Education and debate

Fetal origins of adult disease—the hypothesis revisited

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The idea that stimuli or insults during critical or sensitive periods in early life can have lifetime consequences is well established in developmental biology and has been termed "programming."[1] The first evidence for programming, obtained over 100 years ago, confirmed the critical period for imprinting in birds.[2] Programming stimuli may be generated endogenously (for instance, internal hormonal signals[3]) or they may be environmental. One important type of environmental programming is that induced by early nutrition. Since McCance's studies in the 1960s on the long term effects of early nutrition in rats,[4] numerous animal studies have shown that nutrition in infancy or fetal life can induce lifetime effects on metabolism, growth, and neurodevelopment and on major disease processes such as hypertension, diabetes, atherosclerosis, and obesity.[5-8] If these phenomena applied in humans, it would be a matter of major public health and clinical importance.

Fetal origins hypothesis

The considerable research focused on early programming of adult outcomes in humans has taken two approaches: experimental, using early randomised nutritional interventions with prospective follow up (an approach that we have favoured[9]), and observational. Inferences from data based on observational approaches require more careful interpretation. Some of the most thought provoking observational studies are those of Barker et al.[10] They have shown that small size at birth or in infancy is associated with an increased propensity to adverse health outcomes in adulthood—including abnormal blood lipid values, diabetes, hypertension, and death from ischaemic heart disease. These important primary observations have led to the fetal origins hypothesis.[10] Small body size or body shape at birth (or subsequently) has been seen as a marker of poor fetal nutrition, which, it is suggested, results in fetal adaptations that programme future propensity to adult disease.

Adjusting for subsequent size

Some observational studies show a direct association between small size in early life (for example, low birth weight) and current, adult health outcomes.[11-15] However, in others this relation has emerged only after body size at some later period (notably current weight or body mass index) has been adjusted for.[16-21]

Summary points

The hypothesis that adult disease has fetal origins is plausible, but much supportive evidence is flawed by incomplete and incorrect statistical interpretation

When size in early life is related to later health outcomes only after adjustment for current size, it is probably the change in size between these points (postnatal centile crossing) rather than fetal biology that is implicated

Even when birth size is directly related to later outcome, some studies fail to explore whether this is partly or wholly explained by postnatal rather that prenatal factors

These considerations are critical to understanding the biology and timing of "programming," the direction of future research, and future public health interventions

Adjusting for current size has been justified on the grounds that birth weight or size is positively related to later size, and also that current weight or fatness is positively related to the outcome variable of interest (for example, blood pressure), and if not adjusted for could obscure a negative relation between birth weight and the outcome variable.[22] However, other reasons have been advanced, some of which are hard to understand. In one study of birth weight and later blood pressure in children, adjustment for current weight was said to be "justified … because while childhood body size seems to confound the association, in adulthood this confounding is less apparent."[16] Other authors fail to justify; they simply state that the results were adjusted for adult body mass index.[17]

The statistical implications of adjusting for birth size or size in infancy concurrently with some later measure of size do not seem to have been fully understood, or at least communicated. Yet appropriate statistical interpretation is vital for the biological understanding of nutritional programming, as is shown below.

Statistical interpretation
Suppose that a study using simple regression analysis fails to show a relation between birth weight

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website extra

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(independent variable) and later blood pressure (dependent or outcome variable). A further (independent) variable, current weight, is now added to the statistical model. Suppose birth weight is now significantly negatively related to blood pressure (low birth weight is associated with high blood pressure), and current weight is significantly positively related to blood pressure (heavy individuals have higher blood pressure). Previously, the interpretation would have been that adjustment for current weight had revealed the underlying relation between low birth weight and later higher blood pressure, and that some factor before birth (changed fetal biology) was responsible. However, this interpretation fails to take account of what adjusting concurrently for birth weight and current weight means in statistical terms.

What has been constructed in this example is effectively a regression equation in which the outcome (dependent) variable (blood pressure) is related to both early and later body size, where these two effects work in opposite directions. It is tempting to interpret the negative relation between early body size and later blood pressure as meaning that a low birth weight leads to a poor adult outcome, but this is incorrect. The relation between outcome and early body size can be interpreted only in the context of the other variable—later body size. It is early size adjusted for later size that is the relevant factor, not early size itself. In fact, the critical point is that early size adjusted for later size is a measure of change in size between the earlier and later measurement.

