Papers

The four papers in this section appear here, in the print BMJ, *in abridged form. The full versions appear on our website. The editorial by Delamothe et al explains why we are doing this, and we welcome readers' reactions. One paper (by Whitehead, p 908) appears in two abridged versions, one much shorter than the other; again we welcome readers' reactions on which they prefer, and why*

Twins and maternal smoking: ordeals for the fetal origins hypothesis? A cohort study

Sheila Williams, Richie Poulton

Abstract

Objective To assess the direct and indirect effects of being a twin, maternal smoking, birth weight, and mother's height on blood pressure at ages 9 and 18 years.
Design Longitudinal study.
Subjects Cohort born in 1972-3.
Setting Dunedin, New Zealand.
Main outcome measure Blood pressure at ages 9 and 18 years.
Results Compared with singletons, twins had a systolic blood pressure 4.55 (95% confidence interval 1.57 to 7.52) mm Hg lower at age 9 after adjustment for direct and indirect effects of sex, maternal smoking, mother's height, socioeconomic status, and birth weight, as well as concurrent height and body mass index. Blood pressure in children whose mothers had smoked during pregnancy was 1.54 (0.46 to 2.62) mm Hg higher than in those whose mothers did not. The total effect of birth weight on systolic blood pressure at age 9 was −0.78 (−1.76 to 0.20) mm Hg and that for mother's height was 0.10 (0.06 to 0.14) mm Hg. Similar results were obtained for systolic blood pressure at age 18. The total effect of twins, maternal smoking, and birth weight on diastolic blood pressure was not significant at either age.
Conclusions Twins had lower birth weight and lower systolic blood pressure at ages 9 and 18 than singletons. This finding challenges the fetal origins hypothesis. The effect of maternal smoking was consistent with the fetal origin hypothesis in that the infants of smokers were smaller and had higher blood pressure at both ages. This may be explained by pharmacological rather than nutritional effects. The total effect of birth weight on systolic blood pressure, after its indirect effect working through concurrent measures of height and body mass index was taken into account, was small.

Introduction

Studies reporting an inverse association between birth weight and blood pressure in both children and adults have led to the hypothesis that events occurring before birth may lead to cardiovascular disease in later life.[1 2] It is argued that this is the consequence of the mother's poor nutrition in pregnancy. Although not all findings confirm this hypothesis,[3-5] support comes from several studies of people born in the 1920s and 1930s and from children born more recently. The evidence, as a *BMJ* editorial puts it, is an inductionist's dream; example being piled on example, with each study being somewhat consistent with others but none seriously testing the hypothesis.[6] This editorial suggests ordeals or tests to which the hypothesis might be put, including the effect of being a twin, a group known to experience restricted growth in the third trimester of pregnancy; smoking by the mother, which is a key determinant of birth weight and smoking in the offspring; and social class both at the time of birth and in the mother's family.

This sample from New Zealand provided an opportunity to re-examine the association between birth weight and later blood pressure. Information was available on mothers' height, which can be regarded as a measure of the socioeconomic climate of their childhood as well as the socioeconomic climate prevailing at the time of the children's birth.

Methods

The sample consisted of children enrolled in the Dunedin multidisciplinary health and development study,[7] born between 1 April 1972 and 31 March 1973.

The sample was traced at the time of the children's third birthdays, and consent was given for 1037 of the 1139 still living in Dunedin or Otago to take part. The present study uses data collected at age 9, when 818 children attended the research unit for physical measurements and their mothers were asked about smoking

Editorials
by Delamothe et al and Susser and Levin

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website *e*xtra
The full version of this paper appears on the BMJ's website
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Table 1 Characteristics of males and females at age 9 and 18 years. Values are means (SD)

