European Journal of Clinical Nutrition (2004) 58, 438–448
 0954-3007/04 $25.00
www.nature.com/ejcn

ORIGINAL COMMUNICATION

A supply–demand model of fetal energy sufficiency predicts lipid profiles in male but not female Filipino adolescents

CW Kuzawa[1]* and LS Adair[2]

[1]*Department of Anthropology, Northwestern University, Evanston, IL, USA; and* [2]*Department of Nutrition, Schools of Public Health and Medicine, University of North Carolina, Chapel Hill, NC, USA*

Objective: To test the hypothesis that the balance between fetal nutritional demand and maternal nutritional supply during pregnancy will predict lipid profiles in offspring measured in adolescence.
Subjects and methods: A total of 296 male and 307 female Filipino offspring (aged 14–16 y) and mothers enrolled in a longitudinal birth cohort study (begun in 1983–84) had lipid profiles measured. Data on maternal height (as a proxy for offspring growth potential and thus fetal nutritional demand) and third trimester maternal arm fat area (as a proxy for maternal supply) were used to create four groups hypothesized to reflect a gradient of fetal energy sufficiency.
Results: As fetal energy sufficiency increased among males, there was a decrease in total cholesterol (TC) ($P<0.05$ for trend), low-density lipoprotein cholesterol (LDL-C), and the ratios of TC/HDL-C cholesterol and LDL-C/HDL-C (all $P<0.001$), while HDL-C increased ($P<0.05$). Similar associations were identified when lipid levels were modeled as dichotomous 'high-risk' cut-points used in cardiovascular disease prevention in adolescents. These relationships were stronger, or only present, among offspring of mothers in the lower half of the third trimester energy intake distribution, and were independent of the child's current adiposity, dietary energy and fat intake, maturity, household income, and birth weight. In females, the supply–demand model did not predict any lipid outcome or clinical risk criteria.
Conclusions: Our findings in males support the hypothesis that the balance between fetal nutritional demand and maternal nutritional supply has implications for future lipid profiles. The lack of significant associations in females adds to mounting evidence for sex differences in lipid metabolism programming, and may reflect sex differences in fetal nutritional demand.
Sponsorship: The National Science Foundation, the Mellon Foundation, the Nestle Foundation, and the Emory University Internationalization Program.
European Journal of Clinical Nutrition (2004) **58,** 438–448. doi:10.1038/sj.ejcn.1601826

Keywords: fetal growth; maternal nutrition; serum lipids; cardiovascular diseases; sex characteristics; Philippines; birth weight

Introduction

Risk for cardiovascular disease (CVD) and cardiovascular mortality is elevated among individuals who were at the lower end of the birth weight distribution (Barker *et al*, 1989). The prevailing hypothesis to explain these findings, the 'fetal origins hypothesis', is founded upon the observation that fetal nutrition is a key determinant of fetal growth rate and thus assumes that birth weight functions as a marker of fetal nutritional sufficiency (Barker, 1994, 1995). According to this hypothesis, poor fetal nutrition forces the fetus to slow its overall growth rate to conserve resources, while relative adjustments in organ growth, hormonal set points, and other physiologic responses boost immediate survival. These responses, collectively described as 'programming', are viewed as permanent, and contribute to elevated risk for CVD in postnatal life (Lucas, 1991).

While a growing number of studies have investigated relationships between maternal nutritional status during pregnancy and offspring CVD risk (Forsen *et al*, 1997; Stanner *et al*, 1997; Roseboom *et al*, 2000; Adair *et al*, 2001;

***Correspondence: C Kuzawa, Department of Anthropology, Northwestern University, 1810 Hinman Avenue, Evanston, IL-60208, USA. E-mail: kuzawa@northwestern.edu**
Guarantor: **CW Kuzawa.**
Contributors: **CWK and LSA were responsible for study design, data collection, and securing funds. CWK was responsible for data analysis and drafting the manuscript, which was revised by both authors.**
Received 17 February 2003; revised 23 April 2003; accepted 23 May 2003

Roseboom *et al*, 2001; Kuzawa & Adair, 2003), most tests of the fetal origins hypothesis continue to use birth weight as a marker of fetal nutritional sufficiency (Rasmussen, 2001). Recent reviews present a strong rationale to question this interpretation of birth weight (Godfrey & Robinson, 1998; Waterland & Garza, 1999; Godfrey & Barker, 2000). A small baby may have realized a lower growth potential with adequate fetal nutrition (Chard *et al*, 1993). By the same reasoning, a baby with a high growth potential may attain an average or above-average birth weight despite growth restriction, and be misclassified as having adequate growth.

While unquestionably complicating the interpretation of birth weight, the normal population variability in fetal growth potential also raises important questions about the determinants of fetal nutritional sufficiency. For a fetus aiming for a higher growth target, maternal supply must be greater to avoid fetal nutritional insufficiency and the metabolic and developmental adaptations that restrict growth and elevate CVD risk after birth (reviewed by Godfrey & Robinson, 1998). It follows that fetal nutritional sufficiency and associated postnatal CVD sequelae are not a simple product of the level of nutrition delivered by the mother across the placenta, but the balance of maternal supply relative to fetal demand (Figure 1). A complete test of the fetal origins hypothesis would take both determinants of fetal nutritional sufficiency—maternal supply and fetal demand—into account.

We use data collected prospectively in the Philippines over a 17-y period to develop and test markers of maternal third trimester nutritional supply (arm fat area) and fetal nutritional demand (fetal growth potential as indexed by maternal stature). Subjects are participants in a 1-y birth cohort study who have been followed since the third trimester of pregnancy and had lipid profiles measured when they were 14–16 y of age. We have previously shown that birth weight and maternal nutritional status during pregnancy predict lipid profiles among the males in this population, which is experiencing a rising burden of cardiovascular disease (Kuzawa & Adair, 2003). Here we tested the hypothesis that categorizing individuals based upon the likelihood of having experienced energy shortfall in utero, as indicated by different combinations of high and low maternal supply and fetal demand, would predict lipid profiles measured in adolescence.

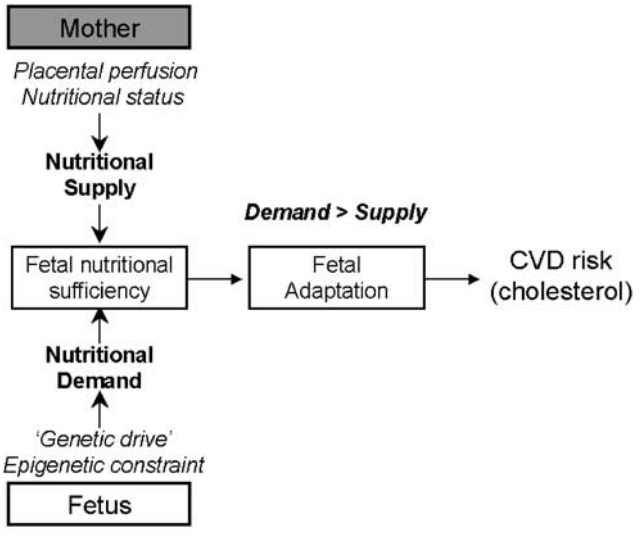

Figure 1 Supply–demand model of fetal nutritional sufficiency and cardiovascular programming.

