Cardiovascular Disease Risk Factors Are Related to Adult Adiposity but Not Birth Weight in Young Guatemalan Adults[1,2]

Aryeh D. Stein,*[3] Andrea Conlisk,*† Benjamin Torun,** Dirk G. Schroeder,* Ruben Grajeda** and Reynaldo Martorell*

*Department of International Health, Rollins School of Public Health, Emory University, Atlanta GA 30322; †Nutrition and Health Sciences Program, Graduate School of Arts and Sciences, Emory University, Atlanta GA 30322; and **Instituto de Nutrición de Centro América y Panamá (INCAP), Guatemala City, Guatemala

ABSTRACT Fetal undernutrition has been hypothesized to program inappropriate metabolic responses to nutritional abundance in later life. Most studies have been conducted in industrialized countries. We studied the relationship between birth weight and risk factors for cardiovascular disease (CVD) among 187 men and 198 women age 20–29 y (mean age 24 y) who had participated in a longitudinal study conducted in Guatemala between 1969 and 1977. In women, birth weight was positively associated with adult body mass index (BMI; $P < 0.01$), systolic ($P < 0.001$) and diastolic blood pressure ($P < 0.05$), but not with glucose or any lipid measure. In men, birth weight was not associated with adult BMI, blood pressure or glucose, and was weakly and inversely related to total cholesterol and LDL cholesterol (test for trend: $P = 0.06$ and $P = 0.09$, respectively). Adult BMI was associated with increased prevalence of CVD risk factors in both men and women. Our data offer no support for the fetal programming of cardiovascular disease risk hypothesis in young adult women, and weak support in young adult men. Overweight in adults is a strong determinant of variance in CVD risk factor prevalence. J. Nutr. 132: 2208–2214, 2002.

KEY WORDS: • *birth weight* • *blood pressure* • *body mass index* • *glucose* • *serum lipids*

Fetal undernutrition may program inappropriate metabolic responses to nutritional abundance in later life (1). The literature relating birth weight (a proxy indicator for fetal nutritional status) to metabolic precursors of cardiovascular disease (CVD),[4] especially blood pressure level, disruption of the glucose-insulin regulatory axis and the multiple metabolic syndrome, has become voluminous (2–7). The excess risk associated with low birth weight is most clearly observable in individuals who become overweight later in life, whereas those who remain lean often show no relation of birth size to risk (8,9). There is also an increasing body of animal and in vitro research supportive of the programming hypothesis (10–13).

Most of the relevant research has been conducted in industrialized countries in which chronic undernutrition has not been a public health problem for several generations. Despite substantial progress in most regions, populations in developing countries continue to be exposed to considerable prenatal undernutrition and risk of infection, and many adults are poor, physically active, and lean (14). CVD rates were historically low in these populations, but are increasing rapidly now (15). There is extensive evidence of epidemic emergence of type-2 diabetes mellitus among populations and migrants who are moving from traditional indigenous lifestyles to modern, "Westernized" ways of life (16–20). Incidence of low birth weight is high (21), which would make these populations more susceptible to CVD when individuals of low birth weight are exposed to improved economic conditions later in life.

A limited number of studies in developing countries have tracked individuals through adulthood. Among individuals born in a hospital in Mysore, India and still living in the same location, the prevalence of CVD (at mean age 45 y) was inversely associated with birth weight. Specifically, the prevalence of CVD declined from 17% of those with birth weights ≤ 2.5 kg to <3% among those born at >2.9 kg (22). Prevalence of type-2 diabetes mellitus (23) and blood pressure (24) were not related to birth weight. In China, birth length and ponderal index were inversely related to systolic blood pressure at age 30 y (25), and low birth weight was associated with elevated plasma glucose, insulin, triglycerides, and blood pressure in 627 men and women with a mean age of 45 y (26). Studies among children and adolescents in developing countries that examined the relationship of birth weight with blood pressure (27–30), and with type-2 diabetes mellitus and/or glucose intolerance (31,32), showed results generally consis-

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[3] To whom correspondence should be addressed.
E-mail: astein2@sph.emory.edu.

[4] Abbreviations used: BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; HDL-C, HDL cholesterol; INCAP, Institute of Nutrition of Central America and Panama; LDL-C, LDL cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

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tent with reports from developed countries, i.e., an inverse association between birth weight and level of the risk factor.

We investigated the relationship between birth weight and risk factors for CVD in a cohort of Guatemalan men and women recruited prenatally and last studied at 19–29 y of age. In the present analysis, we focus on the association between birth weight and adult outcomes because this association has been the focus of much previous research. We hypothesized that birth weight would be inversely related to CVD risk factor levels, and that low birth weight and high adult body mass index (BMI) would act synergistically to increase risk.

SUBJECTS AND METHODS

Population and research design. Between 1969 and 1977, a longitudinal study of growth and development was conducted by the Institute of Nutrition of Central American and Panama (INCAP) in four villages of mixed Spanish-Indian descent, located 40–110 km east of Guatemala City. Pregnant women and their offspring were provided with improved medical care and a dietary supplement containing either proteins, micronutrients and 3.80 MJ (900 kcal)/L, or only micronutrients and 1.35 MJ (330 kcal)/L. Supplement type was assigned at random, with village as the unit of randomization. Complete details about the original study and subsequent follow-up studies are found elsewhere (33,34).

