Chapter 6
The Developmental Origins of Health and Disease: Adaptation Reconsidered

Ian J. Rickard, Ph.D.

Lay Summary The conditions that a foetus experiences in the womb leave their mark on that individual as they grow, and stay with it for its entire life. Evolutionary biologists study similar kinds of effects in animals. They think that the understanding of what the developing body does when it experiences something harmful, such as a reduction in nutrients, can be helped with evolutionary theory. Some argue that a foetus treats such harmful experiences as a forecast of what it will experience later in life, and that it prepares itself for that later life experience by changing its biology. However, there are other ways in which evolutionary theory can be used to understand these effects. For example, if a body cannot grow as big as it would ideally, it may need to change its biology to make the best out of the situation. Also, a foetus may need to adjust its growth when its mother is under stress and not able to provide many nutrients. Deciding which of these different possibilities are and are not true is important, because they mean different things for how we understand patterns of health and illness, and how we go about improving population health.

6.1 Introduction

The field of the Developmental Origins of Health and Disease (DOHaD) examines the consequences of early life conditions for health and disease risk [1]. DOHaD has its origins in some early work showing striking geographical correlations between mortality rates in infancy and—decades later—mortality due to coronary

I.J. Rickard (✉)
Department of Anthropology, Durham University, Durham, UK
e-mail: ian.rickard@durham.ac.uk

A. Alvergne et al. (eds.), *Evolutionary Thinking in Medicine*,
Advances in the Evolutionary Analysis of Human Behaviour,
DOI 10.1007/978-3-319-29716-3_6

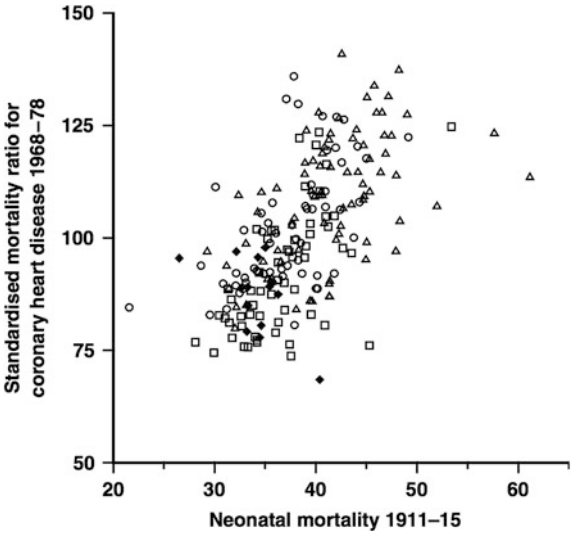

Fig. 6.1 Standardised mortality ratios for coronary heart disease in England and Wales during 1968–79 and neonatal mortality during 1921–25 (*diamonds*—London boroughs; *triangles*—county boroughs; *circles*—urban districts; *squares*—rural districts). Reproduced from Ref. [1]

heart disease (CHD) [2] (see Fig. 6.1). It was subsequently hypothesised that the same environmental conditions that contributed to high infant mortality in a cohort of individuals also caused high rates of CHD in the survivors in their adult life, and specifically that such conditions exerted themselves via intrauterine growth patterns [1]. A prediction generated from this hypothesis was that individuals with lower birthweight are at a greater risk of developing CHD as adults, due to a common role of intrauterine growth restriction in promoting both. This prediction has been supported empirically [3] and extended to other outcomes, including Type II diabetes [4, 5]. Causality of DOHaD effects is typically inferred from studies of animal models [6] and that of cohorts exposed prenatally to famines [7], such as the Dutch hunger winter [8], which experience higher incidences of schizophrenia, diabetes and obesity in adulthood.

Several authors have suggested that applying the theory of evolution by natural selection may improve our understanding of the above patterns [9–13]. This is because natural selection can lead to the evolution of 'developmental plasticity': selection favours genes that cause the developing bodies they are in to actively respond to their environment in such a way that will improve their chances of surviving and leaving behind a large number of descendants (having high evolutionary fitness). We should therefore expect the existence of developmental responses to environmental conditions that cause the body to do better than it would in the absence of such a response. For instance, 'brain sparing' is an apparently adaptive process by which a foetus suffering from placental insufficiency undergoes physiological and anatomical changes that appear to prioritise oxygen supply to the developing central nervous system [14].