Characteristic	Males	Females
Age 9:	(n=419)	(n=376)
Systolic blood pressure (mm Hg)*	107.0 (7.28)	106.1 (7.24)
Diastolic blood pressure (mm Hg)†	68.7 (6.71)	68.5 (7.03)
Body mass index (kg/m^2)	16.3 (1.55)	16.4 (1.77)
Height (cm)	132.7 (5.41)	131.8 (5.77)
Birth weight (kg)	3.4 (0.53)	3.3 (0.52)
Mother's height (cm)	162.7 (5.68)	163.1 (6.01)
Age 18:	(n=444)	(n=407)
Systolic blood pressure (mm Hg)	126.0 (9.38)	115.4 (9.27)
Diastolic blood pressure (mm Hg)‡	56.8 (10.57)	56.8 (9.06)
Body mass index (kg/m^2)	22.7 (3.17)	22.9 (3.17)
Height (cm)	176.1 (6.21)	164.1 (6.08)
Birth weight (kg)	3.5 (0.53)	3.3 (0.51)
Mother's height (cm)	162.7 (5.81)	163.2 (6.13)

*Recorded for 811 children, but analysis restricted to children with no data missing.
†1 Observation missing in each group.
‡13 Observations missing for males and 4 observations missing for females.

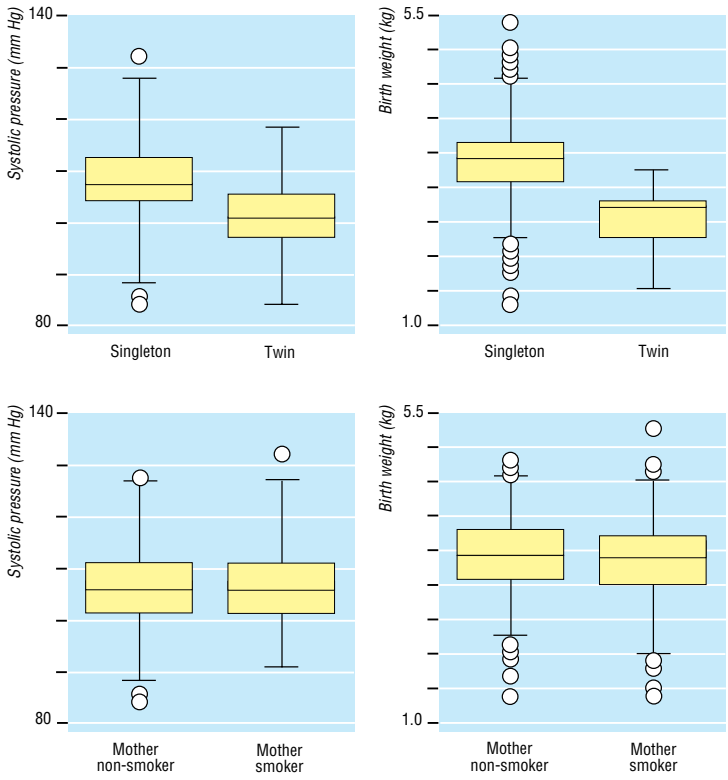

Fig 1 Box and whisker plots for systolic blood pressure at age 9 and birth weight for twins compared with singletons, and children of mothers who smoked during pregnancy compared with children of mothers who did not smoke

in pregnancy, and at age 18, when 879 attended the unit for a full day's assessment.

This cohort was part of a larger study from which birth weight and mother's height were derived.[8] Socioeconomic status for the infants' fathers was recorded, using the Elley-Irving index of socioeconomic status[9]; categories 5 and 6 were defined as low socioeconomic status.

At age 9 the mothers of the children were asked whether or not they had smoked in pregnancy and were classified as smokers or non-smokers. Mother's height was recorded at assessment at age 11, and this was used if mother's height had not been recorded at the time of the child's birth.

Path analysis was used to examine the effect of maternal smoking, mother's height, and being a twin on birth weight as well as their effect on later height, body mass index, and blood pressure. The models were fitted with LISREL using maximum likelihood methods.[10] In the analysis, the temporal nature of the variables was used to examine the causal relations among them. As the mother's height was established and maternal smoking occurred before the baby was born, these variables were regarded as being causally related to birth weight. Birth weight was considered to be causally related to measures taken at ages 9 and 18 years. Although height, body mass index, and blood pressure were collected simultaneously, a causal relation between both body mass index and height and blood pressure was tenable. This mediates the direct and indirect effects of birth weight and other variables on blood pressure.