Outcome data for the present study were gathered between 1997 and 1999 (35). Briefly, names of 762 individuals with data on maternal nutrition during pregnancy, birth weight, and growth for at least part of y 1 of life, were obtained from the 1969–1977 data files. Current residence was derived from a recent census in the villages, and from relatives, friends, and neighbors who provided information to trace individuals who had migrated to nearby villages or to Guatemala City. All individuals who could be located were invited to participate. Migrants were studied in Guatemala City or when they visited the villages on holidays or for family events. The study protocol was approved by institutional review boards at INCAP and Emory University, and all participants provided written consent.

Two field workers interviewed respondents at home and measured blood pressure. Anthropometric measurements were obtained within a few days of the interview, at project headquarters in the villages, or at INCAP headquarters in Guatemala City. Capillary blood samples were obtained after an overnight fast. Socioeconomic indicators on housing and household possessions of village residents were derived from a census taken as part of another ongoing study, or from interviews in Guatemala City.

Blood pressure. Three measurements were taken at 3- to 5-min intervals with an oscillometric digital sphygmomanometer (Model UA-767; A&D Medical, Milpitas, CA). We validated the digital sphygmomanometers against mercury sphygmomanometers. Three observers measured BP simultaneously connecting in parallel a mercury sphygmomanometer (with stethoscopes connected in tandem with T connectors) and the digital sphygmomanometers. Concordance correlation coefficients of the digital sphygmomanometers with the 3 observers were >0.92 for both systolic blood pressure (SBP) and diastolic blood pressure (DBP). When 3 digital sphygmomanometers were compared with each other, concordance correlation coefficients were >0.99 for both SBP and DBP (36). Calibration was checked periodically. The first measurement was taken after sitting comfortably on a chair for at least 5 min, with the left arm at heart level resting on a table. The mean of the last two measurements was used for analysis. In nine cases in which the 2nd and 3rd measures did not coincide within 10 mm Hg, a fourth measurement was taken and the mean of the two closest values was used for analysis.

Blood chemistry. Capillary blood was drawn by finger prick after an overnight fast. Concentrations of total cholesterol (TC), HDL cholesterol (HDL-C), triglycerides (TG) and glucose were determined by solid-phase enzymatic reactions (Cholestech LDX, Hayward CA). The lipid values were calibrated against venous blood assayed at Emory University's Lipid Research Laboratory (37). LDL cholesterol (LDL-C) concentration was calculated with Friedewald's equation (38). Standard criteria were used to classify the results as normal, borderline-high, and high (39).

Anthropometry and body composition. Height and weight were measured in triplicate with weighing scales that were calibrated periodically and steel measuring tapes (40,41). The mean of the three replicates was used for analysis. BMI was computed as weight (kg) divided by height squared (m^2).

Statistical analysis. All analyses were conducted separately for men and women. We computed descriptive statistics. Proportions were compared using standard approaches for categorical data, and means were compared by t test; distributions were examined for normality and transformed if necessary (42). We divided the birth weight distributions into sex-specific tertiles. We then examined the association between birth weight and the individual CVD risk factors. Because this population is young, few individuals meet established criteria for elevated risk. However, the effects of blood pressure, serum lipids and adiposity on cardiovascular disease risk are continuous and graded (43–45), and even variation within the "normal" range is of interest. Furthermore, CVD risk factors both increase in level and track over time, and hence individuals at the upper end of the distribution, even if their levels are within the normal range at the time of assessment, are at increased risk for future attainment of the clinical threshold. We also compared the distribution of the CVD risk factors across tertiles of BMI, again using sex-specific categories. A 1° of freedom test for linear trend was used to assess the significance of any associations observed in the data.

We investigated clustering of risk factors by examining the joint distribution of five risk factors (BMI, SBP, glucose, HDL-C, and TG), and then the subset of four risk factors (excluding BMI), because of the presumed role of overweight in causing adverse CVD risk. We identified individuals with values in the upper sex-specific tertile of the distribution (men: BMI > 22.8 kg/m^2, SBP > 123 mm Hg, glucose > 5 mmol/L, TG > 1.4 mmol/L, HDL-C < 0.9 mmol/L; women: BMI > 24.2 kg/m^2, SBP > 107 mm Hg, glucose > 4.9 mmol/L, TG > 1.4 mmol/L, HDL-C < 0.9 mmol/L). Because one third of individuals were in the upper tertile for each risk factor, we computed the expected joint prevalence of the risk factors based on standard binomial probability as 3^{-n}, where n is the number of risk factors in the set, and an observed to expected ratio was computed and tested using a χ^2 test. Finally, we examined whether the degree of clustering of risk factors was associated with birth weight or with current BMI. All analyses were adjusted for gestational age at birth, treatment type received, age at examination and rural/urban residence using SAS (SAS Institute, Cary, NC) procedures LOGISTIC and GENMOD (46). As suggested by Lucas et al. (47), we tested a model with both birth weight and adult current BMI, and then tested for a birth weight by current BMI interaction. Significant difference was declared at $P < 0.05$, with no adjustment for multiple comparisons, except for tests of interactions, which were declared significant at $P < 0.20$.

