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Early development, survival and reproduction in humans

Virpi Lummaa and Tim Clutton-Brock

Environmental factors commonly influence the growth and early development of individuals in wild populations of mammals. Such influences can exert downstream effects on the phenotypic quality and breeding success of the same individuals in adulthood, as well as on the growth and subsequent reproductive success of their offspring. Recent studies of humans indicate that similar effects occur both in Western human populations and in human populations subject to nutritional stress. Here, we compare evidence for the effects of early development on growth, survival and breeding performance in humans to similar trends in food-restricted populations of other mammals. We highlight the relevance of findings from animal studies to humans and vice versa, and suggest that the integration of wild animal and human studies could increase our knowledge about how early development shapes reproductive performance across generations.

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In food-limited populations of wild mammals, ecological factors affecting growth rates of juveniles before or immediately following birth can have pronounced consequences for their subsequent growth, survival and breeding success [1–3]. In Scottish red deer *Cervus elaphus*, the mean birth weight of calves rises by ~8% for every 1°C increase in mean daily temperature during April and May, the two final months of gestation [4]. Differences in average birth weight among cohorts of calves are associated with intercohort differences in neonatal survival, relative development at specific ages and the age at first reproduction [5]. Other environmental factors that influence early growth can have similar consequences. For example, in Soay sheep *Ovis aries*, high population density in the winter preceding birth is associated with reduced birth weights, as well as with reductions in neonatal survival, adult body size and fecundity [6,7].

In sexually dimorphic species, the effects of adverse environmental conditions during early development are commonly more pronounced in males, leading to either reductions in the relative numbers of males born [1], or reductions in their growth and breeding success [7,8]. In red deer, the proportion of male calves born declines with increasing population density in the preceding winter [9], whereas in bighorn sheep *Ovis canadensis*, sex differences in adult body size decline as population density increases [10]. Similar effects have been recorded under controlled conditions. Restricting food given to golden hamster *Mesocricetus auratus* females during their first 50 days of life causes them to produce smaller litters and female-biased sex ratios during adult life, even after they have been replaced on *ad libitum* diets [11]. In wild house mice *Mus musculus*, experimental food deprivation during gestation has much greater negative effect on the subsequent reproductive success of sons than on that of daughters, possibly because of a disruption in the organizational effects of testosterone in neonatal male mice [12].

Studies of wild mammals also suggest that early development has effects that span generations. For example, cohorts of female red deer characterized by relatively low birth weights produce light calves and the survival of calves born to different cohorts of mothers varies from <10% to >60% [5,6]. Some evidence suggests that, like effects within generations [8], these intergenerational effects are more pronounced in males. For example, in hamsters, the daughters of food-restricted females, themselves reared on *ad libitum* diets, produce smaller litters and relatively fewer sons than do daughters of control females that were not food restricted [13].

Accumulating evidence suggests that similar growth and survival effects also occur in human

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Table 1. Examples of evidence for long-term negative effects of adverse early development in humans[a]

System or organ affected	Response in adulthood	Refs
Growth	Reduced childhood growth and adult size	[19]
Longevity	Increased susceptibility to premature death in adulthood	[30,31]
	Increased suicide risk	[25]
Reproduction	Reduced offspring birth weight	[33,34]
	Reduced offspring early survival	[33,35]
	Reduced probability of marriage	[40]
	Earlier age at menopause	[38]
Ageing	Increased lens opacity score, higher hearing threshold, reduced grip strength, thinner skin	[50]
Brain	Reduced cognitive performance	[51]
	Increased risk of schizophrenia	[52]
Bone	Reduced bone mineral content	[53]
Cardiovascular system	Reduced vascular compliance	[54]
	Increased left ventricular thickness	[55]
	Impaired endothelial function	[56]
	Increased risk of stroke	[57]
Endocrine system	Changes in hypothalamic–pituitary–adrenal axis	[58]
	Changes in glucose–insulin metabolism	[59]
	Changes in growth hormone–insulin-like growth factor 1 axis	[60]
	Changes in gonadotropic axis	[61]
Immune system	Increased susceptibility to autoimmune thyroid disease	[62]
Kidney	Reduced plasma concentrations of inactive rennin	[63]
Liver	Impaired cholesterol metabolism	[64]
	Reduced factor VII synthesis	[65]
Respiratory system	Increased prevalence of obstructive airways disease	[66]
	Increased risk of asthma	[67]
Skeletal muscle	Increased insulin resistance	[24]
	Glycolysis during exercise	[68]

