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Epigenetic Epidemiology: The Rebirth of Soft Inheritance

by Mark A. Hanson et al.

Key insights

Non-communicable disease (NCD) levels are reaching epidemic proportions worldwide. Current interventions largely ignore the role of early life development in modulating the disease risk and instead focus on screening at-risk individuals or the treatment of patients with disease. Based on global trends in NCD statistics, such an approach is no longer tenable. Instead, more emphasis should be placed on preventative interventions in early life.

Current knowledge

Extensive literature shows that the risk of developing NCDs in later life is dependent on early life conditions, such as the maternal condition before/during pregnancy. The pathways to increased disease risk include evolutionary, developmental and demographic dimensions. Recent epigenetic research provides a molecular basis for such observations.

Practical implications

An appreciation of the importance of early life developmental factors and non-genomic inheritance in influencing later life health is crucial for devising effective intervention strategies. Identification of the at-risk individual early in life using epigenetic biomarkers, or treatment with therapeutics with an epigenetic basis, represents a promising step forward in tackling NCDs.

Recommended reading

Gluckman PD, Hanson MA, Buklijas T, Low FM, Beedle AS: Epigenetic mechanisms that underpin metabolic and cardiovascular diseases. *Nat Rev Endocrinol* 2009;5:401–408.

Proposed relative contributions of disease susceptibility determinants and risk: a conceptual shift towards 'soft' inheritance (see text for details).

Epigenetic Epidemiology: The Rebirth of Soft Inheritance

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Key Messages

- Early development plays a central role in determining an individual's susceptibility to non-communicable disease in later life.
- Devising effective intervention strategies against non-communicable diseases will require a greater focus on how developmental pathways lead to greater disease risk.
- New insights into the underlying molecular mechanisms, especially epigenetic processes, offer the hope of devising biomarkers indicating risk and of developing novel interventions.

Key Words

Developmental plasticity • Developmental origins of health and disease • Epigenetics • Gestational diabetes • Mismatch • Non-communicable diseases • Predictive adaptive responses • Soft inheritance

Abstract

Non-communicable diseases (NCDs), such as cardiovascular disease and type 2 diabetes, constitute the main cause of death worldwide. Eighty percent of these deaths occur in low- and middle-income countries, especially as these countries undergo socio-economic improvement following reductions in the burden of infectious disease. The World

Health Organization predicts a substantial increase in the incidence of NCDs over the next decade globally. NCDs are generally preventable, but current approaches are clearly inadequate. New initiatives are needed to implement such prevention, and there needs to be greater recognition that early-life interventions are likely to be the most efficacious. Devising appropriate prevention strategies necessitates an understanding of how the developmental environment influences risk. Progress in this field has been slow due to an excessive emphasis on fixed genomic variations (hard inheritance) as the major determinants of disease susceptibility. However, new evidence demonstrates the much greater importance of early-life developmental factors, involving epigenetic processes and 'soft' inheritance in modulating an individual's vulnerability to NCD. This also offers opportunities for novel epigenetic biomarkers of risk or interventions targeting epigenetic pathways to be devised for use in early life. This may pave the way to much more effective, customised interventions to promote health across the life course.

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Introduction

Non-communicable diseases (NCDs), such as cardiovascular disease, diabetes, chronic lung disease, allergy, some forms of cancer, cognitive decline, osteoporosis, sarcopenia and affective disorders, are the world's biggest killers. They are now endemic in the developed world and are of increasing importance in the developing world [1]. The statistics are sobering: for example cardio-metabolic

disease alone accounts for 35 million deaths per year, i.e. 60% of all deaths globally. The economic and humanitarian costs incurred by NCDs are enormous and may well destabilise the economies of low-income countries, where recent data show that risk markers for these diseases become evident early in the process of socio-economic improvement and well below the level of affluence traditionally associated with them in developed societies [2, 3]. World Health Organization (WHO) statistics suggest that 80% of these deaths occur in low- and middle-income countries [4]. This is especially true as developing countries undergo socio-economic improvement following reductions in infectious disease. More alarmingly, the WHO predicts a global increase in NCDs of 17% over the next decade. Despite the preventable nature of most NCDs, the effectiveness of current intervention approaches is limited, as reflected in the continued increase in prevalence in both developed and developing countries. Currently implemented strategies have mainly focused on developed countries. More promisingly, the United Nations General Assembly recently agreed that an international summit should be held this year to address the challenge of NCDs, especially in low- and middle-income countries (table 1) [5].

