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Historical cohort studies and the early origins of disease hypothesis: making sense of the evidence

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The hypothesis that early-life growth patterns contribute to non-communicable diseases initially emerged from historical cohort studies, consistently associating low birth weight and infant weight gain with later disease risk. Cohort studies offer crucial life-course data on disease aetiology, but also suffer from important limitations, including the difficulty of adjusting for confounding factors and the challenge of interpreting data on early growth. Prospective randomised trials of infant diet appear to provide evidence in direct contradiction to cohort studies, associating faster early growth with disease risk. The present article attempts to resolve this contradiction on two grounds. First, insufficient attention has been directed to inconsistency of outcomes between cohort studies and prospective trials. Cohort studies can assess actual mortality, whereas prospective trials investigate proxies for disease risk. These proxies are often aspects of phenotype that reflect the 'normalisation' of metabolism in response to growth, and not all those displaying normalisation in adolescence and early adulthood may go on to develop disease. Second, a distinction is made between 'metabolic capacity', defined as organ development that occurs in early life, and 'metabolic load', which is imposed by subsequent growth. Disease risk is predicted to be greatest when there is extreme disparity between metabolic capacity and metabolic load. Whereas cohort studies link disease risk with poor metabolic capacity, prospective trials link it with increased metabolic load. Infancy is a developmental period in which nutrition can affect both metabolic capacity and metabolic load; this factor accounts for reported associations of both slow and fast infant growth with greater disease risk.

Early origins of disease hypothesis: Historical cohort studies: Conflicts in evidence: Phenotypic induction

During the 20th century the burden of disease in industrialised countries shifted dramatically from infectious to non-infectious diseases as a result of changes in sanitation, hygiene, living conditions and nutrition[1]. In 1880 infectious, parasitic and respiratory diseases accounted for approximately 50% of all deaths in England and Wales, whereas cancers and diseases of the circulatory system accounted for <10%. By 1990 the corresponding percentages had altered to 17 and 70[1]. The modern killers became known as 'lifestyle' diseases, attributed to behavioural factors such as diet, sedentary behaviour and tobacco smoking, although both genetic factors and broader environmental factors such as pollution were also acknowledged to be important. Public health campaigns to reduce the prevalence of CVD and associated diseases such as type 2 diabetes, hypertension and stroke focused on dietary change (decreased consumption of fat, salt and refined carbohydrate, increased consumption of fruit, vegetables, vitamins and minerals), reductions in smoking and alcohol consumption and the promotion of leisure-time physical activity.

Within the last two decades a major shift in the understanding of the aetiology of these 'lifestyle' diseases has occurred, initiated by the analysis of several historical

Abbreviation: RCT, randomised controlled trials.

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Table 1. Key historical and prospective cohort studies used in research on the developmental origins of adult disease

	Country	Period of births	*n*	Reference
Historical birth cohorts				
Uppsala Academic Hospital cohort	Sweden	1915–29	14 611	Leon *et al.*[69]
Caerphilly cohort	Wales	1920–35	2512	Elwood *et al.*[70]
Hertfordshire birth cohort	England	1931–9	3000	Syddall *et al.*[8]
Helsinki birth cohort	Finland	1934–44	15 846	Eriksson[71]
Boyd Orr cohort*	UK	1918–39	4999	Martin *et al.*[72]
Dutch Hunger Winter cohort	The Netherlands	1943–7	3307	Lumey *et al.*[73]
Aberdeen children of the 1950's cohort	Scotland	1950–6	12 150	Leon *et al.*[74]
Human Capital study*	Guatemala	1962–72	2393	Grajeda *et al.*[19]
Prospective birth cohorts				
1946 National birth cohort	UK	1946	5362	Wadsworth *et al.*[75]
1958 British birth cohort	UK	1958	17 416	Power & Elliott[76]
New Delhi birth cohort	India	1969–72	8181	Bhargava *et al.*[77]
Vellore birth cohort	India	1969–73	10 670	Antonisamy *et al.*[78]
1970 British birth cohort	UK	1970	16 571	Elliott & Shepherd[79]
Pelotas 1982 birth cohort	Brazil	1982	5914	Victora & Barros[80]
Cebu Longitudinal Heath and Nutrition Survey	The Philippines	1983–4	3080	Tudor-Locke *et al.*[81]
Birth to twenty birth cohort	South Africa	1990	3273	Richter *et al.*[82]
Avon Longitudinal Study of Parents and Children	England	1991–2	Approx 14 000	Golding *et al.*[83]
Pelotas 1993 birth cohort	Brazil	1993	5249	Victora *et al.*[84]