The predictive adaptive response (PAR) hypothesis argues that poor growth conditions can be useful as a forecast of later life conditions, and that consequently

humans and other animals have evolved to adaptively change their phenotype in accordance with this information [9]. In particular, it is argued that poor intrauterine growth can be taken to indicate a low-nutrition environment, to which the foetus adapts by altering its insulin–glucose metabolism in such a way that would facilitate survival under nutritionally poor adulthood conditions. However, in the rapidly changing environments of industrialised societies over the course of the twentieth and twenty-first centuries, such forecasts have frequently been incorrect, leading to type II diabetes and cardiovascular diseases as well as other pathologies in later life [9].

Both the DOHaD and the PAR hypotheses hold implications for understanding patterns of health and disease, and which avenues for intervention might be usefully explored. If the first nine months of life, or those immediately preceding it, are of critical importance in determining later health, then it may be opportune to intervene during this period [15–18]. If the PAR hypothesis is correct, then we may infer that once the relevant mechanisms have been identified, it might be possible to change the predictive information that the foetus receives and thus improve its lifelong chances (e.g. through preventing altered insulin–glucose metabolism in individuals with intrauterine growth restriction). However, this requires critical evaluation.

In this chapter, I consider how an understanding of developmental plasticity (beginning with the PAR hypothesis) may be employed so as to understand relationships between early life environment and later life health outcomes. In 'Research Findings', I first evaluate evidence from a range of adjacent biological and biomedical fields that may be brought to bear in order to answer the question of whether developmentally plastic processes may be disrupted to therapeutic benefit, and highlight how much of this evidence points the way to accounts of developmental plasticity that differ significantly from the account given by the PAR hypothesis. In 'Implications for Policy and Practice', I point out how these different accounts are correspondingly associated with different implications for interpretations of patterns of health and disease. Finally, in 'Future Directions', I discuss some avenues of investigation that this alternative perspective suggests would be worthy of attention.

6.2 Research Findings

Beginning from the premise that adaptive developmental plasticity, here I critically evaluate what is arguably the dominant hypothesis that is used to account for DOHaD effects, the PAR hypothesis, as well as consider alternative adaptive perspectives.

6.2.1 Did Environmental Matching Select for Developmental Plasticity in Humans?

The PAR hypothesis gives rise to the clear prediction that the fitness of an individual will generally be higher when the environment it experiences as an adult

matches that which it experienced through the maternal environment during gestation. As a rule, developmental adversity such as poor nutrition tends to permanent damage, or constrain, a body's ability to function optimally in later life [19–24], but it is nonetheless possible that adversity could also simultaneously act as a forecast of the external environment as well as being a constraint [25], allowing individuals to prepare for what is to come. A recent meta-analysis of the fitness benefits of environmental matching across a range of animal and plant species concluded that evidence for it is weak; in other words, individuals experiencing poor early conditions were not better able to later cope with such environments in later life [26]. Furthermore, the fact that a long time period in between development and adulthood increases the potential for the environment to change in the interim reduces the likelihood of beneficial matches occurring. It is therefore of particular importance that such evidence appears thus far absent for animals that are long-lived such as humans [27–29].

A further reason why PARs may be argued to be even more unlikely to be found in humans becomes apparent when we consider the reproductive ecology of humans in a comparative context. We should expect that the effects of the environment on developing offspring would differ dramatically between species according to the extent to which maternal reserves are called upon during reproduction. Rodents, from which comes most of the experimental evidence for DOHaD effects, are 'income breeders', meaning that foetal growth is largely dependent on resources that are consumed during the period of gestation [30]. On the other hand, human foetal growth is heavily reliant on accumulated reserves (capital). As a result, while rodent foetuses are inevitably greatly affected by variation in maternal nutrient consumption during gestation, the human foetus is relatively buffered from such short-term variation [31].

In fact, on close examination, the evidence for changes in maternal nutrition during pregnancy affecting offspring health outcomes does not appear to be particularly strong. Studies of cohorts that were in gestation during famine conditions certainly demonstrate 'proof of concept', i.e. that external nutritional conditions probably do have some effect on later life health outcomes [7]. However, their relevance to understanding relationships between birthweight and adult disease may be too easily overstated, as such extreme conditions are rarely likely to be analogous to the same external influences that give rise to the normal range of birth weights in non-famine conditions. Experimentally, while dietary restriction of pregnant animals can have dramatic effects on offspring phenotype [6], long-term follow-up of the offspring of Gambian, Bangladeshi and British South Asian women given protein-energy or micronutrient supplementation during pregnancy suggests few effects on offspring health outcomes measured in childhood [32–35]. There are thus good theoretical and empirical reasons why we might consider whether maternal factors set in motion long before pregnancy could be more relevant to long-term health than those acting during pregnancy itself. This would make it seem unreasonable to expect that environmental matching via maternal nutrition during pregnancy has been a significant force shaping developmental plasticity in the evolutionary history of humans and human ancestors.

