ORIGINAL ARTICLES

Size at birth and plasma insulin-like growth factor-1 concentrations

C H D Fall, A N Pandit, C M Law, C S Yajnik, P M Clark, B Breier, C Osmond, A W Shiell, P D Gluckman, D J P Barker

Abstract

***Objective*—To test the hypothesis that reduced fetal growth leads to altered plasma insulin-like growth factor-1 (IGF-1) concentrations in childhood.**

***Design*—A follow up study of 4 year old children whose birth weights were recorded, and of 7 year old children whose weight, length, head circumference, and placental weight were measured at birth.**

***Setting*—Pune, India, and Salisbury, England.**

***Subjects*—200 children born during October 1987 to April 1989 in the King Edward Memorial Hospital, Pune, weighing over 2·0 kg at birth and not requiring special care, and 244 children born during July 1984 to February 1985 in the Salisbury Health District and still living there.**

***Main outcome measure*—Plasma IGF-1 concentrations.**

***Results*—In both groups of children, and consistent with findings in other studies, plasma IGF-1 concentrations were higher in taller and heavier children, and higher in girls than boys. Allowing for sex and current size, concentrations were inversely related to birth weight (Pune $p=0·002$; Salisbury $p=0·003$). Thus at any level of weight or height, children of lower birth weight had higher IGF-1 concentrations. The highest concentrations were in children who were below average birth weight and above average weight or height when studied. Systolic blood pressures were higher in children with higher IGF-1 concentrations (Pune $p=0·01$; Salisbury $p=0·04$).**

***Conclusions*—Children of lower birth weight develop higher circulating concentrations of IGF-1 than expected for their height and weight. This is consistent with the hypothesis that undernutrition in utero leads to reprogramming of the IGF-1 axis. The increase of plasma IGF-1 concentrations in low birthweight children may also be linked to postnatal catch-up growth. High IGF-1 concentrations may be one of the mechanisms linking reduced fetal growth and high blood pressure in later life.**

(*Arch Dis Child* 1995; 73: 287–293)

Keywords: insulin-like growth factor-1, birth weight, systolic blood pressure.

MRC Environmental Epidemiology Unit, Southampton General Hospital, Tremona Road, Southampton SO16 6YD
C H D Fall
C M Law
P M Clark
C Osmond
A W Shiell
D J P Barker

King Edward Memorial Hospital Research Centre, Pune, India
A N Pandit
C S Yanjik

Department of Paediatrics, University of Auckland, Auckland, New Zealand
B Breier
P D Gluckman

Correspondence to:
Dr Fall.

Accepted 21 June 1995

Recent studies have shown that men and women who had reduced fetal growth have increased rates of cardiovascular disease[1 2] and hypertension.[3 4] One mechanism proposed as a link between reduced fetal growth and cardiovascular disease is persisting changes in secretion of and sensitivity to the hormones that regulate fetal growth, including insulin and insulin-like growth factor-1 (IGF-1).[4–6] Low birth weight is associated with an increase of plasma insulin concentrations, and insulin resistance, in adult life.[7–12] We recently studied glucose and insulin concentrations during an oral glucose tolerance test in 4 year old children in Pune, India, and 7 year old children in Salisbury, England.[13 14] Children of low birth weight (Pune) or low ponderal index (weight/length^3) at birth (Salisbury) showed evidence of reduced insulin sensitivity. We hypothesised that fetal undernutrition leads to insulin resistance which is present in childhood and persists into adult life.

As yet there are no comparable data for IGF-1. We have measured plasma IGF-1 concentrations in fasting blood samples taken during our studies of glucose and insulin metabolism in children, and examined the relationship of IGF-1 to birth weight, and other measurements of body size at birth. We have also examined the relationship of plasma IGF-1 concentrations to blood pressure.

Subjects and methods

PUNE

The study sample was 404 singleton children, born in the King Edward Memorial Hospital (KEMH) during October 1987 to April 1989, weighing more than 2·0 kg at birth, and admitted to the routine postnatal wards (that is, they did not require special care). They were selected using random number tables

Table 1 Anthropometric data at birth and 4 years in Pune and comparison British data; values are median (3rd, 97th centiles)*

	Boys (n=104)	*Girls (n=96)*
Birth weight (kg)		
Pune	2·750 (2·083, 3·600)	2·700 (2·160, 3·509)
British standards	3·607 (2·918, 4·443)	3·463 (2·773, 4·245)
At 4 years:		
Weight (kg)		
Pune	13·0 (10·6, 16·9)	12·5 (10·0, 17·2)
British standards	16·5 (13·1, 20·4)	16·3 (13·1, 20·2)
Height (cm)		
Pune	97·6 (88·7, 105·7)	97·8 (88·1, 106·6)
British standards	101·6 (93·6, 109·7)	100·4 (92·4, 108·6)

*Standards for British children are from Gairdner and Pearson[17] and Tanner *et al.*[18]

from 1998 live births listed in the labour ward register, in which birth weights are recorded routinely. We wrote to the children's parents inviting them to the hospital, where a paediatrician explained the study and obtained consent. Eighty four children were no longer living at the address listed at birth and could not be traced. The parents of 201 (63%) of the remaining 320 allowed their child to take part.