Subjects and methods

Population and research design

Data come from the Cebu Longitudinal Health and Nutrition Survey (CLHNS), a community-based cohort study of mothers and their infants born in 1983–84. Maternal nutritional status and other characteristics were measured during the third trimester of pregnancy (30 ± 2 weeks gestational age). Mothers and offspring were then followed prospectively from birth to the present. At the 1998–99 survey when cholesterol was measured, 2089 adolescents aged 14–16 y were located and interviewed. Of these, 1969 had available measurements of birth outcomes, gestational age, and current measurements, from which a subsample was selected for blood sample collection. Twin pregnancies ($n = 10$) were excluded and the sample limited to term births defined as a gestational age at birth ≥ 37 weeks. The population selected for blood draws was sampled at random within two birth weight strata. To ensure adequate numbers of lower birth weight individuals for an analysis of the effects of fetal growth restriction on CVD risk (not presented here), we oversampled individuals with birth weights equal to 2600 g or below. Final samples for the lipid analysis include roughly 50% (154/316) of males and females with a birth weight ≤ 2.6 kg and roughly 25% (449/1653) of individuals with higher birth weight. We correct for this sample design in the analysis (discussed below).

The potential for bias associated with attrition after the baseline survey and selection of the subsample was assessed in several ways. First, we compared birth characteristics of all adolescents who were included in the 1998 follow-up with those who were lost to follow-up. Mean birth weight of those lost to follow-up was roughly 50 g less ($P < 0.05$) than those retained in the sample. This is most likely attributable to the higher mortality rates among low birth weight infants. Birth length did not differ significantly in the two groups. Those lost to follow-up were more likely to have been urban residents (82.5% urban *vs* 73.5% in the retained sample), but there were no significant differences in household assets, maternal education or maternal height, age or parity. Next, we assessed potential biases in the subsample selected for lipid analysis. Consistent with sampling design, females included in the CVD study had significantly lower birth weight, current height, and current weight (all $P < 0.05$) compared to those excluded, while these differences were

close to significant in males ($P<0.07$ for birth weight, $P<0.16$ for height, and $P<0.12$ for weight). The lack of significant differences in current anthropometrics among the selected males was in large part due to the greater body size variability in males. The absolute differences between the selected and excluded subsets were quite similar among males and females (eg for current weight, the selected female and male subsets, respectively, were about 0.97 ± 0.44 and 0.67 ± 0.57 kg lighter than those excluded). There were no differences between the included and excluded subsets in current body mass index (BMI), skinfold thickness, household income, or dietary fat intake.

Diet, anthropometrics, and socioeconomic variables

Body weight, height, waist circumference, mid-upper arm circumference, and triceps skinfold thickness were measured in mothers and offspring using standard anthropometric techniques (Lohman *et al*, 1988). BMI was calculated as the ratio of weight (kg)/height (m^2). Arm fat area was calculated from triceps skinfold thickness and mid-upper arm circumference (Frisancho, 1990). During the 1998–99 follow-up, the child's dietary intake was measured using two 24-h recalls on consecutive days. Mean macronutrient intakes from the 2 days were used in analyses. Energy and fat intake were calculated using Philippines Food Composition Tables produced by the Food and Nutrition Research Institute of the Philippines (Institute and Medicine, 1990). In females, prospectively measured age at menarche was used to construct a five-level maturational status variable. Among males, maturational status was assessed by self-rated five-level pubic hair staging, which was validated against physician assessment (unpublished data). Although not directly comparable with one another, the male and female maturity scales were used to control for variation in maturational status within each sex. When data were collected for the 1998–99 survey, girls were completely surveyed before boys. Consequently, boys are roughly 1 y older than girls. Informed consent was obtained from all participants, and all protocols were reviewed and approved by Institutional Review Boards at the University of North Carolina at Chapel Hill, with supplementary reviews by boards at the Emory University Medical School and the University of San Carlos in Cebu, Philippines.

Lipid profiles

For measurement of lipid profiles, participants were asked to fast overnight for 12 h, and blood samples were collected in clinics the following morning using EDTA-coated tubes. After separation, samples were frozen and shipped on dry ice to the Emory Lipid Research Laboratory (Atlanta, GA, USA) for analysis of lipid profiles. All samples remained frozen at $-80^{\circ}C$ until ready for analysis. Total lipids were determined by enzymatic methods using reagents from Beckman Diagnostics on the CX5 chemistry analyzer. High-density lipoprotein cholesterol (HDL-C) and low-density lipoprotein cholesterol (LDL-C) were determined using the homogeneous assay direct HDL-C and direct LDL-C (Equal Diagnostics, Exton, PA, USA). Total cholesterol (TC) was determined with an enzymatic kit, while triacylglycerol (TG) was determined with a glycerol blank as a two-step reaction (Beckman Coulter Diagnostics). The atherogenic ratios of TC/HDL-C and LDL-C/HDL-C were also calculated (Labarthe, 1998). The Emory Lipid Research Laboratory is a participant in the CDC/NHLBI Lipid Standardization Program to ensure accuracy and precision of the determinations.

Maternal nutritional supply

In selecting a measure of maternal nutritional supply, we excluded maternal weight or body mass index, as these in part reflect the weight of the feto-placental unit. Maternal arm fat area (MAFA) measured during the third trimester of pregnancy (30 ± 2 weeks of gestation) was deemed the most appropriate index of maternal nutritional supply as 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 (Adair & Popkin, 1988). Prior research in the Cebu sample has shown that third trimester MAFA or the related measure of triceps skinfold thickness is inversely related to offspring CVD risk as indexed by lipid profiles (Kuzawa & Adair, 2003) and blood pressure (Adair *et al*, 2001). We also use maternal third trimester energy intake to validate our model.

Fetal nutritional demand

We use maternal height as a marker of fetal growth potential and thus fetal demand for nutrients. Of the candidate variables at our disposal, mother's height is among the strongest established predictors of birth weight (Institute of Medicine, 1990) and, compared to other measures of maternal body size, is only weakly correlated with mother's third trimester MAFA ($r=0.18$). We did not have paternal height measurements available for this analysis. This approach is similar to the use of adult height as an index of fetal growth potential in prior fetal origins research (Leon *et al*, 1996; Hennessy & Alberman, 1997). 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.

Constructing the four fetal energy sufficiency groups and hypotheses

We first divided the population into high/low levels of fetal demand based upon a median split (median = 150.4 cm) of maternal height (tall/short), and two levels of maternal supply as indexed by a median split (median = 12.2 cm^2) of high/low third trimester maternal arm fat area (HAFA/LAFA).

Next, we defined four groups representing the four possible combinations of high/low supply and high/low fetal demand (Figure 2). In our model, an individual born to a tall mother with low energy status (Tall-LAFA) has a high fetal demand for nutrients (high growth potential) but a mother with a poor capacity to supply these needs as indicated by her energy stores (LAFA). Thus, offspring of Tall-LAFA mothers are predicted to have highest CVD risk. By the same logic, the offspring of short but well-nourished mothers (Short-HAFA) are predicted to have lowest risk of fetal energy shortfall and thus lowest postnatal CVD risk.

