Birth weight and blood pressure: cross sectional and longitudinal relations in childhood

Peter Whincup, Derek Cook, Olia Papacosta, M Walker

Abstract

Objective—To examine cross sectional and longitudinal relations between birth weight and blood pressure in childhood.

Design—Cross sectional study of primary school children aged 9-11 years, with analysis in relation to previous measurements at 5-7 years in a subgroup.

Setting—20 primary schools in Guildford and Carlisle.

Subjects—1511 children measured at 9-11 years (response rate 79%), including 549 who had been measured at 5-7 years.

Main outcome measures—Blood pressure at 9-11 years, change in blood pressure between 5-7 and 9-11 years, birth weight (based on maternal recall), and placental weight (based on birth records).

Results—At 9-11 years birth weight was inversely related both to systolic blood pressure (regression coefficient -2.80 mm Hg/kg; 95% confidence interval -3.84 to -1.76) and to diastolic blood pressure (regression coefficient -1.42 mm Hg/kg; -2.14 to -0.70) once current height and body mass index were taken into account. Placental weight was inversely related to blood pressure after adjustment for current height and body mass index but placental ratio (placental weight to birth weight) was unrelated to blood pressure. Between 5-7 and 9-11 years systolic blood pressure rose more rapidly in children of lower birth weight (regression coefficient -1.71 mm Hg/kg; -3.35 to -0.07). This effect seemed to be stronger in girls.

Conclusions—Birth weight rather than placental ratio is the early life factor most importantly related to blood pressure in childhood. The results support the possibility of "amplification" of the relation between birth weight and blood pressure, particularly in girls.

Introduction

Barker and colleagues argued that early life factors, acting particularly in utero, may have a strong influence on subsequent cardiovascular risk.¹ An inverse relation between birth weight and subsequent blood pressure (lower birth weight being associated with higher subsequent mean blood pressure) has been reported in adults²⁻⁴ and children,⁵⁻⁸ though not consistently in adolescents.⁹⁻¹¹ Earlier reports also suggested that a large placenta, particularly in the presence of low birth weight, was related to subsequent high blood pressure and the risk of hypertension.³ Recent reports have suggested that the birth weight and blood pressure relation becomes stronger with age ("amplification")¹² and that this may be an example of "programming."¹³ However, the evidence for amplification is based almost entirely on comparison of cross sectional studies with subjects of different ages and times of birth rather than on longitudinal measurements.¹⁴

We studied the relation between birth weight and blood pressure in children. In cross sectional analyses at 9-11 years of age we examined the relations between birth weight and blood pressure and the influence of placental weight. In longitudinal analyses based on children measured at both 5-7 and 9-11 years of age we examined the development of the birth weight and blood pressure relation with age.

Subjects and methods

We present data based on two surveys four years apart (1987 and 1991) in Guildford and Carlisle. The sampling and methods used have been detailed elsewhere.^{15,16} Both surveys were carried out in the same sample of 10 primary schools in each town. The second survey included all children from the earlier survey still attending the schools together with similar numbers of children in the same classes. In both surveys measurements were made by a team of trained nurse observers, who visited schools in the two areas in sequence.

Blood pressure was measured after five minutes' rest with the child seated and the arm supported at chest level. Three blood pressure measurements were made one minute apart on the right arm with the Dinamap 1846SX oscillometric blood pressure recorder (Critikon Inc, United States).¹⁷ All analyses were based on the means of the three readings. At 9-11 years all measurements were made with the adult size cuff (cuff bladder 22 cm × 12 cm); at 5-7 years all measurements were standardised to the child size cuff (cuff bladder 15 cm × 9 cm), as described.¹⁸ These cuff sizes ensured that the minimum cuff bladder width to arm circumference ratio of 40% recommended by the American Heart Association¹⁹ was met for 98% of the study population at age 9-11 years and for 99% of the population at age 5-7 years. Ethnic group was assessed on the basis of the child's appearance.

