Lipid profiles in adolescent Filipinos: relation to birth weight and maternal energy status during pregnancy[1–3]

Christopher W Kuzawa and Linda S Adair

ABSTRACT

Background: The finding that persons with low birth weight have a higher cardiovascular disease (CVD) risk than do persons with higher birth weight remains poorly understood.

Objective: We tested the hypothesis that maternal arm fat area (MAFA) in the third trimester of pregnancy and birth weight of offspring are inversely related to the offspring's risk of CVD.

Design: In a 1-y birth cohort study (1983–1984), 296 male and 307 female offspring were followed up (1998–1999) to measure their lipid profiles. Participants came from randomly selected communities of Cebu, Philippines.

Results: MAFA (log cm^2) was positively associated (β) with HDL cholesterol (0.12 log mg/dL; $P < 0.01$) and inversely associated with total cholesterol (−10.0 mg/dL; $P < 0.10$), LDL cholesterol (−13.1 mg/dL; $P < 0.01$), and the ratios of total to HDL cholesterol and LDL to HDL cholesterol (both $P < 0.001$) in males. These relations were independent of birth weight, present adiposity, energy and fat intakes, maturity, and income. Birth weight ≤ 2.6 kg was associated with elevated LDL cholesterol (9.9 mg/dL; $P < 0.01$) and an elevated ratio of LDL to HDL cholesterol (0.22; $P < 0.10$) only in males. In females, MAFA related positively to total (15.5 mg/dL; $P < 0.05$) and LDL (11.9 mg/dL; $P < 0.05$) cholesterol.

Conclusions: In this Filipino population, mothers with low energy status during pregnancy gave birth to male offspring who had a high CVD risk in adolescence, as indicated by lipid profiles. The findings in females are less consistent with the fetal origins hypothesis and suggest sex differences in the relation between fetal nutrition and postnatal lipid metabolism. *Am J Clin Nutr* 2003;77:960–6.

KEY WORDS Cardiovascular diseases, birth weight, fetal nutrition, pregnancy, cholesterol, lipoproteins, sex differences, adolescence, Philippines, risk factors, dietary fats, programming, fetal origins hypothesis, nutrition transition, maternal energy status, Cebu Longitudinal Health and Nutrition Survey

INTRODUCTION

Cholesterol profiles are among the suite of cardiovascular disease (CVD) risk factors believed to contribute to the inverse relation between birth weight and CVD mortality in human populations (1). The most common finding among studies to date is an elevation of total cholesterol in relation to markers of poor birth outcome, typically indexed by weight at birth (2–5). It is widely assumed that low birth weight (LBW) indicates fetal growth restriction and underlying nutritional insufficiency, which is viewed as the stimulus that triggers fetal adaptations that have long-term physiologic effects on cholesterol metabolism (6).

Because fetal nutritional sufficiency is in part a reflection of the maternal capacity to supply the energy and nutrients necessary for growth, maternal nutritional status during pregnancy may be an important factor influencing patterns of CVD risk in offspring (6). Although maternal dietary manipulation during pregnancy has long-term effects on lipid metabolism in offspring in animal models (7, 8), few studies in humans have investigated the possible role of maternal nutrition during pregnancy in these relations (9). Of the 3 studies of cholesterol that included markers of maternal nutritional status during pregnancy, poor maternal nutritional status was alternately found to increase (10), to decrease (3), or to have no association with CVD risk in offspring (11), as indicated by lipid profiles. Of the 2 studies that investigated famine-exposed populations, 1 showed evidence of an effect of famine exposure during the first trimester on the ratio of LDL to HDL cholesterol in offspring, whereas the second found no significant famine-related differences in lipid profiles in offspring (12, 13).

Despite evidence that LBW is associated with an atherogenic lipid profile and an elevated risk of CVD mortality, the contribution of maternal nutritional status during pregnancy to cholesterol metabolism in offspring remains a matter of speculation. In the present study, we used data collected prospectively over a 17-y period in the Philippines to test the hypothesis that poor maternal energy status during pregnancy and LBW predict elevated CVD risk in offspring during adolescence, as indexed by cholesterol lipid profiles.

