A Critical Evaluation of the Fetal Origins Hypothesis and Its Implications for Developing Countries

Modeling Fetal Adaptation to Nutrient Restriction: Testing the Fetal Origins Hypothesis with a Supply-Demand Model

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ABSTRACT

The fetal origins hypothesis (FOH) proposes that intrauterine nutrition influences the development of various hormonal systems and organs, with lasting effects on adult risk for cardiovascular disease (CVD). The hypothesis has generated considerable interest for its potential insights into health trends in populations experiencing the nutrition transition, where more common problems of poor maternal pregnancy nutrition and low birth weight may be contributing to the emerging CVD epidemic.

The FOH hypothesis gains strongest support from animal models showing that maternal nutritional restriction during pregnancy (3,4) and direct modification of fetal nutrition through restricted uterine or placental blood flow (5–7) result in elevated blood pressure, reduced insulin sensitivity and abnormal cholesterol profiles after birth. However, in humans, fetal nutritional sufficiency must be inferred through the use of proxy measures, most typically birth weight (BW). Although nutrition is a key factor influencing fetal growth rate, the common assumption that BW-CVD risk factor relationships reflect an effect of fetal nutrition is problematic, because BW is also influenced by a wide range of hormonal, genetic and epigenetic (imprinting) factors that vary by individual and across populations. The most important non-growth-related influence on birth size is prematurity, and only some of the many studies using retrospectively collected birth weight data have had access to information on gestational age at birth. But even in a hypothetical population of optimally nourished newborns carried to term, birth weight would follow a normal distribution (8). If fetal nutritional sufficiency is indeed a common pathway through which prenatal factors influence later CVD risk, babies who are “constitutionally” small should not be at increased risk for CVD as adults. While any given small baby is more likely to have experienced growth restriction than a large baby, this interpretation is more defensible if there is evidence that the small baby had a higher growth potential, was born to a nutritionally stressed mother, or both. Using low density lipoprotein cholesterol (LDL-C) and systolic blood pressure (SBP) as markers of CVD risk, the predictions of the model are only met for LDL-C and only in males. There is evidence for an association between maternal nutritional status and male offspring SBP, but this relationship is independent of fetal nutritional sufficiency as defined by the model. Thus, although both the LDL-C and SBP findings support the general hypothesis that the prenatal milieu has long-term implications for CVD risk in males, only the patterns observed for LDL-C are consistent with the prediction that fetal nutritional sufficiency is key to CVD programming.

KEY WORDS: fetal nutrition, cardiovascular disease, maternal nutrition, birth weight
The supply-demand model as a refined test of the fetal origins hypothesis

This logic, which uses a combination of offspring and maternal characteristics to define a de facto conditional probability defining fetal growth sufficiency, provides a basis for a refined test of the FOH, illustrated by the supply-demand model outlined in Figure 1 (11). The model incorporates three functionally distinct markers—measures of maternal supply, fetal demand and birth outcome—to infer fetal nutritional sufficiency. Although not a comprehensive list of hypotheses, the model predicts an elevated risk of CVD among (Hypothesis 1) small babies born to tall mothers (or that otherwise show evidence of a higher growth potential) and (Hypothesis 2) small babies born to poorly nourished mothers (or otherwise born under conditions that suggest poor nutritional supply to the fetus). Finally, confidence in the interpretation that small birth size results from poor nutrition is greatest if (Hypothesis 3) the mother is both tall and poorly nourished during pregnancy.

Although a measure of growth potential may be used to interpret BW, the normal variability in growth potential has broader significance for the model. A fetus with the potential for higher growth requires a higher level of nutrients to avoid growth restriction (12). Thus, the model assumes that fetal demand is a variable in its own right, leading to hypotheses that are independent of birth outcome. For instance, the model predicts that (Hypothesis 4) CVD risk is elevated among babies who have a high fetal growth potential (high demand) but are born to poorly nourished mothers (low supply).

Of course, the converse hypotheses also follow from the model; e.g., large babies born to short and well-nourished mothers are the least likely to have experienced intrauterine nutritional shortfall and growth restriction, and are thus predicted to have the lowest CVD risk. These hypotheses use BW and different combinations of maternal traits to test, in a more targeted fashion, the central premise of the FOH: that fetal nutritional insufficiency both reduces birth size and elevates CVD risk. Expanding our previous analysis of Hypothesis 4 (11), this paper tests the above hypotheses with data from the Philippines, using systolic blood pressure (SBP) and low density lipoprotein cholesterol (LDL-C) in adolescence as measures of CVD risk.

