Association of blood pressure in adolescence with birthweight

P O D Pharoah, C J Stevenson, C R West

Abstract

Aims—To compare the blood pressure of very low birthweight infants with that of normal birthweight controls in adolescence.

Methods—A cohort of all infants of birthweight ≤ 1500 g born to women resident in the county of Merseyside in 1980–1 was followed up at age 15 years with age, sex, and school matched controls. Growth indices and blood pressures were measured under standard conditions. The smoking history of mothers and children and their status for several socioeconomic variables were documented. In a matched pairs analysis systolic and diastolic blood pressures were compared for cases and controls before and after adjusting for height, weight, and body mass index.

Results—There were 172 singleton 15 year old survivors of birthweight <1500 g out of 40 321 live births to Merseyside residents in 1980–1. Of the 172 survivors, 128 (74%) who had no clinical disability and 11 (6%) with a clinical disability but attending normal schools, were assessed with individually matched age, sex, and school controls. Twenty three (13%) had a clinical disability and were attending special schools; these were assessed without controls. Ten (6%) children refused or were unavailable for assessment. The systolic blood pressure was significantly higher in cases than in controls; the mean of the difference was 3.2 mm Hg. The diastolic blood pressure was also higher in the cases, but the difference was not significant. The controls were significantly heavier (4.4 kg), taller (4.0 cm), with larger head circumference (1.5 cm) than the cases. The difference in body mass index was not significant. Adjusting for height, weight, or body mass index increased the difference in systolic blood pressure between cases and controls. There were no significant differences in the socioeconomic variables, but what differences did exist favoured the controls. There was also a higher prevalence of smoking among the children and the mothers of the cases than the controls.

Conclusions—The study supports the hypothesis that in adolescents variation in systolic blood pressure has its origins in fetal development. Some of the variation could be attributed to socioeconomic differences.

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Ecological studies that reported a correlation between past infant mortality and current adult cardiovascular mortality[1][2] led to the hypothesis that the intrauterine and infant environment had an important role in later mortality. Ecological studies, however, are subject to the ecological fallacy[3] and the need for cohort studies to relate measures of fetal and infant development to specific risk factors for cardiovascular disease arose.

Several such studies have reported a negative association between birthweight and blood pressure in childhood[4-8] and adulthood.[9-14] These have largely provided supportive evidence for the hypothesis that fetal and infant development programmes the individual and influences the development of risk factors for subsequent cardiovascular disease such as impaired glucose tolerance[15] and hypertension.[9][12][13] In contrast to children and adults, the association between birthweight and blood pressure in adolescents is inconsistent.[16-20]

We followed up of a geographically defined cohort of low birthweight infants and matched controls from birth. They were assessed when aged 15 years and the correlation between blood pressure and measures of fetal development examined.

Methods

A cohort comprising all infants of birthweight ≤ 1500 g born in 1980 and 1981, to mothers resident in the county of Merseyside, was obtained from birth notifications. The obstetric and neonatal records were abstracted for demographic and clinical details of the mother and the birthweight and head circumference of the child. Subsequently the infants were examined when aged 3 years to determine the prevalence of disability[21] and again when aged 8 years to determine the prevalence of subclinical deficits of cognitive and motor function[22] and of behavioural disorders.[23] At the 8 year follow up, for those children attending normal school, an age and sex matched control from the same school was also assessed. The intention behind matching for schools was that, because primary schools tend to draw children from socially homogenous areas, it would effectively match for important social variables. This premise was tested at the 8 year follow up, when cases and controls were compared for several socioeconomic variables, including social class, current employment status of the father, housing status of the family, parental education and income and the

FSID Unit of Paediatric and Perinatal Epidemiology, Department of Public Health, University of Liverpool, Liverpool L69 3GB
P O D Pharoah
C J Stevenson
C R West

Correspondence to:
Professor P O D Pharoah.

number of children in the family. All these indices were marginally in favour of better social circumstances for the controls but none was significant. The only significant difference was that fewer cases than controls were living with both natural parents.[23]

The children were reassessed when aged 15 years with the same controls, when possible, as at the 8 year follow up. The children have now moved from primary to secondary schools and in some instances cases and controls were at different secondary schools. If the original control from primary school was not available, a new control of the same sex, in the same class at secondary school, and nearest in birth date to the index child was selected.

SURVEY MEASURES
All the assessments were carried out by one examiner (CJS) either at school or in the home. Blood pressure was measured in the left arm after the child had been seated for about 15 minutes during which time s/he completed a questionnaire. Three readings of the blood pressure were made at one minute intervals using a Dinamap 1846SX automated oscillometric monitor and a small adult size cuff. The last of the three readings was used in the analysis. The Dinamap was calibrated daily and serviced at 6 monthly intervals.