A self administered parental questionnaire sent to the parents on the day of examination in the 1991 survey was used to collect information on birth weight and gestational age (assessed on the basis of recall of the number of weeks the birth was early or late). With the permission of mothers, hospital birth record information was collected on subjects born in the two study areas, including birth weight, gestational age based on date of last menstrual period, and (available in Carlisle only) placental weight. Because there was close agreement in birth weight and gestational age between maternal recall and birth record information, analyses of birth weight and blood pressure at 9-11 years were based on maternal recall data.

A total of 924 children aged 5-7 years (84% response rate) took part in the 1987 survey; 1511 children aged 9-11 years (79% response rate) took part in the 1991 survey. All but eight children were of European origin; exclusion of the others had no effect on the results. Among the 1511 children measured in 1991, questionnaires with full birth details were returned for 1230

University Department of Public Health, Royal Free Hospital School of Medicine, London NW3 2PF

Peter Whincup, senior lecturer in clinical epidemiology
Olia Papacosta, research statistician
M Walker, research administrator

Department of Public Health Sciences, St George's Hospital Medical School, London SW17 0RE
Derek Cook, senior lecturer in epidemiology

Correspondence to: Dr Whincup.

BMJ 1995;311:773-6

(81%). Of these, 996 children were born in the study towns; maternal consent to retrieval of birth records was obtained for 995 children. Complete birth records were obtained for 838 (84%) of these children, 473 of whom were Carlisle subjects with data on placental weight. The 1991 survey included 549 children of 699 (79%) who took part in the 1987 survey and were still attending the survey schools. The longitudinal relations between birth weight and blood pressure were examined in 523 of these 549 subjects for whom maternal recall information on birth weight was available.

Statistical analysis—All analyses were carried out with the statistical analysis software (SAS) package.²⁰ Birth weight, placental weight, age, and measures of current body size—height and body mass index (weight (kg) divided by height (m²))—were either treated as continuous variables or ranked and grouped in equal thirds or fifths. Standard linear regression techniques were used throughout and all analyses standardised for the effect of study area. Changes in blood pressure between 5-7 and 9-11 years were examined both as absolute changes and as changes in rank by using standard deviation scores. These were calculated separately for blood pressure at 5-7 years and 9-11 years, standardised for age, sex, height, and body mass index at each age. Changes in standard deviation scores were then regressed on birth weight to examine the relation between birth weight and change in blood pressure rank between 5-7 and 9-11 years.

Results

BIRTH WEIGHT AND CURRENT BODY SIZE (AGE 9-11)

Birth weight showed little or no relation with blood pressure in a model adjusted only for age and sex (fig 1). However, after additional adjustment for height and body mass index (correlation coefficients with birth weight $r=0.19$, $r=0.10$ respectively) birth weight showed a smooth graded inverse relation with both systolic and diastolic pressure (fig 1). The corresponding regression coefficients defining the increase in blood pressure for a 1 kg fall in birth weight were -2.80 mm Hg (95% confidence interval -3.84 to -1.76 ; $P<0.0001$) for systolic pressure and -1.42 mm Hg (-2.14 to -0.70 ; $P<0.0001$) for diastolic pressure. The relations between birth weight and blood pressure were very similar in preterm and term infants, in boys and girls, and in children in the top and bottom thirds of the distribution of height and body mass index. They were also independent of parity, social class, maternal blood pressure, and maternal smoking in pregnancy.

BIRTH WEIGHT AND PLACENTAL WEIGHT (AGE 9-11)

Relations between birth weight, placental weight, and blood pressure were examined in 473 Carlisle children with data on these variables. Placental weight was strongly correlated with birth weight ($r=0.45$). Like birth weight, it showed a smooth inverse relation with blood pressure, particularly systolic pressure, once current height and body mass index were taken

FIG 1—Birth weight and blood pressure at 9-11 years, showing effect of adjustment for current body size. Mean blood pressures and 95% confidence intervals (bars) are shown for each fifth of birth weight. ●—● Adjusted for age and sex only. ○—○ Adjusted for age, sex, height, and body mass index

FIG 2—Systolic blood pressure centiles between 6 and 10 years of age. Centiles are based on data from 549 children studied longitudinally, measured at mean ages of 6.2 and 9.9 years and are standardised for sex, height, and body mass index. (See text for options (a) and (b))

into account. For a 100 g fall in placental weight systolic pressure rose by -0.84 mm Hg (95% confidence interval -1.50 to -0.18 ; $P=0.012$). However, including birth weight in the regression model greatly attenuated the relation between placental weight and blood pressure. Moreover, the placental ratio (placental weight to birth weight) showed no relation either with systolic pressure ($P=0.89$) or with diastolic pressure ($P=0.37$).