MATERIALS AND METHODS

Data are from the Cebu Longitudinal Health and Nutrition Survey (CLHNS), a community-based birth cohort study of mothers and their infants born in 1983–1984. Maternal nutritional status and other characteristics were measured during the third trimester of pregnancy (30 ± 2 wk gestational age). Mothers and offspring were then followed prospectively from birth to the present. The analyses use blood pressure measured in 1050 male and 969 female adolescents included in the 1998 follow-up, when participants were 14 to 16 y of age. Low density lipoprotein cholesterol was measured in fasting morning plasma samples collected in about one-third of this sample, and lipid data for 296 males and 307 females were available for the present analyses. Descriptions of the study population, sample design, selection criteria and potential biases due to loss to follow-up are discussed in detail elsewhere for the blood pressure measurements (13,14) and cholesterol samples (15,16). These papers also include detailed information on the methods used to measure diet, anthropometrics, blood pressure and blood lipids.

Predictor variables: supply, demand and birth outcome

The supply-demand model incorporates measures of maternal supply, fetal demand and birth outcome. Building from the bulk of prior FOH research, birth weight was chosen as a measure of birth outcome. In selecting a measure of maternal nutritional supply, maternal weight and BMI were excluded because they in part reflect the weight of the feto-placental unit. Maternal arm fat area (MAFA) measured during the third trimester of pregnancy (30 ± 4 wk gestation) was deemed the most appropriate index of maternal nutritional supply available for this population because it is a marker of energy balance that is correlated with maternal energy intake (r = 0.2, P < 0.00001) and relates positively to offspring birth weight in this sample (17). Maternal third-trimester energy intake was also used as a complimentary measure of maternal energetics, under the assumption that a mother with low fat stores is even less likely to meet the energy demands of pregnancy when her energy intake is also constrained.

Maternal height was chosen as a marker of fetal growth potential and thus of fetal demand for nutrients. Of the candidate variables at our disposal, maternal height is among the strongest established predictors of birth weight (18) and, compared to other measures of maternal body size, is only weakly correlated with third-trimester MAFA (r = 0.18). Maternal height measurements were not available.

![Figure 1](https://example.com/figure1.png)

**Figure 1** Supply-demand model of fetal nutritional sufficiency incorporating measures of maternal supply, fetal demand and birth outcome. Different combinations of these three classes of variables can be used together to infer fetal nutritional sufficiency.
for this analysis. We assume that a fetus born to a tall mother has, on average, a higher fetal growth potential, thus requiring a greater supply of nutrients to avoid nutritional insufficiency, growth restriction and the suite of adaptations that persist to elevate risk for CVD.

**Statistical analyses**

All analyses were performed with the Stata Statistical Package, Version 8 (Stata, College Station, TX). Means and standard deviations were calculated for each CVD risk factor, predictor and control variable. Because descriptive statistics for the lipid analysis subsample were published previously (11,15,16), descriptive statistics are provided for the total (blood pressure) sample. Mean CVD risk factor levels were adjusted for potential confounding factors with multivariate regression and stratified on two or more of the variables in the supply-demand model, following from the hypotheses outlined above. In stratified analyses, \( P \)-values for the difference between the highest and lowest tertiles of the exposure variable (e.g., tertiles of maternal height) were assessed using dummy variables in regression models stratified on the level of the other predictor variable of interest (e.g., high and low birth weight). Hypothesized interactions were also tested using interaction terms in full regression models.

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**TABLE 2**

Tests of Hypotheses 1, 2 and 4 of the supply-demand model

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>Male, n = 296</th>
<th>Female, n = 307</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tertile 1</td>
<td>Tertile 2</td>
</tr>
<tr>
<td>Maternal height</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothesis 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight ( \leq 3 ) kg</td>
<td>921 ± 40</td>
<td>999 ± 39*</td>
</tr>
<tr>
<td>Birth weight ( &gt; 3 ) kg</td>
<td>874 ± 42</td>
<td>873 ± 42</td>
</tr>
</tbody>
</table>

| Maternal arm fat area | | | |
|-----------------------| | |
| Hypothesis 2 | | |
| Birth weight \( \leq 3 \) kg | 994 ± 36* | 908 ± 47 | 952 ± 35* | 0.05 | 998 ± 34 | 1086 ± 37 | 1121 ± 48 | 0.07 |
| Birth weight \( > 3 \) kg | 903 ± 42 | 937 ± 43 | 849 ± 36 | | 1029 ± 53 | 1089 ± 44 | 1064 ± 44 |   |

| Hypothesis 4 | | |
| Short mother (<150.4 cm) | 924 ± 36 | 905 ± 47 | 930 ± 40 |        | 998 ± 37 | 1086 ± 40 | 1151 ± 48* | 0.04 |
| Tall mother (>150.4 cm) | 1002 ± 43 | 944 ± 45 | 884 ± 33 | 0.002 | 1019 ± 46 | 1092 ± 40 | 1026 ± 43 |        |