[a]Early adverse development including low birth weight, poor postnatal growth rate or exposure to famine *in utero*.

populations [14,15]. However, the complementary and similarity between studies on wild animal and human populations have not yet been fully explored [2,3]. No study of wild mammals has examined the health and survival consequences of early growth to the extent provided by the existing human literature (Table 1), and many human studies are well ahead of studies on wild animals in understanding subtle effects of early growth and their surrounding mechanisms. By contrast, only a few human studies have addressed the effects of early development on reproduction in current or future generations, which are well documented for many animal populations. This review builds on two recent reviews in *TREE* [2,3] focusing on how early conditions experienced by individuals affect their subsequent reproductive strategies and fitness. We show that consideration of both animal and human studies can enhance our understanding of the repercussions that conditions experienced during early development have for subsequent health, breeding success and survival, not only for the current generation, but also for future ones.

Environmental conditions and human births

Although the foetal genome affects human growth potential *in utero* [16], environmental conditions before birth affect foetal growth, birth weight and neonatal survival in all human populations. For example, mothers who were exposed to a short famine in The Netherlands during the winter of 1944–1945 had reduced weight gain during pregnancy and, consequently, produced infants with reduced foetal growth, birth weight and length, and neonatal survival [17]. Similarly, in rural Gambia, where the seasonal environment gives rise to an annual period of hunger, offspring birth weight can vary by 200–300 g depending on birth date [18] (Fig. 1a), with mortality risk being highest for those born during the hungry season, when birth weights are lowest [19]. Foetal growth retardation and subsequent mortality risk during the hungry season were reduced when pregnant mothers were given supplementary food, suggesting that the effects were caused by nutritional stress [18]. Likewise, women with a history of 'voluntary' starvation (e.g. anorexia nervosa) tend to have an increased number of miscarriages and their offspring tend to be born prematurely and with low weight [20].

Early development and survival in humans

Human studies provide detailed examples of how variation in birth weight can have long-term effects on health and survival in adulthood. One line of evidence for such an association is provided by studies that link individual variance in birth weight in populations to probability of death or disease in adulthood. For example, in Western human populations, birth weight commonly predicts the onset of chronic conditions that lead to increased mortality in adulthood [14,15], although causal pathways are often difficult to determine from these data. It has been proposed that many aspects of an individual's life history can be determined before birth via nutritionally dependent changes in gene expression in early life, which lead to increased susceptibility to various diseases (Table 1). Babies whose early growth (both pre- and post-birth) is reduced, or who are exposed to famine *in utero*, tend to show increased rates of coronary heart disease [21], obesity [22], hypertension [23], noninsulin-dependent diabetes mellitus [24] and even suicide [25] in adulthood. These effects can be strong enough to persist over generations: female foetuses constrained by nutrient deficiency show persistent changes in their physiology and metabolism, which can lead to reduced foetal growth and raised blood pressure in their offspring [26]. These intergenerational effects of early nutrition have been verified in controlled laboratory experiments in rodents. Such studies have shown that female rats *Rattus norvegicus* fed on protein-poor diets had offspring (fed *ad libitum*) who were smaller, with reduced glucose utilization capacity, and whose offspring, in turn, also had reduced glucose utilization [27] (see Box 1 for other intergenerational effects). As in other mammals [8,9,11,12], empirical evidence suggests that, under stressful conditions, foetal growth of human males is more likely to be retarded than is that of females [28], and males are more likely to carry

