Thematic Article

Early life influences on later health: the role of nutrition

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Individuals who were small at birth have an increased risk of cardiovascular disease in later life. Barker has put forward a hypothesis to explain this and other associations, known as the 'fetal origins theory of adult disease'. It is proposed that chronic disease is the long-term outcome of physiological adaptations the unborn baby makes when it is undernourished, a process referred to as 'programming'. Maternal nutrition is thought to be a major influence on programming, and growth in childhood as well as obesity in later life may modulate the propensity for disease acquired in the womb. While robust evidence to support specific nutritional interventions during pregnancy is currently lacking, the theory in general affirms broader public health nutritional strategies and policies to improve the social and economic status of women.

Key words: cardiovascular disease, childhood growth, fetal growth, fetal origins of adult disease, later obesity, maternal nutrition.

Introduction

Research conducted over the past decade has revived the understanding[1] that experiences in early life can have long-lasting impacts on health. There is burgeoning interest in the way the early environment may affect brain development and behaviour.[2,3] In the realm of physical health, the focus has been on relationships between growth in early life and later chronic disease, largely inspired by the work of Barker and his colleagues.[4] Barker has put forward a hypothesis known as the 'fetal origins theory of adult disease', which proposes that adverse conditions in the womb can give rise to restricted fetal growth and also result in the resetting of physiological systems, thereby predisposing the individual to chronic disease in later life.[5]

Established associations

Initial reports of a link between birthweight and adult disease were met with considerable scepticism and generated much debate.[6–8] Major criticisms of the epidemiological work concerned selection bias (for example, some cohorts were based on records of individuals born in hospitals, at a time when a large number of births occurred at home) and losses to follow-up (individuals who cannot be located in adulthood or no longer live in the place where they were born, may be healthier, or in other ways different, from those who can be traced and are included in the follow-up data). These are perennial but important problems in cohort studies. In addition, early results lacked consistency. However, the accumulated evidence is now much more robust and, in combination with animal studies, has led to widespread acceptance that associations exist; several organisations have published consensus statements to that effect.[9,10]

Barker and his colleagues drew attention to the association between low birthweight and increased risk of cardiovascular disease (CVD), following suggestive findings from their ecological research.[11] They 'retrospectively' established a series of cohorts, by searching for collections of archived birth records and 'following-up' the individuals named therein. For example, one cohort was based on records for babies born in a part of Hertfordshire, England, between 1911 and 1930. Matching these records with information from National Health Service files showed that the likelihood of death from CVD fell as birthweight increased; the difference in death rates for individuals at the extremes of the birthweight distribution was approximately twofold.[12,13] Since then, with one exception,[14] this association has been confirmed in six studies from countries that include the US, Sweden and India.[15–17] Overall, the results support an association with small size for gestational age, rather than with premature birth.

Birthweight is also inversely related to systolic blood pressure. In two systematic reviews of the literature,[18,19] published reports of this association dating back to the 1970s were found. Evidence from 80 studies indicates that the effect is consistent but modest, with a 1 kg increase in birthweight typically associated with a 2–3 mmHg decrease in systolic blood pressure in later life. This body of reports includes eight studies from five countries in the Asia–Pacific region, namely, Australia, China, India, Japan and New Zealand.

Other major clinical risk factors for CVD are blood lipid profiles and clotting factors, and associations between birthweight and these variables have been examined in a number

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of studies.[5] To our knowledge, however, these reports have not been reviewed systematically; our impression is that the available evidence is inconsistent.

Associations require interpretation

Like all associations, there are a number of possible interpretations, apart from that offered by Barker and his colleagues. Initially, it seemed likely that the associations were simply a product of confounding by socioeconomic status. Individuals of low birthweight are more likely than their counterparts to be born into disadvantaged families, and hence were arguably more likely to behave in ways that were adverse for CVD risk.[20,21] This alternative explanation has now been investigated in detail in a number of independent studies (e.g., Leon *et al*.[16] and Moore *et al*.[22]). Differences in behaviours or socioeconomic circumstances, for the most part, do not account for the association between birthweight and later blood pressure or CVD. Adjustment for risk-related behaviours or socioeconomic status generally reduces the associations a little, but does not eliminate them. It could be argued that assessments of such potential confounders made at one point in time, in a cursory manner, do not adequately capture these lifetime influences. This possibility of residual confounding is not readily resolvable through epidemiological studies and this is where supportive animal data comes to the fore.[23]

It is also unlikely that the associations are principally attributable to genetic inheritance, because of the substantial experimental and other evidence that birthweight is largely determined by supply to the fetus of nutrients and oxygen.[24] Nevertheless, genes do have some influence on birthweight,[25] and the argument that they are only a minor determinant of birthweight does not rule out some role in these associations.