**Systolic blood pressure, mm Hg**

<table>
<thead>
<tr>
<th>Hypothesis</th>
<th>Male, n = 1050</th>
<th>Female, n = 969</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Tertile 1</td>
<td>Tertile 2</td>
</tr>
<tr>
<td>Maternal height</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypothesis 1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Birth weight ( \leq 3 ) kg</td>
<td>106.0 ± 0.7</td>
<td>106.0 ± 0.8</td>
</tr>
<tr>
<td>Birth weight ( &gt; 3 ) kg</td>
<td>105.0 ± 0.9</td>
<td>105.5 ± 0.8</td>
</tr>
</tbody>
</table>

| Maternal arm fat area | | | |
|-----------------------| | |
| Hypothesis 2 | | |
| Birth weight \( \leq 3 \) kg | 106.0 ± 0.7 | 105.6 ± 0.8 | 106.2 ± 0.8 | | 96.1 ± 0.6 | 98.1 ± 0.6 | 97.7 ± 0.7 | |
| Birth weight \( > 3 \) kg | 107.4 ± 0.8 | 105.5 ± 0.8 | 105.0 ± 0.7 | 0.005 | 97.6 ± 0.9 | 97.4 ± 0.7 | 96.8 ± 0.6 | 0.06 |

| Hypothesis 4 | | |
| Short mother (<150.4 cm) | 106.4 ± 0.7 | 104.0 ± 0.8 | 105.2 ± 0.8 | 0.06 | 98.3 ± 0.6 | 98.0 ± 0.6 | 97.1 ± 0.7 |   |
| Tall mother (>150.4 cm) | 106.6 ± 0.8 | 106.3 ± 0.8 | 106.0 ± 0.7 | 0.03 | 97.2 ± 0.7 | 97.6 ± 0.7 | 97.4 ± 0.6 |   |

1 Values are means ± SE. Means were tested for differences between tertile 1 and tertile 3 of maternal height or maternal adiposity during pregnancy. Low density lipoprotein cholesterol means were adjusted for age, maturational status, the child’s height and BMI and household income measured at birth and in 1998. Systolic blood pressure means were adjusted for age, maturational status, the child’s height and BMI and household income measured at birth and in 1998. Means with an asterisk differed by birth weight within tertiles of maternal height or maternal adiposity (\( P < 0.05 \)). Means for short and tall mothers did not differ within strata.

**RESULTS**

Participants had a mean birth weight roughly 0.5 kg below that of the general U.S. population, and were born to mothers with low BMI and relatively low energy intake measured at a mean gestational age of 30 wk (Table 1). Levels of SBP and LDL-C in the offspring are within the range of values documented in other adolescent populations (13).

Hypotheses 1, 2 and 4 are tested in Table 2, which stratifies SBP and LDL-C in males and females by different combinations of variables from the supply-demand model. Values were adjusted for the child’s age, maturational status, current anthropometrics, and diet (for LDL-C). Household income measured at baseline and at the age of CVD risk factor assessment was used to control for differences in the postnatal environment during early life and in adolescence.

**Males: LDL-C and SBP**

The LDL-C data for males were most consistent with predictions. The general pattern is that LDL-C levels were high-

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These are those most likely today to have elevated LDL-C levels. Despite evidence of higher growth potential, or born to levels in males in this population. Individuals born small to a mother who was relatively poorly nourished during pregnancy, are those most likely today to have elevated LDL-C levels. These findings are as expected if fetal nutritional sufficiency, reflected in birth outcome, programs CVD risk. However, the hypothesis that gains the strongest support is Hypothesis 4, which stratifies LDL-C on a measure of growth potential (maternal height) and maternal supply (MAFA) alone. There is a clear dose-response increase in LDL-C with declining MAFA, but only among individuals with higher growth potential, as indicated by being born to a tall mother. This finding suggests that poor maternal nutritional status (low supply) during pregnancy may have implications for lipid profiles in males, but only when there is evidence for higher fetal growth potential (high demand).