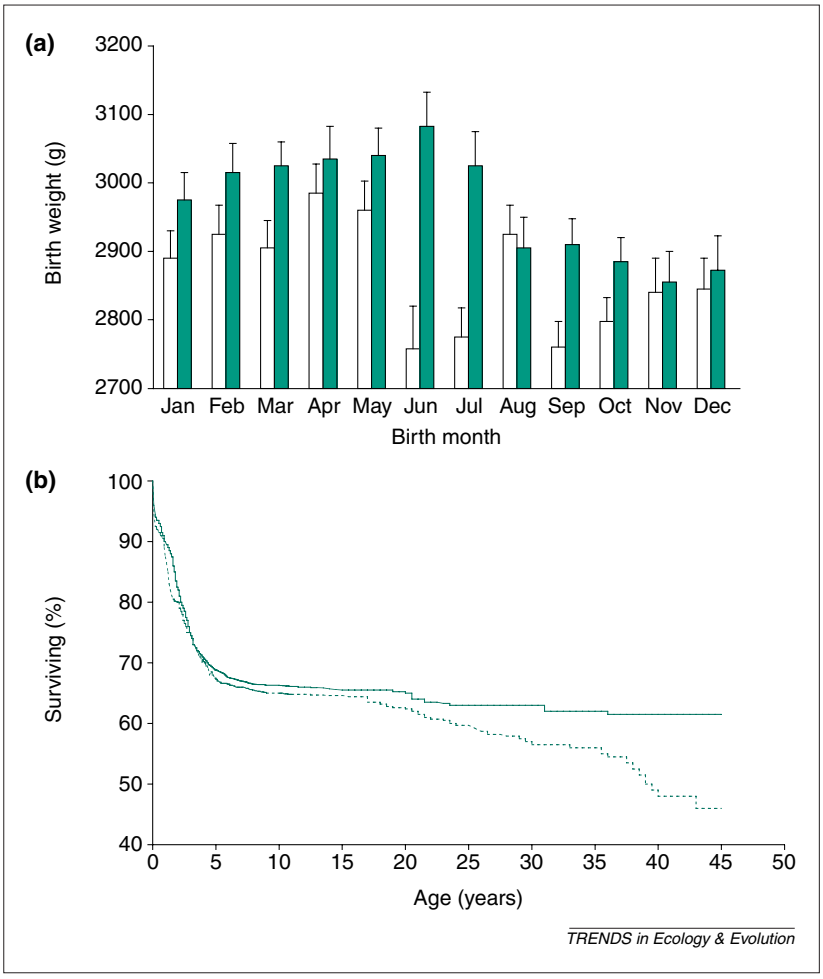

Fig. 1. Effects of season of birth on birth weight and survival in rural subsistence-farming Gambian populations. The annual hungry (wet) season (June–October) is associated with decreases in average birth weight and increases in numbers of babies born with low birth weight (a, open bars). High-energy biscuits given for 20 weeks before delivery improved weight gain in pregnancy and significantly increased birth weight (closed bars), particularly during the hungry season. Perinatal mortality was also decreased (data not shown). The study consisted of the single-born babies ($n = 2047$) delivered in 28 villages of the Gambia during 1989–1994. Reproduced, with permission, from Ref. [18]. (b) Survival plot for rural Gambians according to their season of birth. Those born during the annual hungry season (dashed line) were up to ten times more likely to die prematurely in adulthood compared with those born during the annual harvest season (solid line). From the age of 15, those born in the hungry season showed greater mortality from infectious diseases. Based on data for 3102 births and 1077 deaths occurring in three rural Gambian villages during 1949–1994. Reproduced, with permission, from Ref. [30].

the negative consequences of low birth weight into adulthood (reviewed in Ref. [29]).

Studies of human populations subject to periodic food shortages have produced similar results. For example, rural Gambians born during the annual hungry season are up to ten times more likely to die from infections and pregnancy complications in adulthood than are individuals born at other times of the year [30,31] (Fig. 1b). A permanent effect of malnutrition on the development of the immune system during foetal growth might be an explanation [31]. However, not all studies have found effects of this kind. For example, although cohorts of Finns born during the severe famine of 1866–1868 showed an immediate increase in mortality during and after the famine, they showed no evidence of reduced survival in later life compared with those cohorts born five years preceding and following the famine [32].

Early development and reproduction in humans

Adverse early conditions can also affect later reproduction of humans, although these effects have traditionally gained more attention in studies on wild animals. Some studies of Western humans have found associations between birth weight and reproductive performance in adulthood. Women with reduced early growth and low weight at birth tend to have babies who are small and who have an increased risk of suffering from birth complications and early mortality. In addition, mothers who are themselves born small (≤2 kg) are at elevated risk of birth complications in the future, including a higher risk of bearing a child that subsequently dies, even if the child's birth-weight is relatively high (e.g. modern Americans [33] and Norwegians [34]).

