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ORIGINAL ARTICLE

Newborn size, infant and childhood growth, and body composition and cardiovascular disease risk factors at the age of 6 years: the Pune Maternal Nutrition Study

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Objective: To study associations of size and body proportions at birth, and growth during infancy and childhood, to body composition and cardiovascular disease (CVD) risk factors at the age of 6 years.
Design: The Pune Maternal Nutrition Study, a prospective population-based study of maternal nutrition and CVD risk in rural Indian children.
Methods: Body composition and CVD risk factors measured in 698 children at 6 years were related to body proportions and growth from birth.
Measurements: Anthropometry was performed every 6 months from birth. At 6 years, fat and lean mass (dual X-ray absorptiometry) and CVD risk factors (insulin resistance, blood pressure, glucose tolerance, plasma lipids) were measured.
Results: Compared with international references (NCHS, WHO) the children were short, light and thin (mean weight <-1.0 s.d. at all ages). Larger size and faster growth in all body measurements from birth to 6 years predicted higher lean and fat mass at 6 years. Weight and height predicted lean mass more strongly than fat mass, mid-upper arm circumference (MUAC) predicted them both approximately equally and skinfolds predicted only fat mass. Neither birthweight nor the 'thin-fat' newborn phenotype, was related to CVD risk factors. Smaller MUAC at 6 months predicted higher insulin resistance ($P<0.001$) but larger MUAC at 1 year predicted higher systolic blood pressure ($P<0.001$). After infancy, higher weight, height, MUAC and skinfolds, and faster growth of all these parameters were associated with increased CVD risk factors.
Conclusions: Slower muscle growth in infancy may increase insulin resistance but reduce blood pressure. After infancy larger size and faster growth of all body measurements are associated with a more adverse childhood CVD risk factor profile. These rural Indian children are growing below international 'norms' for body size and studies are required in other populations to determine the generalizability of the findings.
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Keywords: birth size; infant growth; childhood growth; cardiovascular disease risk factors; body composition; India

Introduction

South Asia has the highest rate of rise of type 2 diabetes in the world[1] and cardiovascular disease (CVD) is predicted to become the leading cause of death by 2015.[2] Insulin resistance is an important risk factor for type 2 diabetes and CVD in South Asian populations.[3,4] South Asians develop the insulin resistance syndrome (IRS), and related morbidity and mortality at a younger age and lower body mass index (BMI) than white Caucasians.[5,6] This has been attributed to a characteristic South Asian body phenotype, comprising a low muscle mass, high percentage body fat and tendency to central adiposity[7,8] ('thin-fat' phenotype[9]).

There is mounting evidence that small size at birth is associated with an increased risk of CVD, type 2 diabetes and the IRS.[10–12] In the majority of these studies, the only measurement at birth is weight. Recently, we described the detailed anthropometry of South Asian Indian newborns, and showed that they are markedly light in weight, have a

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reduced non-fat soft tissue mass but are relatively adipose compared with white Caucasian newborns (the 'thin-fat' newborn phenotype).[9,13,14] We do not yet know how this relates to later CVD risk.

The risk of CVD, type 2 diabetes and the IRS is also related to growth in infancy and childhood. Studies in adults have shown that higher weight or BMI at the age of 1 year is associated with a decreased risk of disease, while rapid weight or BMI gain in childhood is associated with an increased risk.[15–20] Studies in children have shown that features of the IRS are elevated in those who had grown heavier, taller or fatter relative to their peers.[21–26] Childhood may be an opportune time to intervene to prevent excessive weight or BMI gain and thus prevent the development of insulin resistance and later disease. However, it is not clear which components of childhood body composition (adipose tissue, lean mass or skeleton) are related to later risk, nor do we know the critical time during childhood when interventions to limit weight gain may be appropriate.[27] Most published studies were retrospective, with large dropout rates, making their interpretation difficult.

The Pune Maternal Nutrition Study is a prospective, population-based study of maternal nutrition, pregnancy outcome and CVD risk in the children, being carried out in a rural community in Western India. For the children, detailed anthropometric measurements were made at birth, and serially every 6 months during infancy and childhood. CVD risk factors were measured at the age of 6 years to test the following hypothesis: low birthweight and the 'thin-fat' phenotype at birth, smaller size in infancy and more rapid childhood growth, especially fat gain, will predict higher levels of components of the IRS. Associations between maternal diet during pregnancy and cardiovascular outcomes in the children will be reported separately.

Patients and methods

The Pune Maternal Nutrition Study methodology has been described previously[9] (Figure 1). We prospectively studied non-pregnant married women from six villages near Pune, to record their menstrual dates and anthropometry. Women who became pregnant were studied twice during gestation, to measure their nutrition and fetal growth. There were 770 deliveries, including 8 stillbirths. The babies were measured within 72 h of birth by one of five trained fieldworkers. Birthweight was measured to the nearest 25 g using a Salter Spring balance, crown-heel length to the nearest 0.1 cm using a portable Pedobaby Babymeter (ETS JMB, Brussels, Belgium), triceps and subscapular skinfold thicknesses were measured to the nearest 0.1 mm, on the left side of the body, using Harpenden skinfold calipers (CMS Instruments, London, UK) and occipitofrontal head circumference and mid-upper arm circumferences (MUAC) were measured to the nearest 0.1 cm using fibreglass tapes (CMS Instruments). Of 762 liveborn babies, 702 were measured at birth. The duration of exclusive breastfeeding was recorded at 1-year follow-up.

