Section I

Overview

Chapter 1

Overview and Introduction to the Second Edition of *Developmental Origins of Health and Disease*

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The concept that early life 'exposures' influence lifelong health was not prominent in the twentieth and twenty-first centuries, although a range of earlier studies had introduced the idea. The thalidomide tragedy and the death of the infant son of President John Kennedy gave impetus to much increased research in perinatology. However, it was not until the 1990s that pioneers, including Professor David Barker, provocatively championed the concept that the risk for common diseases may have origins *in utero*. This created world-wide interest and gave rise to the 'fetal programming' or 'Barker hypothesis'. In 2006, when the first edition of this book was published, the fundamental theory was growing in acceptance but the nomenclature was changing. The acronym DOHaD (developmental origins of health and disease), often abbreviated to 'developmental programming', had just replaced FOAD (fetal origins of adult disease) and fetal programming to include windows of early childhood vulnerability and also to refer to the developmental processes underlying determinants of health as well as risk of later chronic disease. Programming was seen as a rather deterministic metaphor for what came to be understood as environmental influences on the mechanisms of development, either disrupting organogenesis or influencing developmental plasticity. The role of developmental plasticity had become a major focus of evolutionary biology, and the discipline of evolutionary medicine had emerged, both with reciprocal influences on understanding human development. Now, in 2022, DOHaD has been further extended to encompass exposures from both mothers and fathers operating during an important 'new' window of vulnerability the weeks, months and years before conception (Chapter 3).

DOHaD-related concepts are seen by many as offering an intuitively logical approach to understanding the precedents of non-communicable disease, and continue to engage the global research community, as these diseases dominate mortality statistics in most regions. In January 2022 approximately 179,000 publications listed on the National Institutes of Health PubMed database included the term 'developmental programming'. The International Society for the Developmental Origins of Health and Disease has also grown and now has nine associated organizations across the globe and ~1,000 members. Synonymous descriptors of DOHaD have evolved and expanded into common use, most notably the 'the Lifecourse of Health'. Worldwide, academic institutions are abandoning disease- and age-specific research 'silos' in favour of a seamless 'lifecourse' coalition to better understand key transitional stages in disease risk and development from early life onwards. Universities in the United Kingdom, United States, Canada, Australia, and Africa, amongst others, have created 'lifecourse' institutes, centres, schools, departments and training courses. A focus on the importance of the 'first 1,000 days of life' has also become popular, perhaps as a more comprehensible DOHaD message for the general public but also as a result of scientific observations about how powerful developmental effects induced at that time can be later.

Although important, yet often confused by the changing nomenclature, the essence of the DOHaD message lies not in a name, but in the strength of the supporting scientific evidence, and its implications for the development of strategies to promote optimal human capital development and prevent common diseases, which must be the ultimate aim. Contributors to this second edition detail major steps in scientific knowledge, but do not evade the challenges – and indeed failures – in the translation of DOHaD research

to interventions that optimize human potential and reduce the population disease burden.

Chapter 2 describes how the DOHaD phenomena are likely to be underpinned by multiple mechanisms, notably including evolutionary and developmental mismatches in the fetal/child's response to exposures in early development. The conceptual basis for such interpretations is underpinned by the premise that natural selection operates to sustain and promote Darwinian fitness, notwithstanding any antagonistic impacts on health during the post-reproductive age. Chapter 3 sets out the experimental evidence contributing to the vulnerable periods of development in relation to lifelong health, highlighting a new focus on the importance of the preconception period, and also the emergent science indicating the important role of paternal health.

There follow descriptions in Chapters 3–9 of how the DOHaD field has expanded in directions dictated by new or worsening global challenges/exposures encountered by the developing child, including climate change and pollution, the increasing global prevalence of maternal obesity and maternal mental health issues as well as by sustained inequalities, for example, in maternal nutrition. The strength of evidence demonstrating relationships between maternal obesity and dysglycaemia and the development of obesity and glucose intolerance in the child gives cause for great concern; whether this results from *in utero* exposure (supported by animal models), interaction between exposure and genetic variation or simply shared maternal and child environment, the key message is that maternal body mass index (BMI) and weight gain are potentially modifiable, and such modifications should be pursued. Similarly, the abundant evidence for relationships between maternal psychosocial health, anxiety and depression and offspring risk of cognitive and behavioural problems, now supported by structural changes in the infant brain, gives alarm but also cause for hope, as in this domain, there is evidence that interventions to improve maternal mental health can benefit that of the child. Chapter 7 describes how ambient air pollution has a devastating effect on lifecourse health, and the particular vulnerabilities of pregnant women and children. Here, it is described how climate change will inevitably increase exposure to air pollution and chemicals, thereby increasing inequities.

