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Fetal, Infant, and Childhood Growth and Adult Blood Pressure

A Longitudinal Study From Birth to 22 Years of Age

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Background—People who are small at birth tend to have higher blood pressure in later life. However, it is not clear whether it is fetal growth restriction or the accelerated postnatal growth that often follows it that leads to higher blood pressure.

Methods and Results—We studied blood pressure in 346 British men and women aged 22 years whose size had been measured at birth and for the first 10 years of life. Their childhood growth was characterized using a conditional method that, free from the effect of regression to the mean, estimated catch-up growth. People who had been small at birth but who gained weight rapidly during early childhood (1 to 5 years) had the highest adult blood pressures. Systolic pressure increased by 1.3 mm Hg (95% CI, 0.3 to 2.3) for every standard deviation score decrease in birth weight and, independently, increased by 1.6 mm Hg (95% CI, 0.6 to 2.7) for every standard deviation score increase in early childhood weight gain. Adjustment for adult body mass index attenuated the effect of early childhood weight gain but not of birth weight. Relationships were smaller for diastolic pressure. Weight gain in the first year of life did not influence adult blood pressure.

Conclusions—Part of the risk of adult hypertension is set in fetal life. Accelerated weight gain in early childhood adds to this risk, which is partly mediated through the prediction of adult fatness. The primary prevention of hypertension may depend on strategies that promote fetal growth and reduce childhood obesity. (*Circulation*. 2002;105:1088-1092.)

Key Words: blood pressure ■ obesity ■ pediatrics ■ birth weight ■ prevention

Many epidemiological studies have shown that people who are small at birth tend to have higher blood pressure in later life. Recent systematic reviews have emphasized that in both prepubertal children and adults, there is a consistent negative relationship between birth weight and present systolic blood pressure.^{1,2} However, there are difficulties in drawing the straightforward conclusion that factors that retard fetal growth also lead to raised blood pressure. Babies with low birth weight often show accelerated rates of growth in infancy and early childhood, a phenomenon known as catch-up growth. This raises the possibility that it is these postnatal adaptations in growth, rather than fetal growth restriction itself, that result in higher levels of blood pressure later.

This is a matter of more than theoretical interest, because present pediatric practice is to promote catch-up growth in infants with low birth weight. Might it be that this practice is inadvertently leading to higher blood pressure and perhaps a

subsequently higher risk of cardiovascular disease in these children? The epidemiological studies that have linked low birth weight to raised blood pressure suggest that the primary prevention of adult hypertension may depend, at least partly, on interventions in pregnancy and childhood. But a fuller understanding of how patterns of growth in fetal life, infancy, and childhood exert their influence on blood pressure will be needed before such interventions can be rationally designed and evaluated. We have carried out a follow-up study of blood pressure in a contemporary sample of young British adults for whom detailed longitudinal data on childhood growth rates were collected.

Methods

The Brompton study cohort was formed from a total of 2088 consecutive live births at a single hospital in southern England between 1975 and 1977. Excluding refusals to join the study (88), preterm births (105), and multiple births (28), the cohort consisted of 1867 individuals following sequential singleton birth at term. They

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TABLE 1. Characteristics of the Study Participants

	Men (n=161)	Women (n=185)
Birth Weight, kg	3.43 (0.46)	3.31 (0.43)
Weight at 1 year, kg	10.2 (1.0)	9.7 (1.1)
Weight at 5 years, kg†	19.5 (2.2)	19.2 (2.3)
Height at 5 years, cm†	111.0 (4.5)	110.5 (4.7)
Age at interview, y	22.4 (0.7)	22.4 (0.7)
Height, cm	177.1 (6.6)	164.6 (6.5)
Weight, kg*	74.1 (1.16)	61.7 (1.18)
Body mass index, kg/m ² *	23.7 (1.16)	22.8 (1.15)
Systolic pressure, mm Hg	125.6 (10.8)	110.3 (8.7)
Diastolic pressure, mm Hg	72.9 (7.2)	70.3 (6.1)

Values are mean (SD).
 *Geometric mean and geometric SD.
 †Missing for 42 men and 40 women.

were studied at birth, 4 times during infancy, and annually until 10 years of age, when the childhood study finished.³

Our selection criteria were that the subject should have been measured at birth, at 1 year of age, and at least once between 2 and 6 years of age so that we could characterize their infant and early childhood growth. For practical reasons, we only included subjects who were resident in southern England so that we could visit them at home.