RESULTS

We successfully traced and interviewed 473 persons (237 men and 236 women, 19.4–29.5 y old), representing 78% of those known to be living in a study village or in Guatemala City. Three other persons had died of causes unrelated to CVD, 151 had moved to distant or unknown places, 36 could not be contacted despite multiple attempts, 4 were excluded because of serious handicaps and chronic illness unrelated to diabetes or CVD, 25 women were excluded because they were pregnant or nursing babies <6 mo old, and 70 persons refused to participate. Maternal height and nutritional intake, weight, length and socioeconomic characteristics at birth, growth velocity, dietary supplement intake, burden of illness in childhood, and anthropometric and socioeconomic characteristics during adolescence were similar for the 473 participants and the 288 persons who were not studied (35).

A total of 385 individuals (187 men and 198 women) had complete data for this analysis. Reasons for exclusion were as follows: *1*) no glucose or lipids obtained (26 men and 24 women); and *2*) glucose obtained after <4 h of fasting, (7

TABLE 1

Selected characteristics of 187 men and 198 women born during the Institute of Nutrition of Central America and Panama (INCAP) supplementation study in one of 4 study villages in Guatemala, 1969–1976, and examined in 1997–1999[1]

	Men	Women	Gender difference[2] *P*-values
Birth weight (BW), *kg*	3.14 ± 0.5	3.05 ± 0.4	0.07
BW ≤2.50 kg, %	8.0	10.1	0.48
Age, *y*	24.5 ± 2.4	24.3 ± 2.2	0.44
Body mass index (BMI), *kg/m²*	22.1 ± 2.4	23.6 ± 4.2	<0.001
BMI ≥ 30 kg/m², %	1.1	9.6	<0.001
Systolic blood pressure (SBP), *mmHg*	120 ± 10	103 ± 11	<0.001
SBP > 140 mmHg, %	4.3	0.0	0.003
Diastolic blood pressure (DBP), *mmHg*	73 ± 10	65 ± 8	<0.001
DBP > 90 mmHg, %	3.2	0.0	0.01
Fasting glucose (FG), *mmol/L*	4.8 ± 0.6	4.6 ± 0.5	0.002
FG ≥ 6.05 mmol/L, %	3.0	2.0	0.46
Total cholesterol (TC), *mmol/L*	4.1 ± 0.7	4.4 ± 0.8	<0.001
TC ≥ 5.2 mmol/L, %	8.0	16.2	0.01
LDL, *mmol/L*	2.6 ± 0.7	2.7 ± 0.7	0.009
LDL ≥ 3.4 mmol/L, %	10.7	15.7	0.15
HDL, *mmol/L*	1.0 ± 0.2	1.1 ± 0.3	<0.001
HDL ≤ 1.0 mmol/L, %	75.9	54.6	<0.001
Triglycerides (TG), *mmol/L*	1.3 ± 0.7	1.3 ± 0.8	0.88
TG > 2.2 mmol/L, %	11.2	12.6	0.67

[1] Values are means ± SD or %.
[2] *t*-Test for continuous variables; χ^2 test for categorical variables.

men, 7 women) or lipids obtained after <8 h of fasting (3 men, 3 women). Several individuals met >1 exclusion criteria. Selected characteristics of those with complete data are provided in Table 1. Low birth weight (<2500 g) was present in 8% of men and 10% of women. In general, men were lean (mean BMI 22.1 kg/m²) and had few of the CVD risk factors examined. The exception was HDL-C, with 75.9% of men having values <1.0 mmol/L. Relative to men, women had higher BMI (mean 23.6 kg/m²; $P < 0.001$), lower levels of SBP, DBP, and glucose, and a worse lipid profile. TG of men and women did not differ.

In women, birth weight was positively associated with adult BMI ($P < 0.01$), with SBP ($P < 0.001$) and with DBP ($P < 0.05$) (Table 2). There was no association between birth

TABLE 2

Distribution of selected cardiovascular disease (CVD) risk factors across tertiles of birth weight, by sex, among men and women born during the Institute of Nutrition of Central America and Panama (INCAP) supplementation study in one of 4 study villages in Guatemala, 1969–1976, and examined in 1997–1999[1]

	Men (*n* = 187) Birth weight tertile (kg)				Women (*n* = 198) Birth weight tertile (kg)			
	<2.88 *n* = 66	2.88–3.25 *n* = 64	>3.25 *n* = 57	Trend[2] *P*-values	<2.88 *n* = 74	2.88–3.25 *n* = 71	>3.25 *n* = 53	Trend[2] *P*-values
Body mass index, *kg/m²*	22.0 ± 2.1	22.5 ± 2.9	21.7 ± 1.9	0.81	22.9 ± 4.3	23.3 ± 3.5	25.0 ± 4.7	0.005
Systolic blood pressure, *mm Hg*	120 ± 10	121 ± 11	120 ± 11	0.81	101 ± 10	102 ± 10	108 ± 11	0.0004
Diastolic blood pressure, *mm Hg*	72 ± 8	74 ± 8	73 ± 7	0.53	64 ± 7	65 ± 8	67 ± 7	0.06
Glucose, *mmol/L*	4.8 ± 0.5	4.9 ± 0.6	4.7 ± 0.6	0.53	4.6 ± 0.5	4.6 ± 0.4	4.7 ± 0.5	0.43
Total cholesterol, *mmol/L*	4.2 ± 0.7	4.2 ± 0.8	0.4 ± 0.7	0.06	4.3 ± 0.7	4.5 ± 0.9	4.5 ± 0.7	0.53
LDL cholesterol, *mmol/L*	2.6 ± 0.6	2.6 ± 0.8	2.5 ± 0.6	0.09	2.6 ± 0.6	2.8 ± 0.7	2.8 ± 0.7	0.33
HDL cholesterol, *mmol/L*	1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.2	0.51	1.1 ± 0.3	1.1 ± 0.2	1.1 ± 0.3	0.67
Triglycerides, *mmol/L*	1.3 ± 0.7	1.4 ± 0.8	1.1 ± 0.6	0.28	1.4 ± 0.9	0.1 ± 0.7	1.3 ± 0.7	0.91