A concept relatively new to DOHaD lies in the role of the infant gut microbiome. This, it is proposed, may act as a conduit for exposure–outcome relationships. The infant microbiome is normally acquired at vaginal delivery from the mother and during breast feeding, stabilizing in infancy with little substantial change thereafter. It is suggested that divergence from this normal process of bacterial colonization at birth and during infancy, either directly or through indirect biological pathways, can permanently influence immune function, and thereby the risk of childhood atopic disorders such as asthma (Chapter 8). Here, the authors emphasize that researchers should evaluate not only the phylogenetic composition but also the functional consequence of the changes in the functional gut microbiome community, to better define microbiome pathological pathways, perhaps suggesting ways to develop effective maternal, infant or childhood interventions.

Globally, more than eight million babies have been born by assisted reproductive technologies (ART). Given the evidence that the periconceptional gametes and embryo are particularly sensitive to environmental disturbances, Chapter 9 reviews the increasing literature addressing the variety of ART methods and their relationships to clinical outcomes in children born following ART. The authors conclude that amidst a plethora of confounding factors, no firm conclusions can at present be drawn, but clearly there remain important questions. A similar conclusion was drawn from a literature review of relationships between childhood asthma and adult chronic obstructive respiratory disease, where influences of genetic susceptibility and *in utero* and post-natal exposures proved difficult to disentangle (Chapter 11).

Common themes emerge in defining the probable causal mechanisms contributing to developmental exposure–longer-term outcome relationships. Several authors, whether reporting experimental studies in animal models or investigations in humans, elaborate a mediating role for the epigenome, the suggestion being that persistent epigenetically induced changes in offspring gene expression explain how the early environment can frame the offspring child or adult phenotype. Adjustments to the offspring epigenome have been implicated in the lifelong consequences of poor maternal nutrition (Chapter 4), maternal obesity (Chapter 5), maternal psychosocial stress (Chapter 6), air and chemical pollution (Chapter 7) and *in vitro* fertilization (Chapter 9), as well as in the origins of childhood asthma (Chapter 11) and ageing (Chapter 13). However, the evidence that these are mechanistic rather than associative associations remains rather

limited. The authors of Chapter 15, whilst not dismissive of an epigenetic cause, provide a strong reality check to DOHaD scientists, warning of the need to replicate and validate the many reports implicating the epigenome, and to heed pitfalls in design and interpretation. Three clear messages emerge from this helpful review of epigenetics: that the epigenome encompasses multiple biochemical processes and defines the phenotype of every cell, and is therefore cell type specific; that studies of the epigenome should not be cross sectional but longitudinal and that insights that stand the test of time will emerge only if numbers are adequately large for statistical power. We are also informed that the placenta is remarkably vulnerable to changes in methylation status, being almost globally demethylated, and therefore particularly vulnerable to environmental exposures. Measurement of epigenetic marks may in this instance be less challenging than establishing the functional response to epigenetically driven placental gene expression, as a lack of effective functional methods to assess human placental function are a major hindrance to progress (Chapters 16 and 17).

Structural changes in tissues and organs that occur *in utero* or in early post-natal life can seldom be corrected beyond these critical periods of development, and present some of the most incontrovertible evidence for the early origins of disease. In Chapter 6, we are told of the increasing evidence from magnetic resonance imaging (MRI) demonstrating relationships of maternal stress and mood with aberrant structural development of the human infant brain. These seem likely to underpin consistent reports of relationships between maternal stress and depression and childhood disorders of mental health. No doubt, structural changes involve transient readjustment of the tissue-/cell-specific epigenome, but here there is no need to evoke a persistent change in the epigenome. Chapter 14 similarly describes the revolution brought about by new imaging modalities, including optical imaging that offers unprecedented resolution at the cellular level, in the human kidney, liver, pancreas and placenta, as well as the brain. These methods offer real-time evaluation of offspring structure and function from fetal life through to adulthood, a significant advance for DOHaD research, and they also reduce dependence on animal studies.