Approx, approximately.
*Not all those in the cohort were recruited at birth.

cohort studies conducted primarily in European populations. This work has led to the 'developmental origins of adult disease' hypothesis, proposing that patterns of growth and nutrition in early life are strongly predictive of later disease risk. Apparently-contradictory findings relating to this hypothesis now prompt re-evaluation of the strengths and limitations of historical cohort studies and the best way to interpret and utilise their findings in order to integrate them with findings from other study designs.

Historical cohort studies and the developmental origins of adult disease hypothesis

The first major published study deriving from a historical cohort emerged from the follow-up of young adult men, some of whom had been exposed to maternal famine during the Dutch 'Hunger Winter' at the end of the Second World War. A landmark publication showed that compared with adults who had not experienced maternal famine *in utero*, those who had been exposed had higher adult BMI if they had experienced the famine in the first trimester of pregnancy, but lower BMI if they had experienced the famine in the third trimester[2]. These data were collectively suggested to comprise the induction of either adipocyte number or appetite regulation, depending on when the nutritional exposure occurred[2]. A longer-term follow-up reported a similar association between early pregnancy exposure to famine and markers of obesity in middle-aged women, but did not reproduce the earlier findings in middle-aged men[3]. Subsequent work in the same population, building on the ideas of Barker and colleagues[4–6] (which are described later), linked early-pregnancy famine exposure with increased risk of CHD and atherogenic blood biochemistry, while also linking late-pregnancy exposure with increased risk of impaired glucose tolerance and hypertension[7].

Beginning in the mid 1980s, groundbreaking work[4–6] demonstrated inverse associations between birth weight and risk of the metabolic syndrome and CVD across the entire range of birth weight. The statistical significance of birth weight in these associations appeared to implicate fetal nutrition, and these studies in combination with the Dutch hunger winter data thus focused attention on poor nutritional supply *in utero* as a key factor predisposing to CVD and related diseases. This work inspired similar research in a variety of other populations. Over the last two decades, research into the developmental origins of adult diseases has been conducted in a variety of historical cohorts (summarised in Table 1). These historical cohorts are located in industrialised countries, and the data were originally collected because of concern with child health in the early 20th century[8]. Their recent exploitation has involved the follow-up of adults for whom data on maternal phenotype and on offspring growth and infant feeding were available, and in some cases tremendous effort has been required in order to re-establish a viable cohort of survivors for scientific study.

These historical cohort studies have consistently linked early-life experience with an increased risk of a variety of disease in adult life, including CVD, hypertension, stroke and type 2 diabetes[9]. In 1991, capitalising on pioneering work that identified sensitive periods of development[10,11], the concept of 'programming' was proposed, whereby experience during early life exerts long-term effects on later phenotype[12]. Others have likewise referred to 'metabolic imprinting'[13], and there has been much interest in so-called 'critical windows' during which programming effects might be exerted. From an evolutionary perspective, the term programming has been criticised[14], based

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on the argument that early-life experience does not contain specific 'information' about later disease. 'Phenotypic induction' was suggested as a more neutral term, in keeping with other areas of biology. 'Programming' has entered biomedical usage, and in relation to early life the two terms are to some extent interchangeable depending on the audience. However, phenotypic induction is a broader term with important benefits for integrating experience across the life-course and is used in the present article. One limitation of the 'critical window' approach is that physiological variability appears to involve different mechanisms at different life-course periods, and specific sensitive periods become increasingly difficult to define. The recent explosion of research into epigenetic modification of DNA expression has demonstrated one mechanism whereby nutrition in early life may generate long-term effects on phenotype[15], whereas later-life effects may be more attributable to incremental physiological changes.

