

Fetal Malnutrition and Adult Chronic Disease

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Since the fetal origins of adult disease hypothesis was put forward, more than 30 studies around the world have indicated low-birth-weight (LBW) infants have a higher incidence of hypertension and impaired glucose tolerance. India ranks second in incidence of LBW among South East Asian countries and is experiencing a transition of disease pattern from communicable disease to non-communicable disease. Whether this could be explained in part by LBW infants who experienced better nutrition at a later age is explored here. An earlier cohort with accurate birth weights was traced and enrolled into the study. A sample of 50 LBW and 78 normal birth weight (NBW) individuals are reported on here. Though the odds ratio (OR) estimates of risk factors for coronary heart disease and diabetes tended to be higher in LBWs who were better nourished at the time of the study, they were not statistically different. Similarly, OR estimates for risk factors tended to be higher in LBWs who put on more weight than the median of NBWs, but they were not significant. Logistic regressions with several variables indicated significant influence of body mass index on systolic ($P < 0.007$) and diastolic ($P < 0.004$) blood pressures. Since the risk associations are weak, more studies are needed to put the hypothesis on a firm footing.

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Introduction

The fetal origins of adult disease hypothesis originated in the 1980s when an association between low birth weight and the incidence of cardiovascular disease among middle-aged men and women was noted by Barker at Southampton.¹ Later, more than 30 studies around the world indicated low-birth-weight infants to have a higher incidence of hypertension and impaired glucose tolerance, independent of adult social class, smoking, drinking, and other risk factors.²

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It has been postulated that the fetus in a malnourished mother's womb has to adapt to a limited supply of nutrients, thereby changing its physiology, function, and metabolism. Such "programmed" changes may trigger a number of diseases in later life when dietary intakes and lifestyles differ greatly from the deprivation experienced in utero.

In developing countries, the prevalence of low birth weight varies anywhere from 13% to 30%. India ranks second in the number of low-birth-weight infants among South East Asian countries, as 30% of newborns weigh less than 2.5 kg at birth.³ Not all low birth weights fall into one category, and the risk for hypertension, diabetes, CAD, and stroke varies, depending upon the symmetric or asymmetric growth retardation.⁴ It is now well documented that the risk of the above conditions vary with the quantity or quality of nutrition available during each trimester of pregnancy and with differential effects on the development of the brain, internal organs, muscles, adipose mass, etc. Infants whose birth weight is less than 2 kg more often show symmetric growth retardation, while those with higher birth weights exhibit symmetric retardation only 8–10% of the time. Symmetric growth retardation is commonly seen in low-income groups, while asymmetric growth retardation prevails in high-income groups.

At the National Institute of Nutrition, earlier multi-center studies designed to determine the effects of protein-energy malnutrition on physical growth and psychological development of children were carried out. Cohort birth weights were measured by trained staff with standardized balances. The cohort children are now between the ages of 16 and 19 years and 25% to 30% have birth weights less than 2.5 kg.

Objective

The aim of this study is to understand the association between low birth weight and a risk factor profile for coronary artery disease and diabetes.

Subjects and Methodology

Subjects from the above cohort were traced. All subjects who were willing to participate and follow the protocol were enrolled. After collecting clinical data and an-

Table 1. Population Under Study

	Number	Percentage
Number of children with available records	201	100
Enrolled	125	62
Low birth weight (≤ 2.5 kg)	50	55
Normal birth weight (> 2.5 kg)	75	37
Refused/died of accidental causes	49	24
Still to trace	27	24

thropometric measurements, fasting blood samples were collected at their homes. Blood pressure readings were recorded for each individual two times on different days.

Blood samples were placed on ice and transported to the main laboratory for further estimations. Blood glucose, hemoglobin, and fibrinogen levels were analyzed within 6 hours after collection. The lipid profile and insulin levels were analyzed within a month, using standard procedures.

Statistics

Means were tested for significance using Student's *t* test. Chi-square test was used to test for tertile distribution. Risk estimates were worked out for all the response variables. Logistic regression for explanatory variables was fitted for response variables.