Children were admitted to the KEMH, with a parent, the evening before the test, and fasted overnight. Blood pressure was measured in the left arm, during sleep, using an automated device (Dinamap), with a cuff of the recommended size for the measured mid-upper arm circumference. Two measurements were made at an interval of one minute, and the average used in the analysis. In the morning a fasting blood sample was taken after applying local anaesthetic cream (EMLA) to the venepuncture site. The child's weight was measured using a portable (Seca) scale to the nearest 0·5 kg and height using a wall mounted stadiometer (Microtoise) to the nearest 0·1 cm. Ethical permission for the study was given by the KEMH ethics committee.

SALISBURY

Subjects were recruited from 431 singleton children who had been born in Salisbury Health District between July 1984 and February 1985 (total number of singleton births=638) and who had taken part in our earlier study of blood pressure at the age of 4 years.[15] Information on the mother's pregnancy and delivery, and the baby's weight, length, head circumference, placental weight, and gestational age at birth were available from the obstetric records. The 370 children who were listed on the child health computer as still living in the district, and whose general practitioners gave permission, were invited by letter to take part. They were visited at home by a paediatrician or a nurse, who explained the study and obtained consent, and 250 (68%) children agreed to have blood samples taken. A blood sample was taken at a second home visit, in the morning, after the child had fasted overnight. EMLA cream was applied one hour before venepuncture. The child's weight was measured to the nearest 0·1 kg using digital scales, and height to the nearest 0·1 cm using a portable stadiometer (Minimetre).

Blood pressure was not measured during this (7 year) study. We subsequently recontacted the children at the age of 9 years, and the 239 children still living in Hampshire, Wiltshire, or Dorset agreed to have their blood pressure measured. Pressures were measured either at school or at home, in the left arm, using an automated recorder (Dinamap) with the cuff size recommended for the measured arm circumference. After a five minute rest period, with the child seated, three measurements were taken at one minute intervals, and the average used in the analysis. The child's weight and height were measured as before. Ethical permission for the studies was obtained from the Salisbury Health Authority ethics committee.

LABORATORY METHODS

Samples suitable for laboratory analysis were obtained from 200 children in Pune and 244 children in Salisbury. Plasma IGF-1 concentrations were measured in Auckland, New Zealand, using a double antibody radioimmunoassay, after acid-ethanol cryoprecipitation.[16] The primary antiserum (No 878/4) was used at a final dilution of 1:250 000. The cross reactivity of the antibody with IGF-2 and insulin was <0·05% and <0·001% respectively and the minimal detectable dose was 0·07 ng/tube. Recombinant human IGF-1 (batch CPG 35'126, provided by Drs K Mueller and W Maerky, Ciba-Geigy Ltd, Basel, Switzerland) was iodinated by the chloramine T method. Residual IGF binding proteins were blocked by addition of an excess rhIGF-2 (50 μg/tube, Eli Lilly and Co, Indianapolis, Indiana) before addition of ^{125}I labelled IGF-1 tracer and incubation at 4°C for 18 hours. The intra-assay coefficient of variation was 5% and the interassay coefficient of variation was 8%, across the whole range of IGF-1 concentrations. IGF-1 values are expressed in terms of the international reference preparation (IRP IGF-1, batch 87/518).

STATISTICAL METHODS

Among the Pune children, the distribution of plasma IGF-1 concentrations was positively skewed, and values were transformed to normality using logarithms. Among the Salisbury children the distribution of IGF-1 was not markedly skewed and did not require transformation. Data were analysed by tabulation of means and multiple linear regression. Comparisons between the sexes were made using *t* tests. Levels of significance refer to analyses of continuous variables by regression.

Results

IGF-1, SEX, AND CURRENT BODY SIZE

In Pune, the children's ages ranged from 3·7 to

Table 2 Anthropometric data at birth and 7 and 9 years in Salisbury; values are mean (SD)

	Boys (n=124)	*Girls (n=120)*
At birth		
Weight (kg)	3·374 (0·545)	3·344 (0·464)
Length (cm)	51·5 (2·4)	50·8 (2·3)
Head circumference (cm)	34·8 (1·3)	34·3 (1·3)
Ponderal index (kg/m^3)	25·3 (3·1)	25·7 (3·2)
Placental weight (g)	665 (201)	654 (133)
Gestation (weeks)	40·0 (1·8)	40·3 (1·4)
At 7 years		
Weight (kg)	26·3 (4·6)	25·8 (4·1)
Height (cm)	127·3 (6·4)	126·2 (5·4)
At 9 years (n=239)		
Weight (kg)	32·0 (6·3)	31·4 (5·6)
Height (cm)	135·3 (6·7)	133·9 (5·7)

Length at birth was known for 210 children, head circumference for 212, placental weight for 215, and gestational age for 234.