There are a number of strengths characterising historical cohort studies. First, these large cohorts have in common data on birth weight, allowing certain hypotheses relating to associations between birth weight and later health or disease to be tested in different settings. Second, the participants are now middle-aged or elderly, hence analyses of their data offer robust evidence in relation to associations between early-life experience and actual morbidity or mortality in adult life. This factor represents a key strength because, although animal studies can generate life-course data over short time periods, the physiology of rodents may differ substantially from that of human subjects. Third, there is typically at least some data about the socio-economic status of the families, allowing some adjustment for this source of variability. The strengths of this approach have been demonstrated, for example, in the analyses of the Dutch Hunger Winter[2].

However, there are also a number of limitations to such studies. First, the data on early-life experience and confounders such as parental health and socio-economic status tend to be limited, and often incomplete. Second, observational studies of size or weight gain, with poor capacity to adjust statistically for confounders, are not adequate for demonstrating causation at the level of nutrition. As will be discussed, birth-weight data are especially hard to interpret and do not only index fetal experience. Finally, experience 60–90 years ago may not provide an appropriate model for contemporary populations[16]. Given these limitations, researchers increasingly use other study designs to research the developmental origins of adult disease.

First, since the end of the Second World War onwards a number of large prospective birth cohorts have been established, as described in Table 1. These cohorts include national birth cohorts in the UK and more local cohorts in modernising countries. The early 1990s saw the initiation of the Avon Longitudinal Study of Parents and Children (ALSPAC), perhaps the most intensively studied cohort to date. Other cohorts have also been established recently in Brazil, the Philippines, South Africa and India. These newer cohorts, typically of several thousand individuals, have better data on early-life experience and potential confounding factors, more information on the continuous process of development and more frequent physiological measurements than do the historical cohorts. Broadly, they support the hypothesis that low birth weight is associated with increased adult disease risk[17].

Second, building on nutritional supplementation studies, researchers began applying the well-established pharmaceutical model to nutritional research. For example, between 1962 and 1977 all children within a group of Guatemalan villages were eligible for a food supplement, with two neighbouring villages given supplements differing in energy and protein content[18]. These children, now followed up as the 'Human Capital Study'[19], were however not randomised to the two diets and, although unlikely, it is technically possible for the villages themselves to have differed. Treating early-life nutrition from a pharmaceutical perspective, a series of randomised controlled trials (RCTs) were initiated whereby groups of preterm or term infants were allocated to different trial diets of known composition[20–22]. These trials represent a better approach for adjusting for confounding factors, whether known or unknown[16], and are considered to produce the most robust evidence of causation. In particular, such trials are needed to demonstrate that early-life nutrition does indeed induce the later disease profile.

Nevertheless, randomised controlled trials (RCT) themselves suffer from certain limitations. First, they are difficult to perform at most ages (e.g. pregnancy or from early childhood onwards) and breast-feeding remains particularly difficult to study. These factors have resulted in widespread use of RCT with formula milks of differing composition but very little evidence for periods outside early infancy or for the kinds of total diets that individuals consume if not wholly formula-fed. Second, whilst they demonstrate the magnitude of the effect of the intervention, they cannot reveal the physiological mechanism or when during their administration they exert the effect.

Recently, it has become clear that the evidence from historical and prospective cohort studies and RCT contains major apparent contradictions. Whilst some researchers believe that fetal and infant undernutrition is key to the developmental induction of adult disease[23], others argue that overnutrition in the very same time periods is fundamental[24]. This controversy risks polarising research into two opposing schools, detracting from the ability to develop a more holistic model of environmental impacts on disease risk. It also inhibits the formulation of public health policies, whereby the vast amount of research funding directed to the developmental origins hypothesis might generate tangible health benefits.

In the present article, it is argued that apparent controversy derives primarily from inconsistency in research outcomes, terminology, study designs and the interpretation of statistics, and not from either school being correct at the expense of the other. It is proposed that the different study designs emphasise different aspects of the total process of phenotypic induction, and that being more specific about what is induced during any particular developmental period aids the integration of the sum of data more successfully. This approach can therefore resolve the problem of how both under- and overnutrition during early life increase risk for a common set of diseases.