Results

The means and standard deviations for systolic blood pressure, height, body mass index, birth weight, and mother's height are shown in table 1. At age 9 the sample of 419 boys and 376 girls included 22 (2.8%) twins and 261 (32.8%) children whose mothers reported smoking in pregnancy. Information on whether or not the mothers smoked was not available for 40 (5.0%) children. The sample also included 177 (22.3%) children in the low socioeconomic status category and 36 (4.5%) whose mothers were unmarried at the time of their conception. Height and weight at age 9 were missing for five children, mother's height for two, and socioeconomic status for nine.

On average twins had both lower blood pressure at age 9 and lower birth weights than singleton children (difference 5.09 (95% confidence interval 2.03 to 8.16) mm Hg for blood pressure and 0.88 (0.66 to 1.09) kg for birth weight) (fig 1). The children of mothers who smoked in pregnancy had higher blood pressure (difference 1.41 (0.32 to 2.50) mm Hg) and lower birth weights (difference 0.11 (0.03 to 0.19) kg) than those whose mothers did not smoke.

Regressing systolic blood pressure on birth weight in the total population of births showed an inverse relation: a difference of 1 kg in birth weight was commensurate with a decrease in blood pressure of 0.26 (0.70 to 1.21) mm Hg. Mother's height was positively related, with a difference of 1 cm being commensurate with a difference of 0.07 (−0.02 to 0.15) mm Hg. The results of regressing systolic blood pressure at age 9 on all the variables simultaneously is shown in table 2. These are the direct effects of each variable on blood pressure. Being a twin, maternal smoking, the concurrent measures of body mass index and height, as well as birth weight, were all significantly associated with blood pressure. Birth weight was inversely associated with blood pressure, commensurate with a decrease of 1.93 (0.96, 2.89) mm Hg for each kg increase in birth weight. This analysis, however, does not take into account the indirect effects of a number of these variables on blood pressure.

Path analysis was used to estimate both the indirect and the total effects of the measures related to birth

Table 2 Regression coefficients for effects of predictors of systolic blood pressure at age 9 adjusted for other variables in model

	Direct effect (95% CI)	Indirect effect (95% CI)	Total effect (95% CI)
Sex	0.76 (–0.20 to 1.72)	–0.02 (–0.39 to 0.35)	0.74 (–0.27 to 1.75)
Twin	–4.31 (–7.32 to –1.30)	–0.80 (–2.13 to 0.54)	–5.11 (–8.18 to –2.03)
Maternal smoking in pregnancy	1.34 (0.31 to 2.38)	0.20 (–0.19 to 0.59)	1.54 (0.45 to 2.63)
Maternal smoking status (unknown)	1.77 (–0.54 to 4.08)	–0.40 (–1.25 to 0.46)	1.37 (–1.08 to 3.81)
Low socioeconomic status	–0.34 (–1.48 to 0.81)	–0.02 (–0.44 to 0.41)	–0.35 (–1.57 to 0.87)
Mother unmarried	–1.42 (–3.83 to 0.98)	1.24 (0.34 to 2.15)	–0.18 (–2.72 to 2.36)
Mother's height (cm)	–0.02 (–0.11 to 0.07)	0.09 (0.05 to 0.14)	0.07 (–0.02 to 0.16)
Current height (cm)	0.33 (0.23 to 0.43)	—	0.33 (0.23 to 0.43)
Current body mass index (kg/m^2)	0.92 (0.63 to 1.21)	—	0.92 (0.63 to 1.21)
Birth weight (kg)	–1.93 (–2.89 to –0.96)	1.06 (0.67 to 1.46)	–0.87 (–1.86 to 0.13)

