A Critical Evaluation of the Fetal Origins Hypothesis and Its Implications for Developing Countries

Modeling Postnatal Exposures and Their Interactions with Birth Size\textsuperscript{1,2}

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ABSTRACT The fetal origins of adult disease hypothesis postulates that the inverse association between birth weight and later adverse outcome reflects fetal programming that increases the risk of later disease. However, low birth weight is associated with catch-up after birth, and weight gain is itself a risk factor for later disease. It is difficult to disentangle the effects on outcome of the size and growth components of weight change through time. This paper presents the life course plot, a device to display both size and growth effects simultaneously. It is based on the multiple-regression analysis of the outcome on the various weights, expressed as z-scores, and the plot displays the coefficients plotted against the corresponding ages of measurement. Examples from Brazil (Pelotas) and the Philippines (Cebu) relate blood pressure in adolescence to weight through childhood. They show small inverse weight effects in infancy, but early weight is less important than height and weight gain during adolescence. In addition, birth length in the Cebu study affects the strength of the relationship between weight and blood pressure in adolescence. This suggests a fetal programming effect, with children who were relatively long at birth having a more sensitive relationship between blood pressure and weight at age 15. Whether this is a good or a bad thing is not immediately clear. J. Nutr. 134: 201–204, 2004.

KEY WORDS: • fetal origins of adult disease • blood pressure • birth weight • postnatal growth.

There is considerable evidence that size early in life, particularly weight at birth, is related inversely to later chronic disease. Infants of low birth weight are more likely to suffer from such disease as hypertension, diabetes or coronary heart disease as adults. The original interpretation of this inverse association was within the framework of the fetal origins of adult disease hypothesis, i.e., that maternal malnutrition during pregnancy leads to fetal growth restriction and reduced birth weight. Furthermore, this period of restricted growth in some way “programs” the individual to be less well fitted in adulthood to resist the common chronic diseases of affluence.

Many of the markers used as proxies for adult chronic disease (for example, elevated blood pressure or insulin or cholesterol) are strongly positively related to body weight at the time of measurement. This is in contrast to the inverse association between the various markers and weight at birth. In many of the studies reporting this inverse association, the association was strengthened by including a concurrent adjustment for current weight (1).

Lucas et al. (2) pointed out that the implications of the two weight associations operate in opposite directions. The outcome (for example, blood pressure) can be adjusted for the combined effects of weight at birth and weight in adulthood using multiple regression analysis, where the two regression coefficients of weight are of opposite sign. In general, the absolute size of the coefficient is greater for current weight than for birth weight, which is to be expected because the variability of adult weight is approximately 20 times that of birth weight. The coefficients can be made comparable by converting the weights at the two ages to SD scores (z-scores), with a mean of 0, an SD of 1 and a normal distribution.

Once this is done the two coefficients can be compared directly. And it then becomes apparent that the regression equation can be rearranged. Assume the equation is as follows, where $W_1$ and $W_2$ are the early and later weight z-scores and $a_1$ and $a_2$ are the corresponding regression coefficients:

\[ \text{Outcome} = a_0 - a_1W_1 + a_2W_2 + \text{error} \]

Note that $a_1$ is shown with a negative sign, reflecting the inverse association with birth weight, so that $a_1$ and $a_2$ are positive. This equation can be rearranged as follows:

\[ \text{Outcome} = a_0 + a_1(W_2 - W_1) + (a_2 - a_1)W_2 + \text{error} \]
where now the first term is the change in weight \( z \)-score from birth to adult, with the same coefficient as for birth weight in the original equation. The second term is still later weight, but with a smaller coefficient than before.

Now a change in \( z \)-score over time is equivalent to centile crossing, the process of an individual's weight changing centiles on the chart over time. This is the way that growth charts are interpreted clinically, so that \( z \)-score change is a natural way of expressing divergence from normal growth, i.e., increased or decreased velocity.

The rearranged equation shows that the combination of an inverse birth weight association and a direct adult weight association can be interpreted in two quite different ways. The conventional view is that birth weight is a proxy for previous fetal growth (looking backward in time), whereas the alternative view is that birth weight is a baseline for weight change in postnatal life, which highlights increasing overweight as a risk factor for chronic disease in later life (looking forward in time). Both interpretations are valid as far as they go, but the first is couched in terms of size (i.e., weight at the two ages) whereas the second relates to growth (i.e., change in size over time).

Unfortunately, the two interpretations have diametrically opposed implications for public health. The size approach implies the need to improve maternal nutrition in pregnancy and hence fetal growth, whereas the growth approach urges interventions in postnatal life to control weight gain and overweight. Clearly, this duality of interpretation raises important practical questions.