Height was measured using a portable stadiometer (the Leicester Height Measure), to the nearest 0.5 cm, with the child standing on a firm level surface. Weight was measured to the nearest 0.5 kg, with the child lightly clothed, using SECA Patient Scales. Body mass index was determined as weight (kg)/height (metres)^2. Head circumference was measured using a steel tape passing over the occipital protuberance.

A questionnaire to the mothers of cases and controls elicited information on their current smoking habit or whether they had ever smoked. For the control children only, the birthweight of the child was elicited by questionnaire. The birthweight of the index children had been extracted from the obstetric records when the cohort was initially established. The child's current smoking habit was obtained by a self-completed questionnaire.

STATISTICAL METHODS AND POWER CALCULATIONS
Power calculations for the study were based on regional differences in the mean blood pressure of children reported from the Regional Heart Study.[24] The range of mean systolic blood pressures in the regions was 96.7–102.4 mm with a standard deviation range of 8.6 to 8.7 mm. The range of mean diastolic blood pressures was 55.9 to 60.1 mm and the standard deviation range was 5.9 to 6.0 mm. Based on these data, the sample of children available for the study would allow, with an 80% power $(1-\beta = 0.8)$ and $\alpha = 0.05$, detection of a 3.5 mm difference in mean systolic, and a 2.5 mm difference in mean diastolic, pressure between cases and controls.

Statistical analysis was carried out using the Statistical Package for Social Sciences (SPSS). The paired Student t test was used to determine if the mean of the differences between each case control pair differed from zero for the continuous variables. The unpaired Student t test was used for continuous variables when comparing disabled and non-disabled children. McNemar's test for paired data was used to compare the current smoking of cases and controls and smoking during pregnancy of the mothers of cases and controls. Simple linear regression was used to adjust systolic and diastolic blood pressure for height, weight, and body mass index individually before a paired case control comparison.

Results
There were 40 321 live births in Merseyside in 1980–1; 399 weighed ≤1500 g at birth, of whom 219 survived to age 15 years; 172 (79%) of the survivors were singletons and comprise the results reported here. Of the 172 singletons, 128 (74%) were children with no disability attending normal schools for each of whom there was an age, sex, and school matched control. Eleven (6%) children with a disability but attending normal schools were also assessed, each with a matched control; 23 (13%) children with a disability and attending special schools were assessed without matched controls and are reported as a separate group; 10 (6%) children refused assessment, were untraced, or had moved abroad. Of the 219 survivors from the total cohort, 47 were from multiple pregnancies and were excluded from the analysis. This report is of 139 singleton (128 non-disabled + 11 disabled at normal school) children with their matched controls and 23 disabled singleton children at special schools without controls.

The mean birthweight of the 128 non-disabled index cases was 1249 g (range 630 to 1500 g) and for the controls was 3338 g (range 2098 to 4550 g). The gestational age of the index cases ranged from 26 to 37 weeks with a mean of 30.7 weeks. Data on the gestational

Table 1 Comparisons of anthropometric indices in non-disabled and disabled singleton cases and their matched controls and disabled singleton cases attending special schools (who have no controls)

Anthropometric measures	Non-disabled singleton cases (n=128)	Matched controls (n=128)	Mean of differences between cases and controls (95% CI)	Disabled singleton cases (n=11)	Matched controls (n=11)	Mean of differences between cases and controls (95% CI)	Disabled cases with no controls (n=23)
Height (cm)	159.7 (SD 7.9)	163.7 (SD 7.8)	−4.0 (−2.1 to −5.9) p < 0.001	153.8 (SD 5.8)	162.4 (SD 6.8)	−8.6 (−2.3 to −14.9) p < 0.02	151.5 (SD 9.0)
Weight (kg)	50.8 (SD 10.7)	55.3 (SD 10.5)	−4.4 (−1.8 to −7.0) p=0.001	47.8 (SD 9.8)	56.3 (SD 9.3)	−8.5 (−0.8 to −16.2) p<0.05	43.7 (SD 10.1)
Body mass index	19.8 (SD 3.3)	20.6 (SD 3.2)	−0.7 (−1.5 to +0.1) 0.1>p>0.05	20.3 (SD 4.5)	21.2 (SD 2.6)	−1.0 (−3.5 to +1.5) not significant	19.0 (SD 4.0)
Head circumference (cm)	55.1 (SD 1.9)	56.7 (SD 1.6)	−1.5 (−1.1 to −1.9) p<0.001	53.5 (SD 2.0)	56.2 (SD 2.1)	−2.8 (−0.9 to −4.7) p<0.01	53.9 (SD 1.6)

