The programming effects of early growth

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Abstract

Early-life growth patterns predict subsequent disease risk. The ontogenetic development of body composition appears to play a key role in such associations, but details have only recently begun to emerge. Studies in diverse populations consistently associate birthweight with subsequent lean mass. Associations with subsequent adiposity show less consistency, and may be gender-specific, while associations between infant weight gain and subsequent body composition appear to differ systematically between industrialised and developing countries. Existing evidence suggests two primary pathways whereby the body composition development contributes to disease risk. First, poor growth during fetal life and infancy appears permanently to constrain lean mass, thereby constraining metabolic capacity to tolerate a rich diet. Second, rapid catch-up growth and childhood weight gain appear to divert energy disproportionately to adipose issue, particularly in the abdomen, thereby increasing metabolic load. These complementary processes may account for disease risk being greatest in those born small who subsequently become large.

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1. Introduction

Over the last two decades, biomedical research has produced compelling evidence that the risk of a number of diseases of adulthood is associated with experience during early life. Most interest has focused on the metabolic syndrome, stroke, hypertension, type 2 diabetes, obesity and cardiovascular disease. Initial work emphasised low birthweight as a risk factor for these diseases [1]. Subsequent work has shown that greater postnatal weight gain is independently associated with disease risk [2], such that for most outcomes, the risk is greatest in those born small who subsequently become large [3,4].

These associations between early size or growth rate and subsequent disease risk implicate early-life nutrition, and its impact on developmental trajectory, as the key underlying mechanism. Numerous aspects of developmental trajectory may be involved, ranging from epigenetic influence on DNA expression, the development of hormonal axes, and the relative accretion of different tissues and body components. The relative importance of these different mechanisms remains unclear, hindering our ability to develop appropriate public health policies for the general population and treatment strategies for individuals.

Various aspects of body composition are implicated in the induction of adult diseases, but the details of its role have only recently begun to emerge. This area of research is complicated by the difficulty of measuring body composition with accuracy in large, epidemiological studies, and by the challenges of interpreting life-course data where some traits are simultaneously confounding factors and also key out-
comes. The aim of this review is to summarise current understanding, and highlight controversies with a view to stimulating further research.

2. Early-life experience, body composition and disease: a state of confusion

The role of early-life experience in the induction of adult diseases is highlighted by statistical associations between risk and birthweight. However, in the majority of studies, the association emerges most strongly after adjustment for current weight. Thus, for example, when current weight is taken into account, several studies have shown an inverse association between birthweight and risk of cardiovascular disease [1]. The initial interpretation of these data was that low birthweight was a significant risk factor for disease, implicating poor fetal growth (and by inference fetal malnutrition) as the underlying mechanism. Following that line of inquiry, various studies have been conducted into the details of fetal nutrition and its association with cardiovascular risk [5,6].

Others have questioned this model of causation, arguing that if adjustment for current weight is required to reveal such associations, a more appropriate interpretation would emphasise change in size between birth and adulthood as the key predictor of disease [2]. According to this perspective, disease is associated not with being small at birth, but with growing fast afterwards. Indeed, some authors have discounted fetal development entirely, and have proposed that variability in postnatal growth rate is the primary component of the association between low birthweight and disease [1]. The initial interpretation of these data was that constrained development of lean mass may be a critical component of the association between low birthweight and subsequent disease. This hypothesis is consistent with the “thrifty phenotype” hypothesis of Hales and Barker [13], which proposed poor pancreatic development during fetal life as a primary mechanism inducing subsequent risk of diabetes and cardiovascular disease. More broadly, many other aspects of organogenesis are likely to be sensitive to poor fetal growth. For example, low-birthweight babies have reduced nephron number, implicated in increased predisposition to high blood pressure subsequently [14]. The environmental induction of the organs and tissues that comprise lean mass therefore represents an extremely important area for subsequent research, as discussed below.

Second, the literature was far less consistent regarding associations between birthweight and subsequent fat mass. Studies variously reported positive, negative or no association between birthweight and indices of whole-body adiposity [12]. The interpretation of such studies is often confounded by the manner in which the data are presented. Traditionally, relative body fatness is expressed in the format “percentage fat”, or fat as a proportion of body weight. This index is confounded by the level of lean mass, such that a high percentage fat could be due either to high levels of fat, or low levels of lean [15]. Given the association between birthweight and lean mass discussed above, associations between birthweight and percentage fat may not actually represent associations between birthweight and adiposity itself (as discussed in more detail below). In the large ALSPAC cohort, using DXA for body composition assessment, a significant positive association was observed between birthweight and later size-adjusted fat mass, and this association was strengthened if the predictor was birth ponderal index [16]. This study also found a stronger effect in girls than boys, a finding also reported in several other studies [12], and sex-differences in the induction of body composition are thus another area meriting further research. However, the ALSPAC cohort still showed a stronger association of birthweight with later lean mass than with later fat mass [16].