6.2.2 *Reconsidering the 'Environment' that Selects for Developmental Plasticity*

How then, in the absence of selection by matching/mismatching, can the responses of developing individuals to adverse environments be understood? The answer may lie in re-evaluating the premises of the question. Our understanding of developmental plasticity can be limited when we consider the process of selection as something that emerges from a dichotomy between the individual organism and the 'environment' in which it lives (e.g. the physical landscape, the elements of heat and water, the prospects of either eating or being eaten). We may consider the process more inclusively by recognising that selection acts on genes, through their trait products that emergently form cells, tissues, systems, and individuals, and that the 'environment' is simply the context in which that selection takes place. Thus, life is organised hierarchically, and at each level of this hierarchy, the ability of each unit to do its job is dependent on characteristics of other units. One of the best-studied animal models in this context is the mouse mandible, in which bone, muscle and teeth are integrated together into a 'functional complex' [36]. The different components work together to influence the organism's fitness, with a change in the character of one component ideally requiring a change in the character of the others, in order to maintain function. At this level, the phenomenon is known as 'phenotypic integration' [37].

Considering this changes how we look at developmental plasticity. In this light, we may explain many changes within the body as being necessary to maintain overall function when one or more other traits are influenced by external factors. For instance, in DOHaD animal model research, maternal dietary restriction leads to not only altered glucose–insulin metabolism, but also: reduced pancreatic beta cell function [38], reduced hepatic gluconeogenesis [39], altered intestinal enzyme activity [40], a tendency to lay down visceral adipose tissue [41] and increased dietary preference for fatty food [42]. It is possible that such traits facilitate matching between early and late life environment when the environment is nutrition-poor, in accordance with the PAR hypothesis. Alternatively, it is also possible that such traits are in fact optimal in any later environment for an individual whose fitness potential is constrained by their poor start in life. Because the negative effects of poor nutrition in early life are inevitable, some features of the eventual adult body (e.g. skeletal size) can be predicted accurately (see Box: Internal Prediction). Thus, whereas the PAR hypothesis proposes that the aforementioned traits develop in order to facilitate the adaptation of the individual to its environment, the alternative is that such traits develop in order to facilitate adaptation to itself.

Equivalents to phenotypic integration may be observed at other levels of the organisational hierarchy. The foetus experiences its world not directly, but entirely through the prism of the maternal environment. In addition, acting as a buffer between the foetus and the wider environment, the maternal environment also constitutes a powerful selective force, leading to co-adaptation between foetal

growth and maternal provisioning [31]. This co-adaptation is mediated by the placenta, which matches foetal growth with maternal nutrient supply through actively regulating its growth, nutrient transport to the foetus and maternal physiology itself [43]. This dynamic materno-foetal complex must be functionally integrated and responsive to the constraints of the maternal resource base. Maternal endocrine factors act as signals of those constraints [44] and may therefore facilitate adaptation to (integration with) them. Phenotypic integration across diverse and remote tissues and systems is also likely to be controlled by endocrine factors at the within-individual level [45].

6.3 Implications for Policy and Practice

The point of introducing a new theoretical framework to account for natural processes is not merely an intellectual exercise in conjecture. If evolutionary theory is to have any significance for understanding and predicting patterns of health and well-being, then different evolutionary hypotheses should carry different implications for how societies should think about these issues. In this penultimate section, I outline three implications of the preceding arguments that suggest themselves as being of particular importance.

6.3.1 Maternal Diet During Pregnancy Itself May Have Relatively Little Impact on Offspring Health

The PAR hypothesis proposes that environmental matching between the prenatal environment and the postnatal environment determines health, the corollary being that intervention during or before pregnancy may provide a useful avenue for intervention. However, as argued here, the maternal environment is not restricted to what a woman's body does and experiences from the time of conception onwards, nor even by her adult health and behaviour in general, but by the sum of the environmental experiences that she has had up until that point, including her own experience in the womb [31]. Thus, it is likely that any environmental conditions that are responsible for the relationship between birthweight and health in non-famine conditions largely exert themselves through the mother's body long before conception. As we have seen, there is little evidence that even in developing countries, changes to maternal diet during pregnancy have beneficial effects on offspring health outcomes. Clearly, public health interventions to encourage the consumption of balanced diets in new mothers should be pursued where effective, since the consequences of these can potentially extend far beyond pregnancy. However, rather than 'blaming the mothers' [46] we should expect that a more effective way of improving the lifelong health of newborns would be to ensure the health and well-being of their mothers while they themselves are still growing.