Change in size in this context must be defined. Of course all children increase in size with age. What is being considered here, however, is change over time in the centile of size for the child's age—that is, centile crossing.

Thus, returning to the above example, though the previous interpretation of this type of association cannot be rejected entirely, a logical and plausible interpretation is that adult blood pressure is positively related to the magnitude of the weight gain or, equivalently, the change in weight centile, between birth and adulthood. In a model in which weight measurements are so widely separated in time (birth and adulthood),

we cannot pinpoint the most influential period of growth (see below). However, the general implication of this analysis is that it shifts the emphasis, in terms of the timing of possible causative influences on outcome, from the fetus to postnatal life, and flags the potential importance of postnatal growth.

Further examples

In some studies, blood pressure, diabetes risk, waist-hip ratio, or insulin-like growth factor 1 concentrations in cohorts of various ages from Western or developing countries are related to size at birth only after later size has been adjusted for.[16–21] In other studies,[23–26] the unadjusted data are presented according to birth-weight category, but tests of significance are given only after the data have been adjusted for current size, leaving uncertainty on whether the relation with birth weight is significant without this adjustment.

In all these studies, the fetal origins hypothesis was invoked, yet our analysis indicates that the results could reasonably be interpreted as relating to postnatal change in size rather than to some aspect of fetal biology.

Pinpointing the critical period

When change in body size with age is linked to a later adverse outcome, it is the change in size across the whole time interval between the measurements, not just in early life, that is implicated. Of course, early life may be the critical period, but it could be any other period between early and later life.

Examples

We have examined our own studies for examples. In an unpublished investigation (Fewtrell and Lucas), birth weight in preterm babies was unrelated to the insulin concentration at age 9-12 years. However, further adjustment for current weight (at age 9-12), resulted in a significant negative effect of birth weight, suggesting that a change in weight between birth and 9-12 years may have been influential. When weight at 18 months was also introduced into the model, the effect of birth weight became non-significant—only weight at 18 months and current weight were significant. This displacement of size at birth by size at age 18 months suggests that it may have been the change in weight between 18 months and 9-12 years that was related significantly to the later insulin concentration. Thus these findings may not even signify a relation between outcome and size in infancy, let alone in the fetus, but rather some influence of change in body size later in life—a factor that would become apparent only if intermediate body size measurements were available for analysis. Findings in children born preterm would not necessarily apply to those who were born at full term; we cite this example to illustrate the general importance of undertaking appropriate exploratory analyses.

In some studies, size beyond birth was more strongly associated than birth weight with the later outcome. Vijayakumar found that the left ventricular mass was related negatively to weight at 1 year in men aged 60-70 years; the significance of the association was much greater when current body surface area was

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included in the model.[27] However, rather than considering the change in size between 1 year and adulthood as a plausible interpretation, the authors concluded that adult ventricular wall thickness might relate to undernutrition in late gestation causing growth failure in infancy.

Size at birth and later outcome

In some studies, notably those on coronary artery disease, size at birth was directly related to later outcome without any adjustments for later or current size.[11 15] Given the evidence of long term effects of fetal nutrition in some animal studies,[28] programming effects relating to fetal nutrition or growth seem plausible in humans. Nevertheless, our understanding of the biology of growth shows that alternative possibilities must be considered.

Let us say that birth weight is a "snapshot" of body size on the continuum between fetal and adult size. At any point on this continuum, size is correlated with both earlier and later size. The further away two points are on the continuum, the lower the correlation between them. Nevertheless, there may be residual correlation, even at the extremes of life. For instance, small fetuses are statistically likely to become smaller adults. Therefore, without data on postnatal growth we cannot infer that the size of a baby at birth is a proxy for fetal size rather than for postnatal size.