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Table 2. Associations between indices of reduced or greater infant growth with later disease

Disease	Outcome associated with poor infant growth	Reference	Outcome associated with fast infant growth	Reference
Type 2 diabetes	Glucose intolerance	Eriksson *et al.*[85]	Insulin resistance	Singhal *et al.*[28]
CHD	Death rate	Eriksson *et al.*[86]	Endothelial dysfunction	Singhal *et al.*[29]
Hypertension	Blood pressure	Gaskin *et al.*[87]	Blood pressure	Singhal *et al.*[27]

Controversies in the evidence

Birth weight is widely studied in part simply because the data are widely available[25]. The interpretation of associations between low birth weight and later disease risk remains controversial, because birth weight is associated with postnatal growth rate as well as prenatal growth rate. As the statistical significance for these associations tends to depend on adjustment for adult weight, it has been argued that change in size between birth and adulthood is the primary determinant of risk, implicating postnatal growth rather than *in utero* development[26]. For example, data from some RCT consistently demonstrate associations between increased infant growth rate and poorer subsequent metabolic profile[27–29], paradoxically suggesting increased risk of the same diseases that have been associated in observational cohort studies with infant undernutrition (Table 2). According to the perspective discussed earlier[24], birth weight merely acts as a statistical marker of postnatal growth rate in historical cohort data and does not actually implicate fetal growth variability as the cause of adult disease variability.

On the basis of RCT data the 'growth acceleration hypothesis' was proposed[24], which argues that rapid postnatal growth alone is the mechanism whereby early-life experience predicts subsequent risk. It is argued that because in each trial the groups tended to be very similar in terms of birth weight, there could be no contribution of fetal growth to the between-group differences in physiological markers of disease that were subsequently demonstrated. In support of the argument data are cited from animal studies associating early-life growth rate with later indices of function and health[30]. In these studies faster growth during development was shown to be associated with poorer outcome in a range of animal species. The Metcalfe–Monaghan model of 'grow now, pay later' was interpreted literally by arguing that the process of postnatal growth itself becomes harmful at higher rates[24].

This approach immediately raises the question as to why shorter adult stature and reduced leg length relative to total height are so widely associated with poorer health[31,32]. From a broader perspective, animals vary profoundly in their rate of postnatal growth and this trait is a major feature of 'life history', which refers to the schedule of ontogenetic development, a key strategy whereby species adapt to different ecological niches. Ancestral humans (*Homo erectus*) are generally thought to have grown much more rapidly than modern humans[33], and growth rate in *Homo sapiens* is considered to have become hormonally suppressed[34] to aid maternal reproductive energetics, as occurs in many social mammal species[35]. The idea that growth itself is inherently harmful is extremely simplistic, and the dynamics of the growth process require more careful evaluation.

Nevertheless, because both historical and prospective cohort and RCT data derive from large datasets and because each study design tends to generate findings consistent within itself, it is unlikely that either interpretation is wholly incorrect. Rather, it is necessary to be more specific about what exactly each study demonstrates and to understand how different statistical approaches emphasise different aspects of the biology of development.

Interpreting birth weight

Given the prominence of birth weight in many analyses, it is helpful to begin by exploring the notion that birth-weight variability reflects variability in the adequacy of fetal nutritional supply. Genetic factors undoubtedly influence fetal growth; however, studies are relatively consistent in attributing a minority of variability in size at birth to genetic factors[36,37], indicating that most variability can be attributed to environmental factors. Logic suggests that low birth weight is indicative of undernutrition, and the Dutch famine data on those individuals exposed during the third trimester provide support for this hypothesis. Nevertheless, a recent study using ultrasound measurements to identify growth faltering in each trimester of pregnancy has revealed unexpected findings[38].

Whereas infants who faltered during the third trimester of pregnancy had lower weight and subscapular skinfold thickness relative to those who had not faltered during any trimester, those who faltered in the first trimester had higher values than all the other groups[38]. This finding suggests that early faltering may result in a degree of catch-up growth *in utero* and that large birth weight need not necessarily indicate a lack of fetal growth faltering. This factor in turn may contribute to the paradoxical 'U'-shaped association between birth weight and subsequent risk of obesity, as categorised by BMI[39], and diabetes[40].