The notion that early life environmental exposures stimulate or hinder resilience to disease or ageing is an emerging theme. Chapter 20 describes the paradigm whereby pathways of resilience to age-related non-communicable diseases can be permanently modified in early life. Chapter 13 reports studies in ageing rodents showing clear interactions between early life nutritional status and biological markers of the ageing process, whereby maternal overnutrition and protein deprivation both reduce markers of ageing, and longevity itself. Convincing evidence for dysregulation of the offspring's HPA (hypothalamic pituitary adrenal) axis is presented, and this is the same biological system that is widely implicated in interactions between maternal stress and offspring cognitive and behavioural function (Chapter 6). Potential interactions with the so-called epigenetic clocks, which are seen as proxies for biological rather than chronological ageing, are tantalizingly suggested but remain to be explored. Chapters 12 and 13 also introduce the reader to data from animal models that describe how maternal nutrition can influence resilience of the species by adversely affecting offspring reproductive ageing and fertility.

Knowledge of the biological pathways through which early life exposures influence offspring health outcomes has escalated using animal models, stimulated by extraordinary technological advances, including genetically manipulated and humanized mice, single-cell polymerase chain reaction (PCR), imaging sciences and – especially – the 'omics' explosion (epigenome, transcriptome, proteome, metabolome and microbiome).

The majority of DOHaD research in humans has depended upon, and still rests on, longitudinal population cohort studies, which describe associations between early life environmental exposure and offspring phenotype, almost always with substantive statistical adjustment for known confounders. Several authors appropriately caution against claims of causality, because of the inevitable potential for residual confounding. Others also illustrate how application of Mendelian randomization (MR) methods can address contributions of genetic variation in exposure–outcome relationships, although the authors of Chapter 15 caution that MR requires robust instrumental variables (genetic variants that act as proxies for environmentally modified exposures) and a sample size much larger than conventional association studies.

Whilst MR studies have questioned the causal importance of *in utero* exposures versus heritable genetic variants in the risk of disease, a convincing argument against genetic susceptibility as a sole explanation lies in innumerable studies in experimental animals in which the genotype of parent and offspring is controlled.

The synergy of offspring cardiometabolic and renal outcomes observed in response to a maternal exposure across non-human primates, sheep and rodents is, as detailed in Chapter 10, indicative of a mechanistic pathway common to all species, including humans. However, in humans, in a far less controlled environment, the interaction between multiple social and environmental exposures and genetic variants inevitably contributes to a breadth of phenotypes, and the relative contributions of environment and genes remain to be convincingly quantified. Indeed, the dichotomous distinction is not necessarily helpful – there is increasing evidence that the effect of some environmental influences in offspring development are genotype dependent and indeed future studies need to see this framing as core to experimental design and interpretation. This is key to the building of effective strategies to improve intergenerational health.

Translating the DOHaD message to improvement of the human condition may be attempted at both societal and individual levels by introducing change in the environment, parental and infant health or lifestyle at critical windows of developmental vulnerability. It is disappointing that neither approach has yet been shown to be particularly successful in improving long-term health, although improvements in maternal and perinatal health care, particularly in the developing world, have undoubtedly made major gains since the millennium developmental goals were launched in 2000. But this failure is in part a reflection of a failure to incorporate DOHaD knowledge into either public health or personal health care. It is also in part a failure to communicate or place understandings from DOHaD in a policy-relevant and acceptable framing. The DOHaD community may also need to reflect on the priorities within its own agenda to meet these policy needs. As Chapter 20 points out, policymakers for multiple reasons focus on shorter outcomes than the entire lifecourse and will respond to evidence of scalable, practical, affordable and effective interventions that demonstrate unequivocal benefit in childhood – for example, on emotional and cognitive development, which is a good proxy for long-term human capital accumulation.

As described in Chapters 5, 17 and 18, which report many wide-ranging and well-conducted randomized controlled trials, interventions in individuals have been disappointing, with a few notable exceptions. Interventions in pregnant women or in early post-natal life have not been effective, as shown by very modest or absent benefit for the child. The recommendation for beginning sooner – that is, in the preconception period – has become the new focus, predicated on this being a more logical time to intervene, that is, to improve parental health in preparation for pregnancy. However, many of the same challenges pertain here as in pregnancy and the postpartum period. Chapter 17 describes how lifestyle changes in pregnant women are difficult to achieve at the individual level, and the lack of benefits for child health are unsurprising given the modest difference in maternal behaviours induced by interventions. As obesity researchers have long shown, system change is necessary for individual benefit to be achieved.