The two intermediate risk groups (high demand/high supply and low demand/low supply) have an associated level of hypothesized CVD risk that is more ambiguous. While our results are very similar when the two intermediate risk groups are pooled (data not shown), we retained these groups as separate in our analyses to illustrate both the independent and combined effects of MAFA and maternal height. Under the assumption that MAFA is a better index of maternal supply than is mother's height as a marker of fetal growth potential, we expected the group born to Short-LAFA mothers to have higher risk than those born to Tall-HAFA mothers. We thus hypothesized that the four groups would represent the following gradient of fetal energy sufficiency and associated reduction in CVD risk in adolescence: Tall-LAFA < Short-LAFA < Tall-HAFA < Short-HAFA. To allow trend tests in regression models, we defined a four-level ordinal variable ('fetal energy sufficiency') based upon this hypothesized gradient of fetal energy sufficiency, with Tall-LAFA = 1, Short-LAFA = 2, Tall-HAFA = 3, and Short-HAFA = 4:

Lowest energy sufficiency			Highest energy sufficiency
1	2	3	4
Tall-LAFA	Short-LAFA	Tall-HAFA	Short-HAFA

To validate our hypothesis that this four-level variable reflects a gradient of fetal energy sufficiency, we further divided the population based upon a median split of maternal third trimester energy intake. We hypothesized that the gradient in CVD risk across fetal energy sufficiency levels would be stronger, or only present, among offspring of mothers with lower third trimester energy intake.

Statistical analyses

All analyses were performed with version 8 of the Stata Statistical Package (Stata Corporation, College Station, Texas, USA). In order to get an unbiased estimate of distributional characteristics (eg mean LDL-C or dietary energy intake of children), we weighted the observations such that both birth weight strata would be represented in the estimate in proportion to their occurrence in the population. Probability sampling weights (pweights) for each strata were calculated as the inverse of the within-strata sampling fraction (see above), and the svymean procedure of STATA used to estimate distributional characteristics. For all analyses, a *P*-value <0.05 was considered a statistically significant relationship with $p<0.10$ noted as a statistical trend.

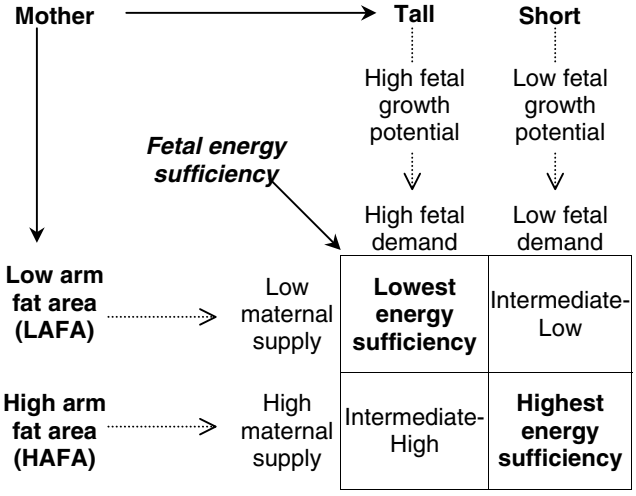

Figure 2 Supply–demand model defining four groups with variable levels of fetal energy sufficiency. Cardiovascular risk factors are predicted to be most elevated in the group at highest risk of energy shortfall (Tall-LAFA), lowest in the group at lowest risk (Short-HAFA), and intermediate in the remaining groups (see the section Subjects and methods for further discussion).

We tested the hypothesis that our four-level ordinal fetal energy sufficiency variable would be inversely related to CVD risk in offspring, as indicated by circulating concentrations of each lipid and the two atherogenic ratios of Total/HDL-C and LDL-C/HDL-C. To clarify the clinical significance of these relationships, we also calculate the prevalence and odds ratios (ORs) for members of each fetal energy sufficiency group being classified as 'high risk' for each lipid outcome, using clinical cut-points developed for use in adolescents (Kwiterovich, 1991). In this analysis, we also calculate a summary risk index reflecting the total number of high risk lipid values for each individual (possible score of 0–6). Diet and adiposity measures and HDL-C and TG were log-transformed to approximate normal distributions before regression analysis.

For each lipid outcome, we first test for significant trends across levels of fetal energy sufficiency, indicated by the significance of the beta coefficient for the four-level ordinal variable in univariate regression models (linear regression for mean values, logistic regression for clinical cutpoints, and ordered logistic regression for the summary risk index). For each lipid outcome, we ran a series of regression models to determine the degree to which any relationships with fetal nutritional sufficiency were independent of potential confounders and the child's weight at birth. We first report a univariate model relating each lipid to the four-level ordinal fetal energy sufficiency variable alone. In model 2 we adjust for factors that might confound associations with prenatal variables, including the adolescent's current adiposity,

energy and fat intake, maturational status, and household income quartile measured at birth and at the age of cholesterol measurement. In model 3, we further adjust for birth weight to assess the degree to which any relationships between fetal energy sufficiency and lipids are independent of birth outcome.

For the purpose of evaluating whether the oversampling of individuals with a birth weight ≤ 2.6 kg in our sample might bias the conclusions drawn from our models, in model 3, we also substituted a categorical variable (≤ 2.6 and > 2.6 kg) for the continuous birth weight measure. By assessing any change in the beta coefficients for the energy risk variable before and after inclusion of birth weight strata variable, we were able to assess whether fetal energy sufficiency–lipid relationships are biased due to over-representation of individuals with a birth weight of 2.6 kg or below. Consistent with our prior work in this sample (Kuzawa & Adair, 2003), sensitivity analyses for all models showed that including the variable reflecting sampling design had negligible effect on the estimates, precision, or significance of regression coefficients for the fetal energy sufficiency variable (not reported). As the fetal energy sufficiency–lipid relationships that we document are independent of low birth weight status, we concluded that they are not biased by over-representation of low birth weight individuals in our sample.

Our prior work in this population revealed highly significant sex differences in the association between prenatal factors and later lipid profiles and blood pressure (Adair *et al*, 2001; Kuzawa & Adair, 2003). Therefore, all models were stratified on sex.

Results

Obesity was nearly absent in the population and the participants had relatively low dietary fat intake (Table 1). There were significant trends for many of the dietary, anthropometric, and socioeconomic variables across the four levels of fetal energy sufficiency. At baseline, the pregnant mothers were marginally nourished as indicated by low energy intake and low mean body mass index measured in the third trimester.