6.3.2 Endocrine Signal Disruption May Not Be a Useful Avenue for Intervention

Other than altering maternal diet during or before pregnancy, another mode of intervention that the PAR hypothesis suggests is alteration of endocrine signalling in order to prevent development of particular traits harmful to health later in life. For example, signalling via leptin, produced by fat cells, is a prospect much discussed in the context of interventions to improve offspring health, due to its important role in programming the metabolic profile of individuals with poor intrauterine growth [18, 47]. However, if natural selection has shaped developmental plasticity in order that an individual's phenotype may be well integrated, then their overall function may be compromised if a therapeutic intervention then disrupts this integration. Recent work on leptin programming in rats favours the rejection of the hypothesis that postnatal administration of leptin can be used to reverse the metabolic consequences of intrauterine growth restriction [48]. Instead, the effects of postnatal leptin may depend on a highly complex interaction between leptin, the degree of growth restriction and the sex of the individual. This complexity might be intelligible if rather than providing information about the nutritional state of the environment, as has been proposed [47], leptin levels were considered to be providing internal information about the animal's phenotype, e.g. level of nutritional reserves. Therapeutic administration of leptin could lead to a disintegrated phenotype, with unpredictable and potentially adverse consequences as a result.

6.3.3 DOHaD Effects May Be Properly Situated Within the Wider Sphere of the Social Determinants of Health

That there are relationships between the early life environment and later life health outcomes is very clear, and despite pleiotropic effects of some alleles on both intrauterine growth and later health outcomes [49], this must be in part ultimately due to the wider environment. Given the arguments above about problems with nutritional intervention and endocrine single disruption, we may ask how we might usefully intervene along this pathway. This leads to the question of what are the major determinants of women's health that could lead to both early life outcomes such as low birthweight and high infant mortality risk (Fig. 6.1) and adverse later life health outcomes, and the hypothesis that intergenerational social determinants of health are what are primarily responsible. Arguing against this, meta-analyses of the relationships between birthweight and Type II diabetes and coronary heart disease have found that they did not change after adjustment for socioeconomic status [4, 5]. However, as the authors of these studies discuss, there are numerous limitations inherent in attempts to adjust for socioeconomic status [50, 51] and this crudity will be exacerbated if the process by which the social determinants of health

begin to come into play occur decades before an individual is even born. An analogy may be found in the existence of both lower birthweight and increased adverse life health outcomes in African Americans compared with European Americans, which is not accounted for after adjustment for socioeconomic status [52, 53]. That such differences are not observed between non-American Africans and European Americans suggests that social structural factors engender long-run aspects of the experience of being African American that are not captured by conventional socioeconomic status measures [54]. This raises the prospect that, beyond the social construct of race, there are also deeply ingrained multigenerational social determinants of health that may affect socially stratified societies broadly, but be elusive currently.

6.4 Future Directions

The PAR hypothesis may be argued to have advanced the cause of population health by articulating to non-evolutionary scientists the value of the predictive framework that evolutionary theory provides. However, there are theoretical and empirical objections to this specific adaptive explanation for human developmental plasticity. I have argued for the value of exploring alternative explanations, and the particular value of reconsidering what kind of adaptation might be driving such plasticity. As highlighted in the previous section, the kind of adaptation that has driven the evolution of developmental plastic processes holds implications for interpretation of patterns of health and disease, as well as which kinds of interventions might ultimately be effective in improving health and well-being. I conclude by suggesting some future research directions that can be used to help answer these questions.

6.4.1 Experimental and Population Studies of Phenotypic Integration

As selection for developmental plasticity acts upon combinations of traits, the limitations of studying small numbers of traits at a time is very clear. There would thus seem to be potential for DOHaD researchers to interact with those studying phenotypic integration. Placing the PAR hypothesis within the framework of this field leads to the very general, but strong, prediction that environmental, developmental and functional patterns of trait integration will correspond closely to one another [37]. This can be studied experimentally—a recent study manipulated the consistency of food received by mice and found that those raised on a hard (versus soft) diet had adaptively altered mandible shape and biomechanical profile, implicating an integrated pattern of developmental plasticity across a number of different, functionally related tissues [55]. Such work shows how taking a

multi-trait and even multi-system approach can enrich understanding of the function of trait plasticity, although caution needs to be exercised in extrapolating too readily between animal models and humans, for reasons outlined in this chapter. Although experimental control cannot be employed easily in human studies, large multi-trait databases (e.g. such as those held by the Danish National Patient Registry [56]) may be analysed to infer the adaptive value of different combinations of traits. One explanation for trait combinations that appear more frequently than would be expected by chance is that such combinations are beneficial for the overall function of the organism [57]. The relationships between traits combination and function/health can also be explored directly.