The key question is why current approaches to address obesity and the associated diseases are generally not achieving the desired goals. Most public health programmes beyond smoking reduction, where price increases have been a particularly successful deterrent, are focused on obesity in adults and in older children. Sustained weight loss remains a difficult objective. Further, the lack of a simple cause-effect relationship between obesity and NCDs confounds our understanding. Not every individual responds to an obesogenic environment in the same way.

Table 1. Non-communicable diseases in low- and middle-income countries

Greatest impact of non-communicable diseases
Disproportionately rapid increase in poor and disadvantaged people
→ Widening health gaps between and within countries

Signals received by the developing embryo, fetus and infant induce adaptive responses that enable the development of phenotypic characteristics appropriate to the environment in which the offspring predicts it will live.

The fundamental challenge we have to address is that of evolutionary mismatch. The modern-day human diet, lifestyle and environment are very different from those during a large part of our evolutionary history. It is only relatively recently that humans have shifted to a high-fat, high-glycaemic-index diet with which we have not evolved the metabolic capacity to cope. This is underscored by observations that a slight increase in the energy

input/output ratio leads to weight gain over a short duration [6]. Coupled with diminishing levels of physical activity, our exposure to a novel obesogenic environment has resulted in a metabolic mismatch in much of the population, thus raising the risk of developing NCDs. But the risk is not constant. Fixed genetic variation places some

individuals at greater risk, but genome-wide association studies have been surprisingly uninformative in explaining a substantial component of this variation in responses [7]. Increasingly, attention is turning to the role of developmental factors, which are the focus of this review. It is important to note from the outset that developmental factors do not cause NCDs; they merely influence the risk of disease in a later obesogenic environment. Moreover, there are several non-mutually exclusive pathways by which increased NCD risk can occur.

Developmental Mismatch

Epidemiological studies across a wide range of countries and over many years have shown that early human development affects the risk of developing NCDs in later life [8]. This field is now internationally recognised as Developmental Origins of Health and Disease (DOHaD; for more information, visit <http://www.dohadsoc.org>), and there is now growing evidence that the molecular basis for this phenomenon involves non-genomic inheritance, including epigenetic mechanisms.

Throughout the developmental stages of early life, aspects of the external environment are transduced by the mother to the fetus, or are experienced directly by the neonate (fig. 1). The parental preconceptional state may also influence the information imparted.

Signals received by the developing embryo, fetus and infant induce adaptive responses that enable the development of phenotypic characteristics appropriate to the en-

Fig. 1. Early-life factors that modulate later-life phenotype. These cues induce PARs that steer the individual to develop an appropriate phenotype that is best matched to its later-life environment. Encountering a different environment from that originally predicted results in a mismatch, thus increasing the risk of NCDs in adulthood.

environment in which the offspring predicts it will live. These responses, which we have termed predictive adaptive responses (PARs) [9], are brought about via the mechanisms of developmental plasticity, which include epigenetic processes. Such mechanisms appear to have evolved because Darwinian fitness is increased by preemptively adapting later-life phenotype to suit the environment. The phenotypic characteristics relate to particular aspects of life course biology such as metabolic control, allocation of fat, skeletal muscle fibre type, cardiomyocyte and nephron numbers, and control systems such as appetite, stress responses, and timing of puberty. Together, they form an integrated phenotype that optimises the ways in which the adult offspring responds to its environment. Alteration of food preference, physical activity propensity and fat deposition will influence the person's risk of NCD. Because the PARs are dependent on developmental history and will be slightly different in each individual, they contribute to the differences in disease risk even between individuals who apparently have very similar adult lifestyles.

Although PARs have arisen to confer adaptive advantages, developmental changes made on the basis of early-life predictions can turn out to be inappropriate – this is termed developmental mismatch. For example, the signals sent by the mother to her offspring may be inaccurate owing to placental dysfunction; the mother may be consuming an unbalanced diet that is not representative of the actual nutritional environment, or the environment may have changed by the time the offspring reaches adulthood. In the event that a mismatch between the predicted and actual environment arises, for example, if a fetus receiving inadequate nutrition experiences a nutrient-replete postnatal environment, the PARs it had made early in life no longer confer a fitness advantage; instead they may have detrimental effects as the offspring is metabolically ill equipped to respond appropriately, and is therefore at higher risk of NCD [10]. Experimental evidence has been provided by studies in rat offspring of

undernourished dams, which develop obesity, insulin and leptin resistance, hyperphagia, and sedentary behaviour in adulthood [11, 12]. Developmental mismatch is particularly important in developing countries undergoing nutritional transition to the modern 'Western' diet. However, we now know that the processes of mismatch can potentially operate across the entire spectrum of environmental signals – for example an unbalanced maternal diet, which is inadequate in a low-income setting, can potentially be as harmful as the high-glycaemic diet of many Western societies.