Tables 2 and 3 present, for males and females, respectively, mean lipid levels for the entire sample and stratified on the

Table 1 Characteristics of mothers during pregnancy and offspring at birth and in 1998 by fetal energy sufficiency groups[a]

		All n=*603*	*Tall-LAFA* n=*130*	*Short-LAFA* n=*173*	*Tall-HAFA* n=*168*	*Short-HAFA* n=*132*	*P for trend*[b]
Mother (3rd trimester)							
Height (cm)		150.7±0.2	154.2±0.3	146.4±0.2	154.8±0.2	147.0±0.2	N/A
Arm fat area (cm^2)		14.7±0.2	10.9±0.2	10.4±0.1	19.4±0.4	17.9±0.4	N/A
Body mass index (kg/m^2)		22.9±0.2	21.2±0.1	21.4±0.2	24.6±0.3	24.3±0.1	<0.0001
Income (pesos)[c]		300±17	249±16	239±19	379±42	324±46	<0.05
Parity		2.4±2.3	2.5±2.2	2.6±2.4	2.2±2.3	2.3±2.3	
Energy (kJ)[d]		6184±378	5699±357	5800±353	7012±491	6055±329	<0.0001
Offspring (birth)							
Birth weight (g)	Male	3064±23	3059±49	3003±42	3166±43	2987±50	<0.01[e]
	Female	3016±23	3048±48	2921±47	3097±48	3014±46	<0.04[e]
Offspring (1998)							
Triceps skinfold (mm)	Male	8.1±0.2	7.8±0.3	6.8±0.2	9.4±0.5	8.0±0.4	<0.2
	Female	14.6±0.2	13.6±0.4	14.4±0.3	15.5±0.4	14.9±0.4	<0.02
Arm fat area (cm^2)	Male	9.3±0.3	8.7±0.4	7.5±0.3	11.3±0.8	8.9±0.5	—
	Female	15.4±0.3	13.9±0.5	15.1±0.5	16.9±0.6	15.9±0.6	<0.01
Maturity[f] median (% >3)	Male	3±46.3	3±46.8	3±48.2	3±46.9	3±42.7	
	Female	3±40.7	3±31.4	3±37.9	4±50.4	3±43.3	<0.02
Energy (kJ)[d]	Male	8064±190	7652±340	7768±379	8630±356	7982±403	—
	Female	5621±132	5437±256	5090±226	5944±239	6158±334	<0.02
Fat intake (% energy)	Male	21.4±0.7	22.2±1.7	20.0±1.2	22.2±1.2	20.4±1.2	—
	Female	22.5±0.7	21.7±1.4	20.2±1.3	23.9±1.4	24.9±1.6	<0.03
Income (pesos)	Male	3719±187	2944±181	3128±326	4988±454	3293±236	<0.05
	Female	3370±209	3131±328	3024±280	3309±217	4183±774	<0.1

[a]Mean±s.e.
[b]Significance of beta coefficient for four-level ordinal supply–demand variable in univariate linear regression model (ordered logistic regression used for maturity scale). Diet variables, income, and arm fat area were log-transformed for analysis.
[c]In 1983, 20 pesos=$1.
[d]1 kcal=4.186 kJ.
[e]From one-way ANOVA.
[f]Median maturity scale value and % with a value >3 for self-assessed five-level pubic hair stage in males, five-level maturity scale derived from menarcheal age in females. *P*-value from ordered logistic regression.

Table 2 Mean lipid levels ± s.e. in male offspring by fetal energy sufficiency groups[a]

	All n=*296*	*Tall-LAFA* n=*60*	*Short-LAFA* n=*78*	*Tall-HAFA* n=*91*	*Short-HAFA* n=*67*	*Model 1*	*Model 2*	*Model 3*
TC (mg/dl)	153.2±1.9	156.8±4.5	154.1±4.1	152.3±3.3	148.6±3.4	0.129	0.06	0.04
LDL-C (mg/dl)	91.8±1.7	97.8±3.9	94.4±3.6	89.0±2.8	85.6±3.1	0.007	0.002	0.0004
HDL-C (mg/dl)	38.3±0.6	36.9±1.5	36.8±1.0	39.7±1.3	39.3±0.9	0.016	0.02	0.02
TG (mg/dl)	73.9±2.2	73.3±4.6	71.1±3.9	73.8±4.2	77.4±4.5	0.7	0.9	0.9
TC/HDL-C	4.2±0.1	4.5±0.2	4.3±0.1	4.0±0.1	3.9±0.1	0.0004	0.0001	0.0001
LDL-C/HDL-C	2.5±0.1	2.8±0.1	2.7±0.1	2.4±0.1	2.3±0.1	0.0002	0.0001	0.0001

[a]Trend test=significance of beta coefficient for four-level ordinal fetal energy sufficiency variable in linear regression model. Model 1=univariate; model 2 adjusts for the child's current arm fat area, energy intake and the percentage of energy from fat, maturational stage, and household income (birth and current); model 3 adjusts further for LBW status (birth weight ≤ 2.6 kg).

Table 3 Mean lipid levels±s.e. in female offspring by energy risk groups

						P for trend[a]		
	All n=*307*	*Tall-LAFA* n=*70*	*Short-LAFA* n=*95*	*Tall-HAFA* n=*77*	*Short-HAFA* n=*65*	*Model 1*	*Model 2*	*Model 3*
TC (mg/dl)	182.5±2.3	183.3±4.5	178.5±4.2	178.1±4.5	192.2±5.2	0.2	0.3	0.8
LDL-C (mg/dl)	104.6±1.7	105.8±3.9	101.4±3.2	102.0±3.2	110.7±3.7	0.4	0.4	0.4
HDL-C (mg/dl)	41.3±0.6	41.6±1.1	39.9±1.0	41.0±1.1	43.2±1.5	0.4	0.8	0.8
TG (mg/dl)	79.6±2.2	78.7±4.2	82.9±4.1	74.0±4.0	82.5±5.5	1.0	0.7	0.8
TC/HDL-C	4.6±0.1	4.5±0.1	4.6±0.1	4.5±0.1	4.6±0.1	0.9	0.6	0.7
LDL-C/HDL-C	2.6±0.1	2.7±0.1	2.6±0.1	2.6±0.1	2.7±0.1	1.0	0.7	0.7

[a]Trend test=significance of beta coefficient for four-level ordinal fetal energy sufficiency variable in linear regression model. Model 1 = univariate; model 2 adjusts for the child's current arm fat area, energy intake and the percentage of energy from fat, maturational stage, and household income (birth and current); model 3 adjusts further for LBW status (birth weight ≤ 2.6 kg).

four levels of fetal energy sufficiency. Lipid values in this population are within the range of values reported for adolescent populations. For instance, in Taiwan, male and female adolescent had total cholesterol values of 151.5 and 164 mg/dl, respectively (Chu *et al*, 1998), while the corresponding values of US males and females were 158 and 161.4 mg/dl (Hickman *et al*, 1998).

In unadjusted male data (model 1), there were significant trends across fetal energy sufficiency levels in LDL-C, HDL-C, and the ratios of TC/HDL-C and LDL-C/HDL-C. The trends were in the direction predicted by the supply–demand model, with CVD risk most elevated among groups classified as high risk for prenatal energy shortfall. Adjusting for the child's adiposity, maturity, energy and fat intake, and household income (birth and 1998) strengthened associations with fetal energy sufficiency, while further adjustment for birth weight (model 3) had negligible effect on any of these models. In contrast to the males, there were no significant differences in any lipid outcome between the four levels of the fetal energy sufficiency variable in females, whether tested as a trend across the four-level ordinal variable (regression) or as multiple comparisons between individual fetal energy sufficiency levels (Bonferonni-corrected ANOVA).

We tested comparable multivariate regression models stratified on lower (kJ $<$ 5710/day) and upper (kJ $=$ 5710/day) halves of maternal energy intake during the third trimester of pregnancy (Table 4). The relationships between fetal energy sufficiency and cholesterol levels were only present, or considerably stronger, among male offspring of mothers with lower energy intake during pregnancy. There were no significant lipid trends across fetal energy sufficiency levels in the females stratified on maternal energy intake (data not shown).

