Chapter 1

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

Lucilla Poston[1], Keith M. Godfrey[2], Peter D. Gluckman[3] and Mark A. Hanson[2]

[1] King's College London, UK
[2] MRC Lifecourse Epidemiology Centre and NIHR Southampton Biomedical Research Centre University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK
[3] University of Auckland, New Zealand

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

https://doi.org/10.1017/9781009272254.002 Published online by Cambridge University Press

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

https://doi.org/10.1017/9781009272254.002 Published online by Cambridge University Press

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.

https://doi.org/10.1017/9781009272254.002 Published online by Cambridge University Press

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

https://doi.org/10.1017/9781009272254.002 Published online by Cambridge University Press

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.

https://doi.org/10.1017/9781009272254.002 Published online by Cambridge University Press