4·4 (median 4·0 years). Their birth weights and anthropometric measurements, shown in table 1, were low in comparison with British children,[17 18] but similar to Indian community averages.[19 20] In Salisbury the children's ages ranged from 7·3 to 8·2 years (median 7·7 years). Their anthropometric data at birth and 7 years are shown in table 2.

Table 3 shows mean plasma IGF-1 concentrations in relation to height and weight, divided by approximate quartiles, for both groups of children and in boys and girls separately. Concentrations were higher in girls than boys (p value for difference: Pune $p<0·001$; Salisbury $p=0·5$). Concentrations were higher in heavier and taller children of both sexes. Among the Pune children they rose by 13%/kg increase in current weight (95% confidence interval (CI) 9 to 18; $p<0·0001$) and by 5%/cm increase in height (95% CI 4 to 7; $p<0·0001$). In a simultaneous analysis of weight and height, both measures were independently related to IGF-1 concentrations ($p=0·01$ and 0·006 respectively). Among the Salisbury children concentrations rose by 3·2 ng/ml/kg increase in weight (95% CI 2·3 to 4·1; $p<0·0001$) and by 1·7 ng/ml/cm increase in height (95% CI 1·0 to 2·5; $p<0·0001$). After allowing for weight, concentrations were not independently related to height (p values were <0·0001 and 0·9 respectively in a simultaneous analysis).

IGF-1 AND BIRTH SIZE

Plasma IGF-1 concentrations tended to fall with increasing birth weight, although the trends were not statistically significant (Pune $p=0·2$; Salisbury $p=0·06$). Birth weight was positively correlated with current weight (Pune $p=0·0006$; Salisbury $p=0·03$) and height (Pune $p=0·002$; Salisbury $p=0·02$). Table 4 shows a multiple regression analysis of plasma IGF-1 concentrations with birth weight, current weight and height, and sex. In both groups of children, after allowing for current size and sex, IGF-1 concentrations were strongly inversely related to birth weight. Table 5 shows mean plasma IGF-1 concentrations according to both birth weight and current weight. Children who had been below average birth weight and were above average weight when studied had high IGF-1 concentrations. Children of above average birth weight and below average weight when studied had low concentrations. There were no statistically significant differences in the trend of IGF-1 with birth weight at different levels of current weight, nor in the trend of IGF-1 with weight at different levels of birth weight. Trends were similar in both sexes.

Among the Salisbury children, who were measured in detail at birth, IGF-1 concentrations, allowing for current weight, were higher in children who were shorter at birth ($p=0·05$), those who had smaller head circumferences ($p=0·08$), and those who had lower placental weights ($p=0·03$), but were not related to ponderal index (weight/length^3; $p=0·7$) at birth. Among the 232 children whose gestational age was known, plasma IGF-1 concentrations were not related to gestation, and allowing for gestational age did not diminish the relation of IGF-1 to birth weight ($p=0·003$), length at birth ($p=0·02$), head circumference ($p=0·04$), or placental weight ($p=0·02$).

IGF-1 AND BLOOD PRESSURE

Among the 4 year old Pune children mean (SD) systolic and diastolic blood pressures were 96 (10) mm Hg and 49 (9) mm Hg respectively. Blood pressure was measured at the age of 9 years in Salisbury (median age 9·3 years, range 8·9 to 9·7). Anthropometric data for the children at 9 years are shown in table 2. Mean systolic and diastolic pressures were 99 (9) mm Hg and 59 (6) mm Hg. As expected, in both groups, heavier children had higher blood pressures. Systolic pressure rose by 1·3 mm Hg (95% CI 0·5 to 2·0; $p=0·001$) in Pune and by 0·4 mm Hg (95% CI 0·3 to 0·6; $p<0·0001$) in Salisbury, for each kg increase in current weight. Systolic pressures were also higher in

Table 3 Mean plasma IGF-1 according to height and weight; figures in parentheses are numbers of children

	Plasma IGF-1 (ng/ml)		
	Girls	*Boys*	*All*
4 Year old children in Pune			
Height (cm)			
≤94·0	43 (24)	33 (26)	37 (50)
>94·0–97·5	51 (22)	34 (25)	41 (47)
>97·5–100·5	69 (29)	42 (24)	55 (53)
>100·5	66 (21)	56 (29)	60 (50)
Weight (kg)			
≤11·5	43 (23)	25 (18)	34 (41)
>11·5–12·5	56 (31)	36 (30)	45 (61)
>12·5–14·0	55 (19)	48 (27)	51 (46)
>14·0	77 (23)	52 (29)	62 (52)
All	56 (96)	41 (104)	48 (200)
SD (geometric)	1·7	1·7	1·7
7 Year old children in Salisbury			
Height (cm)			
≤122	104 (29)	104 (26)	104 (55)
>122–126	111 (28)	108 (23)	109 (51)
>126–130	128 (34)	121 (38)	124 (72)
>130	131 (29)	124 (37)	127 (66)
Weight (kg)			
≤23·0	102 (27)	98 (30)	100 (57)
>23·0–25·5	108 (38)	110 (25)	109 (63)
>25·5–28·0	133 (25)	117 (37)	123 (62)
>28·0	137 (30)	135 (32)	136 (62)
All	119 (120)	116 (124)	117 (244)
SD	33	37	35