To assess the clinical significance of the associations, Table 5 presents the prevalence of males categorized as 'high CVD risk' for each lipid using clinical cut-points developed for use in CVD prevention in adolescents (Kwiterovich, 1991). The tables also report ORs for each level of fetal energy sufficiency (entered as dummy variables) from multivariate logistic regression models predicting each high-risk cut-point, using the highest fetal energy sufficiency group (Short-HAFA) as reference group, and controlling for adiposity, maturity, dietary energy and fat intake, and household income at birth and at present. In females, neither birth weight nor any fetal energy sufficiency group had a significant OR for any clinical CVD risk cut-point whether modeled as crude associations, or controlling

Table 4 Mean lipids in male offspring by fetal energy sufficiency groups, stratified on upper and lower halves of maternal third trimester energy intake[a]

		Tall-LAFA n=*60*	*Short-LAFA* n=*78*	*Tall-HAFA* n=*91*	*Short-HAFA* n=*67*	P *for trend*[b]
TC (mg/dl)	Low kJ	157.1±5.9	157.4±5.5	163.0±5.6	145.1±4.9	0.15
	High kJ	156.4±6.9	149.1±5.9	145.8±3.6	152.9±4.7	0.45
LDL-C (mg/dl)	Low kJ	101.9±4.9	96.1±4.8	92.3±3.8	82.1±4.6	0.002
	High kJ	93.3±6.1	91.8±5.2	86.6±3.9	89.4±3.8	0.282
HDL-C (mg/dl)	Low kJ	34.8±1.4	37.9±1.4	41.1±1.6	39.3±1.3	0.02
	High kJ	39.1±2.8	35.2±1.5	38.7±1.8	39.3±1.3	0.27
TG (mg/dl)	Low kJ	67.1±6.1	69.9±4.5	75.7±6.2	73.1±5.5	0.4
	High kJ	80.1±6.6	72.9±7.0	72.6±5.4	82.1±6.9	1.0
TC/HDL-C	Low kJ	4.63±0.18	4.25±0.15	4.10±0.18	3.79±0.15	0.001
	High kJ	4.26±0.24	4.40±0.20	3.99±0.14	3.97±0.14	0.07
LDL-C/HDL-C	Low kJ	3.03±0.17	2.64±0.16	2.34±0.12	2.19±0.15	0.0001
	High kJ	2.61±0.21	2.77±0.20	2.42±0.13	2.35±0.12	0.07

[a]Low kJ <5710 kJ/day, high kJ $\geqslant 5710$ kJ/day.
[b]*P* for trend controlling for the child's current adiposity, maturation status, dietary energy, % energy from fat, and household income at birth and at the time of cholesterol measurement.

Table 5 Prevalence and OR (95% CI) for male offspring being classified as 'high risk' for each lipid using clinical cut-points for CVD prevention in adolescents[a]

	Tall-LAFA (n=*60*)		*Short-LAFA* (n=*78*)		*Tall-HAFA* (n=*91*)		*Short-HAFA* (n=*67*)	
	%	*OR*[b]	*%*	*OR*	*%*	*OR*	*%*	*OR*
TC $\geq$ 200 mg/dl	15.3	5.8* (1.2, 28.4)	11.9	4.9~ (1.0, 23.9)	12.5	4.0~ (0.8, 19.4)	2.8	1
LDL-C $\geq$ 130 mg/dl	16.5	3.6* (1.03, 12.3)	11.9	2.6 (0.7, 9.3)	7.9	1.0 (0.3, 3.8)	3.9	1
HDL-C $<$ 35 mg/dl	51.4	2.9** (1.4, 6.2)	49.2	2.8** (1.3, 5.7)	32.1	1.2 (0.6, 2.5)	27.2	1
TG $\geq$ 130 mg/dl	10.9	1.2 (0.4, 3.9)	5.2	0.7 (0.2, 2.7)	12.5	0.8 (0.3, 2.6)	9.9	1
TC/HDL-C $\geq$ 5	28.0	3.2* (1.2, 8.4)	18.6	2.1 (0.8, 5.4)	17.8	1.3 (0.5, 3.4)	11.8	1
LDL-C/HDL-C $\geq$ 3	39.9	4.9** (1.8, 10.4)	32.1	3.4* (1.4, 8.0)	23.9	1.5 (0.6, 3.6)	13.8	1
Summary index[c] (0–6)	1.62 (0.22)		1.29 (0.16)		1.07 (0.15)		0.69 (0.13)	

[a]Clinical 'high risk' cut-points for lipids in adolescents (Kwiterovich, 1991). ~$P<0.1$, *$P<0.05$, **$P<0.01$, ***$P<0.001$.
[b]ORs (95% CI) from logistic regression models controlling for current adiposity, maturational status, dietary energy, % dietary fat, and household income at birth and at the time of cholesterol measurement.
[c]Mean number of lipids (+s.e.) classified as high risk per individual (range 0–6). Trend across four-level ordinal fetal energy sufficiency significant ($P<0.00001$) after controlling for adiposity, maturational status, dietary energy, % dietary fat, and household income at birth and at the time of cholesterol measurement (ordered logistic regression).

for confounders or birth weight (P-values ranging from 0.3 to 0.9 for trend tests). We therefore report results for males only.

For each lipid, the percentage of males considered to be ''at high CVD risk'' decreased significantly as fetal energy sufficiency increased; that is, for all five of the cholesterol outcomes, a higher proportion of males were at high CVD risk in the Tall-LAFA group compared to the Short HAFA group. Intermediate levels of fetal energy sufficiency were associated with intermediate ORs for high CVD risk in adolescence. Consistent with these individual models, the summary index (sum of all high-risk lipids) decreased in dose–response fashion across fetal energy sufficiency groups in males. In a multivariate logistic regression model that included only control variables, birth weight was only related to risk for high LDL-C in adolescence (OR [95% CI] = 0.38 [0.03, 0.73] for each 1 kg change in birth weight, $P = 0.043$), a relationship unchanged after inclusion of the fetal energy sufficiency group variable (OR [95% CI] = 0.39 [0.2, 0.76], $P = 0.051$).

Discussion

We hypothesized that the likelihood of having experienced energy shortfall *in utero*, as indicated by different combinations of high and low fetal nutritional demand (growth

potential as indicated by maternal stature) and high and low maternal nutritional supply capacity (maternal energy status), would predict CVD risk among a population of adolescent Filipinos. Our expectations were confirmed in males but not females. Male adolescents who had a high fetal demand for nutrients who were born to mothers who had poor energy status during pregnancy have the highest risk for CVD as adolescents, as indicated by five of six of the lipid outcomes investigated. As the likelihood of having experienced energy shortfall in utero decreased across the four-level supply–demand variable, the levels of TC and LDL-C decreased while HDL-C increased. As a result of these opposing trends, fetal energy sufficiency was strongly inversely associated with the atherogenicity of the lipid profile as indicated by the ratios of TC/HDL-C or LDL-C/HDL-C. These associations were independent of potential confounding factors and were only present, or strongest, among offspring of mothers in the lower half of the distribution of dietary energy consumption during pregnancy. Taken together, these findings support the hypothesis that the balance between fetal demand for nutrients and the maternal capacity to supply these needs has persistent effects on male offspring lipid metabolism.