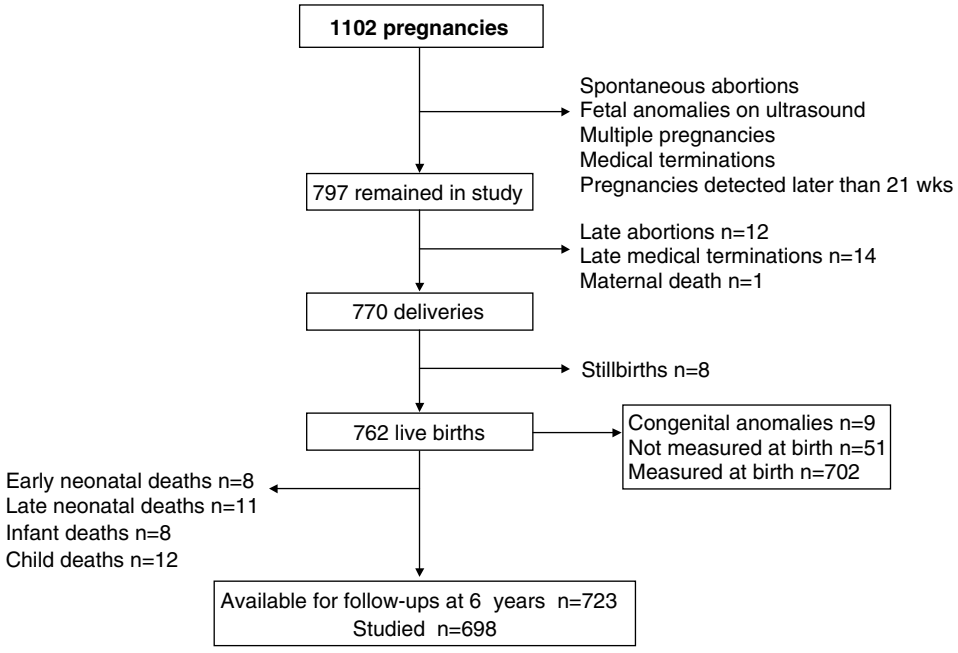

Figure 1 Pune Maternal Nutrition Study.

Post-natal anthropometry
The children were measured every 6 months (±2 months) with follow up rates of more than 90%. Measurements included weight, length or height; MUAC and subscapular and triceps skinfold thickness. Weight was measured to the nearest 0.1 kg using electronic weighing scales (Atco Healthcare Ltd, Mumbai, India). Up to the age of 2 years supine length was measured using the same technique as at birth; from 2 to 5 years standing height was measured to the nearest 0.1 cm using a portable Harpenden stadiometer, and at 6 years using a wall-mounted Microtoise (CMS Instruments Ltd, London, UK). MUAC and skinfold measurements were made using the same protocol as at birth. Inter- and intraobserver variation studies were conducted every 6 months, with retraining sessions as needed, to maintain the quality of measurements, which were made by five observers over the course of the study.

Investigations in the children at 6 years
The children were called for further investigations between 6 and 7 years. Transport was arranged to bring the children and their parents to the Diabetes Unit, KEM Hospital, Pune, in the evening. Children were provided with a standard dinner, and then fasted overnight (nil by mouth except water). In the morning a fasting blood sample was collected, followed by a 1.75 g/kg body weight oral glucose load and two further blood samples 30 and 120 min later. Blood pressure was measured in the supine position, on the right arm, 1 h after the fasting blood sample, using a digital blood pressure monitor (UA 767PC, A&D Instruments Ltd, Oxford, UK) and the appropriate cuff size for the MUAC. Two readings were taken 5 min apart and the second reading was used for analysis. Standardized anthropometric measurements (height, weight, skinfolds, MUAC) were also performed on the parents.

The children's body composition (total fat and lean mass and percentage body fat) was measured by dual X-ray absorptiometry (DXA) (Lunar DPX-IQ 240, Lunar Corporation, Madison, WI, USA). Scans were analysed using Paediatric Software version 4.7.

Plasma glucose and serum cholesterol, high-density lipoprotein (HDL) cholesterol and triglyceride concentrations were measured using a Hitachi 911 automated analyser (Hitachi Ltd, Tokyo, Japan) by standard enzymatic methods. Plasma insulin was measured using a two-site immunoradiofluorimetric (Delfia) assay; the sensitivity of the assay was 4.8 pmol/l and intra- and interbatch coefficients of variation were <4.3 and $<8.8\%$. Relative insulin resistance was calculated from fasting glucose and insulin concentrations using the homoeostasis model assessment of insulin resistance (HOMA-R) equation.[28]

Socio-economic status (SES) at 6 years was measured using the Standard of Living Index designed by the National Family Health Survey.[29] Ethical permission for the study was granted by the KEM Hospital Ethical Committee, and by the local village leaders. Parents gave informed written consent on behalf of their children.

Statistical methods

Variables with skewed distributions (skinfolds, insulin and triglyceride concentrations, and insulin resistance) were log transformed or inverted to satisfy assumptions of normality. All available data were used at each age. Measurements at birth were adjusted to a gestational age of 40 weeks using multiple linear regression. We use the term 'size' to describe anthropometric measurements. Size in infancy refers to measurements at 6 months and 1 year; size in childhood to measurements at 2, 3, 4 and 5 years of age; and current size to measurements at 6 years. Body composition refers to fat and lean mass measured using DXA. Body composition measurements were adjusted to the age of 6 years using multiple linear regression. Associations between earlier size and fat and lean mass are reported using standardized β coefficients (indicating the s.d. change in the outcome per s.d. change in the predictor variable) to enable comparison of the effects of earlier size on these two body composition measurements. Associations between earlier size and CVD risk factors at 6 years were analysed by multiple linear regression, using three models: (1) including early size alone, (2) adjusting for current weight and (3) including the interaction between early size and current weight.[30] Differences between the sexes in associations between earlier size and outcomes at 6 years were examined by including interaction terms (sex × the early size variable) in the regression models.