At the home visit, we measured body size and blood pressure using an automated recorder (Omron HEM-711, Omron Healthcare⁴) and inquired about adult lifestyle. Blood pressure and height were each recorded 3 times, and the mean was used in analysis. Subjects were measured by 1 of 2 observers who did not know the values of the early measurements on the subjects. The study was approved by South and West Multi-Centre Research Ethics Committee and 21 local research ethics committees. Subjects gave informed written consent to participate in the study.

Statistical Methods

We wished to consider the effects of different periods of early growth (prenatal and postnatal) on adult blood pressure. To characterize early growth, we used measurements from all 1184 children who fulfilled the selection criteria for this study. We included 3 measurements for each child: weight at birth, weight at the 1-year visit, and weight at the 2- to 6-year visits that was closest to the fifth birthday (90% had a measurement within 1 year of their fifth

birthday). We constructed growth charts (separately for boys and girls) for the cohort using the multilevel regression method described by Royston.⁵ Estimates from this model are used to derive, for each individual child, standard deviation scores (SDS) of achieved size at each single time point and SDS of growth between successive time points, both unconditional and conditional on previous size. The conditional SDS of growth are independent of each other and also allow the effects of catch-up or catch-down growth to be distinguished from any statistical artifact attributable to regression to the mean.

Data were analyzed by tabulation of means and proportions, Pearson product-moment correlation coefficients, and multiple linear regression. Levels of significance refer to analyses of continuous variables. Adjustments of blood pressures for measurement and adult lifestyle factors were made, where appropriate, by including continuous and categorical variables simultaneously in the multiple regression model. Analyses were performed using the statistical packages Stata⁶ and MLwiN.⁷

Results

Of the 1867 subjects in the birth cohort, 1184 had all 3 required measurements during childhood, and of these, 725 lived in southern England. We visited 346 (161 men and 185 women) of these 725 eligible subjects, a participation rate of 47.7%. Forty-two subjects refused to participate, 324 did not respond to the letter of invitation, and 13 who agreed to participate could not be visited during the fieldwork period.

Table 1 describes the characteristics of the study participants. The subjects' mean birth weight was slightly lower than published standards at that time.⁸ Only 12 subjects had weighed <2.5 kg. At 5 years, the subjects were slightly taller and heavier than published standards.⁹ Their mean heights and weights as adults were similar to those published for a nationally representative sample of similar age.¹⁰ However, their mean systolic blood pressures were lower (by ≈7 mm Hg for men and 11 mm Hg for women).

There were no significant differences in size at birth, postnatal growth, or blood pressure during childhood between the study subjects (n=346) and either those who had the required growth measurements in childhood but did not participate in the study (n=838) or those who entered the original study cohort at birth but did not participate in the

TABLE 2. Interrelationship Between Weight Growth Characterization Variables and Adult Body Mass

	SDS Birth Weight	SDS Weight at 1 y	SDS Weight at 5 y	SDS Conditional Infant Weight Gain*	SDS Conditional Early Childhood Weight Gain†	SDS Unconditional Weight Gain in Infancy	SDS Unconditional Weight Gain, 1–5 y of Age
SDS weight at 1 y	0.37 (<0.001)						
SDS weight at 5 y	0.29 (<0.001)	0.58 (<0.001)					
*SDS conditional infant weight gain	-0.05 (0.3)	0.91 (<0.001)	0.50 (<0.001)				
†SDS conditional early childhood weight gain	0.11 (0.05)	0.04 (0.5)	0.83 (<0.001)	-0.01 (0.9)			
SDS unconditional weight gain in infancy	-0.59 (<0.001)	0.54 (<0.001)	0.25 (<0.001)	0.84 (<0.001)	-0.06 (0.2)		
SDS unconditional weight gain, 1 to 5 y of age	-0.01 (0.9)	-0.27 (<0.001)	0.63 (<0.001)	-0.28 (<0.001)	0.95 (<0.001)	-0.22 (<0.001)	
Adult body mass index	0.004 (0.9)	0.20 (<0.001)	0.42 (<0.001)	0.22 (<0.001)	0.38 (<0.001)	0.17 (0.001)	0.30 (<0.001)