Table 4 Multiple regression analysis of plasma IGF-1 concentration with birth weight and other variables

Variable	Regression coefficient	Standard error	p Value
Pune			
Height (cm)	0·0331	0·0111	0·003
Weight (kg)	0·0842	0·0278	0·003
Sex (boys=0, girls=1)	0·3532	0·0651	<0·0001
Birth weight (kg)	−0·2970	0·0924	0·002
Constant	3·692		
y variable=log plasma IGF-1 concentration (ng/ml)			
Salisbury			
Height (cm)	0·2069	0·5041	0·7
Weight (kg)	3·207	0·6795	<0·001
Sex	4·807	4·117	0·2
Birth weight (kg)	−12·42	4·108	0·003
Constant	115·0		
y variable=plasma IGF-1 concentration (ng/ml)			

Height, weight, and birth weight standardised by subtracting their means. Thus constant=predicted IGF-1 (logIGF-1 in Pune) for a boy of average height, weight, and birth weight.

taller children (Pune p=0·0006; Salisbury p=0·0007), although not independently of weight. Trends were similar for diastolic pressure, though weaker. There was no statistically significant relation between blood pressure and birth weight in either group of children. After allowing for current weight, systolic pressure fell by 0·6 mm Hg (95% CI −4·4 to 3·1; p=0·7)/kg increase in birth weight in Pune, and by 0·5 mm Hg (95% CI −2·6 to 1·6; p=0·6)/kg increase in birth weight in Salisbury.

Children with higher IGF-1 concentrations had higher systolic blood pressures (figure). Among the Pune children, systolic pressure rose by 2·2 mm Hg as plasma IGF-1 doubled (95% CI 0·5 to 3·9; p=0·01). Among the Salisbury children, systolic pressure at 9 years rose by 3·2 mm Hg (95% CI 0·2 to 6·3; p=0·04) for each 100 ng/ml increase in plasma IGF-1 concentration at 7 years. The association of systolic blood pressure and IGF-1 concentrations was not statistically significant in a simultaneous analysis with current weight (Pune p=0·2; Salisbury p=0·7). IGF-1 concentrations were not related to diastolic blood pressure.

Discussion

Consistent with the findings of others,[21] and in both groups of children studied, those who were heavier and taller had higher plasma IGF-1 concentrations (table 3). A new finding was that at any level of current weight or height, children who were lighter at birth had higher plasma IGF-1 concentrations (tables 4 and 5). Gestational age at birth, available for the Salisbury children, was not related to IGF-1 concentrations, suggesting that the higher concentrations in lower birthweight babies are related to intrauterine growth retardation rather than premature birth. Our findings are consistent with the hypothesis that the IGF-1 axis is altered, or 'reprogrammed', in babies who were undernourished in utero, resulting in higher plasma concentrations during childhood.

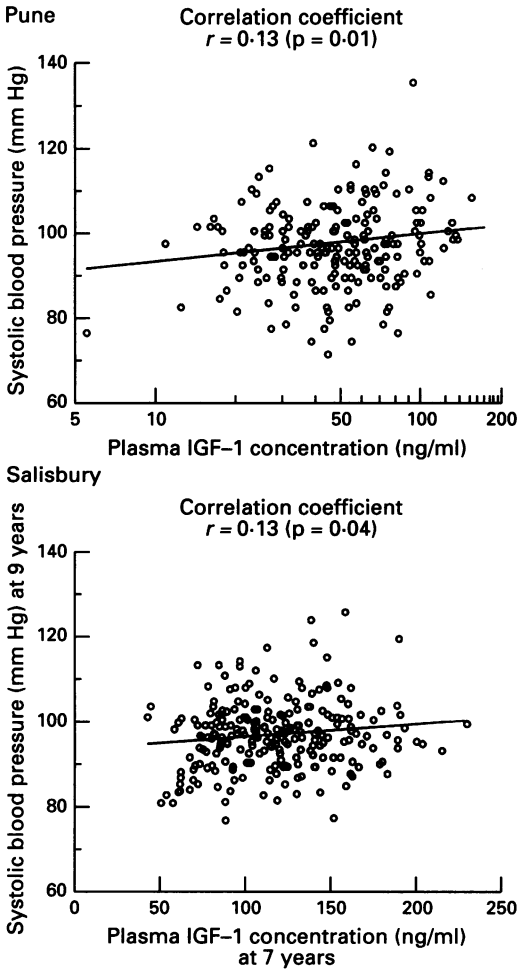
With one exception,[22] studies have consistently shown that plasma IGF-1 concentration and activity are low in umbilical cord blood from small for gestational age fetuses[6 23 24] and neonates.[25–30] In the early neonatal period, both high[31 32] and low[33] plasma IGF-1 concentrations/activity in low birthweight babies have been reported. We can speculate about mechanisms by which low levels in small babies at birth might become raised postnatally. Studies in animals and humans have shown that nutrition is a dominant influence on IGF-1 concentrations prenatally,[6 34–36] and continues to modulate concentrations postnatally,[37 38] undernutrition leading to reduced IGF-1 secretion and to IGF-1 resistance.[39] High concentrations may be a response to adequate postnatal nutrition or alternatively, they may reflect persisting IGF-1 resistance, in an individual who experienced prenatal undernutrition. The fact that, in our study, IGF-1 concentrations were higher in low birthweight babies after controlling for current size, suggests that there is an element of IGF-1 resistance, at least to its growth promoting actions, in the lower birthweight children.