In addition to using individual birth measurements to predict 6-year outcomes, a principal components analysis was carried out to derive composite measures describing the body proportions of the baby. From the original variables (newborn weight, length, head circumference, subscapular and triceps skinfolds, and MUAC) we derived new variables or 'components' that are uncorrelated. In our data, the first principal component had high positive loadings for all birth measurements, indicating that this was a measure of overall body size (Table 1). The second component had strong

Table 1 Principal component analysis of size at birth

Factors	*Components*			
	1	*2*	*3*	*4*
Weight	0.90	−0.11	0.07	−0.05
Height	0.70	−0.45	0.48	0.23
Head circumference	0.73	−0.33	−0.51	0.29
Subscapular skinfold	0.75	0.57	−0.01	0.07
Triceps skinfold	0.74	0.58	0.07	0.05
MUAC	0.80	−0.24	−0.08	−0.52
Variance (%)	59.9	17.3	8.4	6.9

Abbreviation: MUAC, mid-upper arm circumference.

positive loadings for skinfolds and negative loadings for length, head circumference and MUAC. We used this component as an indicator of the 'thin-fat' newborn phenotype. Overall, 76% of the variation in size at birth was explained by the first two principal components. Both principal components were included simultaneously, with and without adjusting for 6-year weight, in multiple regression analyses to predict CVD risk factors at 6 years.

Growth refers to change in size over time. To examine independent associations of growth during different periods (at birth, 6 months, 6 months to 1 year and every year up to the age of 6 years) with outcomes at 6 years, we used Royston's conditional s.d. scores method.[31] Standard deviation scores for all body measurements, and conditional s.d. scores, were calculated at exact ages of 6 months, and every completed year thereafter. Growth charts were constructed (not shown) separately for boys and girls, using a multi-level regression model (MLN software, University of London), from which age- and sex-specific s.d. scores of achieved size at these time points, and s.d. scores of growth between successive time points, conditional on previous size, were derived. These conditional s.d. scores are uncorrelated with each other and indicate whether growth during a particular time period is faster or slower than would be predicted from the average growth of the cohort and the child's size at earlier time points. The conditional s.d. scores can be used simultaneously in a regression model, along with size at birth, to determine associations of faster or slower growth at different time points with later outcomes. For the conditional s.d. scores analysis, we used data from children with complete measurements at birth, 6 months and annually up to 6 years ($n = 566$). Analyses were carried out using SPSS version 11.0 and Stata 7.0. Effects of growth on different outcomes were compared by using the seemingly unrelated regression model (Sureg) command.

Results

Out of the 762 live births, 39 died before the age of 6 years (Figure 1); of 723 children available for follow up at 6 years, 698 children (97%) attended for measurements. Table 2 shows the children's anthropometric measurements at birth, 1 and 6 years, and 6-year CVD risk factor and body composition measurements. Compared with international references (NCHS[32] and WHO[33]) the children were light, short and thin. Compared with a UK skinfold reference[34] (NCHS and WHO do not provide skinfold references) the children were relatively truncally adipose at 6 years, with subscapular skinfold s.d. scores higher than s.d. scores for weight, height and BMI. We limited our analysis to the following outcomes: insulin resistance (HOMA-R), systolic blood pressure and plasma triglyceride; total and HDL cholesterol; glucose concentrations and fat and lean mass.

Table 2 Children's anthropometric measurements (median and interquartile range) at birth, 1 and 6 years, and 6-year CVD risk factors, body composition

	Boys (n = 374)	*Girls (n = 328)*
Birth (n = 702)		
Weight (kg)	2.78 (2.59–2.98)	2.64 (2.45–2.89)
Length (cm)	48.53 (47.4–49.7)	47.8 (46.7–48.8)
Ponderal index (kg/cm^3)	24.0 (22.7–25.5)	24.4 (23.1–25.7)
MUAC (cm)	9.8 (9.3–10.4)	9.8 (9.2–10.4)
Triceps (mm)	4.2 (3.6–4.7)	4.3 (3.7–4.7)
Subscapular (mm)	4.1 (3.6–4.7)	4.3 (3.7–4.8)
Weight s.d. (NCHS, WHO)	−1.56, −1.27	−1.77, −1.43
Length s.d. (NCHS, WHO)	−0.56, −0.73	−0.61,−0.73
% <−2 s.d. for weight (NCHS, WHO)	13.8, 24.4	26.3, 30.2
% <−2 s.d. for length (NCHS, WHO)	8.3, 20.7	12.1, 16.1
1 year (n = 691)	*(n = 367)*	*(n = 324)*
Weight (kg)	8.1 (7.6–8.7)	7.5 (6.8–8.0)
Length (cm)	72.6 (70.8–74.2)	71.2 (69.3–73.1)
BMI (kg/m^2)	15.4 (14.6–16.2)	14.6 (13.9–15.4)
MUAC (cm)	14.1 (13.3–14.7)	13.5 (12.8–14.2)
Triceps (mm)	6.8 (6.0–7.8)	6.8 (5.8–8.0)
Subscapular (mm)	5.6 (4.8–6.4)	5.4 (4.8–6.4)
Weight s.d. (NCHS, WHO)	−2.32, −1.60	−2.37, −1.44
Height s.d. (NCHS, WHO)	−1.22, –1.35	−1.12, −1.11
Triceps s.d. (UK)	−1.76	−1.74
Subscapular s.d. (UK)	−1.37	−1.54
% <−2 s.d. for weight (NCHS, WHO)	63.0, 25.0	71.0, 28.1
% <−2 s.d. for height (NCHS, WHO)	23.0, 26.0	17.0, 20.0
6 years (n = 698)	*(n = 370)*	*(n = 328)*
Weight (kg)	16.4 (15.2–17.6)	15.7 (14.6–16.9)
Height (cm)	109.9 (107.1–113.2)	109.4 (106.4–112.5)
BMI (kg/m^2)	13.5 (12.9–14.1)	13.1 (12.5–13.7)
MUAC (cm)	15.2 (14.5–16.0)	15.1 (14.4–15.8)
Triceps (mm)	5.9 (5.1–6.7)	6.4 (5.5–7.4)
Subscapular (mm)	4.8 (4.3–5.2)	5.1 (4.6–5.9)
Weight s.d. (NCHS)	−1.70	−1.72
Height s.d. (NCHS)	−1.17	−1.11
BMI s.d. (NCHS)	−1.57	−1.60
Triceps s.d. (UK)	−1.34	−1.50
Subscapular s.d. (UK)	−0.35	−0.53
% <−2 s.d. for weight (NCHS)	47%	51%
% <−2 s.d. for height (NCHS)	13%	16%
% <−2 s.d. for BMI (NCHS)	49%	49%
Glucose-insulin (OGTT)		
Fasting plasma glucose (mmol/l)	5.0 (4.72–5.33)	4.83 (4.53–5.16)
30 min plasma glucose (mmol/l)	8.11 (6.94–9.27)	8.22 (7.33–9.19
120 min plasma glucose (mmol/l)	5.38 (4.67–6.17)	5.61 (4.96–6.33)
Fasting plasma insulin (pmol/l)	18.0 (9.6–27.6)	19.8 (10.8–30.6)
30 min plasma insulin (pmol/l)	137.4 (85.8–198.6)	156.6 (109.8–220.2)
120 min plasma insulin (pmol/l)	51.0 (27.0–81.6)	67.8 (19.8 –107.4)
HOMA-R	0.65 (0.35–1.02)	0.74 (0.38–1.10)
Lipids		
Total cholesterol (mmol/l)	3.24 (2.89–3.64)	3.31 (2.87–3.69)
HDL cholesterol (mmol/l)	1.05 (0.92–1.25)	1.05 (0.86–1.21)
Triglycerides (mmol/l)	0.66 (0.56–0.81)	0.66 (0.55–0.82)
Blood pressure		
Systolic (mm Hg)	92 (86–99)	90 (82–98)
Diastolic (mm Hg)	54 (48–60)	54 (47–59)
Body composition		
Fat mass (kg)	2.9 (2.3–3.5)	3.3 (2.6–3.9)
Lean mass (kg)	13.0 (12.2–14.2)	12.1 (11.2–13.0)