[1] Values are means ± SD.
[2] Adjusted for gestational age, supplement type offered in the village of birth, rural/urban residence and age.

TABLE 3

Distribution of selected cardiovascular disease (CVD) risk factors across tertiles of adult body mass index (BMI), by sex, among men and women born during the Institute of Nutrition of Central America and Panama (INCAP) supplementation study in one of 4 study villages in Guatemala, 1969–1976, and examined in 1997–1999[1]

	Men (n = 187) BMI tertile				Women (n = 198) BMI tertile			
	<20.9 n = 62	20.9–22.8 n = 62	>22.8 n = 63	Trend[2] P-values	<21.4 n = 64	21.4–24.2 n = 67	>24.2 n = 67	Trend[2] P-values
Systolic blood pressure, *mm Hg*	117 ± 10	122 ± 11	122 ± 10	0.006	100 ± 9	99 ± 7	110 ± 10	<0.001
Diastolic blood pressure, *mm Hg*	71 ± 8	74 ± 8	73 ± 7	0.20	64 ± 7	62 ± 8	68 ± 7	0.01
Fasting glucose, *mmol/L*	4.7 ± 0.5	4.7 ± 0.6	4.9 ± 0.6	0.16	4.5 ± 0.5	4.6 ± 0.5	4.8 ± 0.5	<0.001
Total cholesterol, *mmol/L*	4.0 ± 0.8	4.2 ± 0.8	4.2 ± 0.6	0.34	4.2 ± 0.7	4.4 ± 0.6	4.7 ± 0.9	<0.001
LDL, *mmol/L*	2.5 ± 0.7	2.6 ± 0.7	2.5 ± 0.7	0.84	2.6 ± 0.7	2.7 ± 0.5	2.9 ± 0.8	0.04
HDL, *mmol/L*	1.0 ± 0.2	1.0 ± 0.2	0.9 ± 0.2	0.03	1.1 ± 0.3	1.1 ± 0.3	0.2 ± 0.2	0.002
Triglycerides, *mmol/L*	1.1 ± 0.5	1.2 ± 0.6	1.6 ± 0.9	<0.001	0.9 ± 0.5	1.2 ± 0.6	1.8 ± 0.9	<0.001

[1] Values are means ± SD.
[2] Adjusted for gestational age, supplement type offered in the village of birth, rural/urban residence and age.

weight tertile and glucose or any of the lipid measures in women. In men, there was no association between birth weight and adult BMI, TG, blood pressure, or glucose, but TC and LDL-C tended to be inversely associated with birth weight ($P = 0.06$ and $P = 0.09$, respectively), with the effect concentrated among men in the highest birth weight tertile. In women, increasing adult BMI was consistently associated with a worsening of the CVD risk factor profile (Table 3; $P < 0.05$ for all risk factors). For SBP and DBP, the effect was concentrated among women in the highest tertile of BMI. In men, the association was found only for HDL-C and TG.

Both men and women were more than four times as likely to have levels of the set of four CVD risk factors in the upper tertile than would be expected by chance alone (Table 4). When high BMI was also included in the analyses, the set of five risk factors was 8.2 times (men) and 10.3 times (women) as likely to be in the upper tertile than would be expected by chance. In women, there was a positive association between both birth weight (test for trend $P = 0.01$) and adult BMI tertile (test for trend $P < 0.001$) and the number of CVD risk factors in the upper tertile (Table 5). In men, there was a weak inverse association between birth weight and number of risk factors in the upper tertile (adjusted test for trend $P = 0.04$), and a strong positive effect of tertile of adult BMI (test for trend $P < 0.001$) on number of other CVD risk factors in the upper tertile. When birth weight and BMI were considered as continuous variables (with or without a quadratic term for birth weight to account for potential nonlinear effects of birth weight), there was no evidence of an interaction between birth weight and adult BMI on the number of CVD risk factors in the upper tertile in men or in women (tests for interaction; $P > 0.30$ and $P > 0.75$, respectively; Fig. 1).