The most specific hypothesis, Hypothesis 3, predicts that the risk of CVD is highest in individuals who had a high fetal growth potential, were born to relatively poorly nourished mothers, and were small at birth. Figure 2A explores this hypothesis for LDL-C levels in the males. Adjusted mean LDL-C level is presented for the total population (dark bars), limited to individuals born to mothers with below-median MAFA (light bars), and further limited to the subset of these mothers who also had below-median energy intake (white bars). This figure incorporates all three elements of the model—supply, demand and birth outcome—simultaneously.

Figure 2A supports the hypothesis that fetal growth restriction due to nutritional restriction is associated with elevated LDL-C levels in males. This interpretation is supported by the fact that below-median birth weight is associated with elevated LDL-C level, but only when there is evidence that the child had a high fetal growth potential (relatively taller mother) and was faced with relatively compromised prenatal nutrition (below-median third-trimester MAFA and energy intake). Regression models were used to test all second-, third- 
and fourth-order interactions among BW, MAFA, maternal height and maternal energy intake treated as continuous variables, while adjusting for the same set of control variables (results not shown). The fourth-order interaction was not significant and was dropped. Three of four of the possible third-order interactions (e.g., BW × MAFA × maternal height), and three of the six possible second-order interactions (e.g., BW × MAFA), were significant ($P < 0.05$). Including all second- and third-order interaction terms in the model substantially increased the explained variance (from 14 to 22%), which was a significant improvement in the model (joint F-test, $P < 0.01$). This is an unwieldy model, but it confirms statistically what is visually apparent in the figure. Moreover, complex interactions of this sort should be present if the premise of the FOH is correct.

In addition to confirming the expectations of the supply-demand model, Figure 2A also illustrates our previously reported finding that maternal nutritional status predicts LDL-C level independent of both fetal growth potential (maternal height) and birth outcome (11). Although the association between elevated LDL-C level and poor maternal nutrition is most apparent among individuals who were small at birth but born to taller mothers, LDL-C level is relatively consistently elevated among offspring of poorly nourished mothers, and this is present among individuals of both above- and below-average birth weight and irrespective of maternal height.

The findings for SBP in males were less consistent with the predictions of the model. Instead, they suggest that maternal energy status or adiposity, as indicated by MAFA and energy intake, are relatively consistent, if modest, predictors of SBP in males, with effects that are independent of size at birth or maternal stature (Fig. 3A). As such, there is no evidence that fetal nutritional restriction reflected in reduced fetal growth programs SBP in the CLHNS males.

**Females: LDL-C and SBP**

We reported previously that the inverse associations between MAFA and lipids and BP in the males are absent in the females in this adolescent sample (13,15). None of the relationships present in the female data were consistent with the predictions of the supply-demand model (Table 2). For instance, among females, LDL-C levels were highest among small babies but only among those born to well-nourished mothers who also had below-median energy intake (white bars). This finding suggests that poor maternal nutritional status (low supply) during pregnancy may have implications for lipid profiles in females, but only when there is evidence for higher fetal growth potential (high demand).

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levels in adolescence. The complex interactions in the LDL-C data for males shown in Figure 2A were supported by higher-order interaction terms in a regression model.

In contrast, there was only a modest association between MAFA and SBP in males that appeared to be independent of birth weight and maternal stature. Because this effect was present at all levels of birth weight and maternal stature, it is probably not mediated through fetal nutritional sufficiency or growth. Findings that do not conform to model expectations may hint at the importance of alternate programming pathways. The most defensible interpretation of the SBP data is that some non-nutritional correlate of maternal adiposity, perhaps hormonal, programs SBP in males (19). Thus, although both the LDL-C and SBP findings support the hypothesis that the prenatal milieu has long-term implications for CVD risk in males, only the patterns observed for LDL-C support the specific prediction that fetal nutritional sufficiency both reduces birth weight and programs CVD risk. Consistent with our prior work at Cebu (13,15), fetal nutritional sufficiency as defined by the model failed to predict either elevated LDL-C level or SBP among the CLHNS females (discussed below).

The present approach differs from most tests of the FOH that incorporate BW, MNS or maternal diet, which typically treat all variables as independent proxies for fetal nutrition (13,15,20,21). Instead, the model interprets birth weight in light of these other measures. What the model loses in simplicity it makes up in specificity. An association between low birth weight and later hypertension is difficult to interpret, as it could reflect a wide range of factors, including genetics, or programming by maternal hormones, stress, or other correlates of birth size. The supply-demand model uses maternal traits in conjunction with BW to isolate individuals who likely were small at birth as a result of compromised nutrition and growth restriction.