The supply–demand model developed here is an extension and refinement of our prior work in this population, which illustrated the importance of MAFA alone as a predictor of offspring male lipids (Kuzawa & Adair, 2003). The gradient in lipid profiles across the four-level fetal energy sufficiency variable (ie Table 5) illustrates the utility of considering both MAFA and maternal stature simultaneously. In the present analyses, male offspring of both low MAFA groups have significantly elevated risk for developing future CVD compared to the reference group born to well-nourished but short mothers. However, offspring of low MAFA-Tall mothers were significantly more likely to be classified as 'high CVD risk' for five lipid outcomes (all but TG), while the offspring of low MAFA-Short mothers were only at increased risk for low HDL-C and high LDL-C/HDL-C, with an additional borderline-significant relationship with high TC. Thus, even within MAFA strata, information on mother's height provides a refined basis for identifying males at risk for CVD. We believe that this finding is consistent with our hypothesis that fetal demand for nutrients—as indicated here by maternal stature—is a variable in its own right, and one with independent effects on the balance of fetal nutritional sufficiency.

Recent commentaries emphasize that the fetal environment is likely to have a minor influence on cardiovascular risk and mortality (Kramer, 2000). Our findings in males suggest that this assessment may be premature, and a reflection of the widespread use of birth weight as a marker of fetal nutritional sufficiency. While weight at birth had little relevance to future lipid profiles in this population, the supply–demand model predicted multiple clinical criteria of high-risk lipid profiles in males. As has been noted previously for relationships between maternal nutrition or nutritional status during pregnancy and offspring CVD risk factors (Roseboom *et al*, 2000; Adair *et al*, 2001), the fetal energy sufficiency variable predicted lipids independent of birth weight. Compared to the group with highest energy sufficiency, males in the lowest energy sufficiency group were about five times more likely to have a level of LDL-C or TC defined as 'high risk' for cardiovascular disease. The lowest energy sufficiency group was also roughly three times more likely to have low levels of beneficial HDL-C, and was five times more likely to have an elevated atherogenic ratio of LDL-C/HDL-C. These findings suggest that fetal nutritional sufficiency, if modeled appropriately, may have greater clinical relevance than suggested by studies that use birth weight as a proxy for fetal nutrition.

Sex differences in lipid programming: hypotheses

The consistency of the findings in males is striking in light of the absence of any significant relationship in females. While support for our model would be stronger if results were also significant in females, these sex differences were not unexpected in light of past research. Our prior work in this population has identified inverse relationships between birth outcomes or maternal nutritional status during pregnancy and offspring lipids (Adair *et al*, 2001; Kuzawa & Adair, 2003), blood pressure (Adair *et al*, 2001), and an interaction between birth length and postnatal growth as an influence on blood pressure (Adair & Cole, 2003) that were only present among males. Based on human epidemiological (Valdez *et al*, 1994; Donker *et al*, 1997; Antal *et al*, 1998; Suzuki *et al*, 2000; Ziegler *et al*, 2000; Stein *et al*, 2002) and animal model research (Lucas *et al*, 1996; Kind *et al*, 1999), evidence for lipid programming is commonly stronger, or only present, in males. Thus, rather than discounting our model, we feel that our findings add to mounting evidence for sex differences in the process of cardiovascular programming, particularly of lipid metabolism.

While no model has been proposed to account for sex differences in cardiovascular programming, the supply–demand model suggests one possible interpretation of these findings. Sexual dimorphism in growth rate begins before birth, and is reflected in the common finding of higher mean birth weight and length among male compared to female newborns (Hindmarsh *et al*, 2002). The greater nutritional demands of the male fetus may render it more precariously balanced nutritionally, and more vulnerable to disruptions in supply. For instance, in rats, surgical reduction in uterine blood flow alleviates the normal sexual dimorphism in size at birth (Oyhenart *et al*, 1998; Dressino *et al*, 2002). A heightened sensitivity of male fetuses to maternal nutrition is suggested in humans by the finding in some studies that nutritional supplementation of poorly nourished mothers disproportionately improves male birth weight (Mora *et al*, 1979; Adair & Pollitt, 1985), and that male embryos or fetuses suffer higher pregnancy losses under conditions of maternal undernutrition (Andersson & Bergstrom, 1998). If

the greater male sensitivity to prenatal nutrition or stress (Stinson, 1985) manifests as sex differences in postnatal lipid profiles or CVD risk, sex differences might be accentuated in this population owing to the marginal nutritional status of the mothers during pregnancy.

Sex differences in lipid programming may also reflect programming of the hypothalamic–pituitary–gonadal axis, which is known to have lasting influence on sex steroid metabolism (Rhind *et al*, 2001). Males experience a prenatal and early postnatal surge in testosterone that 'androgenizes' various target tissues, organs, and endocrine axes, altering their sensitivity and developmental response to the rise in testosterone production initiated at puberty (Forest, 1983). Fetal testosterone production, in turn, is sensitive to maternal nutrition (Rae *et al*, 2002) and stress (Ward & Weisz, 1980; Williams *et al*, 1999). Given the importance of the pubertal rise in androgen production to the establishment of the male-typical adult lipid profile (Berenson *et al*, 1981), any long-term effects of the intrauterine milieu on sex steroids or steroid-sensitive target tissues, such as liver enzymes (Gustafsson & Stenberg, 1974), could influence adult lipid profiles in males. Such dual 'organizational' and 'activational' effects of androgens are well established for numerous tissues and organs (Rhind *et al*, 2001).

Importance of fetal growth potential

Our results add to a small but growing list of 'fetal origins' studies that attempt to account for variation in fetal growth potential. Prior work has used indices of fetal growth potential in combination with birth outcomes as a basis for assessing the sufficiency of growth *in utero*. Leon *et al* (1996) and Hennessy and Alberman (1997) found that inverse relationships between birth weight and blood pressure were strongest among individuals who ended up taller as adults. Based upon the assumption that small size at birth in a tall adult is an indication that growth potential was not attained *in utero*, both authors interpret their findings as evidence that failure to reach fetal growth potential may be critical to blood pressure programming.

In contrast to this approach, our supply–demand model is unique in operationalizing growth potential as an influence on the fetus' risk of nutrient shortfall by determining its level of nutritional demand. While genetics presumably play a dominant role in setting the fetal growth trajectory, epigenetic mechanisms of fetal growth restriction may also be important. Given evidence that the fetal growth trajectory may be reset in response to maternal nutrition or hormonal cues during early pregnancy or the periconceptual period (Godfrey & Robinson, 1998), growth restriction of epigenetic origin might paradoxically *protect* the developing fetus against nutritional insufficiency by lowering the level of nutritional demand during later gestation. Current work on parent of origin effects (imprinting) on IGF-II and a related cluster of genes suggests a possible epigenetic basis for separate regulation of fetal demand and maternal supply, manifesting as differential expression of fetal growth-promoting and placental-supply limiting genes in the fetus and placenta (Reik *et al*, 2003). Our results, along with evidence for sex differences in the transgenerational effect of maternal constraint on birth weight (Price & Coe, 2000), suggest that these processes may vary in important ways in males and females.