Abbreviation: BMI, body mass index; HDL, high-density lipoprotein; HOMA-R, homoeostasis model assessment of insulin resistance; MUAC, mid-upper arm circumference; NCHS, National Center for Health Statistics; OGTT, oral glucose tolerance test; UK, United Kingdom; WHO, World Health Organization. Measurements at birth are adjusted to a gestational age of 40 weeks, and body composition measurements to a post-natal age of 6 years, using linear regression.

Six-year size, body composition and CVD risk factors

Larger current size (weight, height and MUAC) was associated with higher levels of HOMA-R and systolic blood pressure ($P<0.001$ for all), and larger skinfold thicknesses with higher HOMA-R ($P=0.01$) and plasma triglyceride and cholesterol concentrations ($P=0.01$). BMI was related only to systolic blood pressure ($P=0.05$). Higher 6-year fat mass predicted higher HOMA-R, total cholesterol and 120-min plasma glucose concentrations ($P<0.001$); these associations were independent of current height. Lean mass was positively related to systolic blood pressure ($P<0.001$) and inversely related to 120-min plasma glucose concentrations ($P<0.001$) independent of current height.

Size at birth, 6-year body composition and 6-year CVD risk factors

Higher weight, length and MUAC at birth and larger overall newborn size (principal component 1) were associated with higher 6-year fat and lean mass ($P<0.05$ for all). The associations were stronger with lean mass than with fat mass (standardized $\beta=0.13$, (95% confidence intervals (CI) 0.05, 0.21); $P=0.001$ for fat mass and 0.34 (0.26, 0.41); $P=0.001$ for lean mass, per s.d. change in birthweight; $P=0.001$ for the difference between the associations). Skinfolds at birth were not predictive of body composition at 6 years. There were positive associations, of approximately equal strength, between the 'thin-fat' birth phenotype (principal component 2) and both fat and lean mass at 6 years (standardized $\beta=0.11$, $P<0.001$ for fat mass and $\beta=0.09$, $P<0.001$ for lean mass).

Of the individual birth measurements, thinner subscapular skinfold thickness at birth was associated with higher 120-min glucose concentrations (unadjusted $P=0.005$; after adjusting for current weight $P=0.005$; interaction neonatal subscapular $\times$ current weight $P=0.2$). Birthweight was inversely related to blood pressure after adjusting for 6-year weight ($\beta=-3.7$ mm Hg (95% CI -7.0 to -0.5) per kg increase in birthweight; $P=0.02$); however there was no statistically significant interaction between birthweight and current weight ($P=0.7$). There were no associations between the 'thin-fat' birth phenotype and CVD risk factors at 6 years.

Size in infancy, 6-year body composition and 6-year CVD risk factors

Higher weight, length and MUAC at 6 months and 1 year predicted greater 6-year lean and fat mass ($P<0.001$ for all). Standardized β-values for the associations of weight, length and MUAC with 6-year body composition were similar for lean and fat mass (lean mass: 0.38, 0.39, 0.24; fat mass: 0.35, 0.21, 0.28; no significant difference between associations with lean and fat mass). Equivalent values for 1-year weight, length and MUAC were (with lean mass) 0.47, 0.39, 0.25 and (with fat mass) 0.44, 0.26, 0.35 (no significant differences). Larger skinfolds at 6 months and 1 year predicted greater 6-year fat mass (standardized $\beta=0.22$ and 0.26, $P<0.001$ for subscapular and 0.19 and 0.15, $P<0.001$ for triceps) and were unrelated to lean mass at 6 years.