Another possible explanation for the higher concentrations in lower birthweight children is that they are mediated through growth hormone. Growth hormone becomes a major regulator of IGF-1 after birth. It stimulates synthesis and release of IGF-1, and IGF binding protein 3, which prolongs the survival of IGF-1 in circulation.[40] Low birthweight babies have been shown to have high basal growth hormone concentrations and an increased growth hormone response to growth hormone releasing hormone.[31]

In our study the highest plasma IGF-1 concentrations were found in children who had the lowest birth weights but had attained the highest weights or heights when studied (table 5). The increased IGF-1 concentrations in low birthweight children may be linked to the process of catch-up growth, which occurs during infancy in many babies whose growth was reduced in utero. Catch-up growth is

Table 5 Mean plasma IGF-1 concentrations (ng/ml) according to birth weight and current weight; figures in parentheses are numbers of children

Pune						Salisbury					
	Weight at 4 years (kg)						Weight at 7 years (kg)				
Birth weight (kg)	≤11·5	>11·5–12·5	>12·5–14·0	>14·0	All	Birth weight (kg)	≤23·0	>23·0–25·5	>25·5–28·0	>28·0	All
≤2·5	38 (14)	52 (19)	53 (14)	75 (10)	51 (57)	≤3·0	100 (14)	117 (10)	130 (11)	138 (14)	121 (49)
>2·5–2·75	30 (10)	51 (14)	68 (8)	57 (12)	49 (44)	>3·0–3·3	100 (24)	110 (17)	131 (13)	150 (12)	118 (66)
>2·75–3·0	36 (12)	40 (20)	42 (10)	78 (14)	46 (56)	>3·3–3·6	99 (10)	104 (16)	130 (18)	144 (10)	119 (54)
>3·0	28 (5)	38 (8)	48 (14)	48 (16)	43 (43)	>3·6	103 (9)	108 (20)	109 (20)	125 (26)	114 (75)
All	34 (41)	45 (61)	51 (46)	62 (52)	48 (200)	All	100 (57)	109 (63)	123 (62)	136 (62)	117 (244)



Mean systolic blood pressure according to plasma IGF-1 concentration in Pune and Salisbury.

influenced by prenatal growth,[41 42] and by a number of postnatal factors, especially nutrition. During their first year, low birthweight babies whose growth catches up have higher plasma IGF-1 concentrations than those who do not, although concentrations do not exceed those of higher birthweight babies of equivalent infant size.[43] We do not have infant growth data for our children, and where only birth size and current size are known it is not possible to conclude whether the higher IGF-1 concentrations are due to a combination of small size at birth and large current size, or to catch-up growth during a critical period in infancy. Further study is required of IGF-1 concentrations during and after catch-up growth.

High IGF-1 concentrations in low birthweight children may be analogous to the high insulin concentrations found in low birthweight adults.[7–12] The high insulin concentrations in adults reflect insulin resistance, and occur in men and women who were thin, having a low ponderal index, at birth.[8] Length at birth was not available for the Indian children in our study, but higher IGF-1 concentrations in the Salisbury children were associated with shortness at birth, and not with low ponderal index. This suggests that the pattern of fetal growth associated with altered IGF-1 concentrations differs from that associated with altered insulin concentrations.