weight as well as birth weight itself on the height, body mass index, and blood pressure at age 9 (table 2). As the path model estimated a large number of effects, in the interests of parsimony the direct effects which were not statistically significant were removed. The final model provided a good fit for the data ($\chi^2 = 14.07$, df = 11, P = 0.23). The key features of the model are illustrated in figure 2, which shows the standardised regression coefficients. Being male, being a twin, and mother's height were strong predictors of birth weight and later height. Maternal smoking was related to birth weight and later body mass index. In this model the total effect of birth weight on systolic blood pressure included the direct effect, −0.134; the indirect effect acting through height, 0.163 × 0.247; and the indirect effect acting through body mass index, 0.179 × 0.207; leading to total of −0.057. Thus an increase of one standard deviation in birth weight was associated with a reduction of 0.057 of a standard deviation of systolic blood pressure, which is equivalent to a 1 kg increase in birth weight, being commensurate with a decrease of 0.78 (−0.20 to 1.76) mm Hg in blood pressure. The direct effect, and indirect effects operating through birth weight and height, produce a total effect for being a twin of −4.55 (−7.52 to −1.57) mm Hg. The total effect for maternal smoking was 1.54 (0.46 to 2.62) mm Hg, and that for mother's height 0.10 (0.06 to 0.14) mm Hg. The correlation between height and body mass index at age 9 was 0.14. The total effects for the full model are shown in table 2.

When the analysis for systolic blood pressure at age 9 was restricted to the 755 children whose gestational age was believed to be 37 weeks or more, the findings were essentially the same as for the entire sample (see table 3 on website, which also shows key results for diastolic blood pressure at age 9 and systolic and diastolic blood pressure at age 18).

Discussion

Our results are not altogether consistent with a more recent study of 8-11 year old children, which found that the significant inverse association between birth weight and systolic blood pressure held for girls but not boys,[11] nor with a study of 18 year olds in Israel, which found a weak association.[3] It has been argued that body mass index is an intervening variable in the relation between birth weight and blood pressure and that to adjust for it in a regression model is to overcontrol for it.[6] Thus, and because birth weight was not by itself significantly associated with blood pressure in this sample, its importance in the model may be by virtue of its association with other variables.

Statistical considerations

The direct effects in the path analysis were the same as those obtained from multiple regression, so that the measurement for birth weight provided an estimate of its effect on blood pressure after the effects of other variables were taken into account. Adjusting for confounding in this way assumes that none of the variables included in the model are at an intermediate step in the causal pathway. Path analysis, unlike multiple regression analysis, allows for the inclusion in the model of variables such as current height and body mass index which are in the causal pathway. Hence the total effect of birth weight on blood pressure can be estimated from the direct and the indirect effects. The results of this study showed that birth weight was strongly associated with later height and body mass index, which were in turn strongly associated with blood pressure. This resulted in a significant positive indirect effect and, combined with the inverse direct effect, provided an estimate of the total effect.

Ordeals for the fetal origins hypothesis

The most interesting finding of this study was the lower systolic blood pressure of twins. The magnitude of this effect was similar whether or not adjustments were made for birth weight or concurrent height or body mass index. Further, this finding was significant when the analysis was restricted to full term infants at age 9 and when the whole sample was examined at age 18. This finding is not consistent with the fetal origins hypothesis, which argues that poor nutrition in