Lower MUAC at 6 months was associated with higher HOMA-R (unadjusted $P<0.001$; adjusted for current weight $P=0.001$; no significant interaction with current weight, $P=0.5$) (Figure 2). Higher MUAC at 1 year predicted higher systolic blood pressure (unadjusted $P<0.001$; adjusted for current weight $P=0.1$; no significant interaction with current weight $P=0.8$). Larger subscapular skinfolds at 1 year were associated with lower HDL-cholesterol concentrations (unadjusted $P=0.03$; adjusted for current weight $P=0.02$; interaction with current weight $P=0.04$).

Figure 3 shows s.d. scores for measurements from birth to 6 years for children who were above the top quartile for systolic blood pressure and HOMA-R at 6 years. The contrast between MUAC measurements in infancy for children with high 6-year blood pressure (high infant MUAC) and high HOMA-R (low infant MUAC) is shown.

Size in childhood, 6-year body composition and 6-year CVD risk factors

Larger weight, height and MUAC at all ages from 2 to 5 years were associated with higher fat and lean mass ($P<0.001$ for all). Standardized β values for the association between height and 6-year lean mass ranged from 0.57 at 2 years to 0.65 at 5 years, while those between height and fat mass ranged between 0.47 at 2 years and 0.50 at 5 years (P for difference between associations with lean and fat <0.05 for all). Corresponding data for MUAC were (with lean mass) 0.30–0.33 and (for fat mass) 0.34–0.45 (no significant differences). Skinfold thickness measurements during childhood continued to predict fat mass; standardized β values for the association ranged between 0.28–0.34, $P\leqslant0.001$ for subscapular and 0.23–0.40, $P<0.001$ for triceps.

Weight, height and MUAC in childhood, but not skinfold thicknesses, were positively associated with 6-year HOMA-R and systolic blood pressure. These associations strengthened progressively with increasing age (Figure 2). Higher subscapular skinfold thickness at all ages from 2 to 5 years was associated with lower plasma HDL cholesterol concentrations (Figure 2) (unadjusted $P<0.05$; adjusted for current weight $P<0.05$; no significant interaction with current weight). Size in childhood showed no associations with plasma cholesterol, triglyceride and 120-min glucose concentrations (data not shown).

Growth, 6-year body composition and 6-year CVD risk factors

Faster weight and height growth at every age from birth onwards was associated with higher fat and lean mass at 6 years. The effects were stronger with lean mass (Figure 4). Faster growth in subscapular skinfold thickness from 1 year onwards, and in triceps skinfold thickness from 2 years onwards (data not shown), was associated with higher 6-year

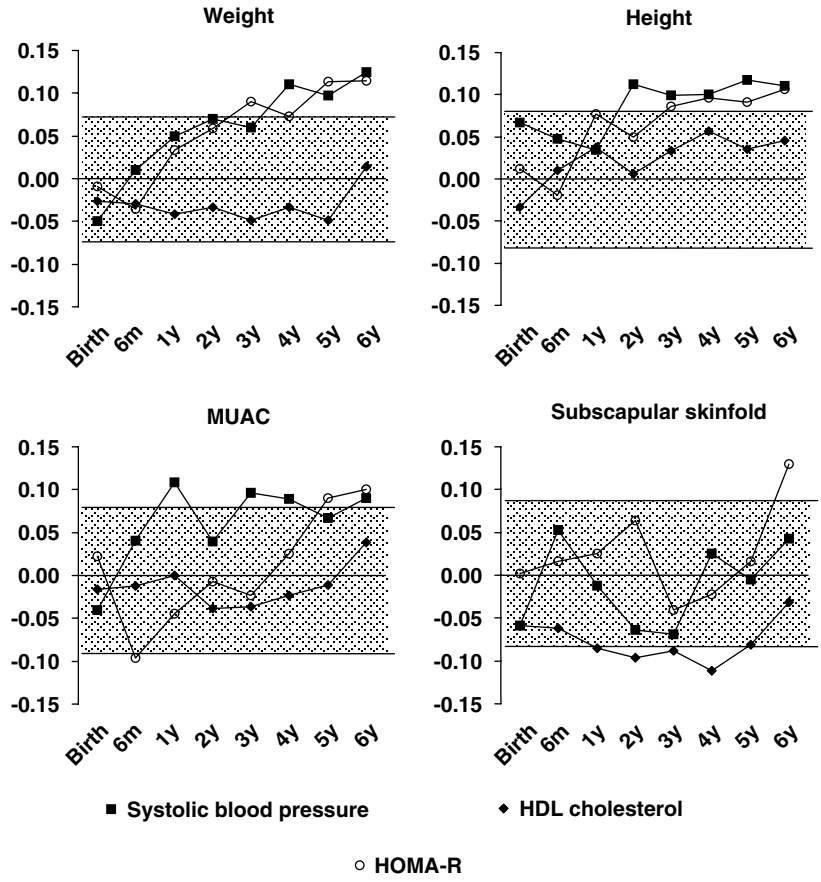

Figure 2 Partial correlation coefficients (adjusted for age and sex) between size measurements from birth to 6 years and CVD risk factors measured at 6 years. (Those outside the shaded band are statistically significant, $P<0.05$.)

fat but not lean mass. Faster growth in MUAC at all ages was associated approximately equally with higher lean and fat mass.

Slower MUAC growth between birth and 6 months was associated with higher HOMA-R at 6 years (Figure 5). There were no other associations between growth from birth to 6 months and 6-year outcomes. Faster growth in weight and height after the age of 6 months or 1 year was associated with higher 6-year systolic blood pressure and HOMA-R (Figure 5). Faster growth in MUAC after 6 months was associated with higher blood pressure, and after 3 years with higher HOMA-R. Faster growth in subscapular skinfold thickness after 3 years was associated with higher blood pressure, and after 5 years with higher HOMA-R. Our conclusions were unchanged if the analysis was carried out using larger time intervals in childhood instead of 1 year intervals. All statistically significant associations in Figure 5 remained so after further adjusting for 6-year lean and fat mass, with the exception of those between height growth and systolic blood pressure. These became non-significant after adjusting for lean mass. Associations were similar in boys and girls.