It might be argued that the fetal origins hypothesis is more probable since fetal life is a vulnerable period of rapid development. However, several studies in rodents and primates show that postnatal life is also important for nutritional programming. Mott and Lewis showed that infant nutrition in primates programmed later obesity,[29] and later atherosclerosis.[30] Human epidemiological studies also indicate the importance of postnatal factors such as the relation between the duration of breast feeding and later ischaemic heart disease.[31]

The implication is that even when birth size is correlated directly (unadjusted for later size) with later outcome, the fetal origins hypothesis must be weighed against a postnatal origins hypothesis. This can be done by adjusting for later size (current or intermediate). This adjustment may attenuate or amplify the correlation between early size and the outcome of interest. If adjustment attenuates or even removes the effect of early size, later size is likely to be more relevant than early body size in the causal pathway (as in the example of Fewtrell and Lucas on insulin secretion, above). Conversely, if adjustment amplifies the effect, it is important to consider whether the change in body size with age may be a relevant or even dominant influence in the causal pathway.

Examples

Where birth weight is related to later outcome, but the relation becomes stronger after adjustment for current weight, both fetal factors and postnatal growth may be influential.[15 25 27 32 33] In studying blood pressure in Swedish men, Leon et al found that for a 1 kg increase in birth weight, systolic blood pressure at 50 years of age fell by 2.2 mm Hg (95% confidence interval –4.2 mm Hg to –0.3 mm Hg).[33] After adjustment for current body mass index, however, the influence of birth weight on later blood pressure was greater—a 1 kg increase in birth weight was associated with a 3.1 mm Hg (–5.0 mm Hg to –1.2 mm Hg) fall in the adult systolic pressure. Thus, both early size and postnatal growth may have influenced later blood pressure. Nevertheless, to explore whether the relation between early size itself and later blood pressure reflects a potential fetal rather than postnatal influence, introducing intermediate body sizes (for example, size at 1 year) into the regression model would be helpful.

Interaction between birth size and later growth

Postnatal growth as a factor for adult disease has been considered in many observational studies, but it has been regarded as a factor that interacts with earlier (fetal) programming. It might be suggested, for instance, that people who are small in early life and then grow rapidly are more at risk than those who remain small. One biological explanation of this could be that people programmed for poor early nutrient intake would be put at risk if their food intake was subsequently increased to a level inappropriate for their programming.

However, it is important to explore whether postnatal growth (magnitude of centile crossing) could influence later health in its own right (as we suggest above) or whether it is simply a modifying factor according to the nature of fetal programming. Is becoming obese later in life only, or most, deleterious in people who were growth retarded at birth? Is centile crossing from a low birth weight more serious in terms of outcome than equivalent centile crossing from a higher birth weight? Again, this is a statistical issue, and it can be approached by using tests for interaction that explore whether early body size affects the relation between outcome and later body size. If the interaction between early and later body size is significant, early body size is acting to modify the effect of later body size on outcome.

Examples

A significant negative interaction between early and later size would support the suggestion that small size in early life works to increase the effect of later size on outcome, as has been reported recently.[15 33 34] For example, the negative association between blood pressure and birth weight in 50 year old Swedish men of above median height was greater in those with a high body mass index or, equivalently, the positive association between blood pressure and body mass index was greater in those of low birth weight.[33]

However, in the example from our data (Fewtrell and Lucas), the interaction between weight at 18 months and in later childhood on insulin concentrations was approaching statistical significance, but positive, suggesting that the effect of increasing weight (or weight centile) during childhood was greatest in subjects who were largest at 18 months.

Another recent study in Finnish men related child growth from birth to 11 years to later coronary heart disease.[35] Birth size was represented by ponderal index, and size at age 11 by body mass index. No significant interaction between early and later size on disease risk was reported. Despite this lack of evidence, the authors

argued that low birth weight followed by catch-up growth was an important risk factor for later disease, over and above low birth weight itself.

Catch-up growth

The concept of catch-up growth raises a further difficulty. Small babies tend to show greater upward centile crossing than larger babies, and this regression towards the mean results in an inherent correlation between birth weight and centile crossing—each, to some degree, a proxy for the other. Adjusting for both early and later size (as discussed above) allows the two effects to be disentangled and identifies which (low birth weight or upward centile crossing) is more relevant to later outcome.

Statistical considerations

Correct interpretation requires that three distinct regression models be fitted (box). For completeness, a fourth model can be fitted in which later size alone is related to outcome. We recommend that investigators report results in the form of these four regression models, and that they interpret their data accordingly. If the fetal origins hypothesis holds, the early model should have a significant and negative coefficient (negative relation of early size to later adverse outcome); this should be possibly more negative in the combined model; and when an interaction between early and later size is found, it should be a negative one. These findings would support, but not necessarily prove, the fetal origins hypothesis; introduction of intermediate sizes into the model is required to test whether birth size is a proxy for some later postnatal size rather than fetal size.