DISCUSSION

Fetal programming, as currently conceived, is a phenotypic response to scarcities during uterine life. In rapidly developing societies or through migration, individuals "programmed" for an environment of food scarcity may instead be exposed to abundance, resulting in obesity, insulin resistance and type-2

TABLE 4

Clustering of cardiovascular disease (CVD) risk factors, based on tertiles of their respective distributions, among men and women born during the Institute of Nutrition of Central America and Panama (INCAP) supplementation study in one of 4 study villages in Guatemala, 1969–1976, and examined in 1997–1999[1]

	Men			Women		
	Observed n (%)	Expected[2] n	O/E Ratio	Observed n (%)	Expected[2] n	O/E Ratio
All 5 risk factors (BMI, SBP, FG, TG, HDL)	6 (3.2%)	0.73	8.2*	8 (4.0%)	0.77	10.3*
All 4 of SBP, FG, TG, HDL	9 (4.8%)	2.2	4.1*	10 (5.1%)	2.4	4.3*
Any 3 of SBP, FG, TG, HDL	16 (8.6%)	6.7	2.4*	26 (13.1%)	7.1	3.7*
Any 2 of SBP, FG, TG, HDL	48 (25.7%)	20.4	2.4*	41 (20.7%)	21.6	1.9*

* $P < 0.001$.
[1] Threshold values used to define upper tertile: Men: body mass index (BMI) > 22.8 kg/m^2; systolic blood pressure (SBP) > 123 mm Hg; fasting glucose (FG) > 91.0 mg/dL; triglycerides (TG) > 1.35 mmol/L; HDL cholesterol < 0.87 mmol/L; Women: body mass index > 24.2 kg/m^2; systolic blood pressure > 107 mm Hg; glucose > 4.80 mmol/L; triglycerides > 1.42 mmol/L; HDL cholesterol < 0.92 mmol/L.
[2] Expected values calculated using binomial probability as 3^{-n}, where n = number of components in the set.

TABLE 5

Clustering of five risk factors for cardiovascular disease (CVD), based on tertiles of their respective distributions, within tertiles of birth weight, and clustering of four adult CVD risk factors (systolic blood pressure, glucose, HDL cholesterol, triglycerides) within tertiles of body mass index (BMI) among men and women born during the Institute of Nutrition of Central America and Panama (INCAP) supplementation study in one of 4 study villages in Guatemala, 1969–1976, and examined in 1997–1999[1]

	Men (n = 187)				Women (n = 198)			
	Birth weight tertile (kg)							
	<2.88 n = 66	2.88–3.25 n = 64	>3.25 n = 57	Trend[2] P-values	<2.88 n = 74	2.88–3.25 n = 71	>3.25 n = 53	Trend P-values
	%				%			
Risk factors, n								
0	13.6	18.8	24.6	0.04	33.8	25.4	20.8	0.01
1	40.9	17.2	38.6		32.4	19.7	24.5	
2	22.7	32.8	19.3		16.2	22.5	20.8	
3	12.1	21.9	7.0		8.1	15.5	11.3	
4	6.1	4.7	10.5		5.4	15.5	15.1	
5	4.5	4.7	0		4.1	1.4	7.5	
	BMI tertile (kg/m^2)							
	<20.9 n = 62	20.9–22.8 n = 62	>22.8 n = 63	Trend P-values	<21.4 n = 64	21.4–24.2 n = 67	>24.2 n = 67	Trend P-values
	%				%			
Risk factors, n								
0	35.5	21.0	12.7	<0.001	46.9	35.8	6.0	<0.001
1	37.1	46.8	30.2		39.1	32.8	23.9	
2	24.2	21.0	31.8		12.5	22.4	26.9	
3	3.2	6.5	15.9		1.6	6.0	31.3	
4	0	4.8	9.5		0	3.0	11.9	

[1] Threshold values used to define upper tertile: Men: body mass index > 22.8 kg/m^2; systolic blood pressure > 123 mm Hg; glucose > 5.0 mmol/L; triglycerides > 1.35 mmol/L; HDL cholesterol < 0.87 mmol/L; Women: body mass index >24.2 kg/m^2; systolic blood pressure > 107 mm Hg; glucose > 4.80 mmol/L; triglycerides > 1.41 mmol/L; HDL cholesterol < 0.92 mmol/L.

[2] Adjusted for gestational age, supplement type offered in the village of birth, urban/rural residence, and age.

diabetes mellitus, and eventually, CVD. A small number of studies, all in industrialized country settings, have reported an association between birth weight and an index or cluster of several CVD risk factors (48–51). The present study in a developing country provides little evidence in support of the fetal programming hypothesis, at least among a population of young adults with a moderate prevalence of low birth weight. In men, there was a weak inverse association between birth weight and the number of CVD risk factors in the upper tertile of the distribution. We did not detect an inverse association between birth weight and any of several accepted risk factors for CVD in women. Indeed, there was a positive association between birth weight and BMI, blood pressure and a clustering of CVD risk factors. In contrast, even in this young and relatively lean population, there was a strong positive association between current BMI and CVD risk factor levels.