The negative effects of mothers having had poor growth rates prebirth on their offspring's birth weight can last for several generations [35] (Box 1). The fertility of women exposed to foetal malnutrition might be impaired because nutritional deprivation can affect development of organs producing and regulating female reproductive hormones [36]. Prebirth exposure to food deprivation during the Dutch famine affected subsequent reproduction of females: those women exposed to famine *in utero* had offspring with lower birth weight and length than did mothers who were not exposed to famine before birth [37], although their fecundity was not depressed [36]. In addition, there was an increase in infant mortality and stillbirths in the second generation, with females who had been exposed to foetal famine being more likely to give birth to offspring that died early [36] (Box 1).

Another correlate of reproductive success in humans that can be influenced by early development is age at menopause. In a follow-up study of women born in England in the first half of the 20th century, Cresswell *et al.* [38] found that menstruation ceased at an earlier age in women who showed low weight gains during their first year of life or who were short at birth. A possible explanation is that poor growth and development in late gestation (a crucial time for ovarian follicular development) leads to a smaller peak number of primordial follicles in the ovary, which leads, in turn, to an earlier menopause [38]. However, another study on contemporary Australian twins failed to detect the association between birth weight and age at menopause [39], possibly because the intrauterine growth of twins might be governed by different influences to that of singletons. Few studies have focused on reproductive consequences of early development in men. However, Phillips *et al.* [40] found that Finnish and English men belonging to generations in which marriage was the social norm (born 1920–1930) were less likely to marry in adulthood if they were small at birth, irrespective of their adult size, social class, income or age.

Box 1. Intergenerational effects

The early growth and development of an individual can influence the reproductive success and survival of its offspring in, for example, many insects [a], some birds [b] and mammals [c], but the mechanisms and consequences of such observations are poorly known. The extensive demographic and medical registers available for many human populations could provide a valuable source of data for examining such consequences, and the possible sex differences in how the long-term effects manifest. Surprisingly few studies have examined the intergenerational effects of early development on survival and reproduction in humans. However, some recent evidence suggests that such downstream effects might play an important role in shaping the reproductive success across generations.

In humans in seasonal environments, the month in which females are born affects their own lifespan [d] and lifetime reproductive success, as well as the fertility (number of lifetime live births) of their daughters (V. Lummaa and M. Tremblay, unpublished). A mother's own weight at birth is related to her weight gain during pregnancy and to her offspring's birth weight, gestational duration, the need for neonatal intensive care and early mortality [e,f]. The downstream effects of starvation events on offspring birth weight and survival can also last over generations. The Dutch famine (1944–1945) was a war-induced starvation that caused food availability to decrease from 1600 kcal day^{-1} to <1000 kcal day^{-1}. The famine led to a sharp decrease in weight gain among women who were pregnant at the time, causing reductions in their infant's birth weight [g]. Women fertilized during the famine had offspring with considerably smaller birth weight and length than did women fertilized before or after the famine (Fig. I). The second generation of babies born after the famine also had reduced survival (Fig. II). Women whose mothers were exposed to famine, especially during the last trimester of their pregnancy, were also at greater risk of losing their own offspring shortly after birth [h].