Values are Pearson r (P).
 *Weight at 1 year conditional on birth weight.
 †Weight at 5 years conditional on weight at 1 year.

TABLE 3. Difference in Systolic and Diastolic Pressure (mm Hg) per SDS Increase in Early Weight Growth Variable, With and Without Adjustment for Adult Body Mass Index

Weight Growth Variable	Regression Coefficient (95% CI)		
	Without Adjustment for Adult BMI	With Adjustment for Adult BMI	<i>P</i> (Interaction Between Weight Growth Variable and Adult BMI)
Systolic pressure			
Birth weight	-1.1 (-2.1 to -0.2)	-1.2 (-2.1 to -0.2)	0.9
Conditional infant weight gain	0.5 (-0.6 to 1.6)	-0.1 (-1.2 to 0.9)	0.3
Conditional early childhood weight gain	1.4 (0.4 to 2.5)	0.4 (-0.7 to 1.5)	0.6
Diastolic pressure			
Birth weight	-0.7 (-1.3 to 0.0)	-0.7 (-1.3 to 0.0)	0.9
Conditional infant weight gain	0.2 (-0.5 to 1.0)	0.0 (-0.8 to 0.7)	0.1
Conditional early childhood weight gain	0.1 (-0.6 to 0.9)	-0.3 (-1.1 to 0.4)	0.04

Each row represents a separate regression analysis. BMI indicates body mass index.

study (n=1521). However, study subjects were significantly less likely to be male (46.5% of study subjects were male compared with 54.7% of nonparticipants with childhood measurements and 53.3% of the original study cohort at birth).

Table 2 shows the interrelationships between the growth variables describing infant and childhood growth and adult body mass. As a consequence of the conditional approach to characterizing postnatal growth, there were only weak or no relationships between birth weight, conditional infant weight gain (weight at 1 year conditional on birth weight), and conditional early childhood weight gain (weight at 5 years conditional on weight at 1 year). These 3 variables were chosen as the main descriptors of early growth, because their independence from each other allowed them to be considered simultaneously.

Systolic and diastolic blood pressures were significantly higher in men than women (Table 1). Systolic and diastolic pressures increased slightly with age and room temperature and were slightly higher in the evening than during the rest of the day. Systolic pressure was 2.4 mm Hg (95% CI, -0.2 to 5.1) lower and diastolic pressure was 0.5 mm Hg (95% CI, -0.9 to 2.0) lower when measured by one of the field workers. This was consistent with differences observed in interobserver studies conducted during the fieldwork. To standardize conditions of measurement and analysis, systolic and diastolic pressures were adjusted for sex, age, field

worker, time of measurement, and room temperature in all subsequent analyses.

As expected, blood pressure increased with adult body mass index. For each geometric standard deviation increase in body mass index, systolic pressure increased by 2.8 mm Hg (95% CI, 1.8 to 3.7) and diastolic pressure increased by 1.1 mm Hg (95% CI, 0.4 to 1.7). Adjustment for adult body mass was made separately to other adjustments to allow comparison with earlier studies.