6.4.2 *Glucocorticoids as Intergenerational Transducers of Social Determinants of Health*

A variety of laboratory treatments of pregnant animals (caloric restriction, protein restriction, iron restriction, fat-feeding, stressors) give rise to similar phenotypic consequences in adult offspring, suggesting a role for common causal pathways [18]. Glucocorticoid (in humans, cortisol) signalling has been implicated in this respect, thus marking it as having a special role in foetal programming, mediating effects not only of nutrient insufficiency, but also other adverse environmental conditions [58, 59]. Glucocorticoids act partially via the placenta through changes in amino acid transport [43] although excess maternal glucocorticoids can bypass the placental barrier [59]. Thus, activation of the maternal stress response system (e.g. through psychosocial stress) can directly affect foetal growth. One study of pregnant German women found that maternal cortisol levels accounted for as much as 19.8 % of the variance in birthweight, after controlling for confounders [60].

From an adaptive perspective, this fits within the wider picture of the functional role of glucocorticoids. In general, glucocorticoid activity serves the adaptive function of temporarily allocating resources away from non-essential activities towards those that are more important in the short term. To the placenta and foetus, high levels of glucocorticoids may act as an internal signal of the short-term level of available circulating resources. Downregulation of foetal growth rate in response to high levels of glucocorticoids can therefore be understood as part of an adaptive strategy. However, if mothers are chronically stressed, then the consequences for the foetus of doing so may be pathological. The experiences of chronic psychosocial stress and ill health are intimately entwined with one another [61]. Individuals with low birthweight have altered cortisol profiles as adults [59], raising the possibility that glucocorticoid transfer from mother to foetus could constitute a major mechanism by which the social determinants of health are transmitted more than two generations. This possibility that the maternal stress response is a major mediator of DOHaD effects hints at opportunities for intervention to improve lifelong health and well-being through social, rather than nutritional or pharmacological intervention.

6.5 Conclusion

Recourse to evolutionary accounts for DOHaD effects may be due to the insufficiency of explanatory models that rely primarily on mechanism and pathology. In this chapter, I have discussed what is arguably the dominant evolutionary explanation employed in this respect, detailed some problems with it, and provided some guidelines for expanding the way DOHaD researchers think about adaptation. I have also argued that these considerations have very real implications for how we think about and understand health and well-being. Thus, when considering the evolutionary story behind DOHaD effects, researchers, policy makers and practitioners should always keep an open mind about the nature of adaptation.

Box 6.1 Internal Prediction

Predicting the future is a tricky business. It may be argued that the more time that elapses between development and adulthood, the more likely it is that the environment will change, and therefore, the more likely that any prediction made about the environment will be invalid by the time an organism reaches adulthood [10–13]. Such individuals will be 'mismatched' to their environment, and run a greater risk of losing out in the evolutionary game of survival and reproduction. However, if we relax our expectations about what constitutes 'the environment', specifically so that it includes internal factors, then the prospect of accurate prediction becomes a lot more realistic [62]. As we might expect, it is reliably the case that adversity in early life compromises the ability of an organism to function well in later life [19–24], e.g. through lower nutrition during development leading to smaller adult size. Therefore, early adversity has predictable consequences for the individual's internal environment. These internal characteristics partially constitute the selective pressures to which developing individuals should adapt. We should therefore expect that natural selection will act on (will have acted on) developmentally plastic processes that facilitate this. Unlike when it requires a match between the individual organism and the external environment, and when developmental plasticity requires co-adaptation between traits, mismatches are prevented. In the parasitoid wasp *Aphaerta genevensis*, experimentally inducing small body size through food restriction limits reproductive potential and causes individuals to change their reproductive scheduling accordingly [63]. In many species, individuals develop profoundly different physical characteristics depending on internal traits [64]. We may ask, does a trait that emerges a consequence of poor foetal growth facilitate the adaptation of an individual to its external environment, or does it instead adapted to its internal environment?

Acknowledgments I thank the editors and members of the Evolutionary Anthropology Research Group and the Anthropology of Health Research Group in the Department of Anthropology at Durham University.