'Buy-in' to the DOHaD message is an absolute requirement if health, educational and social policy, and investment aim to change the focus towards early life vulnerability and shorter-term outcomes. However, the Wikipedia definition of DOHaD (Chapter 20) as an 'approach to medical research in determining the development of human disease in adulthood', if it remains the dominant paradigm of the field, will not convince policymakers of its practical importance. Engagement of the electorate is also essential and the person in the street is unlikely to be familiar with 'DOHaD' per se and may be more comfortable with 'lifecourse' or the 'first 1,000 days'. The International Society, whilst maintaining DOHaD as a name, now subtitles 'Creating Healthy Futures' to identify its mission better. Chapter 19 focuses on the critical importance of imbuing the concept of DOHaD across society, and the ways this must be introduced through education from an early age.

As highlighted in Chapter 20, many of the conditions that adversely influence developmental trajectories are beyond personal choice and are compound by, for example, pollution, climate change, the food system and the obesogenic environment, societal pressures and intergenerational inequalities in societal health and education. Together these may also adversely affect parental mental health and the developmental environment. There is certainly greater recognition that a combination of social, environmental, physical and mental health exposures during periods of developmental vulnerability interact with adult exposures and the individual's genome to define the child's phenotype, which then progresses to greater or less resilience and thus adult health or disease phenotype (Chapters 7, 17, and 20). In parallel, the DOHaD community is moving towards much needed engagement

between biomedical scientists, climate change experts, social scientists and epidemiologists, driven in part by climate change and pollution (Chapter 7) and the COVID pandemic, all of which are generating unparalleled health issues with, and inequalities amongst, women and children. A population-based interventional approach matched in complexity to the range of exposures is clearly the way forward, but requires insight into the 'size effect' of each component, as yet unquantified, as well as substantial investment and local or national government buy-in. Unsurprisingly, this has seldom been attempted, nor has it yet to be fully adopted as a strategy to improve population health.

Systems interventions of the scale required are long term and expensive and not widely embraced by policymakers whose priorities are understandably often guided by short-term gain and cost. Nevertheless, there are encouraging signs that global and national health care policies are shifting towards integrated longer-term strategies which invest in early life, perhaps accelerated by the public health realities and inequalities arising from climate change and the pandemic. Amongst these is the UK Government's 2021 'Best Start for Life', a proposal to make the existing health and community services more effective and joined up for the first 1,000 days of life and the Singapore government's recent commitment to a whole-of-government strategic priority investing in a lifecourse approach to improving human health and potential. The DOHaD research community must seize the opportunity to capitalize on initiatives such as this and – with health and social providers and health economists and policy scholars – provide the robust scientific, economic and social basis required to convince those who make the policy decisions.

Section II Exposures Driving Long-Term DOHaD Effects

Chapter 2

The Evolutionary Basis of DOHaD

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2.1 Introduction

Over the past decade, there has been growing appreciation that our understanding of human health and disease, especially non-communicable disease, can be further deepened by applying an evolutionary and ultimate perspective to complement our knowledge of the mechanistic and proximate basis of disease aetiology. While the research domain of developmental origins of health and disease (DOHaD) has established causal links between early life events and later life disease risk, the emergent field of evolutionary medicine helps to elucidate the ultimate reasons for *why* our bodies are susceptible to disease in the first place [1, 2].

Two of the pathways by which evolutionary processes can influence disease risk are evolutionary mismatch and developmental mismatch. Both pathways draw on the evolutionary principle that selection operates to sustain and promote Darwinian fitness – that is, survival to reproductive age and production of viable offspring – irrespective of the impact on health during the post-reproductive period of the life-course (the exception may be in post-menopausal women, where survival of the grandmother supports survival of the grandchildren). However, despite the shared concept of 'mismatch', it should be noted that they remain distinct concepts. Evolutionary mismatch refers to exposure to an environment or cue that, due to its being either entirely novel or extremely severe in nature, threatens to overwhelm the individual's evolved coping mechanisms. Developmental mismatch involves multiple factors associated with the life-history strategy of the species that enable the developing individual to respond to cues and develop its physiology in ways that evolved to be adaptive; however, later exposure to an environment that is not matched to its physiological phenotype may have maladaptive outcomes.

In this chapter we will frame DOHaD phenomena within these evolutionary contexts, showing that human health and disease risk are dependent on both our evolutionary and our developmental histories. Focusing on nutrition, we demonstrate how the DOHaD phenomena are not unitary and are underpinned by both evolutionary and developmental mismatches, and discuss the evidence for how developmental anticipatory responses may confer adaptive advantage in humans. In addition, we explain the importance of the uniquely evolved human activity of cumulative niche modification in affecting our health in the Anthropocene.