IGF-1 concentrations were low in the Indian children in comparison with those of European children of the same age measured using the same assay method,[21] while concentrations in the Salisbury children were similar. This is consistent with the smaller size of Indian children. Their low height and weight are likely to reflect a degree of chronic undernutrition, although none showed clinical signs of acute undernutrition. Poorer nutrition and growth may explain the greater positive skewness of the distribution of IGF-1 concentrations in the Indian, compared with the British children in our study, requiring log transformation of the data. The consistency of our findings in both groups of children shows that the relationship of high IGF-1 concentrations to low birth weight does not result from the poorer growth of the Indian children. The relationship of IGF-1 concentrations to current size differed in the two groups of children. Among the Indian children increased height and weight both, independently, predicted higher IGF-1 concentrations, while among the Salisbury children, although concentrations rose with increasing height and weight, only weight remained a significant predictor of IGF-1 in a simultaneous regression analysis. We are unable to explain this difference. Published studies of European children report that height and weight (or body mass index) are positively related to IGF-1 concentrations, but do not discuss the interrelationships of height and weight.[21 44 45] In our study, IGF-1 concentrations were higher in girls than in boys, the difference being more marked, and statistically significant, in the 4 year old Indian children. European studies consistently report higher concentrations in girls compared with boys, despite their smaller size, although the differences are not significant.[44–46] We have no explanation for the stronger sex difference among the Indian children.

We did not find the inverse relationship of systolic blood pressure with birth weight in the 4 year old Indian children that has been found in European children of similar age,[47] and in the Salisbury children when studied at 4 years.[15] In European studies this relationship becomes evident after infancy, disappears during puberty, and grows stronger with increasing adult age.[48] The relationship may be absent in the Indian population studied, or the age at which it appears may differ. We plan to measure blood pressure in the same group of children at a later age, and are currently studying blood pressure in Indian adults. The non-significant relationship of systolic pressure to birth weight at the age of 9 in the Salisbury children is consistent with the findings of the Brompton longitudinal study of blood pressure in children.[49] Systolic pressure was significantly inversely related to birth weight at the age of 4 years, but the relationship was weaker, and not statistically significant at 9 years. This may be because the children were approaching puberty, during

which the tracking of blood pressure is known to be perturbed.[48]

In both groups of children plasma IGF-1 concentrations were positively correlated with systolic blood pressure. We do not know whether this is just an association mediated indirectly through current body size, or whether it reflects a biological interaction between IGF-1 and systolic blood pressure. Lever and Harrap have suggested that growth factors which determine somatic growth also determine blood pressure in childhood,[50] and that essential hypertension may be initiated by the action of growth factors on blood vessel development during childhood. IGF-1 is thought to be important for the growth of blood vessels, and is mitogenic for vascular smooth muscle cells in culture.[51-53]

In conclusion we have shown that, after allowing for current size, 4 year old Indian children, and 7 year old British children, of lower birth weight have higher circulating concentrations of IGF-1. At present the mechanisms responsible for this, and the possible consequences on cardiovascular development are unknown.

In Pune, we are grateful to social workers A Vairagar, K N Raut, and V Gaikwad, who traced the subjects, and to research nurses Gokhale and Jadhav. In Salisbury we thank the Department of Community Child Health, Salisbury Health District, the general practitioners who helped us to contact the subjects, and research nurse I Webb. We thank computer staff V M Joshi (Pune), and G Wield and V Cox (Southampton), and C Gibson (Auckland) for assistance with assays. The study was funded by the Wellcome Trust.