The relationship of adult blood pressure to each component of early growth is shown in Table 3. Systolic pressure was inversely associated with birth weight, and this relationship was not changed by adjusting for adult body mass. There was no relationship between conditional infant weight gain and adult systolic pressure with or without adjustment for adult body mass. By contrast, systolic pressure increased with conditional early childhood weight gain. This relationship was attenuated considerably by adjustment for adult body mass index. Diastolic pressure was inversely related to birth weight with or without adjustment for adult body mass index, but the relationship was smaller than that seen for systolic pressure. Diastolic pressure was not related to either conditional infant weight gain or conditional early childhood weight gain. The only statistically significant interaction was between conditional early childhood weight gain and adult body mass index for diastolic pressure.

TABLE 4. Difference in Systolic Pressure (mm Hg) per SDS Increase in Early Weight Growth Variables Considered Simultaneously, With and Without Adjustment for Adult BMI

Weight Growth Variable	Regression Coefficient (95% CI)	
	Without Adjustment for Adult BMI	With Adjustment for Adult BMI
Birth weight	-1.3 (-2.3 to -0.3)	-1.2 (-2.2 to -0.3)
Conditional infant weight gain	0.5 (-0.6 to 1.5)	-0.1 (-1.2 to 0.9)
Conditional early childhood weight gain	1.6 (0.6 to 2.7)	0.6 (-0.5 to 1.7)
Adult body mass index*	...	2.6 (1.5 to 3.7)

*Geometric SDS.

The relationships of adult systolic pressure with birth weight and early childhood weight gain were independent of each other. Thus, the highest systolic pressures were seen in adults who had been light at birth but who gained relatively large amounts of weight between 1 and 5 years of age (Table 4).

To present the results in a format compatible with a recent systematic review,¹ we also calculated the difference in systolic blood pressure per kilogram decrease in birth weight. The difference was 2.7 mm Hg (95% CI, 0.4 to 5.0) for systolic pressure and 1.6 mm Hg (95% CI, 0.1 to 3.2) for diastolic pressure.

The general pattern and size of the relationships between fetal, infant, and childhood growth and systolic or diastolic pressure were similar if additional adjustment was made for socioeconomic status, smoking habit, alcohol consumption, patterns of exercise, and, in women, the use of oral contraceptives (results not presented). Adjustment for duration of gestation in this term cohort slightly attenuated most relationships but did not alter the overall pattern of the results.

Discussion

We found that lower birth weight and greater weight gain between 1 and 5 years of age were associated with higher systolic blood pressure in young adult life. However, weight gain in infancy (the first year of life) was not associated with adult systolic blood pressure. The effects of birth weight and early childhood weight gain were independent, so that adults who had been the lightest at birth but gained most weight in early childhood had the highest blood pressures. Adjustment for adult body mass index did not alter the relationship between birth weight and adult systolic blood pressure. However, children with higher rates of childhood weight gain tended to be fatter as adults (Table 2). Adjustment for adult body mass index attenuated considerably the relationship of early childhood weight gain with adult systolic blood pressure, suggesting that the effect of early childhood weight gain was mediated, at least in part, through its prediction of adult fatness. The relationships between weight at birth and adult systolic blood pressure were independent of duration of gestation and also of characteristics of adult lifestyle. Interactions between adult body mass index and early weights or weight gain were tested in all analyses. The only statistically significant interaction was between adult body mass and early childhood weight gain on adult diastolic but not systolic blood pressure (Table 4). Given the number of tests carried out and the absence of a main effect of early childhood weight gain on diastolic blood pressure, this may be a chance finding.

The men and women in our study sample were from a birth cohort study based on a geographical area in the United Kingdom and, as neonates and children, had been similar in growth characteristics to children forming population standards for the United Kingdom. As young adults, they were also similar in height and weight to a nationally representative sample of the same age,¹⁰ although their mean systolic pressures were somewhat lower. No subjects were diagnosed as having or being treated for hypertension. The response rate was low; 48% of eligible subjects participated in the present study. Their size at birth, postnatal growth, and childhood

blood pressures were not significantly different from those who did not participate, but they were significantly less likely to be male. The low response rate would affect our results only if the association between weight at birth and weight gain during infancy and childhood and adult systolic blood pressure differed between those who did and did not take part in the study. We cannot assess this possibility.