Low-birth-weight infants tend to grow faster (i.e., catch up) postnatally, so low birth weight and rapid later weight gain often occur in the same children. The key question is whether rapid later weight gain is worse, in terms of outcome, among those with a low birth weight. Related to this is the question of whether the timing of the rapid growth period has a critical effect on outcome.

The aim of this paper is to develop a statistical framework for visualizing the impact of size and growth in early life on later outcome. Two examples are used, based on data from published studies of hypertension in adolescence from the developing world.

**MATERIALS AND METHODS**

The data are from studies carried out in Pelotas, Brazil (3), and Metro Cebu, the Philippines (4), investigating the relationship of weight change through infancy and childhood to blood pressure in adolescence. The Pelotas study (\( n = 749 \)) weighed subjects at birth, 20 mo, 42 mo and 15 y and recorded blood pressure (BP) at 15 y. The Cebu study (\( n = 2026 \)) weighed and measured subjects at birth, 2, 8, 11 and 15 (females) or 16 (males) y, and recorded BP on the final occasion. Further details of the studies can be found in the original publications (3,4).

For the present analysis, weights at each age were converted to \( z \)-scores using the CDC 2000 reference (5). The Cebu study presented the outcome as "high BP," defined as systolic BP above the 90th centile adjusted internally for sex, age and height, whereas the Pelotas study presented the outcome as systolic and diastolic BP.

The statistical life-course problem is how to present the relationship between weight, as it changes through childhood, and outcome. Growth is special in that it represents the rate of change of size—weight velocity is the rate of change of weight. Thus, plotting successive weight measurements for an individual on a weight centile chart allows the data to be interpreted both cross-sectionally, as the position of each measurement on the chart, and longitudinally, in terms of the slope of the line joining successive weight measurements. The child’s growth curve therefore indicates both size and growth, in terms of its position and slope, respectively.

In the context of life course, it is not the size or growth of the child that matters, but rather the strength of the association between size and growth on the one hand, and outcome on the other. Multiple regression analysis is conventionally used to establish the separate and independent associations between outcome and weight at each distinct age. The analogy of position and slope representing size and growth can be used here, but applied now to the regression coefficients from the regression analysis. Each coefficient is an age-specific measure of association between outcome and size, whereas the change in coefficient from one age to another indicates the association between outcome and growth over the corresponding time interval. This is in the sense of Lucas et al. (2) as discussed earlier. To make the regression coefficients at each age comparable, weight is expressed as a \( z \)-score for age and sex.

The logical way to present the information is by plotting the regression coefficients (means ± SE) against age. In this way both the values of the coefficients (analogous to size) and their change from one age to another (analogous to growth) are displayed together. Such a chart is here termed a life-course plot.

The first illustration of the life-course plot is the example used by Lucas et al. (2). Figure 1 shows the regression coefficients of weight \( z \)-score at each age, with split pro-insulin at 10 y as the outcome, from a study of 358 children born preterm. The \( y \)-axis shows the effect on insulin of a 1 SD change in weight at each age. There was an inverse effect of weight at 18 mo (regression coefficient = −12%/z) and a direct effect of weight at 10 y (coefficient = 32%/z). The steep slope of the line joining the two points also indicates the importance of weight gain (i.e., change in \( z \)) from 18 mo to 10 y—a unit increase in \( z \) over this period leads to a 44% increase in insulin (adjusted for weight at 10 y). Figure 1 also shows that the adverse outcome is associated with a particular pattern of growth—a child whose \( z \)-score increases from below 0 at 18 mo to well above 0 at 10 y has the greatest risk of a high insulin level. The life-course plot can be thought of as the shape of the growth curve associated with the outcome.

A subsidiary interest is the way that early size interacts with later growth, which tests whether the importance of growth depends on early size. This can be added to the multiple regression equation as an interaction term between early and later size (2), but it is complicated to include in the life-course plot. Instead, it is easier to split the data into two parts on the basis of early size (weight or length), using the median as the cut point, and produce life-course plots for each group separately. This allows differences in the size and growth coefficients to be displayed graphically. They can also be tested formally for significance using appropriate nested regression models.
RESULTS

The first example is from the Pelotas study. Figure 2 shows separate life-course plots for systolic and diastolic BP at 15 y against weight at four ages from birth to 15 y. It shows a negative effect of birth weight on systolic BP and a larger positive effect of weight at 15 y on systolic and less so on diastolic BP. Taken together, the data for the early and later ages indicate that weight centile crossing from birth to 15 y has a dramatic and consistently linear effect on systolic BP at 15 y, with no evidence of a critical period when weight gain is particularly important. The slope of the line indicates that BP increases on average by 0.37 mm Hg/\(z\) unit. For diastolic BP the effect of weight in early life is less clear, but weight gain from 4 to 15 y is still an important influence.

