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ORIGINAL ARTICLE

Size at birth is associated with blood pressure but not insulin resistance in 6–8 year old children in rural Nepal

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Earlier, we reported that antenatal micronutrient supplementation reduced the risk of metabolic syndrome and microalbuminuria among offspring at 6–8 years of age in rural Nepal. In the same birth cohort, we examined associations of size at birth (weight, length and ponderal index), and gestational age, with cardiometabolic risk factors in childhood across all antenatal micronutrient interventions. There was an inverse association between birth weight and systolic blood pressure (SBP, $\beta = -1.20$ mm Hg/kg; 95% confidence interval (CI): −1.93, −0.46) and diastolic blood pressure (DBP, $\beta = -1.24$ mm Hg/kg; 95% CI: −2.00, −0.49). Current child body mass index was positively associated with SBP but not with DBP. Birth weight was unassociated with insulin resistance, but each kilogram of increase was associated with a reduced risk of high triglycerides (odds ratio (OR) = 0.64/kg; 95% CI: 0.41, 0.97) and an increased risk of high waist circumference (OR = 3.16/kg; 95% CI: 2.47, 4.41). In this rural Nepalese population of children 6–8 years of age with a high prevalence of undernutrition, size at birth was inversely associated with blood pressure and triglycerides and positively associated with waist circumference.

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Introduction

There are growing epidemics of diabetes[1] and cardiovascular disease (CVD) globally,[2] with an estimated 80% of the global burden of chronic disease occurring in low and middle income countries.[3] *The Developmental Origins of Health and Disease* hypothesis purports that undernutrition during early life may predispose individuals to a greater risk of chronic disease in adulthood. Small size at birth has been associated with higher blood pressure (BP)[4] and an elevated risk of type 2 diabetes,[5] although the majority of studies have been conducted in developed country settings. There are a few studies among children in India,[6] South Africa,[7] Jamaica,[8] Zimbabwe,[9] Guatemala and Chile[10] that have also noted an inverse association between birth weight and BP, although one Indian study found no association.[11] Birth weight is the most commonly used indicator of fetal nutritional status throughout gestation, however, low birth weight may be caused by intrauterine growth restriction, preterm delivery or a combination of the two. Further, maternal micronutrient intake during pregnancy has been found to impact birth weight.[12]

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We conducted a community-based randomized controlled trial of antenatal micronutrient supplements in rural Nepal, assessing children at birth and during the early school age years (6–8 years). We found that maternal supplementation with folic acid + iron or a multiple micronutrient supplement reduced the risk of low birth weight by 16%–14%, respectively.[13] At the age of 6–8 years, we have also found that folic acid + iron + zinc supplementation increased height by 0.6 cm and reduced triceps skinfold thickness and subscapular skinfold thickness, both by ~0.2 mm,[14] and folic acid supplementation reduced the risk of microalbuminuria and metabolic syndrome (MetS) by 44%–37%, respectively.[15] Because birth weight had not been found to have improved in these two groups, it would suggest that the effects were not mediated through improved birth weight. This study examines whether size at birth and gestational age is associated with cardiometabolic risk factors in children at 6–8 years of age in rural Nepal across the maternal micronutrient intervention groups.

Methods

The study population comprises children who were born to mothers who had participated in a cluster randomized trial of micronutrient supplements from early pregnancy through 3 months postpartum in the rural Sarlahi District of Nepal from 1999 to 2001. Mothers were randomized by cluster to

receive one of the five supplements: (1) vitamin A alone as control or with (2) folic acid; (3) folic acid + iron; (4) folic acid + iron + zinc or (5) a multiple micronutrient supplement containing the former plus vitamin D, vitamin E, vitamin B1, vitamin B2, niacin, vitamin B6, vitamin B12, vitamin C, vitamin K, copper and magnesium. During the initial trial, household socioeconomic status (SES), caste, ethnicity, supplement compliance, birth weight, diet, and morbidity of both the mother and infant were assessed, the specifics of which are provided elsewhere.[13] Birth weight was measured in the home within 72 h of delivery using an electronic scale (Seca 727, Hamburg, Germany) and length was measured using a length board (Shorr Productions, RI, USA).