Determinants of growth

Higher SES predicted faster growth in all body measurements from birth to 6 years ($P=0.04$). Larger maternal and paternal size (BMI and height) predicted faster growth in corresponding measurements at all ages ($P<0.05$ for all, adjusted for SES). Longer duration of exclusive breastfeeding (median 5, interquartile range 3, 6 months) was associated with lower weight gain between 6 months and 1 year ($P=0.004$, adjusted for SES and parental BMI and height) and slower growth in MUAC between 1 and 2 years ($P=0.005$). There were no significant associations between duration of exclusive breastfeeding and CVD risk factors, and no differences in 6-year CVD risk factors between children who were exclusively breastfed for 6 months or less ($n=376$) and those breastfed for longer than 6 months ($n=184$). Duration of exclusive breastfeeding was not associated with fat or lean mass and there was no difference in body composition between children who were exclusively breastfed for 6 months or less and those breastfed for longer than 6 months.

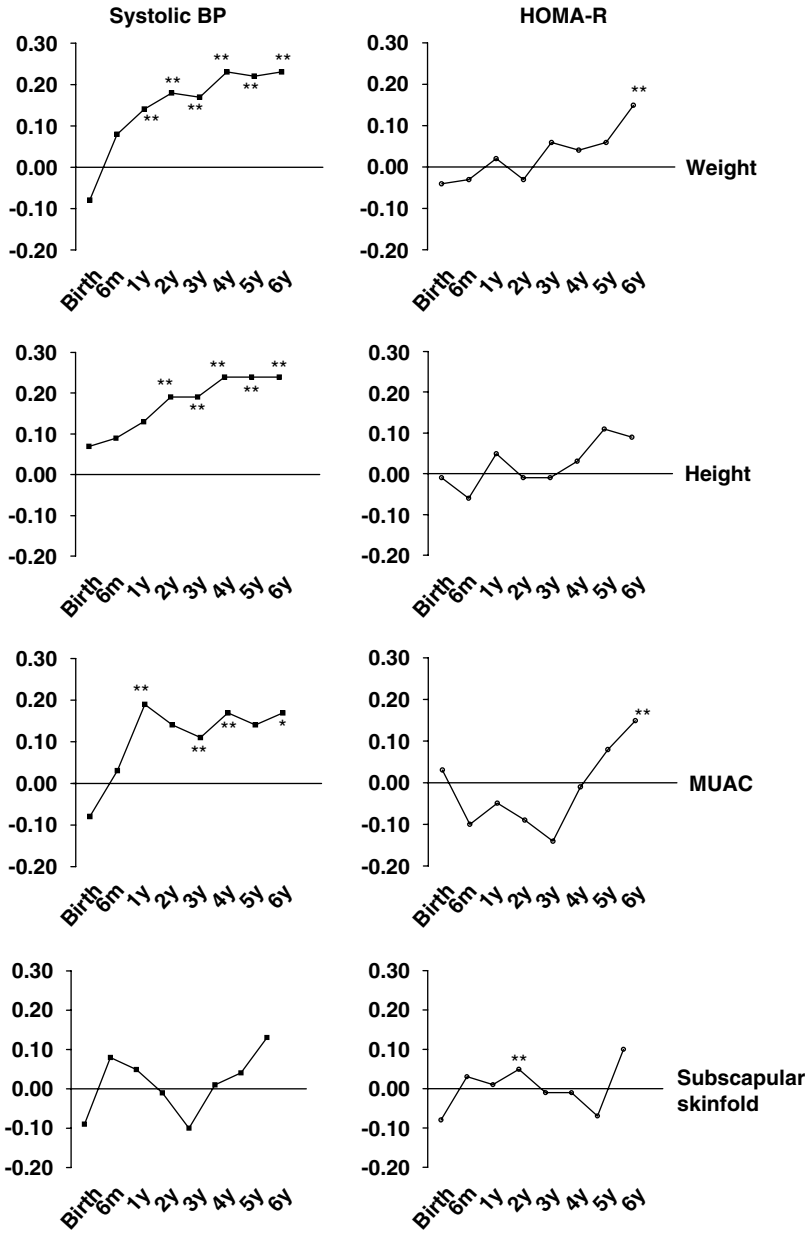

Figure 3 Mean sex-specific within-cohort size s.d. scores from birth to 6 years for children above the top quartile for systolic blood pressure and homoeostasis model assessment of insulin resistance (HOMA-R) at 6 years. Asterisks denote the statistical significance of the difference between s.d. scores of children above the top quartile for blood pressu or HOMA-R and the rest of the cohort; $*P<0.05$; $**P<0.01$.

Discussion

We have measured body composition and risk factors for CVD, in a large population-based cohort of rural Indian children who had serial anthropometry from birth to 6 years. As far as we know this is the first study to incorporate such detailed longitudinal measurements of body size with later body composition and CVD risk factors.

Larger overall size at birth (principal component 1) and larger newborn weight, length and MUAC predicted both fat and lean body mass at 6 years, but showed significantly stronger associations with lean mass. These findings are consistent with other studies in children and adults, and with the suggestion that fetal life is a critical period for the development of later lean body mass.[35–37] Skinfold measurements at birth were unrelated to body composition at 6

