationship was un-

TABLE 2. SBP in CLHNS Adolescents: β -Coefficients From Linear Regression Models

	Boys				Girls			
	Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4
Birth								
Weight, kg	-2.01†	-1.78*	-1.82*	-1.74*	-0.91	-0.83	-0.85	-0.61
Length, cm	0.08	0.13	0.13	0.17	-0.16	-0.16	-0.14	-0.18
Current								
Age	3.67‡	3.47‡	3.45‡	3.07‡	3.80‡	3.80‡	3.71‡	3.79‡
Height, cm	0.15‡	0.22‡	0.23‡	0.21‡	0.21‡	0.24‡	0.26‡	0.25‡
BMI, kg/m ²	1.26‡	1.31‡	1.32‡	1.31‡	0.87‡	0.86‡	0.86‡	0.84‡
Mother's								
Height, cm		-0.15†	-0.16†	-0.16†		-0.07	-0.06	-0.09
Triceps, mm		-0.26‡	-0.24‡	-0.31‡		-0.03	0.04	-0.03
Energy intake			-0.29	-0.16			-0.23	0.01
% energy from fat			-0.03	-0.03			-0.09‡	-0.08‡
% energy from protein			-0.18†	-0.15*			-0.03	-0.02
BP, mm Hg				0.07‡				0.06‡
R^2	0.130	0.141	0.146	0.153	0.103	0.104	0.117	0.126

* $P \leq 0.10$.

† $P \leq 0.05$.

‡ $P \leq 0.01$.

TABLE 3. DBP in CLHNS Adolescents: β -Coefficients From Linear Regression Models

	Boys				Girls			
	Model 1	Model 2	Model 3	Model 4	Model 1	Model 2	Model 3	Model 4
Birth								
Weight, kg	-0.38	-0.33	-0.31	-0.24	0.69	0.83	0.81	1.15
Length, cm	-0.15	-0.11	-0.12	-0.06	-0.27*	-0.26	-0.24	-0.34†
Current								
Age	3.17‡	3.16‡	3.19‡	3.03‡	2.57‡	2.58‡	2.47‡	2.38‡
Height, cm	0.11‡	0.14‡	0.14‡	0.12‡	0.08*	0.12‡	0.14‡	0.14‡
BMI, kg/m ²	0.71‡	0.76‡	0.76‡	0.72‡	0.63‡	0.64‡	0.64‡	0.64‡
Mother during pregnancy								
Height, cm		-0.09	-0.09	-0.08		-0.06	-0.06	-0.08
Triceps, mm		-0.15†	-0.16†	-0.21†		-0.13*	-0.08	-0.12*
Energy intake			-0.01	0.01			-0.20	-0.04
% energy from fat			-0.01	0.03			-0.07‡	-0.07†
% energy from protein			-0.00	-0.02			-0.01	-0.01
BP, mm Hg				0.07‡				0.04‡
R ²	0.073	0.081	0.082	0.096	0.070	0.075	0.085	0.093

* $P \leq 0.10$.† $P \leq 0.05$.‡ $P \leq 0.01$.

changed by the addition of maternal nutrition variables but strengthened with the addition of the mothers' DBP. There was no relationship of birth size to DBP in boys. Maternal skinfold thickness during pregnancy was inversely related to DBP in boys and girls, independent of birth weight and length. A higher fat content in the mother's diet during pregnancy was significantly associated with lower DBP in girls, but there were no significant maternal diet-BP relationships among boys. The mother's DBP was significantly associated with boys' and girls' DBP in adolescence.

Discussion

The inverse relationship of size at birth with BP at later ages is now well established by substantial animal and human epidemiological evidence, although in humans, the relationship is weakest during adolescence.¹ Animal models of dietary restriction during pregnancy implicate inadequate maternal nutrition as the critical determinant of altered physiology leading to elevated BP. Evidence from human studies of maternal nutrition during pregnancy, however, is sparse. Godfrey et al⁷ found an inverse relationship of maternal triceps skinfold thickness at 15 weeks of pregnancy with SBP in a small sample of 10- to 12-year-old Jamaican children, but Laor et al⁸ found no relationship of maternal anthropometry during pregnancy with BP in a large study of 17-year-old Israeli youths. Our study shows that low maternal fat stores at ≈ 30 weeks gestation are associated with higher SBP and DBP in adolescent boys. Consistent with other studies,¹ we also observed an inverse relationship of birth weight to SBP in boys. The SBP-birth weight relationship, however, was attenuated (but not eliminated) when maternal triceps skinfold thickness was taken into account. The significant association of maternal triceps skinfold with BP, independent of birth weight, suggests that maternal nutrition is

indeed an important programming stimulus. Our earlier CLHNS studies show that maternal height and triceps skinfold thicknesses during pregnancy significantly predict infant birth weight and length.¹⁶ Our BP results, however, suggest that important aspects of maternal nutrition during pregnancy are not fully captured by birth weight. At the same time, the marginal birth-weight relationship with SBP in boys after maternal nutrition is accounted for suggests that birth weight serves as a marker for factors unrelated to the aspects of maternal nutrition measured in this study.