References

1. Barker DJP (2007) The origins of the developmental origins theory. J Intern Med 261:412–417. doi:10.1111/j.1365-2796.2007.01809.x
2. Barker DJP, Osmond C (1986) Infant mortality, childhood nutrition, and ischaemic heart disease in England and Wales. Lancet 327:1077–1081. doi:10.1016/S0140-6736(86)91340-1
3. Huxley R, Owen CG, Whincup PH et al (2007) Is birth weight a risk factor for ischemic heart disease in later life? Am J Clin Nutr 85:1244–1250
4. Harder T, Rodekamp E, Schellong K et al (2007) Birth weight and subsequent risk of type 2 diabetes: a meta-analysis. Am J Epidemiol 165:849–857. doi:10.1093/aje/kwk071
5. Whincup PH, Kaye SJ, Owen CG et al (2008) Birth weight and risk of type 2 diabetes: a systematic review. JAMA-J Am Med Assoc 300:2886–2897. doi:10.1001/jama.2008.886
6. Bertram CE, Hanson MA (2001) Animal models and programming of the metabolic syndrome. Brit Med Bull 60:103–121. doi:10.1093/bmb/60.1.103
7. Lumey LH, Stein AD, Susser E (2011) Prenatal famine and adult health. Annu Rev Public Health 32:237–262. doi:10.1146/annurev-publhealth-031210-101230
8. Roseboom TJ, Painter RC, van Abeelen AFM et al (2011) Hungry in the womb: What are the consequences? Lessons from the Dutch famine. Maturitas 70:141–145. doi:10.1016/j.maturitas.2011.06.017
9. Bateson P, Gluckman PD, Hanson M (2014) The biology of developmental plasticity and the Predictive Adaptive Response hypothesis. J Physiol-London 592:2357–2368. doi:10.1113/jphysiol.2014.271460
10. Jones JH (2004) Fetal programming: adaptive life-history tactics or making the best of a bad start? Am J Hum Biol 17:22–33. doi:10.1002/ajhb.20099
11. Kuzawa CW, Quinn EA (2009) Developmental origins of adult function and health: evolutionary hypotheses. Annu Rev Anthropol 38:131–147. doi:10.1146/annurev-anthro-091908-164350
12. Rickard IJ, Lummaa V (2007) The predictive adaptive response and metabolic syndrome: challenges for the hypothesis. Trends Endocrinol Metab 18:94–99. doi:10.1016/j.tem.2007.02.004
13. Wells JCK (2003) The thrifty phenotype hypothesis: thrifty offspring or thrifty mother? J Theor Biol 221:143–161. doi:10.1006/jtbi.2003.3183
14. Baschat DAA (2004) Fetal responses to placental insufficiency: an update. BJOG-Int J Obstet Gy 111:1031–1041. doi:10.1111/j.1471-0528.2004.00273.x
15. Gluckman PD, Hanson MA (2008) Developmental and epigenetic pathways to obesity: an evolutionary-developmental perspective. Int J Obes 32(Suppl 7):S62–S71. doi:10.1038/ijo.2008.240
16. Gluckman PD, Hanson M, Zimmet P, Forrester T (2011) Losing the war against obesity: the need for a developmental perspective. Sci Transl Med 3:1–4. doi:10.1126/scitranslmed.3002554
17. Hanson MA, Gluckman PD, Ma RC et al (2012) Early life opportunities for prevention of diabetes in low and middle income countries. BMC Public Health 12:1025. doi:10.1017/S0029665112000055
18. Vickers MH (2011) Developmental programming of the metabolic syndrome—critical windows for intervention. World J Diabetes 2:137–148. doi:10.4239/wjd.v2.i9.137