When the mean systolic blood pressure for each third of placental weight and birth weight was examined (table I) the highest mean blood pressure was observed in the group in the lowest third of both birth weight and placental weight distributions; subjects with low birth weight and high placental weight did not have a particularly high mean blood pressure. Similar findings were recorded for diastolic pressure (data not shown). There was no evidence of interaction between birth weight and placental weight, either for systolic ($P=0.56$) or diastolic ($P=0.70$) blood pressure. These results were unaffected by exclusion of preterm births (≤ 36 weeks).

CHANGES BETWEEN 5-7 AND 9-11 YEARS

The relative strengths of the birth weight and blood pressure relation at 5-7 and 9-11 years, standardised for

TABLE I—Birth weight (thirds), placental weight (thirds), and systolic blood pressure (mm Hg) at 9-11 years. Figures are means (SE)

Placental weight (thirds)	Birth weight (thirds)			All
	Low (≤ 3120 g)	Mid (3121-3609 g)	High (≥ 3610 g)	
Low (≤ 589 g)	109.4 (1.5)	106.5 (1.7)	106.8 (2.3)†	108.6 (0.8)
Mid (590-689 g)	108.8 (2.0)	103.4 (1.3)	106.0 (1.4)	105.6 (0.8)
High (≥ 690 g)	103.9 (3.2)†	105.4 (1.7)	105.9 (1.2)	105.3 (0.8)
All	108.9 (0.8)	106.1 (0.8)	104.2 (0.8)	106.5 (0.6)

Analyses were based on 473 Carlisle subjects with complete birth record data and were standardised for age, sex, height, and body mass index throughout.

†Based on fewer than 20 subjects.

TABLE II—Birth weight, blood pressure, and change in blood pressure in children measured at 5-7 and 9-11 years

	Systolic		Diastolic	
	Regression coefficient (SE)	P	Regression coefficient (SE)	P
<i>Birth weight and blood pressure†</i>				
Age 9-11 years	-3.95 (0.87)	<0.0001	-1.34 (0.66)	0.03
Age 5-7 years	-2.28 (0.66)	0.0006	-1.10 (0.51)	0.03
<i>Birth weight and change in blood pressure between 5-7 years and 9-11 years‡</i>				
Absolute blood pressure change	-1.71 (0.82)	0.04	-0.08 (0.60)	0.89
Change in blood pressure rank (standard normal deviate)	-0.09 (0.09)	0.28	-0.02 (0.09)	0.83

†Regression coefficients (mm Hg/kg) show difference in blood pressure for 1 kg increase in birth weight at each age.
‡Regression coefficients show absolute change in blood pressure (mm Hg) and change in blood pressure rank (expressed as standard normal deviate) between 5-7 and 9-11 years for 1 kg increase in birth weight.
All analyses were based on 523 subjects followed up between 5-7 and 9-11 years with maternal recall data on birth weight and were standardised for area, age, sex, height, and body mass index at each age.

age, sex, height, and body mass index at each age, were examined in 523 children studied longitudinally and in whom birth weight data were available (table II). The regression coefficients, defining the difference in blood pressure for a 1 kg increase in birth weight, increased between 5-7 years and 9-11 years by 73% for systolic pressure and 22% for diastolic pressure. The corresponding within subject analysis taking into account age, sex, height, and body mass index at both ages showed that the increase in the strength of the systolic relation was significant whereas that for diastolic pressure was not. The increase in the strength of the systolic relation appeared to be more pronounced in girls (regression coefficient -3.42 (SE 1.13) mm Hg/kg) than in boys (regression coefficient 0.03 (1.13) mm Hg/kg) (test for interaction, P=0.03).