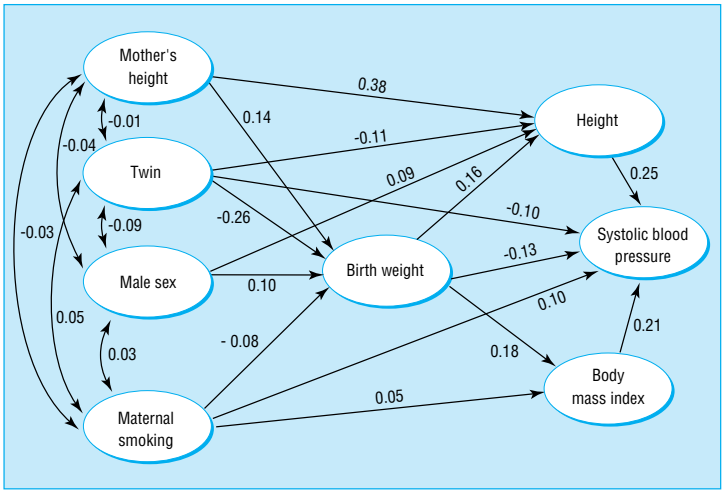

Fig 2 Path diagram for effects of sex, being a twin, mother's smoking, and mother's height on birth weight, and their effects on height, body mass index, and systolic blood pressure at age 9 years

pregnancy leads to higher rather than lower blood pressure. A recent Danish study showed that twins do not have significantly different mortality from cardiovascular disease than the general population, even though they experience intrauterine growth delay.[12] The authors concluded that the fetal origins hypothesis did not apply to the growth retardation experienced by twins. Other studies have found that variables plausibly reflecting poor maternal nutrition, including low maternal body mass index before pregnancy, poor maternal weight gain in pregnancy, and being born small for gestational age, were not associated with higher blood pressure.[13]

The path analysis showed that mother's height had a positive effect on blood pressure, acting indirectly through children's height. Studies that have shown the reverse have not taken into account the indirect effect of maternal height. A study of the British 1946 birth cohort, for example, showed that the 36 year old sons of the tallest mothers had blood pressures 2 mm Hg lower than the sons of the shortest mothers, and this increased to almost 3 mm Hg when adjusted for current weight.[14] The differences were not as clear cut among the women. This effect was also evident among children born in Salisbury in 1984-5.[15] The authors of these reports argue that a woman's physique depends on her nutrition in childhood, and that this may be linked to blood pressure in the next generation. In our sample a difference in height of 10 cm was commensurate with a 1 mm Hg difference in blood pressure.

The model in figure 2 showed that maternal smoking worked in several plausible ways. In some senses this finding is consistent with the fetal origins hypothesis in that maternal smoking was associated with both lower birth weight and higher blood pressure if it is assumed that maternal smoking leads to poorer nutrition for the fetus. As smoking also predicts body mass index at age 9 it seems possible that this is an effect of social environment because it is well known that maternal smoking is associated with low socioeconomic status and lower school achievement and may be a proxy for a poorer home environment or poorer nutrition.[16 17]

Conclusions

The fetal origins hypothesis has been subjected to as tough an ordeal as the data permit. The crucial tests were the effects of being a twin and maternal smoking on the relation with systolic blood pressure. That twins had lower blood pressure at age 9 and 18 challenges the underlying premise of the fetal origin hypothesis. On the other hand, smoking affects both birth weight and blood pressure itself and the associations were consistent with the fetal origins hypothesis provided that its action is explained by poor nutrition. Taken in total, mother's height had a positive effect on blood pressure, suggesting that taller women had larger babies, taller children, and children with higher blood pressure. When the indirect effect of birth weight on current height and body mass index was taken into account, it seems that the direct effect of birth weight on later blood pressure may be overestimated.

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Key message box

- Twins have lower systolic blood pressure at age 9 and 18 years than singletons
- Children of mothers who smoke in pregnancy have a lower mean birth weight and a higher mean systolic blood pressure at age 9 and 18.
- When the indirect effects of birth weight on current height and body mass index are taken into account the effect of birth weight on blood pressure is small at ages 9 and 18

Contributors: SW conceived the idea for this study and carried out the statistical analysis. The paper was written jointly by SW (guarantor) and RP.

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Endpiece

Science is seldom logical

Science seldom proceeds in the straighforward logical manner imagined by outsiders. Instead, its steps forward (and sometimes backward) are often very human events in which personalities and cultural traditions play major roles.

James D Watson, *The Double Helix*, Penguin, 1968