Third, the most controversial issue concerns associations between birthweight and subsequent fat distribution. The

3. Fetal growth and later body composition

Epidemiological interest in the associations between fetal growth patterns and later disease risk must be attributed in part to birthweight representing the first convenient life-course index of growth and development. Early studies on the induction of obesity considered the association between birthweight and BMI [11]. Positive associations tended to be interpreted as larger babies remaining fatter subsequently. In the last decade, a large number of studies have focused in more detail on associations between birthweight and subsequent body composition. Although conducted in a variety of populations, and varying in the quality of the body composition technique utilised, these studies, reviewed recently [12], highlight several important issues.

First, the vast majority of studies were consistent in demonstrating positive associations between birthweight and subsequent lean mass. This association was broadly detected in all populations, across a wide variety of body composition techniques, and remained apparent throughout the life course [12]. The main implication of this finding is that constrained development of lean mass may be a critical component of the association between low birthweight and subsequent disease risk. This hypothesis is consistent with the “thrifty phenotype” hypothesis of Hales and Barker [13], which proposed poor pancreatic development during fetal life as a primary mechanism inducing subsequent risk of diabetes and cardiovascular disease. More broadly, many other aspects of organogenesis are likely to be sensitive to poor fetal growth. For example, low-birthweight babies have reduced nephron number, implicated in increased predisposition to high blood pressure subsequently [14]. The environmental induction of the organs and tissues that comprise lean mass therefore represents an extremely important area for subsequent research, as discussed below.

This controversy is difficult to address. The vast majority of older datasets are restricted to body mass index (BMI, weight divided by height squared) as a generic index of both adult size and adult body composition. BMI is a global index of nutritional status, and though it is strongly correlated with body fat it is equally strongly correlated with lean mass [9]. In epidemiological studies, it therefore represents a very crude index of body composition and cannot be used as a sensitive index of adiposity. Increasingly, studies are demonstrating that both lean mass and fat mass are associated with cardiovascular risk. For example, both lean mass and fat mass are positively associated with blood pressure [10], but the relative importance of high lean mass and high fat mass for hypertension is not known.

It is therefore difficult to interpret the role of adult BMI in the induction of diseases. An increasing number of recent studies have measured body composition directly, and are rapidly improving our understanding of the sensitivity of specific tissues or organs to nutritional intake during particular periods of the life course. Such information is critical for elucidating the aetiology of the metabolic syndrome and associated diseases.
vast majority of studies have addressed this issue using waist circumference, waist–hip ratio or ratios of trunk-to-limb skinfolds as the outcome. Each of these measurements has limitations in this context. Simple ratios rarely adjust one measurement appropriately for another, and this difficulty may be compounded when the association between variables is not linear, as in the case of skinfolds [17]. Only a few studies have examined the association between birthweight and visceral fat measured directly by computed tomography or magnetic resonance imaging. Two adult studies reported no significant association [18,19], while a study of children reported an inverse association in African–American children, but no association in Caucasian children [20]. Current evidence therefore remains inadequate to address this issue, and there is a need for larger studies using high-quality body composition techniques and appropriate statistical analyses to resolve this dilemma. Furthermore, the association between birthweight and infant growth rate requires addressing in this context.

4. Postnatal weight and later body composition

The main finding to emerge from the limited literature on the association between postnatal weight gain and subsequent body composition is that the target of weight gain increasingly shifts from lean mass to fat mass [12]. However, an important confounding influence on this overall pattern appears to be the nutritional status of the population being considered.

In populations from developing countries, greater infant weight gain has been most strongly associated with later lean mass, and is either moderately or not significantly associated with later fat mass [21–23]. In contrast, in populations from industrialised countries, greater infant weight gain has been associated with greater lean and fat masses [24–26], and an increased risk of subsequent obesity [27].

The implication from these studies is that it becomes increasingly difficult to allocate additional energy intake to lean mass from infancy onwards, implicating fetal life and infancy as the primary “critical window” during which nutrition programs total body lean mass. As this hypothetical critical window closes, additional energy intake appears to be targeted instead at fat mass. Such a perspective is consistent with our understanding of linear growth, which is sensitive to nutrition during fetal life and infancy but which becomes canalised towards the end of infancy [28]. The contrasting findings from industrialised versus developing countries are of major significance, indicating that data from western populations may prove an unsuitable basis for public health policies regarding infant nutrition in populations elsewhere. This scenario highlights the importance of the few large cohort studies conducted in developing countries, notably those from Pelotas in Brazil, the Cebu study from the Philippines, and the Birth-to-twenty study from South Africa.