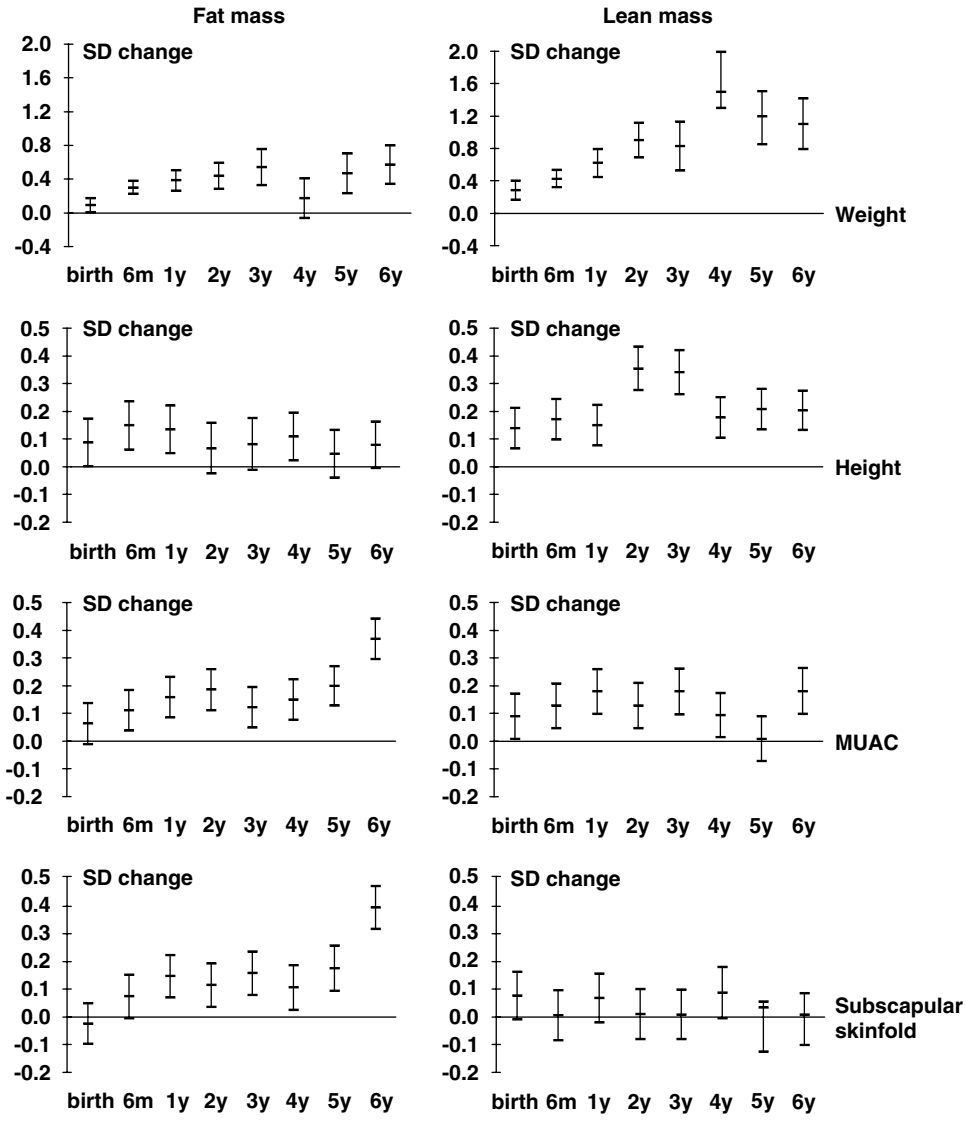

Figure 4 Mean and 95% CI for s.d. change in fat and lean mass at 6 years per s.d. increase in size measurements (weight, height, MUAC, subscapular skinfold) at all ages from birth to 6 years.

years, and the 'thin-fat' newborn phenotype (principal component 2, a contrast between skinfolds and other body measurements), which we expected to be associated predominantly with adiposity at 6 years, was related equally to fat and lean mass.

Birth measurements were largely unrelated to CVD risk factors at 6 years. Lower birthweight was associated with higher systolic blood pressure only after adjusting for 6-year weight. This contrasts with findings in a cohort of 8-year-old urban Pune children, among whom, after adjustment for current weight, lower birthweight was associated with higher blood pressure, HOMA-R and cholesterol concentrations.[24] An explanation could be relatively less post-natal growth in the rural children. Standard deviation scores for weight, height and BMI for the urban children were −1.21, −0.60, −1.60 (boys) and −0.91, −0.41, −1.23 (girls) according to the NCHS reference.[32] We previously speculated that the 'thin-fat' newborn phenotype would be associated with an adverse CVD risk profile at 6 years;[9] however, it was unrelated to CVD risk factors. Our data do not suggest important associations of small size at birth *per se* with an adverse CVD risk factor profile in prepubertal children in this population.

As expected, weight growth was associated with fat and lean mass, height growth with lean mass and skinfold growth with fat mass at 6 years. Somewhat unexpectedly, height growth was also associated with fat mass, which could just reflect larger size of the body. Faster MUAC growth