SUBJECTS AND METHODS

Sample characteristics

Participants were enrolled in the Cebu Longitudinal Health and Nutrition Survey, a community-based birth cohort study of infants

[1] From the Division of Epidemiology, University of Minnesota, Minneapolis (CWK), and the Carolina Population Center, University of North Carolina, Chapel Hill (LSA).

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[3] Address reprint requests to CW Kuzawa, Department of Anthropology, Northwestern University, 1810 Hinman Avenue, Evanston, IL 60208. E-mail: kuzawa@northwestern.edu.

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born in 1983–1984. The study area was metropolitan Cebu, the second largest metropolitan area in the Philippines. The 33 metropolitan Cebu communities randomly selected for the survey included densely populated urban neighborhoods, periurban neighborhoods, and rural villages in the surrounding mountains and 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 1 May 1983 and 30 April 1984 (n = 3327). The child sample (3080 single live births) was thus representative of singletons born during that 1-y interval. Initial refusal rates were low (≈3%), but we do not have information on those who refused to participate. The present analysis used data collected from mothers during the third trimester of pregnancy (1983–1984) and from their offspring at birth (1983–1984) and at 14–16 y of age (1998–1999).

Maternal arm fat area (MAFA) was calculated from triceps skinfold thickness and midupper arm circumference measured during the baseline survey (1983–1984) at a mean (±SD) of 30 ± 5 wk of gestation. Maternal height was measured with a folding stadiometer. Infant length was measured within 6 d of birth by trained project staff using custom-designed length boards. For infants born in hospitals, birth weight was measured by birth attendants using hospital scales. For infants born at home, birth weight was measured by birth attendants who had been provided with Salter (London) hanging-type scales and trained in their use. Gestational age was estimated from the mother's report of the date of her last menstrual period. In cases where this date was unknown, when pregnancy complications occurred, or if the infant weighed < 2.5 kg at birth, gestational age was determined by using the Ballard method (14).

At the most recent follow-up survey in 1998, 2089 adolescents aged 14–16 y were located and interviewed. Of these, 2056 had birth weight, gestational age, and current measurements. From those subjects, a subsample of 307 females and 296 males were selected at random within 2 birth weight strata for blood sample collection. To avoid including subjects who were small at birth because of prematurity, we limited the subsample to subjects who were carried to term, which was defined as a gestational age at birth ≥ 37 wk ($\bar{x}$ ± SD: 39.9 ± 1.8 wk). To ensure adequate numbers of subjects with LBW, we oversampled subjects with birth weights ≤ 2600 g (*see* Statistical Analyses for further details of sample selection and statistical methods used to correct for the design of the study).

We compared the baseline characteristics of the adolescents who were included in the 1998 follow-up with those of the subjects who were in the sample at baseline (single live births). The mean birth weight of the subjects lost to follow-up was ≈50 g lower than that of those retained in the sample. This is most likely attributable to the higher mortality rates among the low-birth-weight infants. Birth length did not differ significantly between the 2 groups. The subjects lost to follow-up were more likely than those retained in the sample to have been urban residents (82.5% compared with 73.5%), but there were no significant differences in household assets or in maternal education, height, age, or parity. We also assessed potential biases in the subsample selected for lipid analysis. The females who were included in the CVD study had significantly lower birth weight, current height, and current weight (all $P < 0.05$) than did the females who were excluded from the study, and this result was consistent with our sampling design; however, among the males, the 2 groups did not differ significantly in these variables. When the subjects who were included in the CVD substudy were compared with those who were not included, there were no significant differences among either sex in body mass index (BMI), skinfold thickness, income, or dietary fat intake.

Data measurement protocol

For measurement of lipid profiles, participants were asked to fast overnight for 12 h, and blood samples were collected in clinics the following morning with the use of EDTA-coated tubes. After separation, samples were frozen and shipped on dry ice to the Emory Lipid Research Laboratory (Atlanta) for analysis of lipid profiles. All samples remained frozen at −80 °C until ready for analysis. Total lipid concentrations were measured by using enzymatic methods with reagents from Beckman Diagnostics on the Beckman Diagnostics CX5 chemistry analyzer (Fullerton, CA). HDL- and LDL-cholesterol concentrations were measured by using the homogenous assays Direct HDL Cholesterol and Direct LDL Cholesterol (Equal Diagnostics, Exton, PA). Total cholesterol concentrations were measured with an enzymatic kit, and triacylglycerol concentrations were measured with a glycerol blank as a 2-step reaction (Beckman Coulter Diagnostics, Fullerton, CA). The atherogenic ratios of total to HDL cholesterol and LDL to HDL cholesterol were also calculated (15). The Emory Lipid Research Laboratory participates in the Lipid Standardization Program of the Centers for Disease Control and Prevention and the National Heart, Lung, and Blood Institute to ensure accuracy and precision of measurements.