Limitations of study

Although prospectively collected data are a strength of our study, we were forced to rely on imperfect measures of both fetal growth potential and maternal supply capacity. The mothers in the Cebu sample have low mean stature relative to Western standards, which is presumably a reflection, in part, of poor postnatal nutrition and unattained growth potential (Siega-Riz & Adair, 1993). This is likely to reduce, but not abolish, the utility of maternal stature as a marker of offspring growth potential. While maternal stature was the most appropriate measure of fetal growth potential available for our sample, prior research has used offspring adult stature (Leon *et al*, 1996; Hennessy & Alberman, 1997) and mother's own birth weight (Skjaerven *et al*, 1997) to similar effect. Our model should be viewed as a preliminary attempt to incorporate variation in fetal nutritional demand into the study of the fetal origins of adult disease.

Similar limitations apply to our measure of maternal supply capacity, as obstructed substrate flow to the fetus secondary to maternal hypertension, placental insufficiency, or other factors may compromise fetal nutrition independent of maternal nutrition and nutritional status (Harding, 2001). We were not able to control for these additional influences on maternal supply capacity. The changes in adipose tissue stores that occur during pregnancy, and the interindividual variability in this process, complicate our interpretation of MAFA. The women in the Cebu sample were marginally nourished during pregnancy, as indicated by low energy intake and a third trimester BMI of roughly 23 kg/m^2. It is thus of interest that the relationships between the fetal energy sufficiency variable and lipids in male offspring were stronger, or only significant, among mothers with below-median energy intake during pregnancy. This strengthens our interpretation that nutritional insufficiency is related to the observed results. The utility of MAFA as a functional measure of maternal supply may have been accentuated by the marginal nutritional status of the women in the sample, and by the fact that it was measured at a mean gestational age (30 ± 2 weeks) just prior to peak energetic demands of pregnancy and fetal fat deposition (King, 2000). Our model may prove most useful in populations experiencing a similar level of energetic and nutritional restriction.

As we are using maternal anthropometric characteristics to predict offspring lipid profiles, we are unable to rule out confounding of the associations by shared genes or features of environment. However, we feel that this an unlikely

explanation for our findings in males. If the associations between fetal energy sufficiency categories and later lipids were the result of shared genetic or lifestyle factors, we would expect the offspring of mothers with greater adiposity to have higher cholesterol. This is the opposite of the observed trend in males. Indeed, it is the nonintuitive association between high offspring cholesterol and low maternal adiposity, especially in combination with low maternal energy intake, that makes it unlikely that our findings are merely due to offspring resembling their mothers. However, these associations are in agreement with the predictions of the fetal origins hypothesis.

In conclusion, our findings in males highlight the potential benefits of considering variation in fetal demand for nutrients in tests of the fetal origins hypothesis, as a complement to current research focused on factors influencing the supply of nutrients to the fetus. Among males, the supply–demand model developed here predicted mean levels and clinical cut-points for five of six lipid outcomes investigated. Lipid risk factors for development of atherosclerosis were most elevated among offspring of taller mothers with low adipose tissue stores, and these associations were strongest when the mothers consumed below-median dietary energy during pregnancy. In contrast, the supply–demand model did not predict any lipid outcome or clinical cut-point among females. We speculate that sex differences in the level of fetal nutritional demand, or sex steroid programming, may help explain these differences.

Acknowledgements

We would like to thank the many mothers and their offspring who have graciously participated in this study for two decades. The Health Departments of the Cities of Cebu, Mandaue, and Lapu Lapu, and Cebu Provincial Health for Region 7 provided generous assistance, including access to clinics and clinic staff. The employees of OPS are warmly thanked for their significant contribution to data collection. Josephine Avila and Joseph Harvey Canete Cadungog assisted in logistics and blood sample collection. Lipid values were measured by Dr Ngoc-Anh Le of the Emory University Medical School. The work was supported by the National Science Foundation, the Mellon Foundation, the Nestle Foundation, and the Emory University Internationalization Program.

References

Adair L & Cole T (2003): Rapid child growth raises blood pressure in adolescent boys who were thin at birth. *Hypertension* **41**, 451–456.

Adair LS & Pollitt E (1985): Outcome of maternal nutritional supplementation: a comprehensive review of the Bacon Chow Study. *Am. J. Clin. Nutr.* **41**, 948–978.

Adair L & Popkin B (1988): Birth weight, maturity and proportionality in Filipino infants. *Hum. Biol.* **60**, 319–339.

Adair LS, Kuzawa CW & Borja J (2001): Maternal energy stores and diet composition during pregnancy program adolescent blood pressure. *Circulation* **104**, 1034–1039.

Andersson R & Bergstrom S (1998): Is maternal malnutrition associated with a low sex ratio at birth? *Hum. Biol.* **70**, 1101–1106.

Antal M, Agfalvi R, Nagy K, Szepvolgyi J, Banto E, Regoly-Merei A, Biro L & Biro G (1998): Lipid status in adolescents born with low birth weight. *Z. Ernahrungswiss.* **37** (Suppl 1), 131–133.

Barker D (1994): *Mothers, Babies, and Disease in Later Life*. London: BMJ Publishing.

Barker D (1995): Fetal origins of coronary heart disease. *BMJ* **311**, 171–174.

Barker DJ, Osmond C, Golding J, Kuh D & Wadsworth ME (1989): Growth *in utero*, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *BMJ* **298**, 564–567.

Berenson GS, Srinivasan SR, Cresanta JL, Foster TA & Webber LS (1981): Dynamic changes of serum lipoproteins in children during adolescence and sexual maturation. *Am. J. Epidemiol.* **113**, 157–170.

Chard T, Yoong A & Macintosh M (1993): The myth of fetal growth retardation at term. *Br. J. Obstet. Gynaecol.* **100**, 1076–1081.

Chu NF, Rimm EB, Wang DJ, Liou HS & Shieh SM (1998): Relationship between anthropometric variables and lipid levels among school children: The Taipei Children Heart Study. *Int. J. Obes. Relat. Metab. Disord.* **22**, 66–72.

Donker GA, Labarthe DR, Harrist RB, Selwyn BJ, Srinivasan SR, Wattigney W & Berenson GS (1997): Low birth weight and serum lipid concentrations at age 7-11 years in a biracial sample. *Am. J. Epidemiol.* **145**, 398–407.

Dressino V, Orden B & Oyhenart EE (2002): Sexual responses to intrauterine stress: body and brain growth. *Clin. Exp. Obstet. Gynecol.* **29**, 100–102.

Food and Nutrition Research Institute (1990): *Food Composition Tables Recommended for Use in the Philippines*. Manila: Food and Nutrition Research Institute of the Philippines.

Forest M (1983): Role of androgens in fetal and pubertal development. *Horm. Res.* **18**, 69–83.

Forsen T, Eriksson J, Tuomilehto J, Teramo K, Osmond C & Barker D (1997): Mother's weight in pregnancy and coronary heart disease in a cohort of Finnish men: follow-up study. *BMJ* **315**, 837–840.

Frisancho AR (1990): *Anthropometric Standards for the Assessment of Growth and Nutritional Status*. Ann Arbor: University of Michigan Press.

Godfrey K & Robinson S (1998): Maternal nutrition, placental growth and fetal programming. *Proc. Nutr. Soc.* **57**, 105–111.

Godfrey KM & Barker DJ (2000): Fetal nutrition and adult disease. *Am. J. Clin. Nutr.* **71**, 1344S–1352S.