5. The role of nutrition

Despite subtle differences in their nature, widespread findings of associations between birthweight or postnatal weight gain and subsequent body composition strongly implicate nutrition as the underlying mechanism. Once growth has become canalised, the association between nutrition and body composition appears relatively clear. Fluctuations in energy intake impact primarily on relative body fatness and fat distribution, although the level of physical activity also impacts on relative muscularity. However, there remains much greater uncertainty regarding the associations between fetal and infant nutrition and subsequent body composition. This in turn stems from the fact that birthweight is an ambiguous index of “fetal growth”.

This is well illustrated by follow-up studies of two cohorts exposed in utero to famine during the Second World War. Initial investigations of survivors of the “Dutch hunger winter” indicated that fetal experience might be predictive of subsequent obesity status [29]. Detailed examination of this cohort demonstrated that the risk of subsequent obesity was dependent upon the trimester of pregnancy during which maternal famine was experienced [30]. Those exposed in the third trimester experienced the lowest birthweight, and had a reduced risk of obesity subsequently. Those exposed in the first trimester showed negligible reduction in birthweight, and an increased risk of obesity subsequently. It is however difficult to interpret these findings, given the observational nature of the study.

First, one alternative explanation for the apparent increased risk of obesity in those exposed in the first trimester could be that fatter mothers, or offspring with particular genotypes, might be more likely to achieve conception during such harsh conditions [12]. These characteristics might then re-emerge in adulthood, manifesting as higher BMI and an apparently increased prevalence of obesity. Second, the importance of birthweight for subsequent fatness may be strongly mediated by postnatal experience. Surviving offspring in the Dutch hunger winter tended to experience rapid infant catch-up growth when the famine ended, whereas another population exposed to famine in Leningrad experienced no such postnatal catch-up, and did not demonstrate associations between early-life exposure and subsequent obesity risk [31].

This issue remains equally controversial concerning the postnatal period. Some studies have proposed stunting to be associated with later obesity [32], with impaired fat oxidation proposed as the underlying mechanism [33]. Other studies have failed to associate indices of childhood undernutrition with later obesity [34]. It is possible that the life-course period when stunting developed many vary between the studies, and account for the different findings. The contribution of episodes of under-nutrition in the induction of body composition is another key area requiring further research.

6. Small at birth or catch-up growth: which is more important?

Our lack of understanding concerning the contributions of fetal and infant growth to the induction of disease is a major hindrance to converting scientific understanding into practical applications, whether in public health policies or the clinical management of individuals. This limitation derives from two separate issues: first, the lack of outcome measurements undertaken during infancy as opposed to later in the life course, and second, the absence of study designs...
capable of differentiating the effects of fetal and postnatal growth.

Whilst most studies investigating the association between early growth and later outcome have been observational, a small number of postnatal randomised trials have also been reported. In preterm babies, those randomised to a low energy diet were subsequently found to have reduced insulin resistance, and this association was independent of birthweight [35]. Some authors of this study argued on the basis of these findings that fetal growth was unimportant in the aetiology of insulin resistance, and that postnatal growth variability could account for its variance [7]. This interpretation has a number of problems. Most important, this study provides a form of evidence which is currently unavailable for fetal life, since comparable interventions have not been conducted during pregnancy. A randomised controlled trial demonstrates the magnitude of effect of a specific intervention, but is not appropriate for attributing causation (in this case of insulin resistance) exclusively to the period of the intervention, as some of the authors have implied.

An evolutionary approach may be informative concerning this debate. Arguably the first evolutionary approach to the induction of disease was the "thrifty phenotype" hypothesis of Hales and Barker [13]. This model considered the low-birthweight baby to have "adapted" to malnutrition in utero, and to be at increased risk of disease if this early malnutrition was followed by nutritional excess in the form of a rich childhood diet. Whilst the notion of contrasting nutritional experience at different periods during the life course inducing deleterious effects is undisputed, the relative importance of malnutrition in fetal growth remains controversial. Fetal nutrition might be considered as a source of "information" about the state of the environment, but it is important to clarify what that information might comprise.