Details of the follow-up procedures have been described earlier.[14,15] Briefly, from 2006 to 2008, surviving offspring of these women, now 6–8 years old, were contacted and assessed during a series of three home visits. During the first visit, data on SES, child education and literacy were collected. Systolic blood pressure (SBP) and diastolic blood pressure (DBP) was measured four times on the child's right arm using an automated oscillometric device (BPM-300, BPTrue, Canada). The first measurement was dropped and the mean of the remaining three measurements was used for analysis. During a second visit, a team of trained anthropometrists measured standing height using a pocket stadiometer (Harpenden Pocket Stadiometer, Crosswell, UK); weight using an electronic scale (Model 881, Seca, Hamburg, Germany); waist circumference using a long insertion tape[16] (Seca 200, Seca, Hamburg, Germany); mid-upper arm circumference using an insertion tape; and triceps skinfold (TSF) and subscapular skinfold (SSF) thicknesses using Holtain precision calipers (Holtain Ltd, Crymych, Wales). All of these were measured in triplicates and the median was used for analysis. Finally, the mothers were asked to answer a brief questionnaire about the child's history of illness in the past 7 days.

Children were then asked to fast overnight and were visited the following morning by a phlebotomist who collected early morning venous blood and urine samples. Blood samples were collected from all assenting children, even if the child had not fasted. Hemoglobin A1c (HbA1c) was tested in whole blood using a DCA 2000 analyzer with standard test kits (Bayer Diagnostics, New York, NY, USA). Data were reported as percentage of HbA1c by the instrument and thus this measure was used for analysis. Total cholesterol, high-density lipoprotein (HDL), triglycerides and glucose were measured in plasma samples using standard enzymatic methods (LDX analyzer, Cholestech, Hayward, CA). Low-density lipoprotein cholesterol was calculated using the Friedewald equation.[17] Plasma insulin was measured using an ultrasensitive sandwich immunoassay (Alpco Diagnostics, Salem, NH, USA). Urinary microalbumin/creatinine ratio was measured using the DCA 2000 analyzer with standard tests kits (Bayer Diagnostics, New York, NY, USA).

The follow-up study received ethical approval from the Institutional Review Boards at Johns Hopkins School of Public Health, Baltimore, MD in the United States and at the Institute of Medicine, Kathamandu, in Nepal.

Statistical analyses

Singleton children who were alive at the end of the original trial were eligible for inclusion into this analysis if they had a birth weight recorded within 72 h of delivery ($n = 3150$). Comparisons were made between children who were lost to follow-up or who had missing data with children who were enrolled in the follow-up study. Birth weight, length, ponderal index, and gestational age, as well as socioeconomic factors, were compared between groups using the *t*-test for continuous variables and χ^2 test for dichotomous variables.

Small for gestational age (SGA) was calculated using a sex specific reference.[18] Low birth weight was defined as <2.5 kg and preterm delivery was defined as gestational duration <37 weeks, based on the last menstrual period. Weight for age, height for age, and body mass index (BMI) for age and BMI z-scores (BMIZ) at birth and follow-up were calculated using the WHO child growth standard.[19,20] Children with z-scores less than 2 standard deviations (S.D.) below the median were classified as underweight, stunted, or low BMI, respectively. BP percentiles were calculated using a United States reference population for children of the same age, height and sex.[21] Although approximately 30% of children had not been fasted at the time of the blood draw, both fasting and non-fasting data were combined for analysis of HbA1c and cholesterol to minimize the amount of missing data that would otherwise arise and because of documented associations between non-fasting lipid profiles and CVD risk.[22,23] Fasting was defined as no food or drink other than water within 8 hours of the blood draw. Models restricting to children who had fasted were also tested and not found to substantially change the interpretation of the analyses. Insulin and triglyceride data were only analyzed for children that had fasted. Insulin resistance (IR) was estimated using the homeostatic model assessment (HOMA): HOMA-IR = (FPI × FPG)/22.5, where FPI is fasting plasma insulin concentration (mU/l) and FPG is fasting plasma glucose (mmol/l).[24]