Body weight, height, waist circumference, midupper arm circumference, and triceps skinfold thickness were measured by using standard anthropometric techniques (16). BMI was calculated as weight (kg)/height^2 (m). In this sample, the child's arm fat area (CAFA), which was calculated from triceps skinfold thickness and midupper arm circumference (16), was more strongly correlated with current lipids than was current triceps skinfold thickness. Thus, arm fat area was used to control the effects of current adiposity on lipids. Prior work showed that third trimester MAFA is a positive predictor of birth weight in this population, and MAFA was therefore used as a marker of maternal energy status (17). During the 1998–1999 follow-up, the adolescents' dietary intake was measured by using two 24-h recalls on consecutive days, and the mean was used in analyses. Energy and fat intakes were calculated by using the *Food Composition Tables Recommended for Use in the Philippines*, which is published by the Food and Nutrition Research Institute of the Philippines (18). Among the males, maturational status was assessed by self-rated, 5-level pubic-hair staging, which was validated against physician assessments (CW Kuzawa and LS Adair, unpublished observations, 2002). For the females, longitudinally assessed menarcheal age estimates were used to construct a 5-level maturational status variable. When data were collected for the 1998–2000 survey, the females were completely surveyed before the males. Consequently, the males were ≈1 y older than the females. Informed consent was obtained from all participants, and human subjects clearance was obtained from the Institutional Review Boards of the Emory University Medical School and the University of North Carolina, Chapel Hill.

Statistical analyses

All analyses were performed with version 7 of the STATA Statistical Package (19). The population was sampled at random within each of 2 strata. In the 1998 survey, we randomly selected

TABLE 1
Anthropometric measures, dietary intakes of energy and fat, and lipid concentrations in adolescents who participated in the Cebu Longitudinal Health and Nutrition Survey[1]

	Males (n = 296)	Females (n = 307)
Age (y)	15.6 ± 0.2	14.8 ± 0.2[2]
Height (cm)	158.4 ± 0.4	148.9 ± 0.3[2]
Weight (kg)	46.6 ± 0.5	41.7 ± 0.4[2]
BMI (kg/m^2)	18.5 ± 0.1	18.8 ± 0.1
Waist-to-hip ratio	0.90 ± 0.00	0.77 ± 0.00[2]
Triceps skinfold thickness (mm)	8.1 ± 0.2	14.6 ± 0.2[2]
Arm fat area (cm^2)	9.3 ± 0.3	15.4 ± 0.3[2]
Birth weight (g)	3064 ± 23	3015 ± 23
Energy (kJ/d)	8060 ± 197	5618 ± 132[2]
Fat		
(g/d)	48.2 ± 2.4	37.6 ± 2.0[2]
(% of energy)	21.3 ± 0.0	22.5 ± 0.0
Lipids		
TC (mg/dL)	153.2 ± 1.9	182.5 ± 2.3[2]
LDL-C (mg/dL)	91.8 ± 1.7	104.6 ± 1.8[2]
HDL-C (mg/dL)	38.3 ± 0.6	41.3 ± 0.6[2]
Triacylglycerol (mg/dL)	73.9 ± 2.1	79.6 ± 2.2[3]
TC:HDL-C	4.16 ± 0.06	4.55 ± 0.06[2]
LDL-C:HDL-C	2.53 ± 0.06	2.63 ± 0.05

[1] $\bar{x}$ ± SE. TC, total cholesterol; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol.
[2,3] Significantly different from males: [2] $P < 0.001$, [3] $P < 0.05$.