We interviewed 78% of eligible individuals and 81% of these had complete data for analysis. There was no evidence of respondent bias (35). Measurement biases are also unlikely because both birth weight and adult CVD risk factors were measured by, or under supervision of, experienced investigators. The use of digital electronic sphygmomanometers and solid-phase blood chemistry reactions, which are not generally used in CVD epidemiologic studies, may raise concerns of accuracy and precision. However, the instruments and methods used in this study showed good reproducibility and little

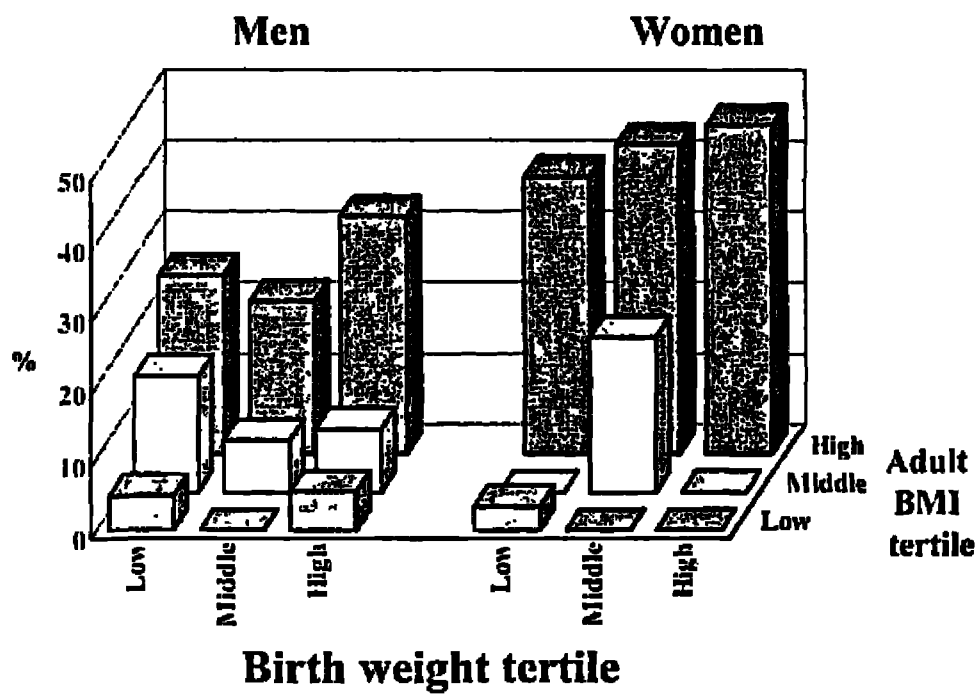

FIGURE 1 Prevalence of cardiovascular disease (CVD) risk factor clustering (percentage of individuals with at least 3 of systolic blood pressure, glucose and triglycerides in the highest sex-specific tertile, and HDL cholesterol in the lowest tertile) within joint tertiles of birth weight and adult body mass index (BMI) among men and women born during the Institute of Nutrition of Central America and Panama (INCAP) supplementation study in one of 4 study villages in Guatemala; 1969–1976, and examined in 1997–1999.

systematic bias compared with conventional methods (36,37). The expected strong association between BMI and CVD risk factors (especially in women) suggests that the instruments are providing data of reasonable precision.

The findings of this study suggest that fetal programming may not be a universal phenomenon, but rather may be observed only under specific circumstances. Understanding these circumstances will advance our understanding of this important area of research. A key difference between this and other studies of fetal and early life programming is that our cohort received nutritional supplementation early in life in a community-randomized trial. It is possible that the additional nutrition received by the cohort altered the birth weight-adult disease risk relationship. However, the findings concerning the relationship between birth weight and CVD risk factors are independent of the type of supplement received. There was no strong effect of type of supplement on birth weight (52), and birth weight was not associated with postnatal supplement ingestion (data not shown). Mean birth weights remained below Western norms, and thus fetal growth retardation is likely to have still occurred. Children receiving Atole grew more in the first 3 y of life than did children receiving Fresco (53), suggesting that growth in these communities was restricted when no supplements were provided.

In conclusion, birth weight was not consistently inversely associated with the prevalence of CVD risk factors in this young adult population. Birth weight was positively associated with adult BMI in women, and adult BMI was positively associated with prevalence of CVD risk factors in both men and women. This supports the notion that prevention of overweight and obesity, which are rapidly reaching epidemic proportions in developing countries, should become a public health priority.

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LITERATURE CITED

1. Barker, D. J. P. (1994) Mothers, Babies, and Disease in Later Life. BMJ Publishing Group, London, UK.

2. Leon, D. & Ben-Shlomo, Y. (1997) Preadult influences on cardiovascular disease and cancer. In: A Life Course Approach to Chronic Disease Epidemiology (Kuh, D. & Ben-Shlomo, Y., eds.). Oxford University Press, New York, NY.

3. Barker, D. J. P. (1992) Fetal and Infant Origins of Adult Disease. BMJ Publishing Group, London, UK.

4. Law, C. M. & Shiell, A. W. (1996) Is blood pressure inversely related to birth weight? The strength of evidence from a systematic review of the literature. J. Hypertens. 14: 935–941.

5. Joseph, K. S. & Kramer, M. S. (1996) Review of the evidence on fetal and early childhood antecedents of adult chronic disease. Epidemiol. Rev. 18: 158–174.

6. Curhan, G. C., Willett, W. C., Rimm, E. B., Spiegelman, D., Ascherio, A. L. & Stampfer, M. J. (1996) Birth weight and adult hypertension, diabetes mellitus, and obesity in US men. Circulation 94: 3246–3250.

7. McKeigue, P. (1997) Diabetes and insulin action. In: A Life Course Approach to Chronic Disease Epidemiology (Kuh, D. & Ben-Shlomo, Y., eds.). Oxford University Press, New York, NY.

8. Frankel, S., Elwood, P., Sweetnam, P., Yarnell, J. & Smith, G. D. (1996) Birthweight, body-mass index in middle age, and incident coronary heart disease. Lancet 348: 1478–1480.