The fetal origins theory of adult disease directs attention to fetal life, rather than to birthweight per se, because birthweight is the outcome of around 9 months of growth in the womb. During that time (and subsequently), tissues and organs of the body pass through 'critical periods' of development. It is a general principle of biology that a stimulus or insult occurring in a critical period can have lasting effects, a process known as 'programming'.[26]

Barker has applied the concept of programming to explain the link between fetal growth and later health, suggesting that fetal undernutrition can permanently change the body's metabolism. In early life, effects may be quite subtle, but over time metabolic differences can be translated into pathology and disease.[5] The work of fetal physiologists in previous decades clearly shows that fetal undernutrition can produce acute physiologic changes, such as redistribution of blood flow to protect the brain, lowered metabolic rate to reduce the use of substrates, and slowing of growth to reduce demand for those substrates (e.g., Campbell *et al*.[27]). Barker argues that such adaptations leave a permanent biological 'memory' of undernutrition.

Possible role for maternal nutrition

It is well established that maternal pre-pregnancy weight and weight gain during pregnancy are related to birthweight of the baby.[28] These variables may be viewed as broad indicators of the availability of energy. Although observational studies concerning maternal diet during pregnancy have been undertaken since the 1930s, few well-replicated associations with birthweight have been identified in western populations.[29] Clinical research has generally been directed towards specific deficiencies in undernourished populations. Nutritional interventions have been the subject of recent systematic literature reviews, as summarised by de Onis *et al.*[30] The methodological quality of the clinical trials was found to be variable, and often poor. However, balanced protein–energy supplementation unequivocally confers a modest improvement in birthweight. Evidence for benefits of zinc, folate or magnesium supplementation is suggestive, but thus far insufficient to reach firm conclusions.

Body proportions at birth and the weight of the baby relative to its placenta provide additional information about fetal growth, possibly reflecting differences in the nature or timing of a growth perturbation. Records of these birth characteristics are rare, but have been available in a limited number of cohorts. Some, but not all, investigations of such detailed birth data have shown that certain birth phenotypes, specifically thinness and shortness at birth and low birthweight relative to placental weight, are linked to adverse health outcomes in later life more strongly than birthweight.[5]

Little is known about the maternal influences that lead to these birth phenotypes. It is widely held that symmetrically small babies have experienced reduced growth throughout gestation, whereas babies exhibiting disproportions at birth have experienced reduced growth in the latter half of gestation. This understanding derives from studies of women who were pregnant during the Dutch famine in World War II[31] and the experiments of McCance and Widdowson in pigs,[32] but other work suggests that this distinction may be oversimplified.[33] While malnutrition has long been suspected as a cause of asymmetrical growth,[34] there is a lack of relevant data, and the available results are conflicting.[35–37] Maternal pre-pregnancy nutrition may have a role, as maternal height and pre-pregnancy weight-for-height, which may be interpreted as long-term and medium-term indicators of nutrition, are determinants of growth of the placenta.[38]

In contrast to the current uncertainty in epidemiological knowledge, recent animal studies strongly suggest that maternal nutrition during pregnancy can induce programming.[23] The animal experiments have focused on two dietary manipulations, an isocaloric low protein diet and varying degrees of global reduction in nutrition. For example, in the study of Langley and Jackson, female rats were fed diets containing either 6, 9, 12 or 18% protein.[39] These rats were then mated, became pregnant and gave birth. Blood pressure of the rat pups was measured 9 weeks after they were born. Blood pressure of the pups was inversely related to the amount of protein in the mother's diet: the highest blood pressures were seen in the pups whose mothers were fed the least protein. As another example, Woodall *et al.* fed female rats either a conventional rat diet or a diet that was 30% less than normal intake throughout pregnancy.[40] Blood pressure of the rat pups was measured several times after 30 weeks of age. Mothers who were fed the restricted diet bore progeny with persistently elevated blood pressure, compared to progeny of the control group.