50% (154 of 327) of the subjects with LBW (birth weight ≤ 2.6 kg) and 25% (449 of 1729) of the subjects with high birth weight for lipid measurement. We used 2.6 kg, rather than the more conventional LBW cutoff of 2.5 kg, to ensure adequate numbers of LBW subjects in our sample. To get an unbiased estimate of distributional characteristics (eg, mean LDL cholesterol or dietary energy intake of the adolescents), we down-weighted the observations in the LBW subjects, so that both birth weight strata would be represented in the estimate in proportion to their occurrence in the population. Probability sampling weights for each stratum were calculated as the inverse of the within-stratum sampling fraction, and the survey mean procedure (svymean) of STATA was used to estimate distributional characteristics.

We used regression analysis to model the relations between birth weight and MAFA as predictor variables with offspring lipid profiles as outcomes. The expansion of the proportion of subjects with LBW in our design adds information, and therefore precision, to an estimate of the relation of blood lipid concentrations to other factors, such as MAFA. However, the oversampling of LBW subjects may create confounding if the LBW variable is related to both the dependent and the independent variables. Therefore, to estimate relations of adolescent blood lipid concentrations to MAFA, we assessed the extent of bias caused by the design by using regression models with and without the variable defining the LBW sampling stratum. An additional difficulty arises because the design variable, LBW, may be in the causal pathway between blood lipid concentrations and several of the predictor variables. We carefully considered the extent to which any effect of including the LBW variable on the regression coefficient of MAFA reflected design-induced confounding, naturally occurring confounding, or overadjustment for a factor in the causal pathway. However, sensitivity analyses for all models relating MAFA to offspring blood lipids in this study showed that the design variable (LBW) had a negligible effect on the estimates of regression coefficients, suggesting that overrepresentation of LBW subjects in our sample was not a significant confounder of MAFA-lipid relations. These findings are reported in Results.

TABLE 2
Mothers' characteristics during pregnancy, 1983–1984[1]

	Value
Age (y)	26.2 ± 0.3
Height (cm)	150.7 ± 0.2
Weight (kg)	52.1 ± 0.3
BMI (kg/m^2)	22.9 ± 0.1
Arm fat area (cm^2)	14.7 ± 0.2
Gestational age (wk)	30.2 ± 0.2

[1] $\bar{x}$ ± SE. n = 603.

Previous studies report sex differences in the association between prenatal factors and later lipid profiles (eg, reference 2). Because initial pooled models (males and females) indicated significant sex × MAFA interactions for 4 of the 6 lipid outcomes analyzed, all subsequent models were stratified by sex. We present a series of regression models designed to assess the relative and independent effects of LBW and MAFA on offspring lipids while investigating any biases in our estimates due to sampling design. Thus, we report results of a base model including only control variables (model 1), to which was added LBW (model 2) or MAFA (model 3), and finally, both LBW and MAFA simultaneously (model 4).

RESULTS

Descriptive statistics for the study participants are shown in **Table 1**. According to growth charts for US children and adolescents from the Centers for Disease Control and Prevention (20), 14 of the 603 adolescents in our sample (2%) were classified as overweight (7 males and 7 females), but only 2 of these adolescents (both male) were classified as obese. American adolescents of comparable age obtained 50% more of their energy from fat than did the participants in the Cebu study (33% compared with 22%) (21). Despite the favorable levels of obesity and the favorable fat intake in the Cebu sample, lipid profiles suggested a relatively high risk of CVD. The mean lipid concentrations in the Cebu sample were roughly comparable to those of US adolescents of the same age (22). For both sexes, mean total cholesterol and LDL-cholesterol concentrations were higher and mean HDL-cholesterol concentrations were lower than the values reported for adolescents in Taiwan (23), Japan (24), and Singapore (25). As expected, most lipid measures were higher in the females than in the males. The characteristics of the mothers during pregnancy are shown in **Table 2**.

Because prior studies reported significant sex differences in the association between prenatal nutrition variables and later lipid concentrations (2), we first tested for sex × MAFA interactions in pooled models (n = 603) controlling for male sex (male = 1), CAFA, energy intake, percentage of energy from fat, maturity, and household income (at birth and in 1998). There were significant male × MAFA interactions for total cholesterol ($P < 0.05$), LDL cholesterol ($P < 0.01$), and the ratio of total to HDL cholesterol ($P < 0.01$) and LDL to HDL cholesterol ($P < 0.01$). Therefore, all models reported are stratified by sex.