Results

Records were available for 186 subjects, of which 125 were willing to participate. Fifty subjects had low birth weight (< 2.5 kg) and 75 had normal birth weights (NBW) above 2.5 kg (Table 1). Blood pressure recordings and blood samples could not be taken in 2 LBWs and 3 NBWs as they were unavailable for blood drawing. Some blood samples were lost or damaged during storage and could not be analyzed.

The mean values of systolic and diastolic blood pressures as well as the other risk factors for CHD were essentially similar between the LBW and NBW groups (Table 2).

LBW individuals were grouped according to current weights into two groups, under- or better-nourished, using the current median weights of NBWs. A higher percentage of LBWs with better current weights (above 44 kg) were in the highest tertile for systolic and diastolic blood pressure, fasting glucose, insulin, triglycerides, and fibrinogen levels, and in lowest tertile for HDL cholesterol. However, none of the differences were significant (Table 3).

Risk estimates for low birth weights based on current weights indicate that individuals with better current weights appeared to have fibrinogen, glucose, insulin, and triglyceride levels that put them at higher risk, whereas those who continued to have low weights had higher risk estimates for systolic and diastolic blood pressure (Figure 1). However, none of the differences were statistically significant.

When risk estimates were calculated among individuals having current weights > 44 kg, LBWs seem to be at higher risk for elevated levels of fibrinogen, glucose, insulin, and triglycerides, and low HDL. Again, these were not significant (Figure 2). When height was taken into consideration, again no significant differences were observed between the groups who had put more height as compared with those who did not (Figure 3).

There was no difference in mean and median body fat between LBW and NBW adolescents. Even the risk estimates were similar between the two groups.

Logistic regressions with all variables such as age, birth weight, current weight, BMI, head circumference, height, and body fat percent were calculated. Only BMI had significant influence on systolic ($P < 0.007$) and diastolic ($P < 0.004$) blood pressures.

Discussion

This cohort has been regularly followed up from the time of birth. Accurate birth weights were re-

Table 2. Mean Levels of Risk Factors for Chronic Diseases

Birth Weight	Blood Pressure (mm Hg)		Fasting Glucose	Fasting Insulin	Cholesterol	Triglycerides	HDL Cholesterol	Fibrinogen
	Systolic	Diastolic	mg/dL	μ U/mL	mg/dL	mg/dL	mg/dL	mg/dL
Low	109.0 \pm 9.5 (48)	73.5 \pm 8.95 (48)	93.4 \pm 11.91 (45)	24.3 \pm 12.73 (46)	121.9 \pm 24.51 (46)	100.0 \pm 42.3 (47)	36.3 \pm 7.91 (47)	201.6 \pm 41.8 (43)
Normal	109.5 \pm 12.7 (72)	72.3 \pm 9.81 (72)	95.5 \pm 14.61 (65)	22.8 \pm 12.23 (68)	117.0 \pm 22.82 (62)	99.1 \pm 46.5 (68)	37.4 \pm 9.52 (64)	189.6 \pm 43.2 (63)

Values are mean \pm standard deviation = number of observations.

Note: HDL = high-density lipoprotein cholesterol.

Table 3. Percentage Distribution of Risk Factors by Tertiles

Risk Factors Cut-offs	Group	A			B			C			D		
	Current Weight	Under			Better			Under			Better		
	Birth Weight	Low			Low			Normal			Normal		
	TERTILES	I	II	III	I	II	III	I	II	III	I	II	III
Systolic BP <106–110–>110	mm Hg	54.2	16.7	29.2	20.8	45.8	33.3	48.6	24.3	27	22.9	40	37.1
Diastolic BP <70–80–>80	mm Hg	54.2	29.2	16.7	50	29.2	20.8	64.9	24.3	10.8	48.6	28.6	22.9
Fasting Glucose <90–102.3–>102.3	mg/dL	37.5	41.7	20.8	33.3	20.8	45.8	40.5	35.1	24.3	25.7	31.4	42.9
Fasting Insulin <18–23–>23	μU/mL	29.2	45.8	25	37.5	20.8	41.7	37.8	29.7	32.4	31.4	42.9	25.7
Total Cholesterol <108–139.5–>139.5	mg/dL	43.5	34.8	21.7	13	73.9	13.0	26.7	43.3	30.0	53.1	31.3	15.6
Triglycerides <108–139.5–>139.5	mg/dL	29.2	50	20.8	29.2	33.3	37.5	30.6	41.7	30.6	37.1	28.6	34.3
HDL Cholesterol >76.5–115.0–>115.0	mg/dL	43.5	30.4	26.1	37.5	45.8	16.7	30.3	36.4	33.3	48.4	35.5	16.1
Fibrinogen <174–221.0–>221.0	mg/dL	33.3	37.5	29.2	29.8	33.3	45.8	37.8	35.1	27.0	28.6	31.4	40.0