1 Osmond C, Barker DJP, Winter PD, Fall CHD, Simmonds SJ. Early growth and death from cardiovascular disease in women. *BMJ* 1993; **307:** 1519–24.
2 Barker DJP, Osmond C, Simmonds SJ, Wield GA. The relation of small head circumference and thinness at birth to death from cardiovascular disease in adult life. *BMJ* 1993; **306:** 422–6.
3 Barker DJP, Bull AR, Osmond C, Simmonds SJ. Fetal and placental size and risk of hypertension in adult life. *BMJ* 1989; **301:** 259–62.
4 Barker DJP. *Mothers, babies and disease in later life.* London: BMJ Publication Group, 1994.
5 Barker DJP, Gluckman PD, Godfrey KM, Harding JE, Owens JA, Robinson JS. Fetal nutrition and cardiovascular disease in adult life. *Lancet* 1993; **341:** 938–41.
6 Langford K, Blum W, Nicolaides K, Jones J, McGregor A, Miell J. The pathophysiology of the insulin-like growth factor axis in fetal growth failure: a basis for programming by undernutrition? *Eur J Clin Invest* 1994; **24:** 851–6.
7 Hales CN, Barker DJP, Clark PMS, Cox LJ, Fall CHD, Osmond C. Fetal and infant growth and impaired glucose tolerance at age 64. *BMJ* 1991; **303:** 1019–22.
8 Phillips DIW, Barker DJP, Hales CN, Hirst S, Osmond C. Thinness at birth and insulin resistance in adult life. *Diabetologia* 1994; **37:** 150–4.
9 Barker DJP, Hales CN, Fall CHD, Osmond C, Phipps K, Clark PMS. Type 2 (non-insulin-dependent) diabetes mellitus, hypertension and hyperlipidaemia (syndrome X): relation to reduced fetal growth. *Diabetologia* 1993; **36:** 62–7.
10 Valdez R, Athens MA, Thompson GH, Bradshaw BS, Stern MP. Birthweight and adult health outcomes in a biethnic US population. *Diabetologia* 1994; **37:** 624–31.
11 Fall CHD, Osmond C, Barker DJP, *et al.* Fetal and infant growth and cardiovascular risk factors in women. *BMJ* 1995; **310:** 428–32.
12 McKeigue PM, Leon DA, Berglund L, Mohsen R, Lithell HO. Relationship of birthweight and ponderal index to non-insulin-dependent diabetes and insulin response to glucose challenge in men aged 50–60 years. *Diabet Med* 1994; **11:** A17, S17 (abstract).
13 Yajnik CS, Fall CHD, Vaidya U, *et al.* Fetal growth and glucose and insulin metabolism in four year old Indian children. *Diabet Med* 1995; **12:** 330–6.
14 Law CM, Gordon GS, Shiell AW, Barker DJP, Hales CN. Thinness at birth and glucose tolerance in seven-year old children. *Diabet Med* 1995; **12:** 24–9.
15 Law CM, Barker DJP, Bull AR, Osmond C. Maternal and fetal influences on blood pressure. *Arch Dis Child* 1991; **66:** 1291–5.
16 Breier BH, Milsom SR, Blum W, Schwander J, Gallaher BW, Gluckman PD. Insulin-like growth factors and their binding proteins in plasma and milk after growth hormone stimulated galactopoiesis in normally lactating women. *Acta Endocrinol (Copenh)* 1993; **129:** 427–35.
17 Gairdner D, Pearson J. Birthweight standards. *Arch Dis Child* 1985; **60:** 1202.
18 Tanner JM, Whitehouse RH, Takaishi M. Standards from birth to maturity for height, weight height velocity and weight velocity: British children, 1965. Part II. *Arch Dis Child* 1966; **41:** 613–35.
19 Mohan Man, Shiv Prasad SR, Chellani HK, Kapani V. Intrauterine growth curves in north Indian babies: weight, length, head circumference and ponderal index. *Indian Pediatr* 1990; **27:** 43–51.
20 Indian Council of Medical Research. *Growth and physical development of Indian infants and children.* New Delhi, India: Indian Council of Medical Research, 1984.
21 Blum WF, Albertsson-Wikland K, Rosberg S, Ranke MB. Serum levels of Insulin-like growth factor I (IGF-I) and IGF binding protein 3 reflect spontaneous growth hormone secretion. *J Clin Endocrinol Metab* 1993; **76:** 1610–6.
22 Wang HS, Lim J, English J, Irvine L, Chard T. The concentration of insulin-like growth factor-1 and insulin-like growth factor-binding protein-1 in human umbilical cord serum at delivery: relation to fetal weight. *J Endocrinol* 1991; **129:** 459–64.
23 Lassarre C, Hardouin S, Daffos F, Forestier F, Frankenne F, Binoux M. Serum insulin-like growth factors and insulin-like growth factor binding proteins in the human fetus; relationships with growth in normal subjects and in subjects with intrauterine growth retardation. *Pediatr Res* 1991; **29:** 219–25.
24 Ashton IK, Zapf J, Einschenk I, MacKenzie IZ. Insulin-like growth factors (IGF) 1 and 2 in human foetal plasma and relationship to gestational age and foetal size during mid-pregnancy. *Acta Endocrinol (Copenh)* 1985; **110:** 558–63.
25 Gluckman PD, Brinsmead MW. Somatomedin in cord blood: relationship to gestational age and birth size. *J Clin Endocrinol Metab* 1976; **43:** 1378–81.
26 Ashton IK, Vesey J. Somatomedin activity in human cord plasma and relationship to birth size, insulin, growth hormone and prolactin. *Early Hum Dev* 1978; **2:** 115–22.
27 Foley TP, DePhilip R, Perricelli A, Miller A. Low somatomedin activity in cord serum from infants with intra-uterine growth retardation. *J Pediatr* 1980; **96:** 605–10.
28 Bennett A, Darrell M, Wilson M, *et al.* Levels of insulin-like growth factors I and II in human cord blood. *J Clin Endocrinol Metab* 1983; **57:** 609–12.
29 Theriot-Prevost G, Daffos F, Forestier F. Serum somatomedin-C and bioassayable growth-promoting activity (thymidine activity) in appropriate and small-for-gestational age human newborns. *Acta Endocrinol (Copenh)* 1985; **110:** 32–5.
30 Verhaege J, Van Bree R, Herck EV, Laureys J, Bouillon R, Van Assche FA. C-peptide, insulin-like growth factors I and II, and insulin-like growth factor binding protein-1 in umbilical cord serum: correlations with birthweight. *Am J Obstet Gynecol* 1993; **169:** 89–97.
31 Deiber M, Chatelain P, Naville D, Putet G, Salle B. Functional hyper-somatotropism in small for gestational age (SGA) newborn infants. *J Clin Endocrinol Metab* 1989; **68:** 232–3.
32 Seminara S, Becherucci P, Chiccoli A, Poggi G, Bettini F, Paparo M, *et al.* Insulin-like growth factor 1 in normal and low birth weight newborns. *Acta Paediatr Scand* 1994; **356** (suppl): 126.
33 Tato L, Dal Moro A, Piemont G, *et al.* A longitudinal study of plasma somatomedin activity in full-term, pre-term and small-for-gestational age newborns. *Biol Neonate* 1981; **39:** 160–4.
34 Gluckman PD. Fetal growth: an endocrine perspective. *Acta Paediatr Scand Suppl* 1989; **349:** 21–5.
35 Oliver MH, Harding JE, Breier BH, Evans PC, Gluckman PD. Glucose but not a mixed amino acid infusion regulates plasma insulin-like growth factor-1 concentrations in fetal sheep. *Pediatr Res* 1993; **34:** 62–5.
36 Straus DS, Ooi GT, Orlowski CC, Rechler MM. Expression of the genes for insulin-like growth factor-1 (IGF-1), IGF-II, and IGF-binding proteins-1 and 2 in fetal rat under conditions of intra-uterine growth retardation caused by maternal fasting. *Endocrinology* 1991; **128:** 518–25.
37 Clemmons DR, Underwood LE. Nutritional regulation of IGF-1 and IGF binding proteins. *Annu Rev Nutr* 1991; **11:** 393–412.
38 Straus DS. Nutritional regulation of hormones and growth factors that control mammalian growth. *FASEB J* 1994; **8:** 6–12.
39 Thissen JP, Underwood LE, Maiter D, Maes M, Clemmons DR. Failure of IGF-1 infusion to promote growth in protein-restricted rats despite normalisation of serum IGF-1 concentrations. *Endocrinology* 1991; **128:** 885–90.
40 Langford KS, Miell JP. The insulin-like growth factor-1/binding protein axis: physiology, pathophysiology and therapeutic manipulation. *Eur J Clin Invest* 1993; **23:** 503–16.
41 Villar J, Smeriglio V, Martorell R, Brown CH, Klein RE. Heterogeneous growth and mental development of intrauterine growth retarded infants during the first 3 years of life. *Pediatrics* 1984; **74:** 783–91.
42 Holmes GE, Miller HC, Hassanein K, Lansky SB, Goggin JE. Postnatal somatic growth in infants with atypical fetal growth patterns. *Am J Dis Child* 1977; **131:** 1078–83.