Gustafsson JA & Stenberg A (1974): Neonatal programming of androgen responsiveness of liver of adult rats. *J. Biol. Chem.* **249**, 719–723.

Harding JE (2001): The nutritional basis of the fetal origins of adult disease. *Int. J. Epidemiol.* **30**, 15–23.

Hennessy E & Alberman E (1997): The effects of own fetal growth on reported hypertension in parous women aged 33. *Int. J. Epidemiol.* **26**, 562–570.

Hickman T, Briefel R, Carroll M, Rifkind B, Cleeman J, Maurer K & Johnson C (1998): Distributions and trends of serum lipid levels among United States children and adolescents ages 4–19 years: data from the Third National Health and Nutrition Examination Survey. *Prev. Med.* **27**, 879–890.

Hindmarsh PC, Geary MP, Rodeck CH, Kingdom JC & Cole TJ (2002): Intrauterine growth and its relationship to size and shape at birth. *Pediatr. Res.* **52**, 263–268.

Institute of Medicine (1990): *Nutrition During Pregnancy. Part I, Weight Gain*. Washington, DC: National Academy Press.

Kind KL, Clifton PM, Katsman AI, Tsiounis M, Robinson JS & Owens JA (1999): Restricted fetal growth and the response to dietary cholesterol in the guinea pig. *Am. J. Physiol.* **277**, R1675–R1682.

King JC (2000): Physiology of pregnancy and nutrient metabolism. *Am. J. Clin. Nutr.* **71** (Suppl), 1218s–1225s.

Kramer M (2000): Association between restricted fetal growth and cardiovascular disease: is it causal? Is it important? *Am. J. Epidemiol.* **152**, 605–608.

Kuzawa CW & Adair LS (2003): Lipid profiles in adolescent Filipinos: relationship to birth weight and maternal energy status during pregnancy. *Am. J. Clin. Nutr.* **77**, 960–966.

Kwiterovich PO (1991): Plasma lipid and lipoprotein levels in childhood. *Ann. N. Y. Acad. Sci.* **623**, 90–107.

Labarthe D (1998): *Epidemiology and Prevention of Cardiovascular Diseases: A Global Health Challenge*. Gaithersburg: Aspen Publishers, Inc.

Leon D, Koupilova I, Lithell H, Berglund L, Mohsen R, Vagero D, Lithell U & McKeigue P (1996): Failure to realise growth potential *in utero* and adult obesity in relation to blood pressure in 50 year old Swedish men. *BMJ* **312**, 401–406.

Lohman T, Roche A & Martorell R (1988): *Anthropometric Standardization Reference Manual*. Champaign, IL: Human Kinetics Books.

Lucas A (1991): Programming by early nutrition in man. *Ciba Found. Symp.* **156**, 38–50; discussion 50–55.

Lucas A, Baker BA, Desai M & Hales CN (1996): Nutrition in pregnant or lactating rats programs lipid metabolism in the offspring. *Br. J. Nutr.* **76**, 605–612.

Mora JO, de Paredes B, Wagner M, de Navarro L, Suescun J, Christiansen N & Herrera MG (1979): Nutritional supplementation and the outcome of pregnancy. I. Birth weight. *Am. J. Clin. Nutr.* **32**, 455–462.

Oyhenart EE, Mune MC & Pucciarelli HM (1998): Influence of intrauterine blood supply on growth and sexual dimorphism at birth. *Growth Dev. Aging* **62**, 187–198.

Price KC & Coe CL (2000): Maternal constraint on fetal growth patterns in the rhesus monkey (*Macaca mulatta*): the intergenerational link between mothers and daughters. *Hum. Reprod.* **15**, 452–457.

Rae MT, Rhind SM, Fowler PA, Miller DW, Kyle CE & Brooks AN (2002): Effect of maternal undernutrition on fetal testicular steroidogenesis during the CNS androgen-responsive period in male sheep fetuses. *Reproduction* **124**, 33–39.

Rasmussen K (2001): The 'fetal origins' hypothesis: challenges and opportunities for maternal and child nutrition. *Annu. Rev. Nutr.* **21**, 73–95.

Reik W, Constancia M, Fowden A, Anderson N, Dean W, Ferguson-Smith A, Tycko B & Sibley C (2003): Regulation of maternal supply and demand for nutrients in mammals by imprinted genes. *J. Physiol.* **547** (Part 1), 35–44.

Rhind SM, Rae MT & Brooks AN (2001): Effects of nutrition and environmental factors on the fetal programming of the reproductive axis. *Reproduction* **122**, 205–214.

Roseboom TJ, van der Meulen JH, van Montfrans GA, Ravelli AC, Osmond C, Barker DJ & Bleker OP (2001): Maternal nutrition during gestation and blood pressure in later life. *J. Hypertens.* **19**, 29–34.

Roseboom TJ, van der Meulen JH, Osmond C, Barker DJ, Ravelli AC & Bleker OP (2000): Plasma lipid profiles in adults after prenatal exposure to the Dutch famine. *Am. J. Clin. Nutr.* **72**, 1101–1106.

Siega-Riz AM & Adair LS (1993): Biological determinants of pregnancy weight gain in a Filipino population. *Am. J. Clin. Nutr.* **57**, 365–372.

Skjaerven R, Wilcox AJ, Oyen N & Magnus P (1997): Mothers' birth weight and survival of their offspring: population based study. *BMJ* **314**, 1376–1380.

Stanner SA, Bulmer K, Andres C, Lantseva OE, Borodina V, Poteen VV & Yudkin JS (1997): Does malnutrition *in utero* determine diabetes and coronary heart disease in adulthood? Results from the Leningrad siege study, a cross sectional study. *BMJ* **315**, 1342–1348.

Stein A, Conlisk A, Torun B, Schroeder D, Grajeda R & Martorell R (2002): Cardiovascular disease risk factors are related to adult adiposity but not to birth weight in young Guatemalan adults. *J. Nutr.* **132**, 2208–2214.

Stinson S (1985): Sex differences in environmental sensitivity during growth and development. *Yearb. Phys. Anthropol.* **28**, 123–147.

Suzuki T, Minami J, Ohrui M, Ishimitsu T & Matsuoka H (2000): Relationship between birth weight and cardiovascular risk factors in Japanese young adults. *Am. J. Hypertens.* **13**, 907–913.

Valdez R, Athens MA, Thompson GH, Bradshaw BS & Stern MP (1994): Birthweight and adult health outcomes in a biethnic population in the USA. *Diabetologia* **37**, 624–631.

Ward IL & Weisz J (1980): Maternal stress alters plasma testosterone in fetal males. *Science* **207**, 328–329.

Waterland R & Garza C (1999): Potential mechanisms of metabolic imprinting that lead to chronic disease. *Am. J. Clin. Nutr.* **69**, 179–197.

Williams MT, Davis HN, McCrea AE & Hennessy MB (1999): Stress during pregnancy alters the offspring hypothalamic, pituitary, adrenal, and testicular response to isolation on the day of weaning. *Neurotoxicol. Teratol.* **21**, 653–659.

Ziegler B, Johnsen SP, Thulstrup AM, Engberg M, Lauritzen T & Sorensen HT (2000): Inverse association between birth weight, birth length and serum total cholesterol in adulthood. *Scand. Cardiovasc. J.* **34**, 584–588.