Specific aspects of the developmental environment, such as the mother's diet or her body composition, stress levels, and her level of physical activity, have also been shown to be risk factors for later disease.

It is important to note that disease risk is graded across the normal range of developmental experiences, at least as determined by proxy measures such as birthweight [13]. Thus, cues experienced during early life do not have to be severe or acute to induce developmental responses. Specific aspects of the developmental environment, such as the mother's diet or her body composition, stress levels, and her level of physical activity, have also been shown to be risk factors for later disease. For example, Gale et al. [14] showed that a mother's energy intake in late pregnancy was related to carotid intima-media thickness (an early marker of vascular disease) in 9-year-old children – an effect amplified by the child's weight at age 9. As these studies were conducted in an unselected population in a European city, they clearly demonstrate how risk is graded across the spectrum of normal human develop-

Fig. 2. Evolutionary novelty of the present-day environment: example of glucose regulation.

ment. Clearly, the effects of developmental plasticity occur in all individuals and are not necessarily accompanied by gross changes in, for example, birthweight. Moreover, a range of trajectories of fetal growth can lead to a similar birthweight [reviewed in ref. 15, 16].

Early-Life Nutritional Excess

Much of DOHaD research was inspired by Barker et al. [17], who linked low birthweight with higher adult risk of cardiovascular disease-related death. Subsequent work has therefore strongly focused on how maternal undernutrition affects offspring phenotype. However, the past few decades have witnessed a worldwide surge in rates of overweight, obesity and diabetes [18]. This has in turn led to increasing numbers of women with gestational obesity and gestational diabetes mellitus (GDM) – both key risk factors for the development of overweight, obesity and the metabolic syndrome in their offspring [19]. GDM leads to fetal hyperinsulinaemia, and mildly raised glucose or insulin levels have been associated with increased neonatal body fat composition and risk of later-life NCD [20]. This is of particular concern because of the potential cyclical nature of affected offspring producing progeny with a similar, elevated risk of disease.

The molecular and cellular mechanisms by which early-life overnutrition promotes a similar outcome to that of undernutrition are not clear, although some animal studies suggest that epigenetic processes may similarly be

involved [21, 22]. Nevertheless, adopting an evolutionary perspective enables a clearer explanation of why (as opposed to ‘how’) disease risk could be elevated. Early-life overnutrition is a relatively recent phenomenon unique to humans, as evidenced by the lack of an evolved upper limit to the level of glucose transferred from mother to fetus. GDM has probably been subject to little selective pressure, given that abundant nutrition would have been rarely experienced throughout our evolutionary history. Maternal insulin resistance during pregnancy appears to promote fetal growth and potentially offspring fitness, suggesting that the placenta may in fact have evolved to buffer against fetal undernutrition rather than overnutrition. This characteristic becomes disadvantageous in the context of the evolutionary novelty of the present-day environment (fig. 2).

Maternal Constraint and Demographic Change

Inappropriate nutrition is not the only means by which NCD risk may be raised. Another factor – one that is increasingly pertinent, given the demographic changes in both developing and developed societies, is the relationship between parity and maternal constraint (i.e. the effect of maternal parity and uteroplacental factors limiting fetal growth in relation to maternal size, so as to facilitate vaginal delivery [23]). First-born children experience a greater degree of maternal constraint during gestation than their siblings [24], and they tend to be born smaller [25].

Fig. 3. An individual's genes, environment and early-life developmental factors converge to influence the nature of later-life phenotype (and hence, disease risk). This is brought about by the organism's capacity for developmental plasticity; epigenetic mechanisms contribute to the mediation of this effect.

Recent studies of a modern UK population have shown that as adults they have higher adiposity and truncal obesity than those born to second or subsequent pregnancies – an association that is independent of current lifestyle factors [26]. It appears that maternal constraint had prompted these individuals to make PARs biased towards a poor nutrition environment, exacerbating their mismatch in contemporary society. The decreasing birth rates observed in many countries, either following socio-economic improvement or legislation, are leading to a greater proportion of first-born children globally, whose more constrained start to life may be contributing to the global incidence of obesity and diabetes.