9. Eriksson, J. G., Forsen, T., Tuomilehto, J., Winter, P. D., Osmond, C. & Barker, D. J. (1999) Catch-up growth in childhood and death from coronary heart disease: longitudinal study. Br. Med. J. 318: 427–431.

10. Holemans, K., Aerts, L. & Van Assche, F. A. (1998) Fetal growth and long-term consequences in animal models of growth retardation. Eur. J. Obstet. Gynecol. Reprod. Biol. 81:149–156.

11. Reynolds, R. M. & Phillips, D. I. (1998) Long-term consequences of intrauterine growth retardation. Horm. Res. 49: 28–31.

12. Spencer, G. S., Robinson, G. M., Berry, C. J. & Dobbie, P. M. (1994) Alteration of maternal growth hormone levels during pregnancy influences both fetal and postnatal growth in rats. Biol. Neonate 66: 112–118.

13. Langley-Evans, S. C., Phillips, G. J., Benediktsson, R., Gardner, D. S., Edwards, C. R., Jackson, A. A. & Seckl, J. R. (1996) Protein intake in pregnancy, placental glucocorticoid metabolism and the programming of hypertension in the rat. Placenta 17: 169–172.

14. James, P., Norum, K. R., Smitasiri, S., Swaminathan, M. S., Tagwireyi, J., Uauy, R. & ul Haq, M. (2000) ACC/SCN. Ending Malnutrition by 2020: an agenda for change in the millennium. Food Nutr. Bull. 21 (Suppl.): 1–88

15. Murray C. J. L. & Lopez A. D. (1996) The Global Burden of Disease. Harvard University Press, Cambridge, MA.

16. Crews, D. E. & MacKeen, P. C. (1982) Mortality related to cardiovascular disease and diabetes mellitus in a modernizing population. Soc. Sci. Med. 16: 175–181.

17. Carter, J. S., Wiggins, C. L., Becker, T. M., Key, C. R. & Samet, J. M. (1993) Diabetes mortality among New Mexico's American Indian, Hispanic, and non-Hispanic white populations, 1958–1987. Diabetes Care 16: 306–309.

18. Schooneveldt, M., Songer, T., Zimmet, P. & Thoma, K. (1988) Changing mortality patterns in Nauruans: an example of epidemiological transition. J. Epidemiol. Community Health 42: 89–95.

19. Nelson, R. G., Morgenstern, H. & Bennett, P. H. (1998) Birth weight and renal disease in Pima Indians with type 2 diabetes mellitus. Am. J. Epidemiol. 148: 650–656.

20. McKeigue, P. M., Miller, G. J. & Marmot, M. G. (1989) Coronary heart disease in South Asians overseas: a review. J. Clin. Epidemiol. 42: 597–609.

21. de Onis, M., Blossner, M. & Villar, J. (1998) Levels and patterns of intrauterine growth retardation in developing countries. Eur. J. Clin. Nutr. 52: S5–S15.

22. Stein, C. E., Fall, C. H., Kumaran, K., Osmond, C., Cox, V. & Barker, D. J. (1996) Fetal growth and coronary heart disease in south India. Lancet 348: 1269–1273.

23. Fall, C. H., Stein, C. E., Kumaran, K., Cox, V., Osmond, C., Barker, D. J. & Hales, C. N. (1998) Size at birth, maternal weight, and type 2 diabetes in South India. Diabet. Med. 15: 220–227.

24. Kumaran, K., Fall, C. H. D., Martyn, C. N., Vijayahumar, M., Stein C. & Shier, R. (2000) Blood pressure, arterial compliance, and left ventricular mass: no relation to small size at birth in South Indian adults. Heart 38: 272–277.

25. Cheung, Y. B., Low, L., Osmond, C., Barker, D. & Karlberg, J. (2000) Fetal growth and early postnatal growth are related to blood pressure in adults. Hypertension 36: 795–780.

26. Mi. J., Law, C., Zhang, K.-L., Osmond, C., Stein, C. & Barker, D. (2000) Effects of infant birth weight and maternal body mass index in pregnancy on components of the insulin resistance syndrome in China. Ann. Intern. Med. 132: 253–260.

27. Levitt, N. S., Steyn, K., De Wet, T., Morrell, C., Edwards, R., Ellison, G. T. & Cameron, N. (1999) An inverse relation between blood pressure and birth weight among 5 year old children from Soweto, South Africa. J. Epidemiol. Community Health 53: 264–268.

28. Margetts, B. M., Rowland, M. G., Foord, F. A., Cruddas, A. M., Cole, T. J. & Barker, D. J. (1991) The relation of maternal weight to the blood pressures of Gambian children. Int. J. Epidemiol. 20: 938–943.

29. Barros, F. C. & Victora, C. G. (1999) Increased blood pressure in adolescents who were small for gestational age at birth: a cohort study in Brazil. Int. J. Epidemiol. 28: 676–681.

30. Law, C. M., Egger, P., Dada, O., Delgado, H., Kylberg, E., Lavin, P., Tang, G. H., von Hertzen, H., Shiell, A. W. & Barker, D. J. (2001) Body size at birth and blood pressure among children in developing countries. Int. J. Epidemiol. 30: 52–57.