The associations of measures of birth size (birth weight, length and ponderal index) and gestational age with BP were analyzed using multivariate linear regression. The microalbumin/creatinine ratio, cholesterol, triglycerides, glucose and HOMA were found to have skewed distributions and were thus described with median and interquartile ranges. The relative mean difference for glucose, insulin and HOMA was estimated on the log scale using generalized linear models with a log link. Coefficients were exponentiated to calculate the percent change and 95% confidence intervals (CI).

A dichotomous variable was created to examine the risk of microalbuminuria (urinary microalbumin/creatinine $\geqslant 30$ mg/g). Because microalbuminuria can be influenced by recent infection, we tested two alternative models: one in which children with reported fever in the previous week were excluded and one in

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which we included those children but controlled for recent fever. Neither of these alternative approaches was found to substantially change the interpretation of the model and thus are not shown here. Additional dichotomous variables were created including low HDL cholesterol (<35 mg/dl), as recommended by the National Cholesterol Education Program (NCEP) report on cholesterol in children;[26] high fasting triglycerides (⩾150 mg/dl), as recommended by the NCEP guidelines for adults[25] and the International Diabetes Foundation guidelines for children;[27] high BP (SBP or DBP ⩾ 90th percentile of the United States reference population)[21] which is used to define prehypertension in children; and high waist circumference (⩾85th percentile of the study population). Few children had a glucose measure greater than the traditionally recommended cut-point of 100 mg/dl, so a cutoff of the 85th percentile was used. In addition, a MetS score was created by summing the S.D. of each of the following risk factors: glucose, triglycerides, SBP, waist circumference, and the inverse of HDL cholesterol, as has been recently recommended.[28] Dichotomous outcome variables were examined using multivariate logistic regression. The MetS score was analyzed using multivariate linear regression.

SES factors at birth and follow-up, maternal education and literacy, paternal occupation, ethnicity and caste were tested as potential confounders in their univariate associations with birth weight and each of the outcome variables. Factors significantly associated with birth weight and any of the primary outcome variables (SBP, HOMA or MetS) were included in all multivariate regression models. Interactions between supplement group and birth weight were tested and found to be non-significant. Finally, child BMI was tested as a potential confounder and an effect modifier in the regression models. An interaction term between birth weight and child BMI, using a dichotomous variable with a cutoff of the 75th percentile, was tested. Data were analyzed using Stata v.10 (Stata Corp, College Station, TX, USA).