The inverse relationship of birth weight with adult systolic blood pressure and the size of the birth weight effect in this study are consistent with the extensive literature, which now includes in excess of 80 studies.¹ We found that the relationship of lower birth weight with higher blood pressure was independent of postnatal growth, adult body mass, or other lifestyle factors. This suggests that at least part of the risk of hypertension is determined in fetal life. Possible mechanisms operating in fetal life that might determine blood pressure include the structural development of resistance arteries, setting of hormone levels, and nephron development.¹¹

We found no relationship between infant weight gain and adult systolic blood pressure. This is consistent with follow-up studies measuring blood pressure in older British adults¹² and in children in Britain,¹³ Sweden,¹⁴ and Australia,¹⁵ where weight at 1 year did not predict systolic pressure once birth weight and present weight or body mass had been taken into account. In contrast, in a study in a young adult population in Hong Kong, those who were thinner at birth and, independently, those who had gained less body mass between 6 and 18 months¹⁶ had higher adult systolic blood pressures. The authors suggested that the difference from other studies may have been attributable to the poor infant growth of individuals in their study sample, who would have been living in disadvantaged circumstances and were likely to have suffered from a high burden of infectious disease. Other differences between their study and ours include their method of analysis, which did not account for the colinearity between birth and infant size, and their measurement of infant growth, which was based on body mass, a measurement that we did not have. Furthermore, in men born in Helsinki, Finland in the 1930s and 1940s, hazard ratios for coronary heart disease were highest in those who were small at birth and, independently, in those who were small at 1 year of age, whether size was measured as weight, length, or index of body mass.¹⁷ Thus, in some populations, reduced infant growth seems to confer additional cardiovascular risk over and above that predicted by birth weight, whereas in others, infant growth is unrelated to cardiovascular risk. Of public health importance, none of the evidence so far indicates that promotion of infant growth increases cardiovascular risk.

In contrast to infant weight gain, children who gained more weight in early childhood than would be expected from their weight at birth and 1 year had higher adult systolic blood pressure. Part of this effect occurred because they were more likely to have higher body mass as an adult, which was itself associated with higher adult systolic blood pressure. Our results are consistent with those of a systematic review of studies relating postnatal weight gain to adult blood pressure.¹ In general, studies in this review showed a positive effect of postnatal weight gain on adult blood pressure. However, most studies were only able to estimate weight gain from the

difference between birth weight and adult size, so the period of postnatal growth that influenced adult systolic blood pressure and its independence from the influence of adult body mass and birth weight could not be determined. We have shown that accelerated weight gain in early childhood, but not in infancy, is associated with higher adult blood pressure. Other studies have found that increased weight gain or adiposity in later childhood or adolescence is associated with higher cardiovascular risk in early adult life.^{18–20} This is compatible with a study of Finnish men and women that found that treatment for hypertension was more likely in people who had been small at birth, who had caught up to average weight and height at 7 years of age, and who were becoming heavier and fatter than average at 15 years of age. However, in this study there was no information on early childhood growth or adult body mass.²¹

Thus, although no single study has assessed the influence of all components of fetal and postnatal growth and adult fatness on blood pressure, the sum of the literature indicates the importance of several phases of preadult life for the development of adult hypertension.

Children who have higher body mass are more likely to become obese as adults, a matter of public health concern in view of the marked rise in both the mean body mass and the prevalence of obesity in children.^{22,23} People who have low birth weight are less likely to be obese as adults but more likely to have central deposition of fat, whatever their level of body mass.²⁴ In our study, the highest blood pressures were found in men and women who had low birth weight but gained the most weight during early childhood. Reduced birth weight and rapid weight gain in childhood is becoming common in some populations, such as children growing up in developing countries where low birth weight is still prevalent, but there is a nutritional transition from chronic undernutrition to Western-type diets. It may also be common among particular groups of children, for instance, those who have suffered from intrauterine growth retardation but grow up in a culture with adequate nutrition and a sedentary lifestyle. Our results indicate that such groups of children are at risk of hypertension in adult life.

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