Recent evolutionary approaches have emphasised that the information entering the fetus in utero is as much about the recent past as it is about pregnancy per se [36–38]. Maternal physiology demonstrates an extraordinary capacity to buffer the developing fetus from short-term perturbations [36,38]. Equally, maternal supplementation studies rarely succeed in generating large increases in birthweight [36–38]. Conversely, a strong predictor of birthweight is maternal birthweight, or even grandmaternal birth size [38]. Such evidence implies that nutritional supply in utero is influenced by a number of factors, including maternal size, and recent matrilineal experience [36–38], and these may be more important than maternal dietary intake itself. Fetal growth is therefore best considered as a process which tracks a number of maternal traits, and the low-birthweight baby is the product of a complex nutritional scenario. Rather than fetal development being relatively unimportant in the induction of adult disease, it is more appropriate to consider that the complexity of fetal development, and its association with past as well as current factors, makes intervention during this stage of the life course more difficult.

Fig. 1 summarises the implications of the existing literature on the contribution of the induction of body composition to the aetiology of the metabolic syndrome. First, fetal life and infancy appear particularly important in the induction of lean mass, with low birthweight

![Figure 1](image-url)
permanently constraining this body component, and by inference constraining the metabolic capacity to tolerate a rich childhood diet. Second, the rate of postnatal weight gain appears particularly important in the aetiology of central adiposity, which is now understood to impose a high metabolic load. These two mechanisms could, together, account for the finding that the risk of cardiovascular disease is greatest in those born small who subsequently large [3,4], imposing a high metabolic load on those least able to tolerate such a burden. However, a key issue here is the relative value of catch-up growth in developing versus industrialised country populations, with the former appearing to experience an extended window during which catch-up is beneficial rather than deleterious.

7. Controversies in the development of body composition

Despite growing evidence that early experience induces subsequent body composition, the underlying mechanism remains unknown. Broadly, two alternatives are plausible. First, early nutrition may impact on epigenetic or hormonal regulation mechanisms, which would then track subsequently and generate effects on body composition in later life. An example of such a hormonal mechanism may comprise the association between low birthweight and insulin metabolism. Studies have shown that low-birthweight babies are born insulin-sensitive [39], which appears to promote catch-up in length during infancy. Where this catch-up continues beyond infancy and early childhood, insulin resistance develops and is associated with central fat accumulation [40]. According to this perspective, the association between low birthweight and later fat distribution may be mediated both by hormonal programming, and the childhood diet.

Second, early nutrition may generate more immediate impact on body composition, which may track subsequently. Few data sets are available for addressing this issue. One study showed a tracking of infant fatness from three months to early childhood [41], and the common finding of associations between low birthweight and subsequent lean mass throughout the life course might suggest that early lean mass variability tracks subsequently. However, unpublished data from our research group suggests that infant fatness may provide energy for subsequent lean mass accretion (Chomtho, Wells, Williams and Fewtrell), hence the details of body composition tracking remain unclear.

Resolution of this issue is becoming easier with the development of a suite of body composition methodologies appropriate for measurements during infancy. In addition to isotope dilution, used over the last two decades [41], magnetic resonance imaging [42] and whole-body plethysmography [43] are now available. Investigation of this issue is of considerable potential importance for clinical practice. Animal studies increasingly demonstrate the capacity for hormonal mechanisms to be targeted by exogenous hormone administration. For example, administration of leptin during lactation to growth-retarded rats has been shown to constrain the development of adverse metabolic profile subsequently [44]. If however body composition variability itself emerges and consolidates within the infant period, tracking through childhood subsequently, a different type of intervention is likely to be required.

It is highly plausible that lean mass and fat mass will not have identical profiles within this context, and may be amenable to differing intervention strategies. Indeed, the available evidence suggests that lean mass development may be most amenable to interventions on the mother, prior to as well as during pregnancy. In contrast, the lack of clear associations between birthweight and subsequent adiposity suggests that infancy and childhood may prove to be valuable windows for interventions aimed at addressing the risk of obesity.

8. Conclusions

Existing data offer strong indications that the development of body composition plays an integral part in the induction of adult diseases, but much further work is required in order to elucidate which tissues and organs are sensitive in which periods, and to clarify the apparent differences in findings between industrialised versus developing countries, and between the genders. Other reviews have emphasised the multi-generational component of the induction of cardiovascular disease, suggesting that fetal growth may be more sensitive to matrilineal experience than maternal nutritional intake during pregnancy. It might be assumed that trans-generational transmission is an inappropriate target for intervention, due to the lengthy time required for beneficial effects to emerge. I would rather argue that the trans-generational component of the aetiology of these diseases is ideal for public health policies, intended to maximise health over generations. However, such an approach would ideally be complementary to the application of the same scientific knowledge in the management of individuals, especially those born small or large.

References