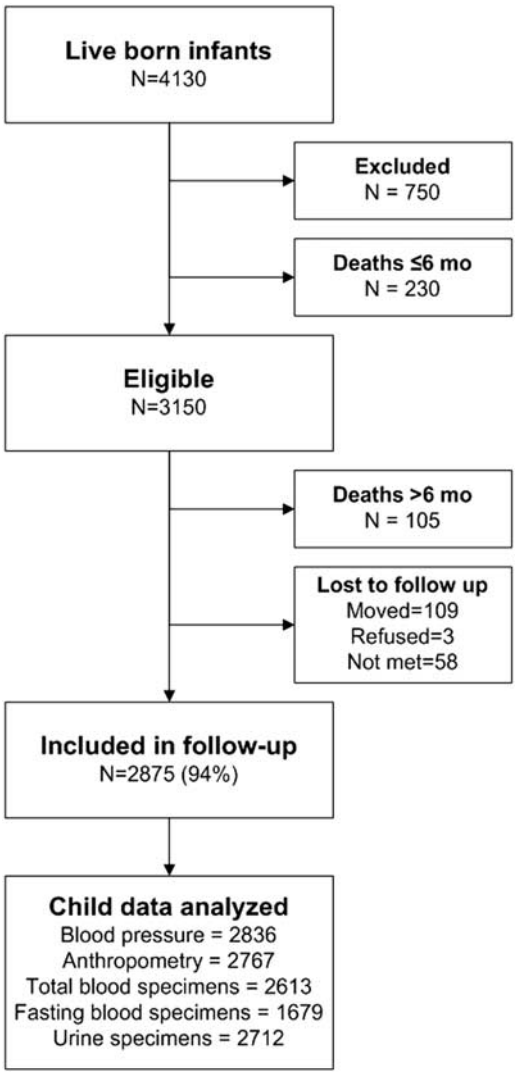

Fig. 1. Enrollment, follow-up and sample sizes for each of the primary assessments. Exclusion criteria included missing birth weight measurement, anthropometry measured ⩾72 h after birth and multiple births.

Results

Of the 4130 live born infants, 230 died before 6 months of age and 750 did not meet the selection criteria for this analysis, leaving 3150 as eligible children. Of these, 105 had died before the follow-up visit and 170 were otherwise lost to follow-up. We thus included 2875 children in this analysis, ~94% of eligible surviving children (Fig. 1). There were missing blood samples because of the refusals ($n = 146$, 5.1%) or not finding the child at home at the time of the household visit ($n = 116$, 4.0%) and an additional 934 (35.7%) had not adhered to fasting instructions. The children lost to follow-up or who had missing biospecimen data were more likely to be Madheshi, an ethnic group originating from northern India (72% *v.* 66%, $P < 0.001$), and less likely to have had any schooling (63% *v.* 68%, $P = 0.011$) or be from land owning families (73% *v.* 80%, $P < 0.001$). Those with missing biospecimen data also had a slightly lower BMI (13.9 kg/m^2 *v.* 14.0 kg/m^2, $P < 0.001$) at follow-up compared with children with complete data. There were no significant differences between those with or without missing data in terms of birth weight ($P = 0.08$), length ($P = 0.07$), or ponderal index ($P = 0.98$), however.

A summary of the children's characteristics at follow-up is shown in Table 1. There was a high prevalence of undernutrition at birth and at follow-up. More than one third were born low birth weight (<2.5 kg), 55% were born SGA and 20% were born preterm. The prevalence of stunting and underweight was 20%–29%, respectively. At follow-up, the prevalence of stunting, underweight, and low BMI was 46%, 53%, and 27%, respectively. Yet, ~20% of children were classified as hypertensive or at risk of hypertension (SBP or

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Table 1. *Summary of anthropometric measurements and biomarkers of cardiovascular risk at birth and during childhood*

Characteristic	N[a]	Mean	S.D.
At birth			
Weight (kg)	2875	2.65	0.41
Length (cm)	2867	47.5	2.02
Ponderal index (kg/m^3)	2866	24.7	2.4
Low birth weight (<2.5 kg, %)	1040	36.2	
Small for gestational age (%)	1565	54.5	
Preterm (<37 weeks, %)	586	20.4	
Stunted (HAZ <−2, %)[b]	570	19.9	
Underweight (WAZ <−2, %)[b]	832	28.9	
In childhood			
Age (years)	2875	7.46	0.44
Anthropometry			
Height (cm)	2764	113.45	5.45
Weight (kg)	2764	18.03	2.26
BMI (kg/m^2)	2763	13.97	1.05
Triceps skinfold thickness (mm)	2763	5.85	1.45
Subscapular skinfold thickness (mm)	2763	4.77	0.99
Waist circumference (cm)	2757	51.24	3.02
Stunted (HAZ < −2, %)[b]	1271	46.0	
Underweight (WAZ < −2, %)[b]	1461	52.9	
Low BMI (BMIZ <−2, %)[b]	758	27.4	
Cardiometabolic risk factors			
Systolic BP (mm Hg)	2836	95.3	8.1
Diastolic BP (mm Hg)	2836	63.8	8.4
HbA1c (%)	2613	5.10	0.27
Fasting insulin (μIU/ml)[c,d]	1654	2.62	1.56–4.36
Fasting glucose (mg/dl)[c,d]	1678	70	64–76
Fasting HOMA-IR[c,d]	1616	0.45	0.26–0.77
Total cholesterol (mg/dl)[c,e]	2613	112	<100–128
HDL cholesterol (mg/dl)[c,e]	2613	27	21–33
LDL cholesterol (mg/dl)[c,e]	1670	73	62–83
Fasting triglycerides (mg/dl)[c]	1679	88	67–115
Urinary microalbumin/creatinine ratio (mg/g)[c]	2710	11	8–16