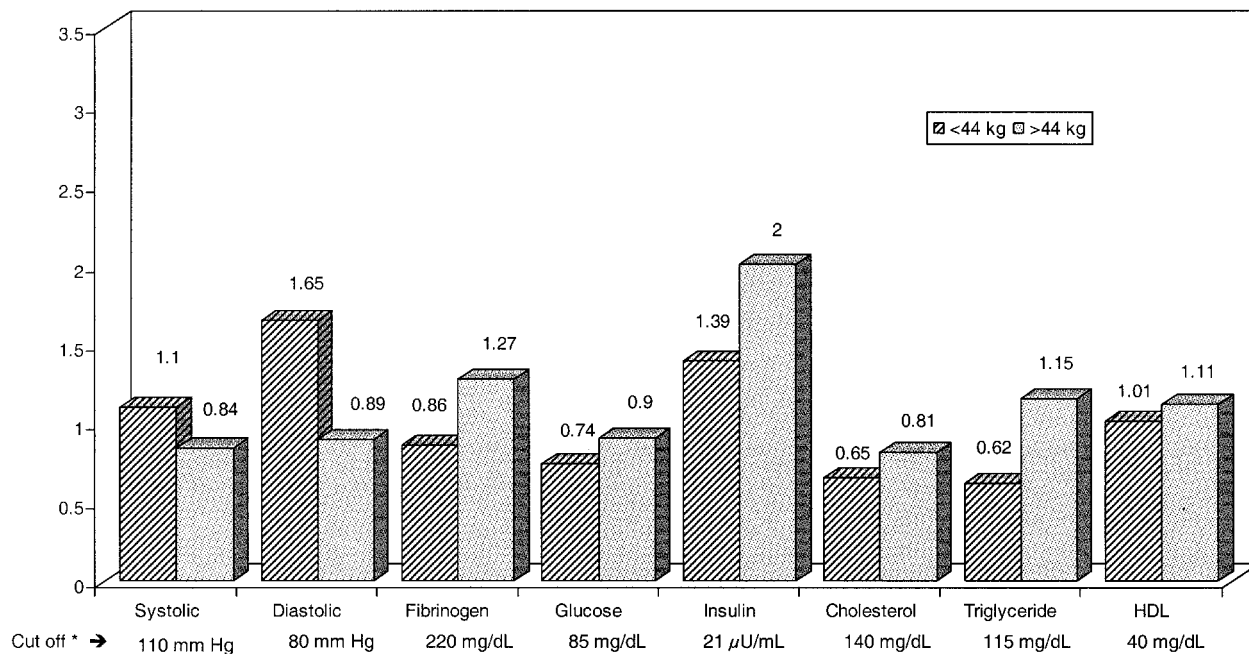
Comparisons between A versus C and B versus D—NS.

Birth weight cut-off = 2.5 kg; current weight cut-off = 44.0 kg.

HDL = high-density lipoprotein cholesterol.

corded within 12 hours of birth. Most of the children continued to remain in the semi-urban and rural areas.

Several animal experiments indicate that early over-nutrition has significant effects on body weight and body metabolism.⁵ Similarly, people who become obese



Chi-square test was nonsignificant.

*Based on 67th percentile of normal birth weights or from literature; 44 kg was median weight of normal birth weight children.

HDL = high-density lipoprotein cholesterol.