TABLE 3
Regression models relating low birth weight (LBW) and maternal arm fat area (MAFA) in the third trimester of pregnancy to lipid concentrations in male adolescents from Cebu, Philippines[1]

	Model 1[2]		Model 2[3]		Model 3[4]		Model 4[5]	
	β	R^2	β	R^2	β	R^2	β	R^2
TC (mg/dL)								
LBW	—		6.6 (−2.3, 15.5)		—		6.5 (−2.3, 15.5)	
MAFA (log cm^2)	—		—		−10.0[6] (−21.5, 1.5)		−10.0[6] (−21.4, 1.5)	
		0.052		0.069		0.062		0.068
LDL-C (mg/dL)								
LBW	—		10.0[7] (2.4, 17.6)		—		9.9[7] (2.4, 17.4)	
MAFA (log cm^2)	—		—		−13.3[7] (−23.1, −3.4)		−13.1[7] (−22.9, −3.4)	
		0.086		0.107		0.108		0.128
HDL-C (log mg/dL)								
LBW	—		0.01 (−0.06, 0.07)		—		0.01 (−0.06, 0.07)	
MAFA (log cm^2)	—		—		0.12[7] (0.03, 0.20)		0.12[7] (0.03, 0.20)	
		0.011		0.011		0.034		0.034
Triacylglycerol (log mg/dL)								
LBW	—		−0.001 (−0.13, 0.13)		—		−0.002 (−0.14, 0.13)	
MAFA (log cm^2)	—		—		−0.07 (−0.25, 0.10)		−0.07 (−0.25, 0.10)	
		0.054		0.054		0.057		0.057
TC:HDL-C								
LBW	—		0.11 (−0.17, 0.40)		—		0.11 (−0.17, 0.39)	
MAFA (log cm^2)	—		—		−0.71[8] (−1.08, −0.35)		−0.71[8] (−1.08, −0.35)	
		0.057		0.059		0.104		0.106
LDL-C:HDL-C								
LBW	—		0.22[6] (−0.04, 0.49)		—		0.22[6] (−0.04, 0.48)	
MAFA (log cm^2)	—		—		−0.65[8] (−0.98, −0.31)		−0.65[8] (−0.98, −0.31)	
		0.068		0.077		0.113		0.121

[1] 95% CI in parentheses. n = 296. LBW was defined as a birth weight ≤ 2.6 kg. TC, total cholesterol; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol.
[2] Base model including the adolescents' arm fat area, energy intake, percentage of energy from fat, maturity scale, and household income (both in 1998 and at birth).
[3] Base model + LBW.
[4] Base model + MAFA.
[5] Base model + MAFA + LBW.
[6] $P < 0.10$.
[7] $P < 0.01$.
[8] $P < 0.001$.

In **Tables 3** and **4**, results are shown for multivariate regression models in the males and females, respectively, that relate each lipid outcome to a set of control variables (model 1), to which was added LBW (model 2) or MAFA (model 3) or both LBW and MAFA simultaneously (model 4). In multivariate models, LBW was associated with a significant elevation in LDL cholesterol in the males, yielding a borderline significant elevation in the ratio of LDL to HDL cholesterol (model 2). Results were similar when birth weight was modeled as a continuous variable, with birth weight (in kg) modestly related only to LDL cholesterol in the males (β ± SE = 7.2 ± 3.7 mg/dL; $P = 0.051$). In the females, neither LBW nor birth weight modeled as a continuous variable were significantly associated with any lipid outcome. Although all participants were from term births, controlling for gestational age at birth had no measurable effect on the β coefficients for either LBW or birth weight as a continuous variable in any lipid model.

There were several significant relations between MAFA and offspring lipids in both sexes (model 3). In the males, MAFA was significantly inversely related to LDL and total cholesterol and positively related to HDL cholesterol. As a result of these relations, MAFA was strongly inversely related to both atherogenic ratios (total cholesterol:HDL cholesterol and LDL cholesterol:HDL cholesterol) in the males and roughly doubled the explained variance in both ratios. In the females, there were significant positive relations between MAFA and both LDL and total cholesterol (model 3). Including a variable defining the gestational age at which the MAFA measurement was made had no effect on any of the regression coefficients relating MAFA to offspring lipids in either sex.