HAZ, height for age z score; WAZ, weight for age z score; BMI, body mass index; HbAC1, hemoglobin A1c; HDL, high density lipoprotein; LDL, low density lipoprotein.

[a] Varying sample sizes are due to missing data on certain indicators. Missing biomarker data were due to refusal ($n = 146$) or child not at home ($n = 116$). Missing fasting glucose, insulin and HOMA data were due to non-fasting status ($n = 934$).

[b] Z-scores calculated using the WHO growth standard.[8,9]

[c] Median and interquartile range are presented for insulin, glucose, HOMA, total cholesterol, HDL cholesterol, LDL cholesterol, triglycerides and microalbumin/creatinine ratio.

[d] Insulin, glucose and HOMA estimates were only analyzed among children that had fasted.

[e] About 28% of total cholesterol data under detectable range (<100 mg/dl) and thus the lower quartile value is displayed as '<100'; 34% of LDL cholesterol data could not be calculated due to total cholesterol, HDL cholesterol or triglyceride values under the detectable range.

DBP ⩾ 90th percentile of the referent population). Nearly 73% of children had low HDL cholesterol (<35 mg/dl) and 9% of children had high triglycerides (⩾150 mg/dl). Only 65 children (2.5%) had high fasting glucose (⩾100 mg/dl) and no children (0%) had high HbA1c (⩾7%). A total of 110 (4%) of children had microalbuminuria (⩾30 mg/g creatinine).

Birth weight was positively associated with BMI ($P < 0.001$), waist circumference ($P < 0.001$), and the sum of skinfold thicknesses ($P < 0.001$) in childhood. After controlling for the child's age, gender, ethnicity, maternal literacy, and family radio ownership, each kilogram of increase in birth weight was associated with 0.59 kg/m^2 increase in BMI (95% CI: 0.50, 0.68), 1.69 cm increase in waist

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Table 2. *Associations between blood pressure and size at birth or current body size in children at age 6–8 years in rural Nepal, adjusted for potential confounding factors*

		Systolic BP	Diastolic BP
	N	β (95% CI)[a]	β (95% CI)[a]
Birth measures			
Weight (kg)	2819	−1.20** (−1.93, −0.46)	−1.24** (−2.00, −0.49)
Length (cm)	2811	−0.16* (−0.32, −0.01)	−0.19* (−0.34, −0.03)
Ponderal index (kg/m^3)	2810	−0.14* (−0.26, −0.01)	−0.14* (−0.27, −0.01)
Gestational age (weeks)	2819	−0.12* (−0.22, −0.03)	−0.12* (−0.22, −0.02)
Child measures (at 6–8 years)			
Weight (kg)	2713	0.27*** (0.12, 0.42)	0.07 (−0.08, 0.23)
Height (cm)	2713	0.06* (0.00, 0.13)	0.04 (−0.03, 0.10)
BMI (kg/m^2)	2712	0.52** (0.22, 0.82)	0.07 (−0.24, 0.38)
Waist circumference (cm)	2706	0.08 (−0.02, 0.18)	−0.03 (−0.14, 0.08)
Sum of skinfolds (mm)	2712	0.20** (0.06, 0.34)	0.07 (−0.08, 0.22)

CI, confidence interval; BMI, body mass index.