An additional strength of the model is its flexibility, because it can be tested using a wide range of maternal and offspring characteristics (Fig. 2). In theory, variables representing any two or more of the supply-demand model’s categories—supply, demand or birth outcome—should provide a more refined criteria of growth sufficiency than any single variable used in isolation. This flexibility also warrants caution, however, as it is likely that in any population there will be some combination of predictors that yields significant results. For this reason, analyses should be limited to tests of a priori and biologically informed hypotheses. Analytically, there are many possible approaches to testing the model, which will vary by the type of data available, the goals of analysis, and the sample size. In addition to formal testing of interaction terms, the consistency, biological plausibility and dose dependence of any set of interactions should be assessed. Visual inspection of the stratified male LDL-C data revealed a relatively clear set of relationships that support the model and its predictions. The regression model confirmed the significance of the interactions, but would have been difficult to interpret on its own owing to the need to consider multiple interaction terms.

**What sets fetal growth potential?** A central assumption of the supply-demand model is that the “sufficiency” of BW or of a given level of nutritional supply is best evaluated against the benchmark of that fetus’s unique growth potential, indexed here by maternal stature. Previously, Leon et al. (22) and Hennessy and Alberman (23) used the child’s adult stature to index fetal growth potential, an approach that is arguably less capable of distinguishing an effect of fetal growth restriction from that of postnatal catch-up growth. In a study predicting mothers. Levels of LDL-C were also elevated among babies born to mothers who were well-nourished and short, a group predicted by the model to have the lowest CVD risk. The highest LDL-C levels were found among small babies born to tall mothers, but also among large babies born to short mothers (both nonsignificant). For SBP, the only significant relationship was a modest increase in SBP with declining MAFA, but only among individuals who had above-median birth weights. None of these relationships support the hypothesis that fetal nutritional sufficiency has long-term effects on CVD risk among the CLHNS females. The absence of any clear patterns in Figures 2B and 3B and of interactions in the regression models (not shown) further support this interpretation.

**DISCUSSION**

We reasoned that if fetal nutritional insufficiency restricts growth and elevates CVD risk, there should be evidence for interactions among markers of growth potential (demand), maternal nutritional status (supply), and birth weight in models predicting SBP and LDL-C level. Specifically, we hypothesized that small size should be associated with elevated CVD risk, but only when there is evidence that an individual had a higher fetal growth potential, was born to a nutritionally stressed mother, or both. In the CLHNS sample, only the LDL-C data for males corroborated these expectations. Males born small to tall mothers who were relatively poorly nourished during pregnancy tended to have the highest LDL-C
Sex differences in the long-term effects of the prenatal environment

Sex differences in the relationships between BP or LDL-C and markers of fetal nutritional sufficiency were evident in the CLHNS sample, with few relationships present in females. Lucas (25) hypothesizes that programming effects could be stronger in males owing to their greater size and demand for nutrients (reviewed in 11). A recent study in Boston found that mothers bearing males consumed 10% more energy during pregnancy than mothers bearing females (26). Consistent with this, CLHNS mothers who gave birth to males had increased energy intake late in pregnancy, when energetic requirements are likely near their peak (Fig. 4). Such findings suggest that the nutritional plane below which a fetus is forced to adapt might be higher in males. It is important to note that in the CLHNS data, the excess in energy intake associated with a male fetus was most pronounced among mothers from households with above-median income, perhaps indicating that they had greater opportunities to meet the excess requirements of a male fetus. Sex differences in CVD programming might be greatest when fetuses of poorly nourished mothers are limited in their opportunities to adapt their energy requirements, such as by reducing expenditure.

Several limitations of the present analyses warrant caution. First, participants were at various stages of maturation when their SBP and LDL-C levels were measured. Although the models were adjusted for age and maturational status, confounding by differences in maturational status, or obscuring of relationships due to the hormonal changes of puberty (27), cannot be ruled out. Second, the measures of maternal supply and fetal demand used here are at best rough approximations, and may not be sufficiently robust proxies to test the model. Growth potential is difficult to measure, and might be better approximated with measures that were not available, such as maternal birth weight (9). That said, confirmation of the model’s predictions for LDL-C levels in males suggests that the variables at our disposal provide a reasonable basis for testing the model. Finally, the supply-demand model ignores nonnutritional programming stimuli. In sheep, small size at birth and adult hypertension may be programmed by nutrient restriction but also by maternal stress hormones (3,28). Although a relationship between BW and CVD risk could be due to a wide range of factors, the present approach moves a step closer to testing the specific hypothesis that fetal nutritional restriction, per se, programs CVD risk.

LITERATURE CITED