The extent to which birth weight was related to change in blood pressure rank between 5-7 and 9-11 years was examined by determining the standard normal deviate of blood pressure in each subject at 5-7 and 9-11 years separately (taking into account age, sex, height, and body mass index at each age) and studying the relation between birth weight and change in standard normal deviate (table II). Overall, birth weight had little or no relation to change in the rank of blood pressure between these ages. However, birth weight seemed to be inversely related to a change in blood pressure rank in girls (regression coefficient -0.26 (SE 0.12)) rather than in boys (regression coefficient 0.09 (0.12)) (test for interaction, P=0.05).

Discussion

The inverse relation between birth weight and blood pressure after standardisation for current body size was consistent with the findings of earlier studies in children.²⁻⁴ The associations seen at 9-11 years were similar to those observed by Cater and Gill⁵ but considerably stronger than those reported by other

workers.^{2,12} The association was smoothly graded, with no evidence of the U shaped relation suggested by Launer *et al.*²¹ The results are consistent with our earlier report in suggesting that attained birth weight is the important factor in the relation between birth weight and blood pressure,⁸ regardless of the degree of intrauterine growth retardation.

PLACENTAL WEIGHT AND BLOOD PRESSURE

Our results do not support the hypothesis that placental weight or the ratio of placental weight to birth weight is a useful marker of higher subsequent blood pressure. In this study, as in an earlier, small study of 7 and 18 year olds,²² placental weight was inversely related to blood pressure. However, placental weight showed little relation with blood pressure once birth weight was taken into account, and placental ratio was unrelated to blood pressure.

CHANGE IN RELATION WITH AGE

This is one of the first longitudinal studies to examine the way in which the birth weight and blood pressure relation develops with age directly—an issue of direct relevance to the possibility of programming.¹³ Our results suggest that the inverse relation between birth weight and blood pressure emerges during the first five years after birth and that the relation becomes stronger (that is, “amplified”) between 5-7 and 9-11 years. The increasing strength of the relation is not an artefact of cuff size or of other aspects of the measuring procedures used. However, it is observed only for systolic pressure and seems to be more pronounced in girls. This is surprising given the greater physical maturity of girls at this age and the inconsistent findings of earlier studies of the birth weight and blood pressure association in adolescence.⁹⁻¹¹ However, the greater strength of the relations between birth weight and blood pressure at 9-11 years in this study compared with earlier studies^{2,12} emphasises the importance of substantiating the finding in other longitudinal studies.

It is also important that the relation between amplification and “programming” is defined. In particular, agreement is needed on whether amplification alone is evidence of programming or whether a particular mechanism of amplification is required. Theoretically, the birth weight and blood pressure relation could be amplified simply by blood pressure tracking combined with the dispersion of the blood pressure distribution which occurs with age (fig 2). Whether amplification occurring by this mechanism (option (a)) is evidence of programming or whether evidence of systematic upward “detracking” across the blood pressure distribution by children of low birth weight (option (b)) is required (fig 2) has still to be established. Our present results provide some support for the possibility of detracking—though only in girls—and emphasise the need for further longitudinal studies of the relation between early life factors and cardiovascular risk factor development.

Two of us (PW and MW) were supported by the British Heart Foundation and one (OP) by the Stroke Association. We thank the research team (Jane King, Susan Wright, Joan Branthwaite) and the education authorities, schools, parents, and children for their cooperation and local directors of public health and hospital medical records departments for their help.

Funding: Medical Research Council and Coronary Artery Disease Research Association.

Conflict of interest: None.

1 Barker DJP, ed. *The fetal and infant origins of adult disease*. London: BMJ Publishing Group, 1992.
2 Barker DJP, Osmond C, Golding J, Kuh D, Wadsworth MEJ. Growth in utero, blood pressure in childhood and adult life, and mortality from cardiovascular disease. *BMJ* 1989;298:564-7.