2.2 Evolutionary Mismatch

Human cultural evolution, which in turn is underpinned by our organic evolution, is characterised by our species' capacity for innovation facilitated by our advanced cognitive, communication and language skills and ability to build and exploit collective expertise. Unlike other species that have evolved adaptive traits or behaviours to help buffer against environmental variation, such as river dam construction by beavers or mounds by termites, humans modify their environments without regard to sustaining Darwinian fitness. Thus, rather than *constructing* our niche to generate an equilibrium, as a species we have actively engaged in continual niche *modification,* at least in the last 10,000 years, without consideration of reaching or maintaining equilibrium [3, 4]. Indeed, we have modified much of our built, sociocultural and nutritional environments at an accelerating rate, particularly during our recent evolutionary history. As a result of the speed and scale of these modifications, we are continually exposed to marked changes in our environments compared to those in which pre-modern humans evolved. However if our genetic repertoire cannot provide adequate means for coping, evolutionary mismatch may occur.

Evolutionary mismatch may arise upon exposure to an environment that is extreme in nature. A classic example is how modern industrial-scale food

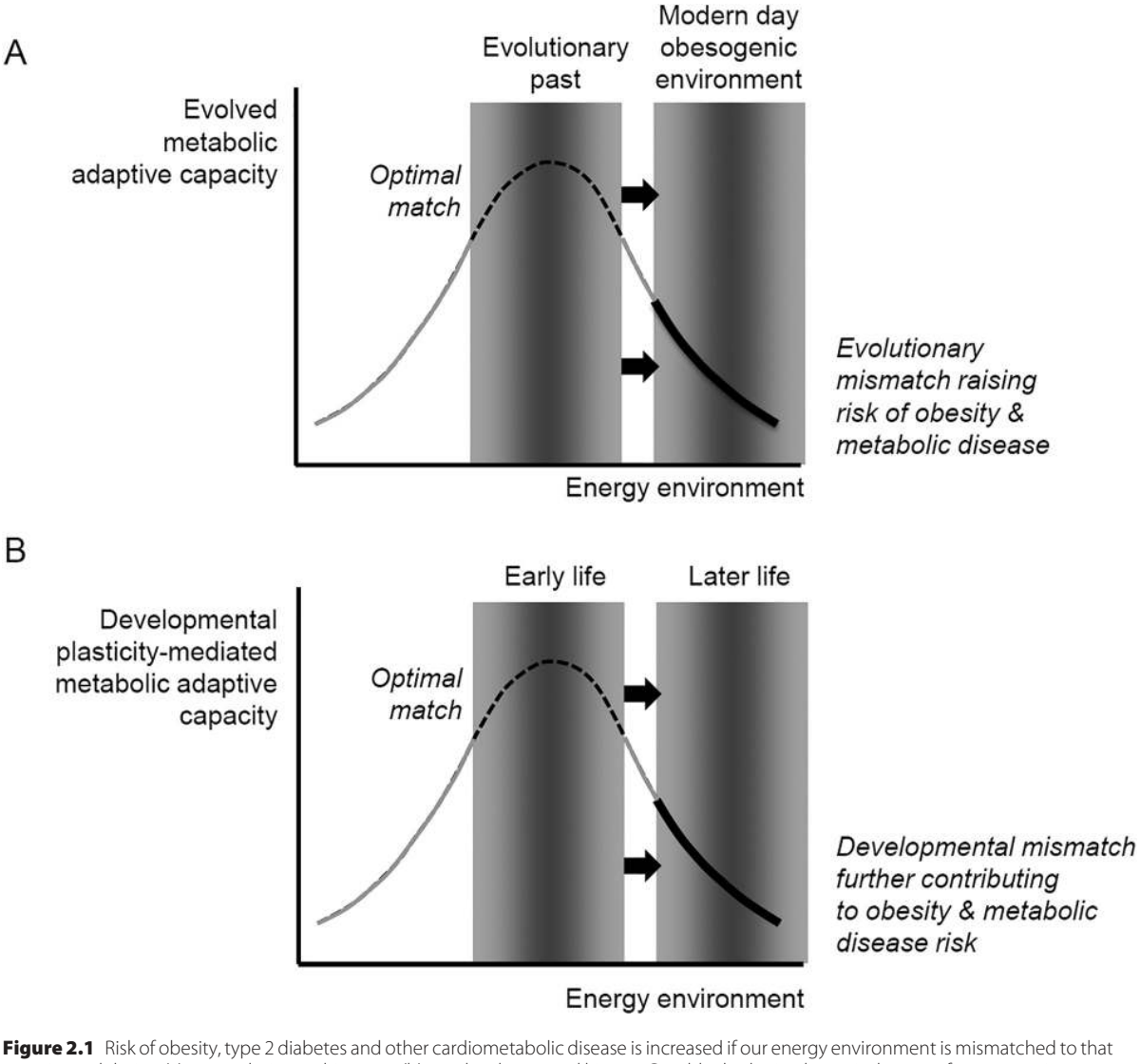

Figure 2.1 Risk of obesity, type 2 diabetes and other cardiometabolic disease is increased if our energy environment is mismatched to that experienced during (a) our evolutionary history or (b) our developmental history. Grey blocks depict the typical range of energy environments experienced. Dotted lines represent the optimal match between our evolved or developed metabolic capacity; bold lines represent the evolutionary or developmental mismatch to modern-day or later-life nutritional environments. Figure adapted from [50], with permission.

technologies have promoted the ready availability of highly processed, nutritionally poor yet energy dense and tasty food, and this together with the tendency of our built environment to facilitate sedentary lifestyles has contributed to an obesogenic setting. This overabundance of nutrition is highly discordant with the hunter-forager diets that humans and their hominin ancestors were likely to have experienced, and by which human metabolism would have been shaped [5]. Our evolved metabolic physiology therefore lacks the capacity to adapt, resulting in increasingly widespread prevalence of obesity and its associated comorbidities such as type 2 diabetes [6] (Figure 2.1a). This has become a more pressing global health concern as low-income countries are increasingly becoming more economically advanced and exposed to 'Western' diets.

Evolutionary mismatch may also occur when encountering an environment that is completely novel in terms of prior exposures over the course of our evolutionary history. For example, the rise in prevalence of gestational diabetes mellitus (GDM), especially in countries undergoing the nutritional transition,