[a] Each row represents the β coefficients (95% CI) from separate multivariate linear regression models for SBP or DBP, adjusted for child age, sex, ethnicity, maternal literacy and radio ownership.

*$P<0.05$; **$P<0.01$; ***$P<0.001$.

circumference (95% CI: 1.42–1.95), and 0.57 mm increase in the sum of skinfold thicknesses (95% CI: 0.38, 0.77). Both birth length and ponderal index were also positively associated with these outcomes ($P<0.001$ for all), but gestational age was not associated with any of the outcomes in adjusted models.

Using simple linear regression models, birth weight and ponderal index were inversely associated with SBP in childhood. However, neither birth length nor gestational age was significantly associated with SBP. In adjusted analyses, each kilogram of increase in birth weight was associated with a −1.20 mm Hg decline in SBP and −1.25 mm Hg decline in DBP (Table 2). Increasing ponderal index was modestly associated with SBP and DBP ($P<0.05$). The measures of current body size were associated with SBP but not with DBP. Each unit increase in child BMI was associated with an increase in SBP of 0.52 mm Hg (0.22, 0.82) and each millimeter increase in the sum of TSF and SSF was associated with an increase in SBP of 0.20 mm Hg (0.06, 0.34). However, waist circumference was not associated with SBP or DBP. In a model including both birth weight and the child's current BMI, the association of birth weight with SBP ($\beta=-1.71$; 95% CI: −2.48, −0.94; $P<0.001$) and DBP ($\beta=-1.41$; 95% CI: −2.21, −0.61; $P=0.001$) became stronger (data not shown). However, there was no evidence of an interaction between birth weight and child BMI on child BP ($P>0.1$).

Size at birth was associated with some, but not all, of the cardiovascular risk factors (Table 3). There was no association between birth weight and the risk of high glucose, low HDL cholesterol, or microalbuminuria after adjustment for confounding factors. However, with every kilogram increase in birth weight, there was a reduction in the risk of high triglycerides (0.64/kg; 95% CI: 0.41, 0.97) and high BP (odds ratio (OR): 0.64/kg; 95% CI: 0.51, 0.81) and a three-fold increased risk of high waist circumference (OR: 3.16/kg; 95% CI: 2.47, 4.41), after adjusting for confounding factors. Birth length was associated with a reduced risk of high BP but an increased risk of high waist circumference. Ponderal index was modestly associated with a reduced risk of high BP, but an increased risk of high waist circumference. Gestational age was not associated with any of the cardiometabolic risk factors, however.

Using multivariate linear regression, there were no significant associations between birth weight or length and HbA1c, fasting glucose, insulin or HOMA-IR after adjustment for potential confounders (data not shown). Each unit of increase in ponderal index at birth was associated with a 2% reduction in HOMA-IR (−2.4%; 95% CI: −4.7, −0.1), but it was not significantly associated with HbA1c, fasting glucose or insulin. The child's BMI, waist circumference, and sum of skinfold thicknesses were not associated with HOMA-IR. Birth weight and length were positively associated with the MetS score after adjustment for confounders ($P<0.01$). Ponderal index and gestational age were not associated with the MetS.