Of importance for this debate are two issues: first, birth-weight variability is difficult to interpret as a marker of fetal growth faltering; second, fetal-growth variability (which is not the same as birth-weight variability) may nevertheless contribute to later disease risk. Confirming the latter hypothesis requires the effect of postnatal growth to be taken into account; however, this approach is challenging because although both early and later markers of growth have been associated with risk of same diseases, insufficient attention has been paid to the interpretation of different physiological markers of a given adult disease.

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Research outcomes and different windows of induction

A second critical issue in unravelling apparent inconsistencies in the literature is the different outcomes assessed. Long-term cohort studies have typically been able to use mortality (e.g. death from CVD) or morbidity (e.g. diabetes, hypertension) as the primary outcome. Low birth weight consistently emerges as a strong predictor of such diseases, but in most cases only after adjustment for current weight. As these diseases emerge slowly throughout the life course, those conducting research on younger individuals are obliged to focus on proxy markers of disease, e.g. arterial distensibility rather than atherosclerosis, blood pressure rather than hypertension or fasting split proinsulin levels (proposed to reflect insulin resistance) rather than diabetes[27–29]. For the youngest age-groups it is possible only to study physiological traits, such as size, body composition or hormonal concentrations, for which clear association with adult disease risk has yet to emerge.

This disparity in research outcomes is a major contributing factor to conceptual confusion, for two related reasons. First, it is difficult to integrate the different outcomes within a simple model of disease (see earlier). Second, study findings may on occasion conflict drastically, according to the age of the participants. This conflict can occur because not all those with apparent markers of disease at young ages go on to develop the disease. These issues may be clarified by elucidating how different periods of growth contribute to the induction of adult phenotype.

Growth may be broadly divided into two generic periods, one in which the offspring's immediate environment comprises maternal physiology, and a subsequent one in which the offspring is directly exposed to the external environment[41]. Organogenesis occurs primarily within the first period, hence this critical period of development could be argued to be induced not by the external environment but by maternal phenotype[41,42]. The duration of this maternal induction varies according to the trait in question. During pregnancy maternal and fetal haemodynamics interact, generating differential growth of peripheral *v.* central organs[43]. The offspring can respond adaptively, but its strategy is also open to maternal manipulation[41,44]. This opportunity for direct haemodynamic interaction ceases at parturition. In contrast, offspring metabolism remains sensitive to maternal phenotype during the window of lactation, through hormonal effects on milk output and composition. Physiological traits such as nephron number[45], cardiac structure[46] and pancreatic β-cell mass[47] are therefore strongly (although not necessarily exclusively) associated with fetal experience, whereas insulin metabolism is further sensitive to infant experience[48]. It has been argued, from an evolutionary perspective, that the offspring adapts to the 'niche' of maternal metabolism and that the mother manipulates her offspring to optimise her own reproductive strategy[41,42]. As many aspects of organ phenotype are essentially fixed from birth or early infancy onwards, as a result of the majority of rounds of cell division having been achieved[49], aspects of phenotype induced during this developmental period track subsequently into adulthood. Thus, reference can be made to the 'maternal induction' of offspring 'metabolic capacity', which is closely associated with certain aspects of organ phenotype.

The influence of maternal phenotype on offspring development must inevitably weaken with offspring age, but the schedule of this change depends on ecological factors. Until the development of agriculture, early postnatal growth would likewise have been strongly influenced by maternal phenotype, via lactation. Even after weaning, the tendency for human offspring to be provisioned by their mother would maintain a link between maternal phenotype and offspring growth rate[41]. Such extended maternal care confers coherence on offspring development throughout the period of pregnancy, infancy and childhood[42]. In recent millennia, most notably in industrialised populations, it has become possible for this maternal influence to be weakened or negated, exposing the offspring to stochastic growth patterns as early as 30 weeks post conception in those born preterm. It is this incoherence in nutritional experience that appears most strongly to predict subsequent disease.