19. Doblhammer G, van den Berg GJ, Lumey LH (2013) A re-analysis of the long-term effects on life expectancy of the Great Finnish Famine of 1866–68. Pop Stud-J Demog 67:309–322. doi:10.1080/00324728.2013.809140
20. Ekamper P, van Poppel F, Stein AD, Lumey LH (2014) Independent and additive association of prenatal famine exposure and intermediary life conditions with adult mortality between age 18–63 years. Soc Sci Med 232–239. doi:10.1016/j.socscimed.2013.10.027
21. Rickard IJ, Holopainen J, Helama S et al (2010) Food availability at birth limited reproductive success in historical humans. Ecology 91:3515–3525. doi:10.1890/10-0019.1
22. Song S (2010) Mortality consequences of the 1959–1961 Great Leap Forward famine in China: debilitation, selection, and mortality crossovers. Soc Sci Med 71:551–558. doi:10.1016/j.socscimed.2010.04.034
23. van Abeelen AF, Veenendaal MV, Painter RC et al (2011) Survival effects of prenatal famine exposure. Am J Clin Nutr 95:179–183. doi:10.3945/ajcn.111.022038
24. van den Berg GJ, Lindeboom M, Portrait F (2013) The Dutch Potato Famine 1846–1847: a study on the relationships between early-life exposure and later-life mortality. In: Lumey LH, Vaiserman A (eds) Early Life Nutrition and Adult Health Development. Nova Science Publishers, New York, pp 229–249
25. Monaghan P (2008) Early growth conditions, phenotypic development and environmental change. Philos Trans R Soc Lond B Biol Sci 363:1635–1645. doi:10.1016/j.biopsycho.2006.01.009
26. Uller T, Nakagawa S, English S (2013) Weak evidence for anticipatory parental effects in plants and animals. J Evol Biol 26:2161–2170. doi:10.1111/jeb.12212
27. Douhard M, Plard F, Gaillard JM et al (2014) Fitness consequences of environmental conditions at different life stages in a long-lived vertebrate. P Roy Soci B-Biol Sci 281:20140276. doi:10.1530/eje.1.02233
28. Hayward A, Rickard IJ, Lummaa V (2013) Influence of early-life nutrition on mortality and reproductive success during a subsequent famine in a pre-industrial population. P Natl Acad Sci USA 110:13886–13891. doi:10.1073/pnas.1301817110
29. Hayward A, Lummaa V (2013) Testing the evolutionary basis of the predictive adaptive response hypothesis in a preindustrial human population. Evolution 106–117. doi:10.1093/emph/eot007
30. Drent RH, Daan S (1980) The prudent parent: energetic adjustments in avian breeding. Ardea 68:225–252
31. Wells JCK (2010) Maternal capital and the metabolic ghetto: an evolutionary perspective on the transgenerational basis of health inequalities. Am J Hum Biol 22:1–17. doi:10.1002/ajhb.20994
32. Hawkesworth S, Prentice AM, Fulford AJ, Moore SE (2009) Maternal protein-energy supplementation does not affect adolescent blood pressure in The Gambia. Int J Epidemiol 38:119–127. doi:10.1093/ije/dyn156
33. Hawkesworth S, Walker CG, Sawo Y et al (2011) Nutritional supplementation during pregnancy and offspring cardiovascular disease risk in The Gambia. Am J Clin Nutr 94:1853S–1860S. doi:10.3945/ajcn.110.000877
34. Hawkesworth S, Wagatsuma Y, Kahn AI et al (2013) Combined food and micronutrient supplements during pregnancy have limited impact on child blood pressure and kidney function in rural Bangladesh. J Nutr 143:728–734. doi:10.3945/jn.112.168518
35. Macleod J, Tang L, Hobbs FDR et al (2013) Effects of nutritional supplementation during pregnancy on early adult disease risk: follow up of offspring of participants in a randomised controlled trial investigating effects of supplementation on infant birth weight. PLoS ONE 8:e83371. doi:10.1371/journal.pone.0083371.s001
36. Zelditch ML, Wood AR, Bonett RM, Swiderski DL (2008) Modularity of the rodent mandible: integrating bones, muscles, and teeth. Evol Dev 10:756–768. doi:10.1111/j.1525-142X.2008.00290.x