For all the lipid outcomes investigated, inclusion of the LBW variable had a negligible effect on the β coefficient or significance level for the relation with MAFA (model 4). Because the MAFA-lipid relations in this sample were independent of LBW status, overrepresentation of LBW subjects in our sample was not a confounder of the MAFA-lipid relations documented here. There were no significant MAFA × LBW interactions in any of the models (data not shown).

In this sample, offspring adiposity correlated with lipids and both MAFA ($r = \approx 0.26$ in both sexes) and birth weight ($r = 0.09$ and 0.15 in the males and the females, respectively), which could confound associations between MAFA or LBW and offspring lipids. We investigated this potential source of confounding by considering the change in the β coefficients for MAFA and LBW after removal of CAFA from multivariate models (models 2 and 3). In the males, the coefficients relating log MAFA to LDL (−7.9 mg/dL; 95% CI: −17.2, 1.5; $P < 0.09$) and total (−4.5 mg/dL; 95% CI: −15.5, 6.4; $P > 0.4$) cholesterol were reduced to nonsignificance after removal of CAFA. Coefficients relating MAFA

TABLE 4
Regression models relating low birth weight (LBW) and maternal arm fat area (MAFA) in the third trimester of pregnancy to lipid concentrations in female adolescents from Cebu, Philippines[1]

	Model 1[2]		Model 2[3]		Model 3[4]		Model 4[5]	
	β	R^2	β	R^2	β	R^2	β	R^2
TC (mg/dL)								
LBW	—		1.9 (−8.4, 12.1)		—		3.0 (−7.2, 13.3)	
MAFA (log cm^2)	—		—		15.0[6] (0.7, 29.3)		15.5[6] (1.03, 29.9)	
		0.039		0.040		0.053		0.054
LDL-C (mg/dL)								
LBW	—		−0.06 (−7.7, 7.5)		—		0.86 (−6.7, 8.5)	
MAFA (log cm^2)	—		—		11.7[6] (1.2, 22.3)		11.9[6] (1.2, 22.5)	
		0.055		0.055		0.070		0.070
HDL-C (log mg/dL)								
LBW	—		−0.02 (−0.08, 0.04)		—		−0.01 (−0.07, 0.05)	
MAFA (log cm^2)	—		—		0.06 (−0.03, 0.14)		0.05 (−0.03, 0.14)	
		0.061		0.062		0.066		0.066
Triacylglycerol (log mg/dL)								
LBW	—		0.06 (−0.05, 0.18)		—		0.06 (−0.05, 0.18)	
MAFA (log cm^2)	—		—		−0.02 (−0.18, 0.15)		−0.01 (−0.17, 0.16)	
		0.051		0.055		0.052		0.055
TC:HDL-C								
LBW	—		0.11 (−0.15, 0.37)		—		0.12 (−0.14, 0.38)	
MAFA (log cm^2)	—		—		0.14 (−0.23, 0.50)		0.15 (−0.21, 0.52)	
		0.094		0.096		0.096		0.098
LDL-C:HDL-C								
LBW	—		0.02 (−0.18, 0.22)		—		0.03 (−0.17, 0.23)	
MAFA (log cm^2)	—		—		0.15 (−0.13, 0.43)		0.16 (−0.13, 0.44)	
		0.110		0.110		0.113		0.113

[1] 95% CI in parentheses. n = 307. LBW was defined as a birth weight ≤ 2.6 kg. TC, total cholesterol; LDL-C, LDL cholesterol; HDL-C, HDL cholesterol.
[2] Base model including the adolescents' arm fat area, energy intake, percentage of energy from fat, maturity scale, and household income (both in 1998 and at birth).
[3] Base model + LBW.
[4] Base model + MAFA.
[5] Base model + MAFA + LBW.
[6] $P < 0.05$.