- 3 Barker DJP, Bull AR, Osmond C, Simmonds SJ. Fetal and placental size and risk of hypertension in adult life. *BMJ* 1990;301:259-62.
- 4 Gennser G, Rymark P, Isberg PE. Low birth weight and risk of high blood pressure in adulthood. *BMJ* 1988;296:1498-500.
- 5 Cater J, Gill M. The follow-up study: medical aspects. In: Illsey R, Mitchell RG, eds. *Low birth weight, a medical psychological and social study*. Chichester: John Wiley, 1984:191-205.
- 6 Whincup PH, Cook DG, Shaper AG. Early influences on blood pressure: a study of children aged 5-7 years. *BMJ* 1989;299:587-91.
- 7 Law CM, Barker DJP, Bull AR, Osmond C. Maternal and fetal influences on blood pressure. *Arch Dis Child* 1991;66:1291-5.
- 8 Whincup PH, Cook DG, Papacosta O. Do maternal and intrauterine factors influence blood pressure in childhood? *Arch Dis Child* 1992;67:1423-9.
- 9 MacIntyre S, Watt G, West P, Ecob R. Correlates of blood pressure in the west of Scotland. *J Epidemiol Community Health* 1991;45:143-7.
- 10 Seidman DS, Laor A, Gale R, Stevenson DK, Mashiach S, Danon YL. Birth weight, current body weight, and blood pressure in late adolescence. *BMJ* 1991;302:1235-6.
- 11 Mattes JWA, Lewis PA, Davies DP, Bethel JA. Relation between birth weight at term and systolic blood pressure in adolescence. *BMJ* 1994;308:1074-7.
- 12 Law CM, de Swiet M, Osmond C, Fayers P, Barker DJP, Cruddas AM, et al. Initiation of hypertension in utero and its amplification throughout life. *BMJ* 1993;306:24-7.
- 13 Lucas A. Programming by early nutrition in man. In: Buck GR, Whelan J, eds. *The childhood environment and adult disease*. Chichester: John Wiley, 1991:38-55. (Ciba Foundation symposium No 156.)
- 14 Whincup PH, Papacosta O, Cook DG. Initiation of hypertension in utero. *BMJ* 1993;306:584.
- 15 Whincup PH, Cook DG, Shaper AG, Macfarlane D, Walker M. Blood pressure in British children: associations with adult blood pressure and cardiovascular mortality. *Lancet* 1988;ii:890-3.
- 16 Whincup PH, Cook DG, Papacosta O, Walker M, Perry I. Maternal factors and development of cardiovascular risk: evidence from a study of blood pressure in children. *J Hum Hypertens* 1994;8:337-43.
- 17 Whincup PH, Bruce NG, Cook DG, Shaper AG. The Dinamap 1846SX oscillometric blood pressure recorder: comparison with the Hawksley random-zero sphygmomanometer under field study conditions. *J Epidemiol Community Health* 1992;46:164-9.
- 18 Whincup PH, Cook DG, Shaper AG. Blood pressure measurement in children: the importance of cuff size. *J Hypertens* 1989;7:845-50.
- 19 Frohlich ED, Grim C, Labarthe DR, Maxwell MH, Perloff D, Weidman WH. Recommendations for human blood pressure determinations by sphygmomanometers. Report of a special task force appointed by the steering committee, American Heart Association. *Circulation* 1988;77:502-14A.
- 20 SAS Institute Inc. *SAS user's guide: basics and statistics (version 5)*. Cary, North Carolina: SAS Institute, 1985.
- 21 Launer LJ, Hoffman A, Grobbee DE. Relation between birth weight and blood pressure: longitudinal study of infants and children. *BMJ* 1993;307:1451-4.
- 22 Williams SA, St George IM, Silva PA. Intrauterine growth retardation and blood pressure at ages seven and eighteen. *Journal of Chronic Diseases* 1992;45:1257-63.

(Accepted 14 July 1995)

FcεRI-β polymorphism and risk of atopy in a general population sample

M R Hill, A L James, J A Faux, G Ryan, J M Hopkin, P le Süeuf, A W Musk, W O C M Cookson

Abstract

Objective—To establish the prevalence of *FcεRI-β* polymorphisms *Leu181* and *Leu181/Leu183* on chromosome 11q13 in the general population and to examine whether when maternally inherited they confer a risk of atopy.

Design—A population based survey for measures of atopy (skin prick test reactions, specific IgE titres, total serum IgE concentration), bronchial hyper-responsiveness, and carriage of *FcεRI-β Leu181* and *Leu181/Leu183*.