37. Klingenberg CP (2014) Studying morphological integration and modularity at multiple levels: concepts and analysis. Philos Trans R Soc Lond B Biol Sci 369:20130249. doi:10.1111/j.1558-5646.2009.00857.x
38. Petrik J, Reusens B, Arany E et al (1999) A low protein diet alters the balance of islet cell replication and apoptosis in the fetal and neonatal rat and is associated with a reduced pancreatic expression of insulin-like growth factor-II. Endocrinology 140:4861–4873. doi:10.1210/endo.140.10.7042
39. Burns SP, Desai M, Cohen RD et al (1997) Gluconeogenesis, glucose handling, and structural changes in livers of the adult offspring of rats partially deprived of protein during pregnancy and lactation. J Clin Invest 100:1768
40. Pinheiro DF, Pacheco PDG, Alvarenga PV et al (2013) Maternal protein restriction affects gene expression and enzyme activity of intestinal disaccharidases in adult rat offspring. Braz J Med Biol Res 46:287–292. doi:10.1590/1414-431X20122561
41. Guan H (2004) Adipose tissue gene expression profiling reveals distinct molecular pathways that define visceral adiposity in offspring of maternal protein-restricted rats. Am J Physiol-Endoc M 288:E663–E673. doi:10.1152/ajpendo.00461.2004
42. Bellinger L, Lilley C, Langley-Evans SC (2007) Prenatal exposure to a maternal low-protein diet programmes a preference for high-fat foods in the young adult rat. Brit J Nutr 92:513. doi:10.1079/BJN20041224
43. Díaz P, Powell TL, Jansson T (2014) The role of placental nutrient sensing in maternal-fetal resource allocation. Biol Reprod 91:82. doi:10.1095/biolreprod.114.121798
44. Fowden AL, Forhead AJ (2009) Hormones as epigenetic signals in developmental programming. Exp Physiol 94:607–625. doi:10.1113/expphysiol.2008.046359
45. Lancaster LT, McAdam AG, Sinervo B (2010) Maternal adjustment of egg size organizes alternative escape behaviour, promoting adaptive phenotypic integration. Evolution 64:1607–1621. doi:10.1111/j.1558-5646.2009.00941.x
46. Richardson SS, Daniels CR, Gillman MW et al (2014) Society: don't blame the mothers. Nature 512:131–132. doi:10.1038/512131a
47. Gluckman PD, Lillycrop KA, Vickers MH et al (2007) Metabolic plasticity during mammalian development is directionally dependent on early nutritional status. P Natl Acad Sci USA 104:12796–12800. doi:10.1073/pnas.0705667104
48. Ellis PJI, Morris TJ, Skinner BM et al (2014) Thrifty metabolic programming in rats is induced by both maternal undernutrition and postnatal leptin treatment, but masked in the presence of both: implications for models of developmental programming. BMC Genom 15:49. doi:10.1186/1471-2164-15-49
49. Shields BM, Freathy RM, Hattersley AT (2010) Genetic influences on the association between fetal growth and susceptibility to type 2 diabetes. J Devel Orig Health Dis 1:96. doi:10.1017/S2040174410000127
50. Braveman PA, Cubbin C, Egerter S et al (2005) Socioeconomic status in health research—One size does not fit all. JAMA 294:2879–2888. doi:10.1001/jama.294.22.2879
51. Shavers VL (2007) Measurement of socioeconomic status in health disparities research. J Natl Med Assoc 99:1013–1023
52. Jasienska G (2009) Low birth weight of contemporary African Americans: an intergenerational effect of slavery? Am J Hum Biol 21:16–24. doi:10.1002/ajhb.20824
53. Geronimus AT (2013) Deep integration: Letting the epigenome out of the bottle without losing sight of the structural origins of population health. Am J Public Health 103:S53–S56. doi:10.2105/AJPH.2013.301380
54. Kaufman JS, Cooper RS, McGee DL (1997) Socioeconomic status and health in blacks and whites: the problem of residual confounding and the resiliency of race. Epidemiology 8:621–628
55. Anderson PS, Renaud S, Rayfield EJ (2014) Adaptive plasticity in the mouse mandible. BMC Evol Biol 14:85. doi:10.1186/1471-2148-14-85

56. Hollegaard B, Byars SG, Lykke J, Boomsma JJ (2013) Parent-offspring conflict and the persistence of pregnancy-induced hypertension in modern humans. PLoS ONE 8:e56821. doi:10.1371/journal.pone.0056821
57. Schluter D, Nychka D (1994) Exploring fitness surfaces. Am Nat 143:597–616
58. Cottrell EC, Holmes MC, Livingstone DE et al (2012) Reconciling the nutritional and glucocorticoid hypotheses of fetal programming. Faseb J 26:1866–1874. doi:10.1096/fj.12-203489
59. Reynolds RM (2013) Glucocorticoid excess and the developmental origins of disease: two decades of testing the hypothesis—2012 Curt Richter Award Winner. Psychoneuroendocrino 38:1–11. doi:10.1016/j.psyneuen.2012.08.012
60. Bolten MI, Wurmser H, Buske-Kirschbaum A et al (2011) Cortisol levels in pregnancy as a psychobiological predictor for birth weight. Arch Womens Ment Health 14:33–41. doi:10.1007/s00737-010-0183-1
61. Thoits PA (2010) Stress and health: major findings and policy implications. J Health Soc Behav 51:S41–S53. doi:10.1177/0022146510383499
62. Rickard IJ, Frankenhuis WE, Nettle D (2014) Why are childhood family factors associated with timing of maturation? A role for internal prediction. Perspect Psychol Sci 9:3–15. doi:10.1177/1745691613513467
63. Thorne AD, Pexton JJ, Dytham C, Mayhew PJ (2006) Small body size in an insect shifts development, prior to adult eclosion, towards early reproduction. P Roy Soci B-Biol Sci 273:1099–1103. doi:10.1093/beheco/12.5.577
64. Gross MR (1996) Alternative reproductive strategies and tactics: diversity within sexes. Trends Ecol Evol 11:92–98