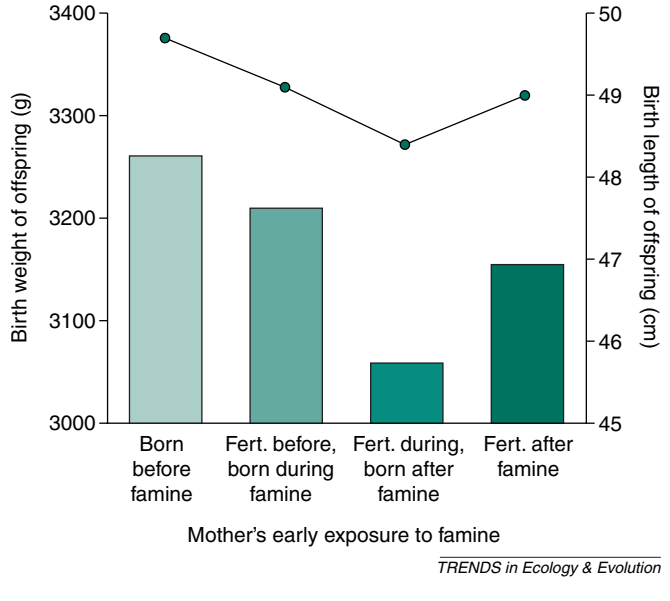

Fig. I. Effects of the Dutch famine for the second generation of offspring born to women whose mothers experienced the famine whilst pregnant. Offspring birth weight (columns) and birth length (line) are shown for offspring according to their mother's early exposure to famine. Women fertilized during the famine were exposed to malnutrition during the second and third trimesters of gestation; mothers exposed only during the first trimester did not show reductions in their offspring size and are not shown here. Data taken from Ref. [g].

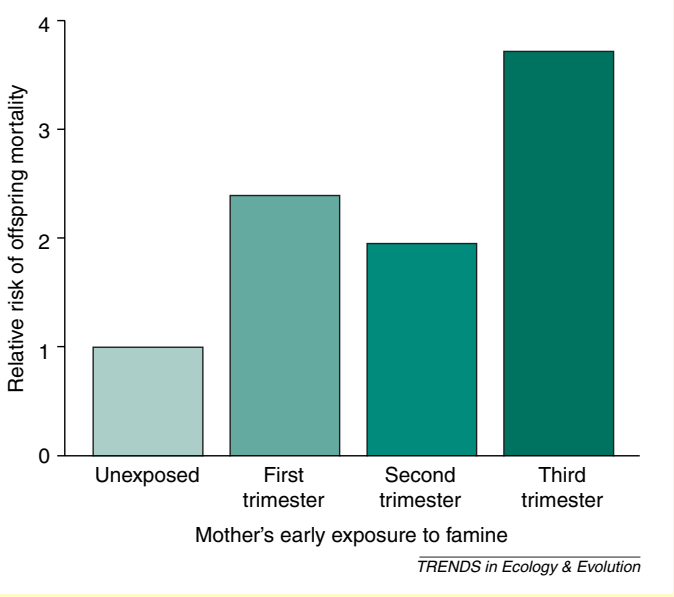

Fig. II. The relative risk of perinatal death (stillbirths and deaths within seven days of delivery) in unexposed controls and in offspring whose grandmother was exposed to famine during first, second or third trimesters of pregnancy. Data taken from Ref. [g].

The mechanism for why women with reduced early growth should themselves produce small babies is likely to be only partially heritable, for even identical twins can differ dramatically in their birth weight [i]. Future studies need to unravel the mechanism for the intergenerational correlations detected for reproductive outcome in humans and other mammals.

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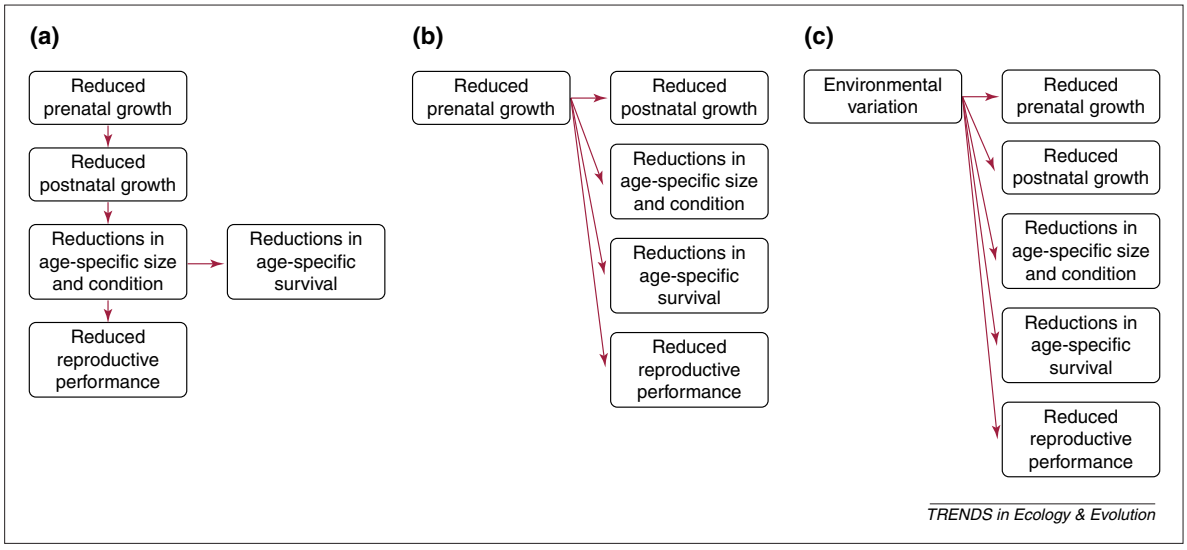