to HDL cholesterol (0.11 log mg/dL; 95% CI: 0.02, 0.17) and to the ratios of total to HDL cholesterol (−0.49; 95% CI: −0.84, 0.14) and LDL to HDL cholesterol (−0.47; 95% CI: −0.79, −0.15) were attenuated but remained significant (all $P < 0.02$). There were similar effects of removing CAFA on the coefficients relating LBW to LDL cholesterol (9.5 mg/dL; 95% CI: 1.8, 17.1; $P < 0.02$) and the ratio of LDL to HDL cholesterol (0.20; 95% CI: −0.06, 0.47; $P < 0.121$). In the females, the slope and precision of β coefficients relating MAFA to LDL (13.7 mg/dL; 95% CI: 3.0, 24.3; $P < 0.01$) and total (16.9 mg/dL; 95% CI: 2.7, 31.1; $P < 0.02$) cholesterol were strengthened after removal of CAFA. Thus, the inverse relations between MAFA and CVD risk in the males were strengthened after the adolescents' own adiposity was controlled for, and some portion of the positive relations between MAFA and CVD risk in the females was probably confounded by positive associations between MAFA and the adolescents' own adiposity.

DISCUSSION

In this sample of adolescent Filipinos, maternal energy status during pregnancy had opposite relations with CVD risk in the male and female offspring. The relations in the males were consistent with the expectations of the fetal origins hypothesis: poor maternal energy status, as reflected in third trimester MAFA, predicts elevated CVD risk in offspring, as indicated by LDL-, HDL-, and total cholesterol concentrations and the ratios of total to HDL cholesterol and LDL to HDL cholesterol. The relations with MAFA in the males were strong and independent of the adolescents' own energy and fat intakes, adiposity, maturity, and household income (both at the age of the cholesterol measurement and at birth). Our results in the males provide some of the strongest evidence yet published that poor maternal energy status during pregnancy has persistent effects on offspring lipids, thus elevating CVD risk.

In contrast with the males, MAFA was positively related to LDL cholesterol and total cholesterol in the female offspring. The finding of a positive relation between maternal nutritional status during pregnancy and offspring CVD risk is infrequently reported (10). It is unclear whether the relations in the females in our sample reflect a positive effect of MAFA on CVD risk in offspring (through "programming") or merely the effect on blood cholesterol of the adolescents' own adiposity, which is positively correlated with MAFA during pregnancy. The latter interpretation is supported by the finding that the slope and significance of the relations between MAFA and both total and LDL cholesterol were strengthened after removal of CAFA from the models in females. Thus, we are unable to rule out confounding of the positive associations of MAFA with LDL and total cholesterol in the females by residual variance in the adolescents' adiposity that

was not indexed by their arm fat area. In the males, removal of CAFA from the models had the opposite effect on the regression coefficients with MAFA, reducing both their slope and precision. A tentative interpretation of these findings is that there is a pathway relating low MAFA during pregnancy to elevated CVD risk in male but not female offspring and that this pathway is strongest once positive correlations between maternal and child adiposity are held constant.

Although the slope and significance of the β coefficients were attenuated in the models that did not include CAFA, most MAFA-lipid relations documented in the males remained significant after removal of this measure of postnatal body size. This may indicate that lipid programming is less dependent on postnatal growth than has been suggested for other CVD risk factors (26). For instance, the finding that inverse relations between birth weight and blood pressure are often significant only when postnatal body size is controlled for has been interpreted as evidence for a role of postnatal growth in these relations (26, 27).

Few prior studies have explored the association between maternal pregnancy nutrition and offspring lipids, and contradictory findings limit our ability to generalize. Our results in the males are most similar to findings among Chinese adults studied by Mi et al (3), who found that maternal BMI measured at 15 wk of gestation was inversely associated with total and LDL cholesterol and triacylglycerol in offspring. In this sample, BMI measured close to term (38 wk of gestation) was not significantly related to any lipid in offspring. The positive association between MAFA and total cholesterol in the females in our sample is similar to findings from Jamaica in which first-trimester maternal BMI was positively correlated with total cholesterol in offspring during childhood (10). Cowin and Emmett's (11) finding of no association between maternal BMI before pregnancy and offspring lipids may be less comparable because of the young age of the sample (31–43 mo).