may also promote fetal exposure to nutrient-related evolutionary mismatch. GDM is likely to be an evolutionary novelty given its association with fetal macrosomia and the maternal and perinatal mortality risks it poses, and also because its risk factors – maternal obesity and excessive gestational weight gain – are likely to have been rare in pre-modern times. Accordingly, there has been little selective pressure to evolve a saturable transport mechanism to limit transplacental glucose transfer, leading to fetal exposure to high levels of glucose in women with uncontrolled GDM [7]. This stimulates hyperinsulinemia and adipogenesis, leading to the neonate being highly susceptible to hypoglycemia. Although modern health care has reduced morbidity and mortality rates of mother and neonate, these babies are at greater risk of adiposity and impaired glucose tolerance in later life [8].

Another example of evolutionary novelty is the replacement of direct suckling of breast milk with bottle feeding of infant formula. Cow's milk differs from human breast milk in its macronutrient, micronutrient and caloric content, as well as its hormonal and immunological profile. Unlike the relative homogeneity of a given brand of formula, human breast milk composition changes with lactation duration, likely in response to the changing nutritional requirements of the growing infant [9]. Feeding from a bottle also interferes with milk intake as the infant is less likely to self-determine cessation of feeding, which may interfere with the proper development of satiety responsiveness. Indeed, there is some evidence linking formula feeding to excessive weight gain and poorer cognitive development, especially in preterm infants [10, 11].

2.3 Developmental Mismatch

2.3.1 Environmentally Induced Responses During Development

Compared to its beginnings a few decades ago, the field of DOHaD is now replete with robust epidemiological, clinical and experimental data in both humans and animal models demonstrating that often subtle experiences in fetal and infant life can induce phenotypic changes that only become apparent later in life [12]. More recently, epigenetic methodologies have been employed to investigate the underlying molecular mechanisms and strengthen the biological plausibility of the findings. Much of the data have focused on nutritional cues, and in particular maternal diet during pregnancy and infant nutrition, although there is increasing focus on other factors such as stress and environmental toxicants.

During development, the fetus is exposed to numerous environmental cues that may influence its mature phenotype in different ways depending on the nature of the cues and their severity. Cues that are especially extreme may have teratogenic effects and irreversibly induce outright disruption of development. For example, maternal infection with the Zika virus causes fetal microcephaly, while overconsumption of alcohol during pregnancy may lead to damage in the fetal central nervous system. However DOHaD interests must be distinguished from teratological phenomena and generally involve cues that are less extreme, or indeed fall within a normal range of physiological conditions, such as modest variations in maternal nutrition or maternal stress. These rather more prosaic cues may instead induce developmentally plastic responses that confer potential adaptive benefit, allowing the organism to adjust its phenotype to better cope with stresses and match its perceived future environment [13]. The strategy is to invest maximal resources into promoting survival until at least reproductive age so that offspring are produced, but this is achieved at the expense of later life health and longevity due to suboptimal maintenance and repair mechanisms, or because the prediction of the future made in early life may no longer be appropriate in adult life (see later).