Discussion

In this rural population where the mean (S.D.) birth weight was 2.64 kg (0.41), birth weight was negatively associated with BP and triglycerides among 6–8 year old children. Birth weight was also positively associated with BMI, waist circumference, and the sum of skinfold thicknesses in childhood. Yet, there was no association between birth weight and any measures of insulin resistance. Other measures of size at birth, including birth length and ponderal index, were not as

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Table 3. *The association of measures of size at birth with the cardiovascular risk factors in children aged 6–8 years*

	Risk factor[a]					
	High glucose	Low HDL cholesterol	High triglycerides	High blood pressure	High waist circumference	Microalbuminuria
Children at risk: n/total, (%)	432/2613 (17)	2084/2875 (72)	151/1679 (9)	576/2729 (21)	424/2757 (15)	110/2493 (4)
	OR (95% CI)[b]					
Birth weight (kg)	1.14 (0.88, 1.49)	1.02 (0.82, 1.28)	0.64* (0.41, 0.97)	0.64*** (0.51, 0.81)	3.16*** (2.47, 4.41)	1.20 (0.74, 1.93)
Birth length (cm)	1.05 (0.99, 1.11)	1.02 (0.97, 1.07)	0.93 (0.85, 1.01)	0.93** (0.88, 0.97)	1.23*** (1.16, 1.30)	1.04 (0.95, 1.15)
Ponderal index (kg/m^3)	0.99 (0.95, 1.03)	1.00 (0.96, 1.04)	0.96 (0.89, 1.03)	0.97 (0.93, 1.00)	1.09*** (1.04, 1.14)	1.01 (0.93, 1.09)
Gestational age (weeks)	1.00 (0.97, 1.04)	1.01 (0.98, 1.04)	0.99 (0.94, 1.05)	1.00 (0.96, 1.03)	1.00 (0.97, 1.05)	1.01 (0.95, 1.08)

[a] Risk factors were defined as: glucose ⩾85th percentile, HDL cholesterol<35 mg/dl, fasting triglycerides ⩾150 mg/dl, SBP or DBP ⩾ 90th percentile of the referent population,[10] waist circumference ⩾85th percentile, and microalbuminuria ⩾30 mg/g.

[b] Each cell represents the odds ratio and 95% confidence interval for each factor using logistic regression models, adjusted for child age, sex, ethnicity, maternal literacy, and radio ownership. Glucose and HDL cholesterol models additionally adjusted for fasting.

*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$

strongly associated with these outcomes. Birth weight was positively associated with the MetS risk score. In comparison to other populations studied, this one would more aptly be characterized as undernourished rather than overweight. The prevalence of stunting and underweight was 20%–29% at birth and 46%–53% at follow-up, respectively. Thus, it is more likely that children experienced growth faltering rather than rapid catch-up growth between birth and childhood.

Despite their overall low BMI, we observed an inverse association between birth weight and BP, in both crude and adjusted models, that was comparable in magnitude to the findings of those of a number of other studies among children.[6–10] A proposed mechanism through which a poor fetal environment may influence BP may be through the growth and development of the kidney.[29] However, we were unable to document an association between birth weight and microalbuminuria in childhood, in spite of the observed association with BP. Contrasting this, we had observed a reduced risk of microalbuminuria, although no effect on BP, with maternal folic acid supplementation in this same population.[15] This would suggest that the effects of folic acid on kidney function and birth weight on BP were mediated through different pathways. One possible explanation is that lower birth weight may have hindered vascular development[30] or promoted greater levels of inflammation[31] without measurable effects on microalbuminuria.

Similar to what has been described by others,[32] we found an inverse association between size at birth and BP, a positive association between size at birth and in childhood, and a positive association between these measures of current body size and BP. It is possible that more rapid weight gain among lower birth weight babies could have contributed to an elevation inBP.[33] Low birth weight infants are more likely to experience catch-up growth during the first year,[34] which likely occurred to some degree in our cohort. However, in other low and middle income country settings, rapid growth in infancy seems to carry no additional risk of high BP, yet weight gain after the age of 2 years has been found to be positively associated with BP.[35] Unfortunately, we are unable to differentiate these periods of weight gain in this cohort.