Fig. 2. Three examples of the causal mechanisms of how correlations between early conditions, growth and subsequent survival and reproduction can arise. (a) Reductions in early growth rates exert causal effects on subsequent growth and age-specific size, which, in turn, influence survival and reproductive performance. (b) Variation in prenatal growth exerts independent effects on subsequent growth, survival and reproductive performance. (c) Environmental factors generating variation in prenatal growth rates have independent effects on subsequent growth, survival and breeding success.

The causes of long-term effects of early development

Although the existence of correlations between early growth and subsequent fitness is now well established, the causes are still largely unknown. It is commonly assumed in studies of wild mammals that reductions in early growth rates exert causal effects on subsequent growth and age-specific size, which, in turn, influence survival and reproductive performance (Fig. 2a). However, there are many other possibilities [6]. Variation in prenatal growth might independently affect subsequent growth, survival and reproductive performance (Fig. 2b). Alternatively, environmental factors might have independent effects on growth, survival and breeding success (Fig. 2c). Between these extremes lies a wide range of possible interactions, including a mixture of dependent and independent effects.

Our understanding of the causation of sex differences in the effects of early development is equally limited. Although these differences are commonly attributed to sex differences in growth, and the available evidence suggests that they are most pronounced in mammals showing strong sexual dimorphism, they are slight or absent in some dimorphic species and occur in some monomorphic ones [1]. Alternative potential factors that might be involved include sex differences in: metabolic rates independent of size [41]; immune response and parasitic load (K. Wilson, *et al*. unpublished); and age-specific expenditure on reproductive behaviour or secondary sexual characteristics [42].

Rather more is known about the mechanisms underlying the downstream effects of early development in humans. As in animals (Fig. 2), some correlations might be a consequence of correlated environmental parameters rather than causal relationships. For example, because the final size at birth in humans is determined by maternal body size and the growth and nutrition of the mother throughout her life, size at birth tends to be correlated with maternal family history and level of parental education – the least-educated and poorest mothers commonly give birth to the smallest babies, even in industrialized countries [43]. Family background, such as education and income, might, in turn, influence survival and reproductive patterns of the offspring, for example via shaping risk factors (e.g. diet or smoking) for chronic diseases, thus generating correlations between birth weight, later survival and reproductive success. Many studies have controlled for such socioeconomic factors of the mothers at adulthood but only a few have done so at the time of their birth. Future studies controlling for early family circumstances and growth environment of individuals born with differing size and/or early nutrition are therefore needed to clarify the mechanism for the detected downstream effects of birth weight in human populations. Encouragingly, some studies of wild mammals that have controlled statistically for potential confounding variables around the time of birth have found associations between birth weight and future breeding success [6–8], and experiments confirm these causal relationships [11].

In some cases, early development might influence some measure of physiological performance that subsequently affects survival and breeding success. For example, early development might affect the development of the immune system and this, rather than growth itself, might affect survival and breeding success in adulthood. There is evidence that adverse factors that impair foetal growth can also hinder immunological maturation so that infants small for their age show atrophy of the thymus and impairment of cell-mediated immunity for years after birth [44]. Consequently, small offspring tend to suffer from increased infection and mortality rates.