Developmental plasticity operates in a wide range of taxa and allows for the generation of multiple phenotypes from a single inherited genotype [14]. This may be seen at the molecular level, such as epigenetic modifications resulting in altered gene expression, to the cellular level, such as changes in number of cells in an organ, through to the wider physiological level, such as the adjustment of metabolic set points or changes in neurodevelopmental behaviour.

Organisms with a high reproductive rate such as bacteria adopt a risk-spreading strategy of 'bet hedging', where daughter cells stochastically develop a range of phenotypes within a given environment, and these may be variously better suited to the current or future environments. In comparison, in species that are much less fecund and generally monotocous such as humans, developmental plasticity occurs in a directional rather than stochastic manner. The capacity for plasticity is maximal during the period of early development and declines with age; this limited timeframe of operation is due to the energetic costs of its maintenance and

the inherent structural or physiological constraints arising as developmental pathways are established. In humans, the most critical window of sensitivity is generally regarded as the period from conception to weaning – or what is often referred to as the 'first 1,000 days of life' [15, 16].

2.3.2 Immediate and Predictive Adaptive Responses

The mechanisms of developmental plasticity may prompt responses that provide immediate survival advantage, usually for cues that, while not as severe as a teratogen, still pose a survival or fitness threat. A demonstration of this is the restriction of fetal growth due to poor maternal nutrition, which lowers the use of already limited energy resources and maximises the chance of survival until birth. Preterm birth is also frequently triggered in response to maternal infection, which may avert fetal death *in utero* [17]. Such immediately adaptive responses (IARs) incur a trade-off – in these examples, growth restriction or prematurity means that babies are born small and are at greater risk of morbidity and mortality, but the immediate survival value is deemed to outweigh potential post-natal costs. Neonates born small are also more insulin sensitive at birth, possibly to maximise building of fat stores to protect the metabolically expensive brain and its need for fatty acids to develop neurons [18, 19].

Due to the relatively short window in the life-course during which developmental plasticity can operate without other more disadvantageous effects, a further type of response affecting physiology may also be made to confer delayed adaptive advantage in an anticipated future environment. Termed predictive adaptive responses (PARs), or anticipatory parental effects [20, 21], these serve to modify the fetal or infant phenotype to better match the predicted future environment. They are elicited by subtle cues that often fall within the normative range of experiences, such as slight variations in maternal diet. There are numerous ecological examples of the operation of PARs. An example is the desert locust developing into either a solitary or a gregarious form in adulthood depending on the chemical signals received shortly after hatching. Prediction of a lower population density favours the low-mobility solitary form, while signals indicating a crowded environment favour the gregarious form that is better suited to competing for food due to greater flight and dietary capacity [22]. In snowshoe hares, offspring whose mothers were exposed to predator-induced stress during pregnancy have higher baseline cortisol levels and are more sensitive to stressors, both of which provide post-natal survival advantage [23]. In humans, the developing fetus relies on maternally transmitted cues to gauge the nature of the external environment and make appropriate PARs so that it is optimally suited to the predicted environment. If the fetus receives cues indicating poor nutrition, for example, it will predict a similar post-natal environment of limited nutrient availability and respond accordingly with PARs that promote energy conservation, such as preferential accumulation of fat stores. This strategy confers considerable fitness advantage as the individual is better matched to their environment [24]. As humans have a long gestational period, there must be a degree of inertia in developmental responses to buffer against brief environmental fluctuations [25].

The concept of anticipatory responses requires careful parsing to discern appropriately their role in evolutionary processes, especially those pertaining to humans. A specific cue may induce both IARs and PARs – for example, poor maternal nutrition leads not only to the IAR of fetal growth restriction but also PARs that later manifest as insulin resistance in childhood and through to adulthood (see next section) [26]. Yet, PARs may also be induced independently of IARs. This can be seen from a study of children of normal birth weight, where the nature of the maternal diet during early pregnancy was associated with epigenetic alterations at birth, which in turn were linked to the children's levels of adiposity in childhood [27]. Another important characteristic of PARs is that they generally do not manifest as an observable phenotype unless developmental mismatch occurs.