There are several possible explanations for this finding. First, our limited measures of maternal nutrition during pregnancy most likely leave much variation in these factors unmeasured. The birth-weight effect in boys might have been further reduced if we had more comprehensive measures of maternal nutritional status. Alternatively, birth weight may be a proxy for some nonnutritional aspect of the maternal or fetal environment. For example, fetal exposure to maternal glucocorticoids triggered in response to stress reduces fetal growth in rats and permanently programs activity of the hypothalamic-pituitary-adrenal axis in offspring, with effects on postnatal BP regulation.¹⁷

Little is known about which specific aspects of maternal diet serve as programming stimuli. Most animal models of fetal programming of BP impose maternal dietary protein restriction during gestation,⁵ although one study¹⁸ imposed a 30% energy restriction. The generalizability of these results to human populations may be limited, because highly restricted protein or energy intakes in the absence of other nutrient deficiencies are not typically seen in humans. We examined total energy intakes and the relative contribution of protein and fat in the maternal diet during pregnancy. Among adolescent boys, SBP was inversely related to the mother's percentage of energy intake from protein during late gesta-

tion, independent of birth weight and maternal triceps skinfold thickness during pregnancy. This is consistent with animal models that document elevated BP in the offspring of rats fed a protein-deficient diet during pregnancy.^{5,19} In girls, SBP and DBP were inversely related to the mother's percentage of energy intake from fat during pregnancy.

In a study of Aberdeen adults, Campbell et al²⁰ found different effects of the mother's carbohydrate intake on BP, depending on the level of animal protein in the diet, with low-carbohydrate, high-protein intakes related to reduced placental size and increased BP later in life. These relationships diverge from our findings, which suggest a BP-lowering effect of maternal protein intake during pregnancy, as indicated by the percentage of calories derived from protein. Our findings are consistent with the recent observations of Roseboom and colleagues,¹² who find evidence for an inverse association between the ratio of protein to carbohydrates in the maternal diet during the third trimester and offspring BP but no association between total calories, protein, fat, or carbohydrates and offspring BP. Our findings are similar in showing a lack of association of total maternal energy intake with offspring BP but an inverse association with percentage of calories from protein. These results suggest an effect of diet composition rather than total intake. Given the potential for future public health preventive measures through altered maternal diet during pregnancy, there remains a need to clarify the role of the macronutrient and micronutrient composition of the maternal diet and its consequences for offspring physiology.

We find marked sex differences in relationships of early exposures to BP. Other studies find inconsistent sex differences: some find effects in boys, others in girls, but as yet, no physiological models have been proposed to explain these findings. Among adolescents, maturational stage, insulin resistance, and sex steroid levels are believed to alter BP during puberty.²¹ Inclusion of maturation variables did not reduce sex differences in our results, nor did maturation status modify or confound the relationship of birth weight or maternal nutritional status with adolescent BP. Measurements of sex steroids are needed, however, to clarify the physiological basis for sex differences in relationships between prenatal exposures and later risk for cardiovascular disease.

The present study helps fill important gaps in the fetal programming literature. First, few studies have been conducted on adolescents in a developing country context, where fetal programming may have the greatest importance. In countries undergoing a nutrition transition, high rates of fetal growth retardation in previous decades are now being followed by substantial improvements in socioeconomic status and a concomitant increase in exposure to cardiovascular disease risk factors, such as sedentary lifestyle and increased energy and fat intakes, which are contributing to increasing obesity prevalence.²² Our results suggest that maternal nutrition during pregnancy and fetal growth outcomes have long-term implications for BP regulation in a population relatively early in the nutrition transition.

Second, other studies have raised questions about the degree to which the relationship of maternal nutrition or birth weight to BP is confounded by exposure to other risk factors

in the period between birth and the measurement of BP. We observed no confounding by the adolescent's diet, activity, maturational status, or indicators of socioeconomic status.

Third, our study may contribute to the debate surrounding the possible role of genetic factors with common influences on fetal growth and BP regulation²³ by assessing the role of the mother's BP. Although we do not directly assess specific genetic factors, our inclusion of maternal BP provides indirect evidence of a possible role of genetics. Inclusion of maternal BP in multivariate models strengthened associations between birth length and BP in girls and between maternal nutritional status and BP in boys. Thus, although there may be some genetic determination of BP (as shown by the positive association of maternal and adolescent BP), the associations that we document are not likely to be explained by genetic factors with common effects on BP and our perinatal predictor variables.

In summary, this study supports the hypothesis that maternal nutritional status during pregnancy has long-term implications for offspring BP regulation in humans. Low maternal energy stores during pregnancy predict higher SBP and DBP in adolescent boys. Although inconsistent in boys and girls, the inverse association of maternal protein intake and offspring BP is consistent with findings in animal models and deserving of further exploration in human populations.

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