43 Thierot-Prevost G, Boccara JF, Francoual C, Badoual J, Job JC. Serum insulin-like growth factor 1 and serum growth-promoting activity during the first post-natal year in infants with intra-uterine growth retardation. *Pediatr Res* 1988; **24:** 380–3.
44 Bala RM, Lopatka J, Leung A, McCoy E, McArthur RG. Serum immunoreactive somatomedin levels in normal adults, pregnant women at term, children at various ages, and children with constitutionally delayed growth. *J Clin Endocrinol Metab* 1981; **52:** 508–13.
45 Juul A, Bang P, Hertel NT, *et al.* Serum insulin-like growth factor-1 in 1030 healthy children, adolescents and adults: relation to age, sex, stage of puberty, testicular size and body mass index. *J Clin Endocrinol Metab* 1994; **78:** 744–52.
46 Argente J, Barrios V, Pozo J, *et al.* Normative data for insulin-like growth factors (IGFs), IGF-binding proteins, and growth hormone binding protein in a healthy Spanish pediatric population: age- and sex-related changes. *J Clin Endocrinol Metab* 1993; **77:** 1522–8.
47 Whincup PH, Cook DG, Shaper AG. Early influences on blood pressure: a study of children aged 5–7 years. *BMJ* 1989; **299:** 587–91.
48 Law CM, Barker DJP. Fetal influences on blood pressure. *J Hypertens* 1994; **12:** 1329–32.
49 Law CM, de Swiet M, Osmond C, *et al.* Initiation of hypertension in utero and its amplification throughout life. *BMJ* 1993; **306:** 24–7.
50 Lever AF, Harrap SB. Essential hypertension: a disorder of growth with origins in childhood. *J Hypertens* 1992; **10:** 101–20.
51 Ferns GAA, Motani AS, Anggard EE. The insulin-like growth factors: their putative role in atherogenesis. *Artery* 1991; **18:** 197–225.
52 King GL, Goodman D, Buzney S, Moses A, Kahn CR. Receptors and growth-promoting effects of Insulin and Insulin-like growth factors on cells from bovine retinal capillaries and aorta. *J Clin Invest* 1985; **75:** 1028–36.
53 Nakao-Hayashi J, Ito H, Kanayasu T, Morita I, Murota S. Stimulatory effects of insulin and insulin-like growth factor 1 on migration and tube formation by vascular endothelial cells. *Atherosclerosis* 1992; **92:** 141–9.