Table 2 Comparisons of blood pressure in non-disabled and disabled singleton cases and their matched controls and disabled singleton cases attending special schools (who have no controls)

Blood pressure	Non-disabled singleton cases (n=128)	Matched controls (n=128)	Mean of differences between cases and controls (95% CI)	Disabled singleton cases (n=11)	Matched controls (n=11)	Mean of differences between cases and controls (95% CI)	Disabled cases with no controls (n=23)
Systolic	114.7 (SD 12.8)	111.5 (SD 10.6)	3.2 (0.4 to 6.0) p<0.05	112.1 (SD 14.9)	111.0 (SD 7.8)	1.1 (−9.3 to 8.8) not significant	110.0 (SD 12.9)
Diastolic	59.4 (SD 8.2)	58.3 (SD 7.5)	1.1 (−0.7 to +2.9) not significant	59.0 (SD 7.4)	58.5 (SD 7.1)	0.5 (−4.9 to 6.9) not significant	62.0 (SD 11.8)

age of the controls were not obtained, but the mean and range of birthweights indicate that most must have been term infants.

ANTHROPOMETRIC MEASURES

There were highly significant differences between both non-disabled and disabled cases and their matched controls in height, weight, and head circumference, with the cases being smaller for all variables. Cases also had a lower body mass index than controls but the difference was not significant (table 1).

A comparison of 128 non-disabled cases with all 34 disabled cases showed that the latter were smaller for all anthropometric indices; there was a 6.4 cm difference in height (p<0.001), a 1.1 cm difference in head circumference (p=0.001), and a 5.0 kg difference in weight (p<0.01). The 0.34 unit difference in body mass index did not quite attain the conventional level of significance (p<0.07).

Within the group of disabled children, those attending special schools for whom there were no controls, were even shorter and lighter than those who attended normal schools, though the differences were not significant (table 1).

SMOKING HABIT

Among the non-disabled group, 20/127 (16%) of the cases and 5/127 (4%) of the controls were current smokers. The difference was significant (McNemar's exact test; p<0.01). Similarly, among the mothers, current smoking status (ever *vs* never smoked) or smoking status at the time of the pregnancy was significantly different in cases and controls. Among the cases, 87/126 (69%) of mothers compared with 59/126 (47%) control mothers have ever smoked (McNemar's χ^2, 1df = 6.7; p<0.01).

BLOOD PRESSURE

The systolic blood pressure was significantly higher in the non-disabled cases than controls; the mean of the differences in each case control pair was 3.2 mm Hg, p<0.05. The diastolic pressure was also higher in cases than controls but the difference was not significant. Systolic and diastolic blood pressures were higher in disabled cases than their controls, but with only 11 disabled case control pairs, the differences were not significant. Comparison of non-disabled with the disabled cases showed no significant differences in either systolic or diastolic blood pressure (table 2).

There was a significant positive correlation between systolic blood pressure and height, weight and body mass index, for cases and controls. The regression coefficients—the gradient of the association, of systolic pressure with height, weight and body mass index— were greater for cases than for controls, although the differences in gradients were not significant (table 3).

In contrast to the systolic pressure, there was no association between diastolic pressure and height in cases or controls. Weight and body mass index were significantly associated with diastolic pressure but the association was weaker than that for systolic pressure. The regression coefficients for the cases were greater than those for the controls, but the differences were not significant (table 3).

In a multiple regression of systolic and diastolic blood pressures on the anthropometric variables and mother and child's smoking status, no significant associations were observed.

Because blood pressure correlated positively with the anthropometric variables, the systolic and diastolic pressures were adjusted for height, weight, and body mass index separately and a paired case control comparison of blood pressure was made. Adjusting for each anthropometric variable increased the case control differences in systolic pressure and these differences remained highly significant. The case control differences in diastolic pressure also were marginally increased but remained non-significant (table 4).

Table 3 Correlation of blood pressure with height, weight, body mass index and head circumference

	Non-disabled cases (n=128)		Controls (n=128)	
	Correlation coefficient	Regression coefficient β (SE of β)	Correlation coefficient	Regression coefficient β (SE of β)
Height				
Systolic BP	0.30	0.49 (0.14) p=0.001	0.17	0.23 (0.12) p=0.06
Diastolic BP	0.01	0.01 (0.09) not significant	0.07	−0.06 (0.09) not significant
Weight				
Systolic BP	0.50	0.59 (0.09) p<0.0001	0.36	0.37 (0.08) p < 0.0001
Diastolic BP	0.20	0.15 (0.07) p=0.02	0.17	0.12 (0.06) p=0.06
Body mass index				
Systolic BP	0.43	16.6 (3.1) p<0.0001	0.35	11.3 (2.7) p=0.0001
Diastolic BP	0.25	6.2 (2.1) p=0.004	0.26	6.0 (2.0) p=0.003
Head circumference				
Systolic BP	0.22	1.43 (0.57) p<0.05	0.18	1.10 (0.58) p=0.06
Diastolic BP	0.03	0.14 (0.38) not significant	0.05	0.24 (0.42) not significant