Postnatal growth contrasts with prenatal growth by increasingly impacting on tissue size rather than fundamental structure, especially from late infancy. Postnatal growth, the sum of both size and somatic tissue (lean and fat), may thus be conceptualised primarily as generating 'metabolic load'. The relative magnitude of growth, and the load it imposes, is associated with homeostatic adaptations in metabolic traits. For example, blood pressure increases systematically during the growth process[50], influenced independently by both somatic size (lean mass)[51] and adiposity[52], with each contributing to the total metabolic load. Even weight gain in the first 3 months demonstrates such effects on blood pressure by 1 year of age[53]. These increases in blood pressure have been attributed to larger bodies imposing a greater load on the kidneys[50], invoking haemostatic changes in order to maintain renal homeostasis. In other words, variability in blood pressure during childhood and adulthood reflects the normalisation of metabolic load for a given metabolic capacity.

This process of normalisation evident for blood pressure is merely one example of a broader pattern whereby metabolic traits mediate the impact of growth-generated metabolic load on metabolic capacity. For example, insulin resistance and insulin secretion are closely related, such that in healthy individuals insulin resistance can be accommodated by increases in insulin secretion to maintain glycaemic control[54]. However, the understanding of this normalisation perspective remains incomplete because of the tendency to target research primarily at those who are unwell, unduly emphasising, for example, the deleterious aspects of hypertension rather than the adaptive function that occurs over the entire range of blood pressure.

The notion that disease is the result of disparity between metabolic capacity and metabolic load was essentially described in the thrifty phenotype hypothesis[47], and this conceptual model remains capable of integrating the findings of diverse developmental origins research studies. What has not been sufficiently appreciated as yet is the shift in the target of growth, from metabolic capacity to

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metabolic load, and the effects of this shift on the induction of diseases.

Disentangling the contributions of fetal *v.* postnatal growth

Differentiating growth into periods targeting metabolic capacity or metabolic load clarifies in several ways the apparent controversy between the 'low birth weight' and 'growth acceleration' schools.

First, it is easier to appreciate apparent inconsistencies relating to outcomes. Low birth weight has been associated with risk of diabetes[55], while rapid infant growth has been associated with insulin resistance[28]. However, since diabetes represents a 'two hit' phenomenon, in which insulin resistance is accompanied by β-cell defect preventing compensations in insulin secretion[54], the epidemiology of diabetes need not be identical to the epidemiology of insulin resistance. Put simply, the life-course induction of physiology (e.g. β-cell mass, nephron number) differs from that of physiological function (e.g. glycaemic control, blood pressure), which in turn differs from that of disease (e.g. diabetes, hypertension). Whether the insulin resistance induced by faster infant growth[28] actually leads to diabetes in later life is likely to be mediated by β-cell function, and hence by fetal developmental experience.

Second, it is possible to resolve apparent inconsistencies relating to statistical models. Studies of older adults with CVD show that, holding current weight constant, those with low birth weight have an increased disease risk[17,56], which implicates the induction of metabolic capacity in early life through strong effects on traits such as nephron number or β-cell mass, as discussed earlier. Studies of younger adults show that rapid infant weight gain is associated with increased physiological markers of risk, regardless of birth weight[27,28], which implies the environmental induction of increased metabolic load. The greatest disparity between metabolic load and metabolic capacity occurs in those individuals who are born small and become large, for whom the risk of CVD and the metabolic syndrome is greatly increased[57–59]. Recent studies further suggest that different periods of childhood growth impact differentially on the risk of specific diseases[60,61]. Each statistical approach may therefore be considered merely to emphasise one component of the dynamic process whereby metabolic load is superimposed on metabolic capacity.