Alternatively, early development might exert direct effects on subsequent growth, development and ultimate fitness. One possibility, known as foetal programming, is that the lifelong effects of birth weight occur because some stimulus or insult during a crucial period of early life has permanent effects later in life [45]. Such stimuli or insults can permanently affect

body structure, physiology and metabolism through reduction in cell numbers, changes in the distribution of cell types and in organ structure, and the resetting of hormonal feedback and metabolic activity [46]. This hypothesis proposes that the foetus might monitor its environment and set growth projections according to nutrient availability. Therefore, there would be a reaction norm with a range of adult phenotypes produced by a single infant genotype according to the early environmental conditions it is subjected to. In an environment with poor nutrient supply, for instance, it would be advantageous to be small. Offspring with placental insufficiency or impaired nutrition might 'interpret' their environment as being nutrient poor and, perhaps irreversibly, set themselves up for shorter stature. Although the changes occurring [46] are beneficial to survival under poor nutritional conditions, low birth-weight individuals who have possibly adapted to low supplies of resources, and who later experience plentiful conditions, might suffer the greatest downstream effects of a poor early start [47] (so-called 'catch-up growth', reviewed in [3]). The exact mechanism for the metabolic imprinting is unknown, but results from animal studies and preliminary human evidence suggest that adverse events in early life might influence the neuroendocrine development of the foetus (reviewed in [29]). One possible candidate system at the level of cells and genes that could mediate the ecological, physiological and evolutionary effects of early growth into adulthood is the insulin-dependent signalling pathway.

However, a genetically determined signalling pathway that influences both birth weight and health in adult life could also explain the correlations between early growth and later life events. It has been proposed that insulin-mediated foetal growth could be affected by foetal genetic factors that regulate either foetal insulin secretion or the sensitivity of foetal tissues to the effects of insulin [48]. Consequently, low birth weight, measures of insulin resistance in adulthood, and diabetes and hypertension (and diseases caused by them) could all be products of the same insulin-resistant genotype [48]. Evidence that at least some of the detected later-life consequences of birth weight are caused by such genetic factors come from studies comparing the birth weight within monozygotic and dizygotic twins where only the other twin develops a disease in adulthood. Findings from such studies suggest that, in dizygotic twins, it is the smaller twin that commonly develops chronic disease in adulthood [49]. In monozygotic twins, who not only share the same early maternal and socioeconomic circumstances but also the same genes, the likelihood of having chronic adulthood conditions associated with early growth is not linked to being the smaller twin in a pair [49]. Such twin studies have provided the best opportunities to control for the many confounding family-linked factors common in studies on human subjects and, given the large established twin databases around the world, might provide a very useful future approach.

Prospects

Studies of wild mammals have shown that correlations between early growth and subsequent survival or breeding success can have important implications for population demography and dynamics [2]. For example, where several 'good' or 'bad' cohorts occur in succession as a consequence of stochastic environmental variation, populations can increase or decrease several years later as a result. Such demographic consequences of correlations between early development and subsequent survival or breeding success in humans are still unexplored. Famines could affect birth and death rates in a population decades later, when the cohorts born during the famine mature, leading to unexpected changes in population growth rate or disease patterns. For example, there is some evidence that blood pressure levels in some Western human communities depend partly on the nutritional experience of previous generations of mothers [26]. The greater vulnerability of males to downstream effects of adverse early conditions might lead to sex differences in these consequences, although little is currently known about the extent or importance of such differences.

In addition, as yet, relatively few attempts have been made to explore how early development interacts with other biological and environmental factors that affect survival and breeding success in humans. It is particularly important to explore these effects in human populations that are subject to periodic resource limitation, because studies of animals suggest that it is here that the strongest downstream effects of early development are likely to be found on subsequent reproduction and survival. Furthermore, recent evidence for the importance of catch-up growth in determining the magnitude of downstream effects of poor early growth [3,47] predicts that the delayed effects of early development might play the most important role in those human populations where living conditions are rapidly improving. Studies comparing the long-term effects of food shortages in human populations suggest that such effects are greatest in hitherto and afterwards well-nourished populations as compared with chronically malnourished ones, but studies on animals could shed more light on how and why such patterns emerge. These findings from human populations support the results from studies on some other mammals that show catch-up growth to be a property of domestic animals and non-food-limited wild populations, whereas individuals living in resource-restricted conditions rarely get an opportunity to compensate for a bad start (T.H. Clutton-Brock, unpublished). The challenge for future research is to understand how breeding decisions and lifetime reproductive success across generations are shaped by early environmental conditions in humans, and whether growth and reproduction of males and females respond differently to early stress, as studies of other mammals suggest.

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