The second example is from the Cebu study, which originally concluded that among males, those most at risk of high BP were relatively thin at birth and heavy in adolescence, whereas there were no obvious early risk factors among females (4). Thinness at birth (i.e., low BMI) is defined by low birth weight adjusted for birth length. Thus the difference between low weight and thinness is length, and as a proxy for fetal growth, birth length is just as valid as birth weight. Interactions of either with later weight would constitute evidence in favor of fetal programming.

Figure 3 shows the findings for males, with separate life-course plots for subjects above and below the 33rd CDC centile for birth length, which is the median for the cohort. For the groups together the coefficients in early life are all small, whereas those at 8 and 16 y are highly significant and of opposite sign, indicating that weight gain from 8 to 16 y (i.e., into and through puberty) is an important risk factor for high BP at 16 y.

Though the individual early coefficients are not significant, and birth length has no effect, there are differences \(P < 0.05\) between the two groups for the effects from 1 to 2 y and at 16 y. An increase in weight centile from 1 to 2 y increases the risk in long infants, but reduces it in short infants. Weight at age 16 has more than twice the impact on risk among those who were long in infancy. This shows that weight gain from 8 to 11 y has a similar effect on later high BP irrespective of birth length, but long infants are sensitive to weight gain from 11 to 16 y (i.e., during puberty), whereas short infants are not (the coefficient is unchanged from 11 to 16 y in this group, so weight gain has no effect).

DISCUSSION

The life-course plot examples emphasize the substantial impact of later weight on high BP in adolescence, which tends to swamp the smaller inverse effects of early weight. At the same time, the plots highlight the importance of weight gain.
(i.e., weight centile crossing upward in later childhood) as a further risk factor for later high BP.

The importance of later weight, and of weight gain from early to later ages, suggests that obesity is the relevant factor in terms of growth. Indeed, Adair showed previously (4) that the pattern of growth predicting high BP was the same as that predicting high BMI at the same age. Weight and weight change in early life appear to be less important in the two examples here, up to 2 y in Cebu and 4 y in Pelotas. Birth weight affects systolic but not diastolic BP in Pelotas, and there is no sign of a trend in coefficient from birth to 2 y in either study.

There is conflicting evidence from the literature about early weight gain, for a variety of outcomes. Barker and colleagues have claimed that first-year weight gain is inversely associated with later heart disease in the Helsinki cohort (6), though their interpretation of the evidence is not universally accepted (7). In the opposite direction, Ong (8) found that weight gain in the first 2 y is positively associated with obesity at age 5 in a recent British cohort (ALSPAC), whereas Stettler (9) reported a positive link between weight gain in the first 4 mo and obesity at age 7 in a large sample of U.S. children born in the early 1960s. Most recently, Singhal (10) has highlighted the importance of rapid weight gain in the first two weeks, among those born preterm, as a risk factor for insulin resistance at ages 13 to 16. There may be a difference between the developing and developed worlds here.

There are two particular issues regarding interpretation of the life-course plot. The first question is exactly what the plot represents. The second is how it helps to distinguish between the fetal-origins and postnatal-origins explanations for the early weight association.

The life-course plot indicates the age-specific effect on the outcome of body weight 1 SD above the median throughout the age range, as compared with median weight. It also shows the effect on the outcome of weight change from one age to another. However, its most important function is to emphasize the dual nature of size and growth, so that both appear in the same graph.

Regarding the second question, whether the life-course plot supports the fetal or postnatal explanation for the association between early growth and later outcome, all the examples show that later weight is by far the most important factor in predicting outcome. Thus, evidence in support of fetal programming must affect this later regression coefficient, as indeed it does in Figure 3. The effect of later growth on high BP is twice as great in those who were long at birth compared with those who were short; the excess of 0.9 log odds units corresponds to an odds/birth-weight SD ratio of 2.4.

Therefore, greater body length at birth leads to greater sensitivity to body weight of BP in adolescence. This is not to say that long neonates are necessarily at greater risk of high BP later, because the extra sensitivity works both ways—a weight z-score of −1 at age 16 leads to substantially reduced BP. However, the fact that the sensitivity of the association between later weight and BP depends on birth length fits with the idea of programming.

Of course, it is possible that the risk factor is reduced sensitivity in those born short, rather than the converse. As an analogy, flow-mediated dilatation, which measures the elasticity of the vessel wall as a proxy for vascular health, is reduced in individuals with vascular disease (11). Thus, in this context reduced elasticity (i.e., reduced sensitivity to a stimulus) is a risk factor. Perhaps the same principle applies to reduced sensitivity in the weight–BP relationship. There is clear evidence for some form of fetal programming, but it is not immediately clear how to interpret it—ar longer or shorter infants at greater risk? No doubt time will tell.

**LITERATURE CITED**