Figure 1. Comparison of risk estimates between low birth weight and normal birth weight individuals for current weight either below or above median current weight of normal birth weight individuals.

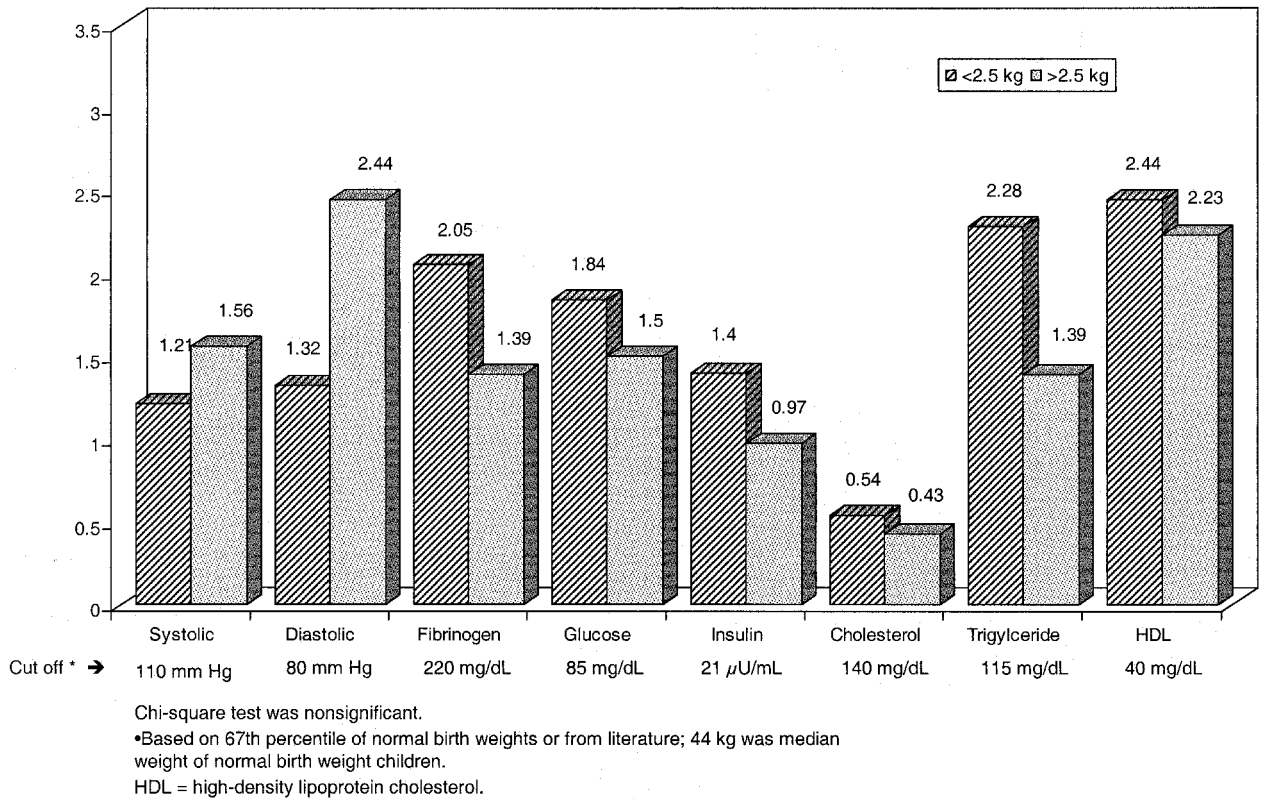


Figure 2. Comparison of risk estimates for current weight above versus below median current weight of normal birth weight children in low and normal birth weight children.

