Birth Size, Growth, and Blood Pressure between the Ages of 7 and 26 Years: Failure to Support the Fetal Origins Hypothesis

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The “fetal origins hypothesis” asserts that birth weight is inversely related to later blood pressure. Data from a cohort of 891 infants born in Dunedin, New Zealand, in 1972–1973 whose blood pressure was measured at 2-year intervals from age 7 years to age 15 years and at ages 18 and 26 years were used to test this hypothesis. Three regression models based on standardized scores for weight and height were used. The first showed that at any of the ages at which the cohort was assessed, an increase in birth weight of one z score (one standard deviation) was commensurate with a decrease of 0.29 mmHg (95% confidence interval: –0.17, 0.76) in blood pressure. The second model showed that a one-z-score increase in weight between birth and a subsequent age was associated with an increase in systolic blood pressure of 0.96 mmHg (95% confidence interval: 0.53, 1.38). This estimate applied to all ages. The third model showed that the effect of an interaction between birth weight and later weight was not significant; thus, there was no evidence to suggest that children with a low birth weight who became overweight or obese had extra high blood pressure. Similar results were obtained for height. These results fail to support the fetal origins hypothesis. Am J Epidemiol 2002;155:849–52.

The inverse association between birth weight and adult blood pressure that has been reported in many studies provides the basis for the “fetal origins hypothesis.” A recent summary showed that the effect was consistent across a number of different study samples and different age groups (1). Questions about the correct interpretation of the results of such studies have been raised, because in many studies the effect of birth weight must be amplified by adjusting for current size for the effect to become statistically significant (2). One suggestion is that change in body size with age may be an important effect in the causal pathway and that this may explain the inverse association with birth weight. The hypothesis, which was initially based on fetal growth and its association with poor maternal nutrition, now encompasses catch-up growth (3, 4).

The use of three key regression models in the statistical analysis of such studies has been proposed (2). The first model, the “early model,” includes birth size alone. The second or “combined” model combines birth size with current size, and the third model, the “interaction model,” adds an interaction term. Data from a New Zealand birth cohort provided an opportunity to examine these models for blood pressure observations made in childhood, adolescence, and young adulthood. Since data were available for both height and weight, it was possible to consider what has been described as skeletal and nonskeletal catch-up growth (1). Because this was a longitudinal study, it was also possible to find out whether the effect of birth size was similar for measures collected across a 19-year age span. If blood pressure were positively related to change in size rather than birth size, the implications for public health policy would differ (5).

MATERIALS AND METHODS

The sample consisted of people enrolled in the Dunedin Multidisciplinary Health and Development Study. Persons included in the cohort were born at Dunedin’s only obstetric hospital between April 1, 1972, and March 31, 1973, when the mothers were residing in the Dunedin metropolitan area. Consent to take part was given for 1,037 of the 1,139 children still living in the province of Otago who were traced at the time of their third birthday. The sample was seen at 2-year intervals from age 3 years to age 15 years and again at ages 18, 21, and 26 years (6). Blood pressure measurements were obtained at ages 7, 9, 11, 13, 15, 18, and 26 years.

Blood pressure was measured using a London School of Hygiene and Tropical Medicine blind mercury sphygmomanometer (Cinetronics Ltd., Mildenhall, United Kingdom) up to age 18 years. Systolic blood pressure was taken as the first Korotkoff sound and diastolic pressure as the fourth
Korotkoff sound. Blood pressure was based on the mean of either two or three measures taken in the recumbent position up to age 18, except at age 15, when the mean of one measurement made in the recumbent position and one measurement made in the sitting position was used. At age 26 years, blood pressure, assessed as the first and fifth Korotkoff sounds, was measured three times according to a standard protocol using a Hawksley random-zero sphygmmomanometer (Hawksley and Sons Ltd., Sussex, United Kingdom) with a constant deflation valve (7). Stature was measured to the nearest millimeter using a portable Harpenden stadiometer. Weight was recorded to the nearest 0.1 kg using a Lindell beam balance up to age 18 years and using calibrated scales at age 26 years, the participants’ being weighed in light clothing. The assessment of blood pressure was one of a number undertaken by the participants, and it was not always completed because of time constraints or because the participants did not come to the Dunedin unit for their assessment. Data for women who were pregnant at the time of their assessments were excluded.

Standardization of weight and height

Birth weight and birth length were derived from a larger study in which details on both antenatal events and perinatal events were recorded for babies born at Queen Mary Hospital between 1967 and 1973 (8). Mean weight and length values and standard deviations were obtained for each week of gestation among single liveborn infants with two umbilical arteries and no major congenital defects (n = 7,886). Duration of pregnancy was measured from the date of the last menstrual period. Infants whose mothers were hypertensive or had gestational or insulin-dependent diabetes were excluded. Provided that gestational age was known, weight and birth length for all children in this study were standardized using these mean values and standard deviations. Standardized scores from age 7 years onward were obtained using all the available data from this cohort.

Statistical analysis

Generalized estimating equations, with an independent working matrix and robust standard errors, were used to analyze the data (9). Through the simultaneous use of all blood pressure measurements and adjustment for concurrent measures of height and weight in the combined and interaction models, it was possible for us to discover whether the effect of birth weight or length on blood pressure was the same at all ages by testing for an interaction effect between birth size and age. Using the independent working matrix meant that the generalized estimating equations procedure produced the least-squares estimates for each age (10). Because multiple measures were used for each person, the observations were not independent; therefore, the robust variance estimator was used to adjust the standard errors (9, 10). The model included terms for age and sex and their interaction to account for the presence of different blood pressure values at different ages. Interaction terms for the interactions of age and sex with weight and height between age 7 years and age 26 years were also examined.