Table 4   Case control differences in adjusted systolic and diastolic blood pressure (128 unimpaired case-control pairs)

	Means of differences between cases and controls	
	Systolic blood pressure (95% CI)	Diastolic blood pressure (95% CI)
Adjusted for height	4.4 (1.8 to 7.0); p=0.001	0.9 (−0.9 to +2.7); not significant
Adjusted for weight	5.1 (2.7 to 7.5); p<0.001	1.6 (−0.2 to +3.4); not significant
Adjusted for body mass index	4.2 (1.6 to 6.8); p=0.002	1.5 (−0.3 to +3.3); not significant

Discussion

The advantages of this study are that it reports a total population of low birthweight children from a geographically defined area and that a high follow up rate of 95% was achieved so that any non-response bias will be small. However, a possible bias could result from the high neonatal mortality among the cases, and the infants who died were probably among the most preterm and most growth retarded. This being so, the case control differences reported here would err towards being an underestimate of the true differences.

Unlike other studies that have been quoted which examine cohorts of children across the whole birthweight frequency distribution, the study we report here is unique in that it focuses on cases which were from one extreme of the birthweight frequency distribution with a birthweight cutoff point of 1500 g. This will enhance differences between cases and controls that are attributable to birthweight. Furthermore, because the cutoff was determined by birthweight and not gestational age, the cases will have a disproportionate number of intrauterine growth retarded infants included. Therefore, any association between fetal growth retardation and blood pressure will be accentuated in the comparison between cases and controls.

Infants who were of low birthweight continued to show significant differences in all the important parameters of growth at the time of adolescence compared with their normal birthweight controls. The association between increased weight and body mass and hypertension in adults is well recognised and, therefore, the difference in growth shown by the cohort of low birthweight adolescents has potentially important implications for subsequent levels of blood pressure, particularly if the growth trajectories are maintained into adulthood, leading to more pronounced differences in height, weight, and body mass index.

At 15 years of age the important difference between the low birthweight cases and their age and sex matched controls was in their systolic blood pressures; their diastolic blood pressures were not significantly different. As the cases were smaller than their controls in all the anthropometric indices, adjusting for these indices only served to increase the case control blood pressure differences. The difference in systolic blood pressure became more pronounced but the diastolic blood pressure difference remained non-significant. Birthweight is, therefore, independently associated with adolescent systolic, but not diastolic, blood pressure. This confirms the report of a cross sectional study of 8–11 year old children in which it was found that birthweight was inversely related to blood pressure after adjustment for current body size.[25]

A difference of 4–5mm Hg in systolic pressure between cases and controls shows how much the frequency distribution curve for systolic pressure is shifted to the right in the low birthweight cases compared with the controls. In populations this is a major difference. As systolic rather than diastolic blood pressure is the important determinant of cardiovascular disease risk and curtailment of life,[26][27] the observation that birthweight and intrauterine growth retardation primarily are associated with systolic blood pressure differences has important implications for subsequent ill health and mortality.

The regression coefficients—the gradients of the increase in blood pressure with height, weight and body mass index—were greater, though not significantly so, for the cases than the controls. Even though there was a failure to achieve significance, nevertheless, the differences could be real and are likely to persist through adolescence into adult life. It is also likely that the growth trajectories are maintained and the differences in the anthropometric indices will be further widened in adult life. If so, a multiplicative effect between gradient of the rise in blood pressure and the increase in height, weight, and body mass index will mean that adult differences in blood pressure attributable to birthweight will be even more pronounced than in adolescence.

The results support the hypothesis that birthweight and intrauterine growth retardation are positively associated with adolescent anthropometric indices and inversely associated with blood pressure after adjustment has been made for known confounding variables. However, the effects of social and economic factors acting postnatally and in early childhood cannot be discounted. Although matching cases and controls for school attenders, effectively matched for a variety of social and economic variables to the extent that no significant differences between cases and controls were found, nevertheless, the marginal differences observed all favoured the controls.[22] Also, a higher proportion of the low birthweight children and their mothers are smokers compared with the controls. It is plausible that adverse social and economic influences initiate their cardiovascular effects during fetal development and are compounded during childhood, adolescence, and adulthood. The difficulty is to determine the proportional contribution during the different phases of development.

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