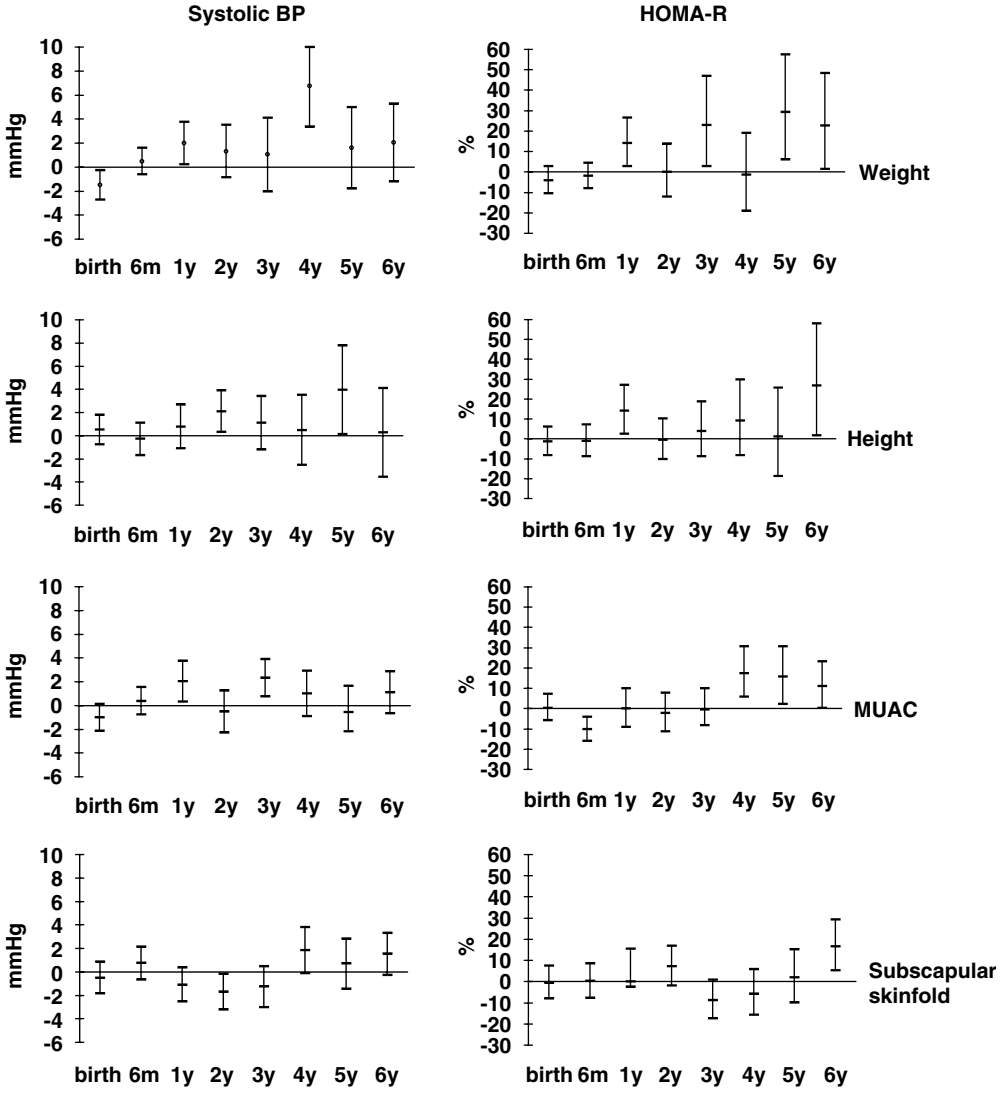

Figure 5 Mean and 95% CI for change in systolic blood pressure (BP) and percentage change in HOMA-R at 6 years per s.d. increase in size measurements at all ages from birth to 6 years.

predicted lean and fat mass approximately equally as expected from the components of MUAC (bone + muscle + fat). Previous studies have shown associations of weight, weight gain and length gain in infancy with lean mass in later life.[37–40] Unlike the previous studies (systematically reviewed),[41,42] we are able to predict fat and lean mass more specifically.

There is little information on associations between growth in early life and cardiovascular risk factors in childhood. In our study, slower MUAC growth between birth and 6 months was associated with higher insulin resistance at 6 years. This may be a chance finding, or indicate an association between growth of both fat and lean mass in the early post-natal period and the later development of insulin resistance. Larger body size or faster growth from birth to 6 months did not predict an adverse CVD risk factor profile at 6 years. There is currently controversy over the long-term effects of infant weight gain. Studies in adults suggest that lower weight or BMI at 1 year predicts an increased risk of CVD and type 2 diabetes.[11,15,17–19] However, among children born preterm who took part in randomized controlled trials of different infant feeds, those with more rapid weight gain in early infancy had increased CVD risk factors in childhood.[43] Our data do not suggest strong effects one way or the other of changes in body size during the first 6 post-natal months on CVD risk factors.

After 6 months, higher weight and height and faster growth in these measurements were associated with higher 6-year blood pressure and insulin resistance. The mechanisms linking rapid growth to CVD risk factors are unknown. Lever[44,45] proposed that the endocrine 'drivers' of growth also stimulate vascular smooth muscle hypertrophy. Another

possible mechanism is through changes in body composition, for example increased fat mass relative to lean mass. However, faster weight and height gain predicted lean mass more strongly than fat mass at 6 years. Larger earlier size or faster growth could be proxies for larger current size. Our findings would then imply that simply having larger fat and lean mass has adverse effects on CVD risk factors. The association between fat mass and insulin resistance probably reflects an excess release of fatty acids and adipocytokines. The link between larger lean mass and higher risk factors is difficult to explain. It could reflect functional characteristics or intramyocellular fat deposition.[46] Blood pressure is physiologically higher in taller people, and height is positively correlated with lean body mass. However, our data showed a positive association between 6-year lean mass and systolic blood pressure, independently of height, and other studies have shown positive associations between muscularity and blood pressure.[47,48] Brenner[49] has proposed that the number of renal nephrons, which is fixed during early development, may become inadequate later in life in the face of higher body weight, especially lean body mass, leading to hypertension.

In conclusion, our data show that larger size at birth and more rapid growth in early childhood is associated with higher lean body mass and increased CVD risk factors at 6 years. It is striking that these associations are found in a rural Indian population, among children who are growing slowly, and many of whom may be categorized as 'undernourished' according to WHO definitions.[50] The findings may not be generalizable to populations in Western countries where children are born heavier and remain larger throughout childhood, but would be applicable to a large number in developing countries. The effects we observed were small; an increase of one-third of an s.d. in weight in any year after infancy was associated with, on average, an increase of 6% in 6-year insulin resistance and 0.6 mm Hg blood pressure. However, even such small changes, when observed in childhood and across the normal range in a population can translate into important effects in public health terms.[51] Associations between 6-year CVD risk factors and growth during infancy were smaller compared to growth later in childhood. It has been recommended that weight gain should be promoted during infancy in undernourished populations. This is based on the evidence that this favours immediate survival,[52] and may prevent stunting and improve neurocognitive development.[53–55] Our findings do not conflict with this advice. However, children who grow rapidly at later ages in childhood may be at increased risk of type 2 diabetes mellitus and CVD.

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