31. Bavdekar, A., Yajnik, C. S., Fall, C. H., Bapat, S., Pandit, A. N., Deshpande, V., Bhave, S., Kellingray, S. D. & Joglekar, C. (1999) Insulin resistance syndrome in 8-year-old Indian children: small at birth, big at 8 years, or both? Diabetes 48: 2422–2429.

32. Dabelea, D., Pettitt, D. J., Hanson, R. L., Imperatore, G., Bennett, P. H. & Knowler, W. C. (1999) Birth weight, type 2 diabetes, and insulin resistance in Pima Indian children and young adults. Diabetes Care 22: 944–950.

33. Habicht, J. P. & Martorell, R. (1992) Objectives, research design and implementation of the INCAP longitudinal study. Food Nutr. Bull. 14: 176–190.

34. Martorell, R., Habicht, J. P. & Rivera, J. A. (1995) History and design of the INCAP longitudinal study (1969–77) and its follow-up (1988–89). J. Nutr. 125: 1027S–1041S.

35. Torun, B., Stein, A. D., Schroeder, D. G., Grajeda, R., Conlisk, A. J., Rodriguez, M., Mendez, H. & Martorell, R. (2002) rural-to-urban migration and cardiovascular disease risk factors in young Guatemalan adults. Int. J. Epidemiol. 31: 218–226.

36. Torun, B., Grajeda, R., Mendez, H., Flores, R., Martorell, R. & Schroeder, D. (1998) Evaluation of inexpensive digital sphygmomanometers for field studies of blood pressure. FASEB J. 12: S5072. (abs.).

37. Flores, R., Grajeda, R., Torun, B., Mendez, H., Martorell, R. & Schroeder, D. (1998) Evaluation of a dry chemistry method for blood lipids in field studies. FASEB J. 12: S3061 (abs.).

38. Friedewald, W. T., Levy, R. I. & Fredrickson, D. S. (1972) Estimation of

the concentration of low-density lipoprotein cholesterol in plasma without use of the preparative ultracentrifuge. Clin. Chem. 18: 499–502.

39. National Cholesterol Education Program. (2001) Third Report of the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults. National Institutes of Health/National Heart, Lung and Blood Institute, Washington, DC.

40. Gibson, R. S. (1990) Principles of Nutritional Assessment. Oxford University Press, New York, NY

41. Lohman, T., Roche, K. A. & Martorell, R., eds. (1991) Anthropometric Standardization Reference Manual. Human Kinetics, Champaign, IL.

42. Fleiss, J. (1981) Statistical Methods for Rates and Proportions. J. Wiley & Sons, New York, NY.

43. Willett, W. C., Manson, J. E., Stampfer, M. J., Colditz, G. A., Rosner, B., Speizer, F. E. & Hennekens, C. H. (1995) Weight, weight change, and coronary heart disease in women. Risk within the 'normal' weight range. J. Am. Med. Assoc. 273: 461–465.

44. Stamler, J., Wentworth, D. & Neaton, J. D. (1986) Is the relationship between serum cholesterol and risk of premature death from coronary heart disease continuous and graded? Findings in 356,222 primary screenees of the Multiple Risk Factor Intervention Trial (MRFIT). J. Am. Med. Assoc. 256: 2823–2828.

45. Neaton, J. D. & Wentworth, D. (1992) Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease. Overall findings and differences by age for 316,099 white men. Multiple Risk Factor Intervention Trial Research Group. Arch. Intern. Med. 152: 56–64.

46. Neter, J., Wasserman, W. & Kutner, M. H. (1983) Applied Linear Regression Models, p. 346-348. Richard D. Irwin, Ltd., Homewood, IL.

47. Lucas, A., Fewtrell, M. S. & Cole, T. J. (1999) Fetal origins of adult disease: the hypothesis revisited. Br. Med. J. 319: 245–249.

48. Haffner, S. M., Valdez, R. A., Hazuda, H. P., Mitchell, B. D., Morales, P. A. & Stern, M. P. (1992) Prospective analysis of the insulin resistance syndrome (syndrome X). Diabetes 41: 715–722.

49. Barker, D. J. P., Hales, C. N., Fall, C. H. D., Osmond, C., Phipps, K. & Clark, P. M. S. (1993) Type 2 (non-insulin dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. Diabetologia 36: 62–67.

50. Yarbrough, D. E., Barrett-Connor, E., Kritz-Silverstein, D. & Wingard, D. L. (1998) Birth weight, adult weight, and girth as predictors of the metabolic syndrome in postmenopausal women. Diabetes Care 21: 1652–1658.

51. Vanhala, M. J., Vanhala, P. T., Keinanen-Kiukaanniemi, S. M., Kumpusalo, E. A. & Takala, J. K. (1999) Relative weight gain and obesity as a child predict metabolic syndrome as an adult. Int. J. Obes. 23: 656–659.

52. Lechtig, A., Habicht, J. P., Delgado, H., Klein, R. E., Yarbrough, C. & Martorell, R. (1975) Effect of food supplementation during pregnancy on birthweight. Pediatrics 56: 508–520.

53. Rivera, J. A., Martorell, R., Ruel, M. T., Habicht, J. P. & Haas, J. D. (1995) Nutritional supplementation during the preschool years influences body size and composition of Guatemalan adolescents. J. Nutr. 125: 1068S–1077S.