Differences between studies in the age at which maternal nutritional status measurements were made may have contributed to some of these inconsistencies. Maternal nutritional status may have different implications for fetal growth or nutritional sufficiency depending on when it is measured because both preconception nutritional status and nutrition during pregnancy may have independent as well as interactive effects (28). There is presently no consensus on the timing of critical periods in lipid metabolism programming. The studies of Mi et al (3) and the Dutch famine study (13) suggest a role for early pregnancy nutritional status or diet in offspring lipid programming, whereas animal model research, though sparse, suggests an effect of nutrition during late gestation and the early postnatal period (7). In the present analysis, most of the women were measured between 27 and 34 wk of gestation, thus representing early third-trimester nutritional status. However, accounting for gestational age at the time of measurement did not significantly alter the relations documented here. Our third-trimester measure of MAFA is probably reflective of cumulative energy sufficiency throughout pregnancy and is therefore incapable of clarifying the timing of critical periods in lipid metabolism programming. Prospective studies with detailed repeat measures of maternal nutritional status and diet during pregnancy will be necessary to establish more definitively whether human lipid metabolism is sensitive to maternal nutrition, and if so, during which stage or stages of gestation.

Among the males, adding MAFA to the base model improved the model $R^2 \approx 25\%$ for LDL cholesterol (from 8.6% to 10.8% of variance explained) and 82% for the ratio of total to HDL cholesterol (from 5.7% to 10.4%). Thus, although much of the variance in lipid concentrations remained unexplained by our models, MAFA contributed substantially to the variance that was explained. The magnitude of the relations in the males is in line with that of prior research. In the sample studied by Mi et al (3), the offspring of mothers in the lowest quartile of the 15-wk BMI distribution had mean LDL- and total cholesterol concentrations that were 15 and 17 mg/dL higher, respectively, than those of the offspring of mothers in the highest quartile. Although we used a different marker of maternal nutritional status, there were similar lipid differences across the MAFA distribution in the males. In our sample, a 1-SD change in MAFA was associated with a 4.6-mg/dL change in LDL-cholesterol concentration and a 0.25-unit change in the ratio of total to HDL cholesterol.

Our finding of significant sex × MAFA interactions for most lipid measures is also in agreement with past research documenting sex differences in the relations between prenatal factors and postnatal lipids. Studies of fetal influences document sex differences more often for lipids than for other CVD risk factors, such as blood pressure, and associations between lipids and birth weight are more common among males than among females (2, 29–33). The few animal model studies that investigated lipid metabolism programming by maternal pregnancy nutrition showed similar evidence for sex differences, with effects most (7), or only (8), evident in males. In the sample in the present study, we also found that relations between maternal adiposity during pregnancy and blood pressure in offspring during adolescence were more consistent among males (27). It will be important to follow up our population as they enter adulthood to establish whether these sex differences are persistent or are transitory effects of the hormonal changes of puberty (34). However, the consistency of sex differences in the relation between prenatal factors and lipid profiles in humans and animal models provides a strong incentive to investigate mechanisms of sex differences in lipid programming.

Relations between MAFA and offspring lipids were independent of birth weight, suggesting that maternal energy status during pregnancy may influence lipid profiles in offspring in the absence of measurable changes in birth outcomes. This finding is in agreement with the findings of past research on lipid metabolism in other populations (3, 13). Among the survivors of the Dutch famine (13), the ratio of LDL to HDL cholesterol was elevated in offspring of mothers who experienced the famine during the first trimester of pregnancy, despite no significant decline in birth weight. In the Cebu sample, we previously documented inverse relations between maternal triceps skinfold thickness during pregnancy and blood pressure in offspring that were independent of birth weight (27). The present findings underscore the limitations of birth weight as a marker of the nutritional or related prenatal exposures that influence long-term CVD risk.

CVD is rapidly becoming a key public health challenge in many developing nations, particularly in the Asia-Pacific region (35). Our findings illustrate significant relations between maternal energy status and CVD risk in offspring in an adolescent population with low obesity levels and a low intake of dietary fat. The strongest postnatal predictors of individual lipid outcomes in our sample were current body fat measures, which in turn are responsive to diet and activity patterns. On the basis of trends observed in the full sample of mothers in the Cebu Longitudinal Health and Nutrition Survey, the percentage of energy consumed from fat has increased from

17% to ≈22% in the past 15 y, and rates of overweight are also increasing. Thus, we expect a trend toward more atherogenic risk profiles in the population. Our findings suggest that males in particular will experience this transition to a more atherogenic lifestyle differentially, depending on the energy status of their mothers during pregnancy. Optimizing the cardiovascular health of future generations of Filipinos may require efforts to attenuate the emergence of overweight among youth and adults while ensuring that mothers are well nourished during pregnancy.

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