Of note, changes in the cardiovascular and metabolic functioning or health outcomes of animals were sometimes

evident in response to altered maternal diet, even when there were no overt reductions in body size of the offspring.[23] For humans, this points to the possibility that birthweight does not have to be significantly reduced for the physiological consequences of poor nutrition during pregnancy to be manifest in the children. Thus, the public health importance of the relationship between fetal growth and subsequent blood pressure or CVD may well be underestimated by the studies mentioned previously, which have only related birthweight to later health outcomes.[12–19]

Possible role for nutrition in childhood and later obesity

A range of observations in humans and animals provide general support for the idea that postnatal growth could influence cardiovascular health. For example, there have been many demonstrations that adult height is inversely related to the risk of coronary heart disease (CHD), particularly in men, and adult height is strongly influenced by the childhood environment in addition to genetic inheritance. More elaborate evidence along this line is provided by the Carnegie cohort, which is based on a survey of diet and health conducted in Britain in 1937–39. Recent analysis of mortality data for survey participants shows that leg length in childhood is inversely associated with risk of CHD.[41] Leg length is a more specific marker of prepubertal growth than adult height, and in the Carnegie cohort it was the component of childhood height most strongly associated with diet and socioeconomic factors. Unfortunately, there is no information on birth size for this cohort.

In papers pre-dating those of Barker and colleagues, Forsdahl proposed that CVD was partly as a result of a mismatch between nutrition experienced in early and later life.[42,43] Overtones of this notion are detectable in emerging work undertaken in the context of the fetal origins theory of adult disease.

The second systematic review of literature concerning birthweight and later blood pressure,[19] mentioned previously, also considered postnatal 'catch-up' growth. Although the measures of postnatal growth were usually indirect and incorporated birthweight in their calculation, the available evidence suggests that accelerated postnatal growth is positively associated with blood pressure, and that the highest blood pressure values occur in individuals whose birthweight was low but whose growth rate was subsequently high. In general, however, the reports on catch-up growth in childhood is complicated by the variety of definitions employed, and it is possible that catch-up in height or lean tissue is beneficial, whereas gains in fat mass are not.

Only two studies provide information on birth size, postnatal growth and death from CVD. Data for the Hertfordshire cohort includes weight at 1 year old (but not height). Among men, but not women, those of low birthweight who experienced a relative improvement in weight by 1 year had a reduced risk of CVD, compared with those who were small at birth and remained so a year later.[13] In another cohort born in Helsinki in 1924–33, measurements of height and weight between 7 and 15 years are available, in addition to details of birth size.[44,45] Among men, the highest death rates for CHD were seen in those who had been thin at birth, but whose relative weight had increased, so that they had an average or above average body mass index (BMI) from at least age 7. Among women, the highest death rates were seen in those who had been short at birth, but who subsequently caught up in height.

Differences between the results of these two studies and findings for men and women are at present unexplained, but these data have been used to support the argument that the impact of postnatal growth or nutrition on CVD risk is contingent on growth or nutrition before birth. The idea is that later overnutrition or obesity relative to birth size (as a summary of growth prebirth) may have implications for CVD risk, regardless of the absolute magnitude of obesity. In other words, individuals may differ in the degree to which a BMI above 25 kg/m^2 constitutes a metabolic challenge and conveys an increase in CVD risk, depending on their programming.

Imbalances in growth could be deleterious through changes to body composition, as babies who are thin at birth are lacking in muscle rather than fat,[46] and later increases in BMI may mean that they have a disproportionately high fat mass. Alternative explanations in terms of overgrowth of a limited cell mass or adverse changes to hormonal profiles have also been offered.[47]

Obesity as conventionally defined may also compound the risk of disease acquired through poor growth in early life.[48] Currently, evidence is sketchy and appropriate statistical tests for interactions have rarely been undertaken.[49] However, in our work with a cohort of young adults born in Adelaide, South Australia, there was an interaction of birthweight and current size on blood pressure at 20 years old, such that effects of low birthweight were enhanced among overweight individuals.[22] Thus, the importance of adult lifestyle may, in fact, be reinforced by the fetal origins theory.