The routine use of this four model principle would make studies in this area comparable. Indeed, it would be valuable if these analyses could be released for previously published studies so that they could be interpreted or reinterpreted appropriately. The results of our study on insulin concentrations at 9-12 years related to current weight and early weight in a cohort of 358 children born preterm, interpreted in terms of these four regression models are presented on the *BMJ* website, as is information on expanding the regression models.

Conclusions

The primary observations on the relations between size in early life and adult disease are of great interest and clearly require explanation. Although the fetal ori-

Regression models

• Early model: regression used simply to relate early size to later outcome

• Combined model: includes both early and later size, obtained by adding later size to the early model

• Interaction model: adds the interaction of early and later size to the combined model. The interaction term is calculated as the product of early and later size

• Late model: later size alone is related to outcome, which helps to interpret the relative importance of early and later size separately and together

Implications of flawed interpretation

• Our observations broaden greatly the potential biological mechanisms and opportunities for influencing or programming long term health in humans

• Our conclusions are relevant to the direction of research effort aimed at understanding the antecedents of adult disease

• Perhaps most importantly, public health strategies designed to manipulate the biology of fetal growth are more daunting than those that aim to influence postnatal growth and nutrition; detection of postnatal influences on adult health would offer a greater likelihood that practical public health interventions could be devised and investigated in this emerging field.

gins hypothesis is plausible, and is likely to be pertinent to some epidemiological observations, evidence cited for it is often flawed because of misinterpretation and inappropriate analysis of growth data. Previous flaws in interpretation may have deflected attention from potentially important areas of postnatal development that could prove influential for adult health (box). The most robust test of either the fetal or postnatal origins hypotheses is the randomised intervention study, which has proved, at least in some areas, to be feasible.[9] Until such studies are performed, the problem of proving causation using correlative analyses of early size and later outcome will remain.

These issue have never been clearly stated before, and published studies have not generally taken them into account. We recommend that each of the models we discuss above is clearly shown in future publications and that the interpretation of results takes account of the arguments we raise.

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The private finance initiative

The politics of the private finance initiative and the new NHS

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We began this series by arguing that the private finance initiative, far from being a new source of funding for NHS infrastructure, is a financing mechanism that greatly increases the cost to the taxpayer of NHS capital development.[1] The second paper showed that the justification for the higher costs of the private finance initiative—the transfer of risk to the private sector—was not borne out by the evidence.[2] The third paper showed the impact of these higher costs at local level on the revenue budgets of NHS trusts and health authorities, is to distort planning decisions and to reduce planned staffing and service levels.[3]

All this raises questions about the direction of government policy on the NHS. Recent government commitments to increase clinical staffing levels and reverse the decline in bed capacity sit uneasily with a policy that seems to lead in the opposite direction. The government has consistently argued that the private finance initiative is no more than a procurement policy, with no implications for services other than increased efficiency. However, this ignores the importance of public-private partnerships to the government's overall agenda.

The private finance initiative, as an explicit move towards the private provision of public services, is central to government policy. The Cabinet Office white paper states: "Distinctions between services delivered by the public and the private sector are breaking down in many areas, opening up the way to new ideas, partnerships and opportunities for devising and delivering what the public wants."[4] The private finance initiative in the NHS is part of a wider policy agenda affecting all government departments. The aim, according to the European Union, is to produce major savings in public

Summary points

The private finance initiative does not provide new money for public services as the government claims

The high costs of capital under the private finance initiative translates into service and workforce cuts

The reduction in public provision of long term care, NHS dentistry, optical services, and elective surgical care shows the trajectory for the NHS under the private finance initiative

In the NHS, shrinkage in service provision combined with budget constraints could force primary care trusts to redefine entitlement to NHS care and to seek privately funded solutions for those who can afford to pay, leaving a rump service

The private finance initiative is a regressive instrument and is likely to increase inequalities in health and in wealth

This is the last of four articles on Britain's public-private partnership in health care

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