Third, it is beneficial to differentiate between study designs and possible sensitive periods of growth. The findings of intervention studies conducted in both preterm and full-term infants during the immediate postnatal period have been used to argue that postnatal growth is implicated as the key 'critical window' in which susceptibility to CVD is induced[24]. However, such studies only demonstrate the magnitude of effect of an intervention conducted during a specific period. As RCT typically begin in the immediate postnatal period, when (under natural conditions) breast-fed infants normally receive little nutritional intake and lose up to 10% of their birth weight[62], the interventions are likely to overload metabolism in this particularly sensitive period of development, and hence disproportionately target the induction of metabolic load rather than metabolic capacity. Where catch-up growth is distributed over longer time periods it is possible that it may more successfully target metabolic capacity, and given the benefits of catch-up growth for survival in many settings[63] this hypothesis requires further research. Metabolic load may be enhanced throughout postnatal life, not only by infant or childhood 'growth acceleration' as suggested, but also by adult obesity once growth has ceased.

This interpretation does not therefore support the model that CVD is essentially induced by postnatal experience alone, as suggested previously[24]. Although it is claimed that the hypothesis of 'growth acceleration' being harmful is supported by data from a range of animal species, the vast majority of such animal studies describe catch-up growth following initial nutritional insult, while the remaining studies involve genetically variant animals[27] and so cannot attribute adult phenotypic variability to early-life environmental variability. Again, these animal studies implicate an inherent link between different growth periods in the aetiology of later disease, one earlier period exerting deleterious effects on metabolic capacity and the other imposing an increased metabolic load on that capacity.

Fourth, it is possible to differentiate alternative pathways whereby public health policies might beneficially impact on health. The close association between birth weight and subsequent lean mass[64], and the fact that organogenesis is largely completed by birth, suggests that interventions on the mother, during her own development or during pregnancy, may represent the optimum approach for benefitting offspring metabolic capacity. Birth-weight supplementation studies tend to have limited efficacy[41,42], hence nutritional intervention earlier in the maternal life course may be most successful. Animal studies, for example, show that maternal effects continue to act on offspring phenotype across several generations[65]. Alternatively, during pregnancy maternal metabolic control may represent a better candidate for intervention than maternal diet[41], as it is the nutrient concentration gradients between fetus and mother that determine fetal supply. In contrast, postnatal interventions may prove most beneficial in preventing the induction of excess metabolic load. Public health policies such as breast-feeding and the promotion of healthy childhood diets and activity levels all have the capacity to target this component of development.

It is well established that babies with low birth weight tend to experience catch-up growth in postnatal life[66]. In the Avon Longitudinal Study of Parents and Children cohort indices of *in utero* growth retardation were found to be strongly associated with rapid postnatal growth rate [66], while researchers using animal models have likewise admitted that they are powerless to prevent such catch-up occurring under natural conditions (S Ozanne, personal communication). Although the magnitude of this catch-up may potentially be regulated through control of diet or feeding schedule, the capacity for such manipulation is limited in breast-fed infants in whom nutritional intake is essentially 'invisible'. Associations between birth weight and adult disease risk thus partly reflect the fact that low birth weight is associated with both poor fetal growth and

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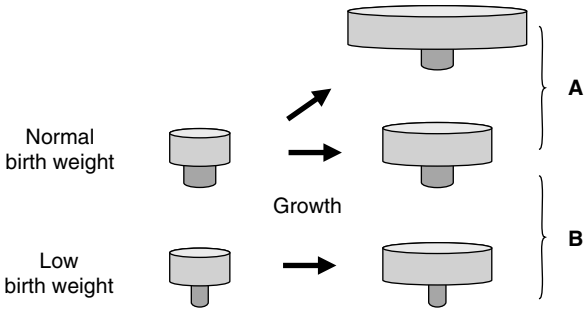

Fig. 1. Schematic diagram illustrating the different emphases of randomised controlled trials (RCT) *v.* historical cohort studies. Disease is attributed to a high metabolic load (deriving from postnatal growth) being exerted on metabolic capacity (organ phenotype determined primarily by fetal experience). RCT investigate the effects of growth on metabolic load and show that rapid weight gain exacerbates metabolic load independent of birth size (A). In contrast, historical cohort studies show that holding current size (i.e. metabolic load) constant, disease risk is greatest in those born small, which can be attributed to their reduced metabolic capacity (B). (■), Metabolic capacity; (□), metabolic load.