Implications for the region

If correct, the fetal origins theory potentially offers new means to prevent CVD in the next generation, through attention to the living conditions, health and nutrition of young women, pregnant mothers and their children. It is potentially a way to reduce social inequalities in health, and may be especially relevant for indigenous groups, for whom rates of chronic disease are escalating. In the Northern Territory of Australia, policy makers appear keen to recognise early life influences on later health[50] and the fetal origins theory resonates with initiatives such as their 'Strong Women, Strong Babies, Strong Culture' program for Aboriginal communities.[51]

While reliable national statistics on birthweight are unobtainable in much of Asia, according to the most recent estimates, more than half of the world's low birthweight babies (defined as less than 2500 g) are born in South Asia.[52] Many variables other than maternal nutrition have been examined and implicated as contributors to low birthweight.[53] From a public health perspective, what matters most is whether a factor is modifiable, how widespread it is, and the degree of influence it has on birthweight.

It is difficult to make concrete recommendations as the region is geographically, economically and culturally diverse. Sachdev has emphasised the need for policies that are specific to the communities or countries concerned.[54] Sachdev's list of interventions that hold most promise

includes efforts to: delay child-bearing among adolescents; provide nutritional advice and/or food supplementation for pregnant women; improve access to antenatal care; encourage rest during pregnancy to reduce energy expenditure; prevent or treat malaria in areas where it is endemic; stop smoking and tobacco chewing. Currently, there is little information on the relative cost-effectiveness of these approaches at a population level.

Apart from the *lack of evidence* of efficacy (as opposed to evidence of *lack of efficacy*) in relation to specific nutritional interventions, there are other reasons for caution. Some trials have found protein supplementation to be adverse for birthweight.[55] Harding *et al.* have pointed out that the timing of interventions needs greater attention, as attempts to reverse impaired fetal growth during pregnancy by the additional supply of one nutrient may result in increased demand for another.[56,57] If not met, this next limitation in nutrient supply may be disadvantageous or even lethal for the fetus. Greater attention to overall nutrition before pregnancy may therefore be a safer strategy.

Given the uncertainty regarding benefits of specific nutritional interventions during pregnancy, Sachdev[54] has suggested that at this stage, it may be pragmatic to devote health promotion efforts to sound nutritional advice, as this has at least proved effective in increasing energy and protein intake of women in developing countries.[58] In westernised countries, the underlying problem may be one of a poor quality diet, even in the presence of overnutrition, so further promotion of good nutrition during pregnancy may also be appropriate.

Taking a broader stance, improvements in socioeconomic conditions, particularly education of women, should be supported for many reasons, including the likely flow of benefits to fetal and child health. UNICEF has a 'Care Initiative' to improve nutrition, which recognises the fundamental importance of political, ideological, historical and economic structures in determining nutrition.[59] Among other things, UNICEF urges greater autonomy for women and respect within the family. The political and social implications of globalisation are currently the subject of intense debate; we believe that there is a clear imperative for ensuring that economic development is linked and judged according to public good, including reductions in deprivation-related disease.

The possibility that obesity in later life could exacerbate the propensity for CVD acquired in the womb is also of great importance, especially in view of the transition to a nutritionally dense diet in many developing countries. Not only is the prevalence of obesity increasing, being marginally overweight may be more hazardous for cardiovascular health in developing countries than it is currently accepted in western countries, if adult size relative to birth size is a crucial feature of increased risk. In other words, it is possible that individuals in developing countries cannot afford to be as obese as individuals in western countries, where low birthweight is less widespread and the general standard of nutrition in women improved some generations ago. Thus, strategies to reduce obesity (or maintain optimal bodyweight) should continue to be given a high priority in the region.

Conclusion

In conclusion, although quite widely accepted, the fetal origins theory continues to be challenged[60] and Barker is regularly accused of 'over-enthusiastic inductive reasoning'.[8] Scientific progress depends on creative thinking and bold conjectures, which then need to be subjected to rigorous inquiry, and we endorse a critical approach to the fetal origins debate. Further research to elucidate the mechanisms that link fetal growth to later health is required, as well as a much better understanding of the role of nutrition. An ongoing exchange between scientists undertaking epidemiological studies, clinical trials and animal experiments, as well as involvement of health anthropologists, sociologists and policy makers, is essential. Finally, we reinforce the position of Leon[61,62] and others, that it is undoubtedly desirable to improve the nutritional status of women, but whether this is a means to prevent CVD remains uncertain, even though the basic propositions of the fetal origins theory appear to be correct.

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