Missing values

Information on gestational age was not available for 122 participants, and a further 24 either did not have blood pressure measurements or did not have measures of weight and height. Children whose gestational age was not known were 0.12 g lighter than those included in the study but did not differ in terms of birth length. The differences for blood pressure, weight, and height were not significant when children whose gestational age was known were compared with those whose gestational age was not known.

RESULTS

Data on systolic blood pressure, current weight and height, birth weight and length, and gestational age were available from at least one occasion for 891 people. Numbers of observations made and mean values and standard deviations for each age are presented in table 1.

In model 1, the early model, blood pressure was regressed on birth weight, with adjustment for sex, using generalized estimating equations. Since the interaction effect between birth weight and age was not significant, we present in table 2 a single estimate for the effect of birth weight on blood pressure at all ages. This estimate shows that a one-z-score increase in birth weight was commensurate with a change of −0.29 mmHg (95 percent confidence interval (CI): −0.76, 0.17) in systolic blood pressure. This is equivalent to a reduction of 0.55 mmHg (95 percent CI: −0.32, 1.46) in systolic blood pressure for a 1-kg increase in birth weight.

Model 2, the combined model, included measures of concurrent weight and height as well as birth weight. Again the interaction effect between age and birth weight was not significant. The effect of a one-z-score increase in birth weight on systolic blood pressure, when adjusted for current size, was −0.96 mmHg (95 percent CI: −1.38, −0.53). Because both birth weight and current weight were included in the model, this should be thought of in terms of change in weight rather than in terms of birth weight alone. The measures of weight were standardized to have a mean of 0 and a standard deviation of 1 at every age, so a change in weight alters the position of an individual in the distribution or brings about what is often described as a centile change. In this case, a one-z-score increase in weight between birth and a later age led to an increase in systolic blood pressure of 0.96 mmHg (95 percent CI: 0.53, 1.38).

Model 3, the interaction model, included an additional term for the interaction between birth weight and later weight. This allows for an extra increment in blood pressure for persons who move from a very low position in the birth weight distribution to being overweight or obese in later life. Since this effect was not different for different ages, one term for birth weight and one term for the interaction are presented. The interaction term was not significant, so there is no evidence to suggest that moving from a very low birth weight centile to a much higher centile later makes an extra contribution to a person’s blood pressure.

The analysis was repeated for birth length and later height. The results indicated a similar pattern of findings (table 2).
A similar, albeit weaker, pattern of results was observed for diastolic blood pressure. A one-\(z\)-score increase in weight between birth and later ages was associated with an increase of 0.12 mmHg (95 percent CI: 0.07, 0.17) in diastolic pressure, and a one-\(z\)-score increase in height was associated with an increase of 0.21 mmHg (95 percent CI: 0.19, 0.25) in blood pressure.

**DISCUSSION**

The results of this study do not provide support for the fetal origins hypothesis, because they fail to meet two of the three conditions stipulated by Lucas et al. (2). The first is that weight, or body size, should have a statistically significant inverse association with later blood pressure. This was not the case in our study. The second is that the magnitude of this effect should be greater but still negative when the statistical model includes current size, which was the case. The third condition is that the interaction between early size and later size should be negative and statistically significant; this was not found.

In this study, the association between birth size and later blood pressure was not significant. This was consistent with earlier findings from this sample (11), as well as findings from other studies, where correlations between –0.07 and 0.09 were reported (12–16). As in other studies, the magnitude of the effect for birth weight increased and only became statistically significant when current size was included in the regression model (model 2). What is really being considered here is change in size (2). All infants change in size as they grow, but since the weights and heights were standardized, the estimate provides an indication of change in blood pressure related to a person changing size relative to other people in the sample. Thus, our findings show that an increase in weight or height between birth and later ages, measured in terms of change in \(z\) score, is associated with an increase in blood pressure. This is consistent with several longitudinal studies of blood pressure which showed that changes in blood pressure are associated with changes in relative body size that occur as part of the life course (17–22).

Changes in body size, in terms of changes in \(z\) scores, could be due to large babies’ appearing to grow more slowly.
and small babies more quickly because of regression to the mean, which makes larger increases in smaller infants more probable. It is also possible that poor nutrition in utero, maternal smoking, or some other insult could lead to some babies’ being small, and catch-up growth could enable them to meet their genetic potential. Experimental studies have shown that nutrition practices in the postnatal period may have major biologic effects in later life (23, 24). An observational study, although longitudinal, cannot distinguish between pre- and postnatal effects of growth.

Reports summarizing the results of several studies have asserted, without necessarily applying a formal test, that the effect of birth weight was amplified with age (25) or attenuated in adolescence (1). Although our findings have been interpreted in terms of growth rather than as an effect of birth weight, the results of this study, which was based on repeated measures of blood pressure in the same sample, suggest that the effect measured in terms of z score was constant across this age span. Blood pressure itself did show some unexpected differences: It was slightly higher at age 9 years than it was at ages 7 and 11 years, for instance. This is likely to have been due to systematic differences between raters across time. A different type of sphygmomanometer was used at age 26 years, and the fifth Korotkoff sound rather than the fourth was used to determine diastolic blood pressure. However, omitting observations for one assessment did not change our results.

In conclusion, these results do not support the fetal origins hypothesis as applied to blood pressure regulation. Our findings are consistent with those of many other studies in this area (1), but our conclusion is based on a different interpretation of the analysis. When two measures of size are included in a statistical model, the effect of the early variable (birth size) must be interpreted in the context of the other (late size), making early size adjusted for later size a measure of change in size (2). The finding that later blood pressure is related to postnatal growth rather than fetal growth is important, because it has been argued that public health policies designed to change postnatal growth would be easier to devise and investigate than strategies to modify fetal growth (2).

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REFERENCES