2.3.3 Malprediction Leading to Developmental Mismatch

As PARs merely reflect the 'best guess' of predicted future environments, the organism's phenotype may not necessarily end up accurately matched to the conditions encountered in later life, reflecting a situation of developmental mismatch (Figure 2.1b). Erroneous predictions may occur because of inaccurate maternal–fetal transmission of cues, generally due to maternal pathophysiological factors, resulting in a misleading representation of the actual environment. An example is placental dysfunction limiting nutrient availability to the fetus, prompting an incorrect prediction

of a nutritionally deficient post-natal environment. A more common way that erroneous predictions may arise is if the organism experiences marked changes to its environment *after* PARs have been established – that is, after the period of greatest plasticity. This often involves behavioural or socioeconomic factors such as migration from a poor nutritional environment to an environment of plenty (as in the case of rural-to-urban migration or emigration to more prosperous countries), or the adoption of a diet substantially different from that experienced *in utero* [28, 29]. In this regard, human niche-modifying activities such as urbanisation, changes in food production and processing and the nutritional transition of the wider environment are important contributing elements that may exacerbate developmental mismatch.

Developmental mismatch is associated with increased risk of chronic non-communicable diseases such as obesity and type 2 diabetes that have major impact on the individual's quality of life. Yet, anticipatory responses would have evolved because of the adaptive advantage of being phenotypically prepared for low-nutrition environments that would have prevailed through our evolutionary history. The fitness advantage they confer is, by definition, limited to the age of reproductive competence, and has no bearing on health status later in the life-course. In addition, modelling studies demonstrate the adaptive value of anticipatory responses even when predictions do not reach a very high level of accuracy [30]. PARs are especially important in humans given our species' low fecundity, relatively long gestation, altricial state at birth, the relatively short maternal reproductive life span, and the high level of investment in each pregnancy.

One specific aspect of the human life history suggests that fetuses are likely to receive intrinsic cues that favour prediction of a low-nutrition post-natal environment. Compared to other primates, humans have not only a relatively narrow pelvis but also a large fetal head to body ratio. Consequently, to reduce the risk of labour dystocia, the mother limits the growth of the fetus below its genetic potential in a phenomenon known as maternal constraint [31]. Maternal constraint is a normative experience – a large study of more than 1.1 million clinical records found that the highest perinatal survival rates were seen for birth weights not at the median but around the 80–84th centile, likely reflecting the operation of maternal constraint limiting fetal growth to a level far below the optimum weight for maximum survival [32]. This bias towards PARs that adjust the mature phenotype for a low-nutrition environment likely magnifies the extent of mismatch within a modern-day obesogenic environment.

In understanding and interpreting the concepts of developmental plasticity and anticipatory responses, it is fundamentally important to recognize that the processes of plasticity and PARs themselves do not contribute to disease risk. Rather, they alter the organism's sensitivity to its post-natal environment, and it is only when developmental mismatch occurs that disease risk is elevated.

2.3.4 PARs in Humans

Many studies have demonstrated the operation of anticipatory responses in a wide range of animals, including mammals [23, 33], insects [22, 34–36], microorganisms [37] and crustaceans [38]. Testing for PARs requires evidence of a fitness advantage, as measured by impact on survival. This naturally presents a challenge when seeking evidence in humans. In this case, retrospective analyses of natural experiments can serve as an alternative, though any demonstration of fitness effect should be biologically plausible and supported by experimental data where possible.

One such natural experiment involves a cohort of Jamaican people who had survived severe acute malnutrition as infants. This extreme form of nutritional stress manifests as two distinct clinical syndromes – kwashiorkor or marasmus – each with very different metabolic physiology and other clinical outcomes. While children with marasmus tend to have very low weight-for-height due to severe wasting, those with kwashiorkor present with less wasting but instead are oedematous, exhibit multiorgan dysfunction and are more susceptible to infections [39]. Metabolic profiling reveals that, unlike marasmic infants who are still able to sustain intermediary metabolic pathways, infants with kwashiorkor are unable to adequately draw on their available fat and protein stores, affecting amino acid and lipid supplies for protein and energy metabolism [40]. This apparently metabolically wasteful pattern is a sharp contrast to the metabolic thriftiness of marasmus, and consequently a higher mortality rate is observed among kwashiorkor sufferers [41].

Since both conditions are observed in children undergoing apparently the same nutritional insult, the differences in metabolism appear to have a prenatal basis, where divergent anticipatory responses