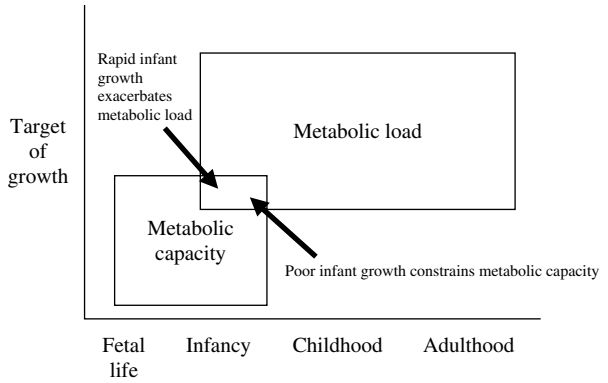

Fig. 2. Schematic diagram illustrating the change in the target of growth with increasing age through the life course. Early-life growth primarily promotes metabolic capacity, whereas later growth induces metabolic load. Infancy reflects a time period when both outcomes can be influenced, with the relative effect on metabolic capacity *v.* metabolic load varying according to current nutritional status and previous growth patterns. Such a model can explain why both poor and rapid growth in infancy have been associated in different studies with poorer health outcomes.

rapid infant growth. However, excess childhood, adolescent and adult weight gain all increase metabolic load, and the deleterious effect of low birth weight cannot therefore be attributed entirely to its inverse association with infant growth, as is emphasised by recent studies[60,61,67].

How different study designs merely emphasise different components of the process whereby nutritional experience contributes to adult disease risk can now be reconsidered. The historical cohort studies highlight how, holding adult weight (or metabolic load) constant, disease risk is greatest in those born small. The physiological evidence attributes this effect of low birth weight primarily to reduced metabolic capacity, deriving from traits such as compromised β-cell mass, nephron number and cardiac structure although low birth weight also contributes to disease risk by inducing catch-up growth. Postnatal RCT demonstrate how increasing metabolic load exacerbates disease risk. This outcome can be achieved in any individual, regardless of initial size, but studies consistently show that those of low birth weight tolerate the increased load least well. Fig. 1 illustrates the different aspects of a single model of the developmental origins of disease that are investigated by observational cohort studies *v.* RCT.

The conflicting results for infancy presented in Table 2 can be attributed to the fact that this period of development incorporates both the later stages of the development of metabolic capacity and the early stages of the generation of metabolic load. Cohort studies associating poor infant weight gain with later disease risk indicate the continued suppression of metabolic capacity. For example, although β-cell mass is strongly associated with birth weight, it continues to increase during infancy[68] and is therefore predicted to be deleteriously influenced by poor infant weight gain. In contrast, RCT associating faster infant growth with increased adolescent blood pressure[27] or insulin resistance[28] imply the imposition of increased metabolic load, possibly through overloading metabolism during the sensitive period immediately after birth. To elucidate this issue further, RCT manipulating growth should be delayed until after the first weeks of life and should then generate physiologically-relevant differences in infant weight gain, rather than extremes. More broadly, the optimal magnitude of infant growth for later health remains a key topic for research, especially in those born small, with the optimal level likely to reflect a trade-off between counterbalancing risks. Fig. 2 illustrates the shifting target of growth across the life course and the contrasting effects of infant undernutrition *v.* overnutrition.

Conclusions

The present article has aimed to probe the value of historical cohort studies in research into the developmental origins of adult disease. Recently, apparent contradictions in the scientific evidence for such disease aetiology have led to some researchers questioning the value, or interpretation, of these observational studies. It has been argued that these contradictions can be attributed to inconsistencies between studies in their design, study populations, outcomes and statistical interpretation. Understanding the changing association between growth and metabolic capacity *v.* metabolic load during the process of ontogenetic development improves the integration of research findings and clarifies two generic complementary pathways whereby public health interventions may reduce the risk of non-communicable diseases. Optimal adult health is predicted to derive from minimising two counterbalancing risks, i.e. the development of poor metabolic capacity *v.* the development of excess metabolic load. Infancy appears a particularly sensitive component of development because both risks manifest during this period. Public health policies may address each of these risks, and a coherent approach across the life course will avoid the disparity of growth between different developmental periods that appears most strongly associated with disease.

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