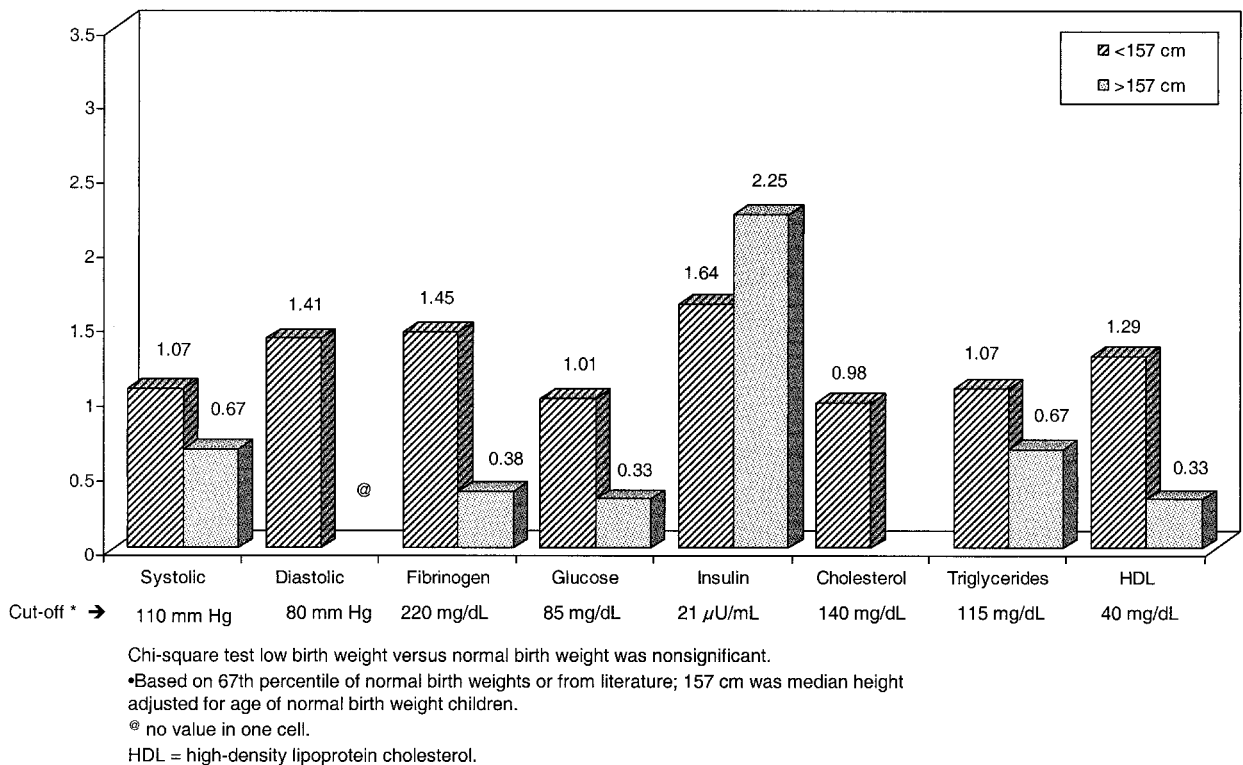


Figure 3. Comparison of risk estimates for low birth weight children whose current heights are below versus above the median current height of normal birth weight children.

during childhood continue to be obese as adults.⁶ It is now clear that undernutrition in different periods of gestation leads to variations in growth retardation. It has been suggested that individuals who had undernutrition in late gestation and early infancy tend to remain thin in adult life.⁷

Perhaps subjects in our study continued to be undernourished and therefore they are less likely to show changes in body composition or biochemistry that are risk factors for cardiovascular disease, diabetes, or other chronic diseases.

Earlier studies conducted in similar populations that mainly tried to determine the effect of childhood undernutrition on glucose tolerance, blood pressure, and serum lipids in adult life noted similar observations. It was concluded that the negative influence of in utero malnutrition is concealed by the persistent undernutrition in adult life.⁸

To categorically indicate the risk potential of LBW children who grow up to be obese adults, it is necessary to increase the sample size of the present study from other cohorts available. The present findings also suggest that the risk for cardiovascular disease may be low when the low-birth-weight individuals continue to be thin.

Our cohort had accurate birth weights, but measurements at birth that can reliably indicate the time in gestation at which undernutrition and growth retardation occurred are unfortunately not available. Neither is information on head circumference at birth available. Stud-

ies indicate small head circumference correlates with raised death rates from cardiovascular causes.⁹ Improving health and nutrition in pregnant women to raise birth weights appears to be a better strategy for decreasing the burden of chronic disease.

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