Setting—The rural coastal town of Busselton, Western Australia.

Subjects—1004 members of 230 two generation families identified through adults aged under 55.

Results—*FcεRI-β Leu181/Leu183* was identified in 45 subjects (4.5%). All 13 children who had inherited the variant maternally were atopic. Six had asthma and nine rhinitis. The odds ratio of a positive skin prick test reaction to house dust mite or grass pollen in these children compared with the other 523 children was 7.37 (95% confidence interval 1.62 to 33.60). The 95% confidence interval for the odds ratio of a positive specific IgE response (radio-allergosorbent test) was 3.00 to ∞, and the odds ratio for bronchial hyperresponsiveness was 3.70 (1.21 to 11.60). By contrast, the eight children who had derived the variant paternally had negative skin prick and radioallergosorbent test results and did not have increased bronchial responsiveness.

Conclusion—*FcεRI-β Leu181/Leu183* when inherited maternally identifies a genetic risk factor for atopy and bronchial hyperresponsiveness.

Introduction

Atopy is a familial syndrome of asthma, rhinitis, and eczema which is due to the interaction of genetic and environmental factors. Genetic linkage of atopic IgE responses to chromosome 11q13¹ was initially controversial² but has now been replicated by several groups³⁻⁵. Linkage was strongest in maternally derived alleles,^{5,6} which may contribute to the maternal inheritance of atopy evident from many studies.⁷⁻¹¹ The gene for the β chain of the high affinity receptor for IgE (*FcεRI-β*)

is a candidate for the chromosome 11q13 effect.¹² Sequencing of *FcεRI-β* has detected polymorphisms (variants)—*FcεRI-β Leu181/Leu183* (*Leu 181/Leu183*) and *FcεRI-β Leu181* (*Leu181*)—which were associated with atopy.¹³

We examined the prevalence of *Leu181* and *Leu181/Leu183* in an Australian general population sample and tested whether when inherited maternally the polymorphisms endowed a risk of atopy.

Subjects and methods

The subjects were from the rural coastal town of Busselton, South Western Australia. The aim was to recruit young nuclear families. Children under 5 were excluded because they could not complete respiratory testing. Families were identified through adults aged 55 or under from an electoral roll of around 9000. Families were serially recruited until a predetermined target of 1000 subjects was reached. The final sample comprised 1004 members of 230 nuclear families.

A total of 1867 subjects were approached. Of these, 177 refused to take part; 140 were not contactable; and 434, though contacted, had not been tested by the end of the study. Seven hundred and eight subjects were excluded because their spouses were aged over 55 or because they were not married with two or more natural children over the age of 5. The remaining 408 subjects and their spouses and children not on the electoral roll completed the study. Subjects knew the respiratory interest of the investigation before agreeing to participate. We emphasised that normal people were important to the study.

Clinical protocol—Testing took place in May, June, and July 1992. A respiratory questionnaire based on the American Thoracic Society questionnaire but including questions on rhinitis and allergies was administered. Skin prick testing to house dust mite (*Dermatophagoides pteronyssinus*), mixed grass pollen, cat and dog dander, *Aspergillus fumigatus*, *Alternaria alternata*, and a negative control (Dome-Hollister-Steir, Spokane, United States) was carried out as described.⁶ Weal diameters were calculated minus the negative control. Bronchial responsiveness to methacholine (maximum dose 12 μmol) was measured.^{14,15}

Nuffield Department of Clinical Medicine, University of Oxford, John Radcliffe Hospital, Oxford OX3 9DU
M R Hill, postdoctoral scientist
J A Faux, postdoctoral scientist
W O C M Cookson, Wellcome senior clinical research fellow

Department of Respiratory Medicine, Queen Elizabeth II Medical Centre, Perth, Western Australia 6009
A L James, consultant physician
G Ryan, consultant physician
A W Musk, head of department

Oxler Chest Unit, Churchill Hospital, Oxford OX3 7LJ
J M Hopkin, consultant physician

University Department of Paediatrics, Princess Margaret Hospital, Perth, Western Australia
P le Süeuf, associate professor

Correspondence to: Dr Cookson.

BMJ 1995;311:776-9