We observed no association between birth weight or length and insulin resistance. Data from other studies examining the insulin resistance in children have been mixed. Some studies have reported an inverse association between size at birth and insulin resistance,[36] no association,[37,38] or an inverse association only among children of high BMI.[39] In a comparable population to our own, Joglekar *et al.* found no association between birth weight and measures of insulin resistance or cholesterol among a cohort of 6-year-old in rural India,[6] which differed from that group's earlier findings among a cohort of 8-year-old children in a more urban neighboring area where birth weight was negatively associated with HOMA.[40] Among adults, there is more consistent evidence in support of a link between birth weight and insulin resistance or type 2 diabetes.[5] The lack of an observed association in our study between size at birth and insulin resistance could

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be due to the younger age of follow-up in our cohort of children. Also, rapid weight gain after the age of 2 years may be a necessary intermediary between low birth weight and insulin resistance. Evidence from animal studies provides support for these two explanations.[41,42]

MetS is a clustering of risk factors for CVD, including a combination of obesity, hypertension, dyslipidemia and impaired glucose tolerance.[26] In our study, larger size at birth was associated with a reduced risk of both hypertension and high triglycerides. In contrast, higher birth weight was associated with an increased waist circumference in childhood. There seemed to be a positive association of birth weight and MetS score, likely driven by the strong positive association between birth weight and waist circumference. This contrasts with our earlier finding in this cohort that maternal folic acid supplementation during pregnancy reduced the risk of MetS in childhood, despite a lack of effect on each of the components individually.[15] Therefore, it appears as if birth weight is associated with some, but not all, of the components of MetS, while maternal intake of folic acid may be associated with cardiometabolic risk through alternative pathways.

Our study adds to the literature by presenting data from a large community-based study in rural South Asia, a population for whom the *Developmental Origins of Health and Disease* research is most relevant because of the high incidence of intrauterine growth restriction. These data illustrate that the associations between birth size and later life outcomes are different than the effects of antenatal micronutrients; presented previously.[15] Our study's strengths include its large sample size and high rate of follow-up. Unfortunately, there was a low level of compliance with a request for fasting, resulting in substantial missing data on certain biomarkers. For this reason and because of the documented association between non-fasting lipid profiles and cardiovascular risk, we chose to analyze both fasting and non-fasting cholesterol data. This was not performed with insulin, HOMA, and triglyceride measures because of their responsiveness to recent food intake, but the consistency between the HOMA findings, reported only in children who had fasted, with HbA1c, measured in all children, would indicate that bias could not entirely explain the negative results. We have also attempted to control for potential confounding variables, but as with any observational study, there is the possibility of unmeasured residual confounding. Finally, if indeed the mismatch between prenatal and postnatal environment is an important factor programming an elevated risk of chronic disease,[43] then this population undernourished during gestation may not have experienced the obesogenic postnatal environment to begin to show signs of insulin resistance.

Conclusions

Among 6–8 year old children in rural Nepal, we found an approximate 1.0 mm Hg reduction in SBP and DBP per kilogram of increased birth weight and prevalence of hypertension that was twice the rate among children in the United States. Even mildly elevated BP in childhood can have adverse effects on vascular structure and function[21] and small differences in BP could be amplified with age.[4] At the population level, a 2 mm Hg reduction in mean BP among adults has been shown to be associated with 4.3%–6.5% reduction in deaths because of CHD and stroke.[44] Even in this population, where the mean difference in BPor triglycerides was small, the reduction in risk of hypertension and high triglycerides was substantial with a 1 kg increment in birth weight. Assuming a more modest 0.5 S.D. shift in the birth weight distribution (~ 200 g), one might expect a 7% reduction in this risk of hypertension or high triglycerides. Yet, few interventions during pregnancy have been found to improve birth weight by this amount. Thus, the most critical question is how to effectively improve fetal growth and development in settings where intrauterine growth retardation is common.

There is much still to be learned about the complex factors influencing cardiovascular risk in South Asia. This study provides a window into a population that has been understudied with regard to these long-term effects of undernutrition in early life. It will be important to follow these children in the future to better understand the determinants of cardiometabolic risk given their poor start to life.

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Statement of Interest

None.

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