Mechanisms of Soft Inheritance

We increasingly find that the predominance of reductionist thinking in biomedical science in recent decades is not helping us to address contemporary health problems. Nowhere is this clearer than in the outcomes of genome-wide association studies, where a relatively small proportion of risk of the common conditions such as heart disease and diabetes can be explained [7]. A deterministic approach has particularly compromised progress in understanding of development and inheritance. For many years, the fields of developmental science such as embryology were dominated by the concept of the genetic 'programme' for development, with environmental influences being given minimal consideration and viewed as merely experimental error. This gave priority to the 'hard' inheritance of fixed genomic variations. The idea that environmental factors could influence phenotype and that they could be passed between generations appeared reminiscent of the discredited theory of Jean Baptiste Lamarck. In his great oeuvre, *Philosophie Zoologique*

[27], Lamarck gave emphasis to learning and development, especially in the origin of malformations. Like many biologists in the ensuing 150 years, he accepted some notion of 'soft' inheritance, but his name became pejoratively associated with the inheritance of acquired characteristics – a concept he did not invent and a phrase he did not use. But after neo-Darwinian ideas took hold and led to the Modern Synthesis (the fusion of Darwin's theory of natural selection with Mendelian genetics), little attention has been paid to intergenerational influences beyond hard genomic inheritance. Soft inheritance and the role of development both came to be written out of biomedical endeavours as non-Mendelian intergenerational effects were regarded as experimental 'noise' [28].

But soft inheritance has now been reborn: the demonstration of developmental epigenetic processes provides a solid molecular basis for understanding how environmental influences can affect the phenotype of the next generation, or even those which follow, including susceptibility to chronic disease [29]. Such developmental epigenetic processes were thought to be involved mainly in genomic imprinting (the expression of a gene depending on the parent origin of the allele), in X chromosome silencing in mammalian females, in reactivation of the embryonic genome soon after fertilisation and in regulating cell lineage differentiation. However, animal studies have shown that environmental influences such as maternal diet or maternal care behaviour can affect offspring phenotype through epigenetic changes on a range of non-imprinted genes, e.g. the glucocorticoid receptor and nuclear receptors such as the peroxisome-proliferator-activated receptors [30, 31], beyond the embryonic period, throughout gestation and into early postnatal life. Epigenetic mechanisms involve concerted changes in DNA methylation, in histone structure and through non-cod-

ing RNAs [32, 33]. They can have a plethora of downstream effects on patterns of gene expression, and might function to change the ‘canalisation’ of phenotype development (i.e. the process by which distinct genotypes tend to produce the same phenotype) in ways reminiscent of Conrad Waddington’s ideas when he coined the term ‘epigenetic’ in 1940 [34]. These pathways not only mediate the differentiation of pluripotent stem cells but additionally affect more subtle metabolic control processes such as mitochondrial function and fatty acid oxidation [35]. These processes are thus highly relevant to the predisposition to later chronic disease.

The range of experimental, clinical and epidemiological data which now link the conditions around early life to later health status is now overwhelming. The size of the population to whom such effects apply could well be substantial. Hence, whereas earlier studies focused on children who were born small and who might therefore constitute only a small proportion of a population, it is now clear that the developmental environment has an impact on the developmental trajectory of every child. The story does not end at birth, as developmental plasticity can extend through early postnatal life, providing a window of epigenetic lability. Later-life phenotype can be influenced by how the child is fed after birth, how it is cared for, by infection or allergen exposure and perhaps by how its gut is colonised with commensal bacteria [36, 37]. Phenotypic outcomes having long-term consequences involve the interplay between genetic, developmental and environmental influences (fig. 3). It is impossible for each to be treated independently of the others.

A New Synthesis

In contrast to the fatalism of a deterministic view based on the (now rather forlorn) hope that the sequencing of the human genome would reveal the genes ‘for’ certain diseases, a new softer synthesis gives scope for optimism. In cancer biology, epigenetic biomarkers and drug targeting of epigenetic machinery are burgeoning fields; attention is now being given to the possibility that lifestyle interventions in early life might be used to correct the epigenetic component of risk of other chronic NCDs. This could be important because the way we interact with our environment as adults – from food preference, appetite control to mood and exercise capacity – has been shown experimentally to be influenced by our development. It is therefore questionable whether the efficacy of interventions that currently form the mainstay of NCD risk reduction in adults could be greater than that

obtained from interventions made earlier in life. We have recently shown that methylation at the promoter region of *RXRA* measured at birth is positively correlated with adiposity in children aged 6 or 9 years [38] – this offers potential opportunities for early identification of individuals and groups at increased risk and for appropriate intervention. Indeed, several animal studies have demonstrated proof of concept for the reversibility of developmentally induced phenotypes. For example, various features of the metabolic syndrome seen in offspring whose mothers were undernourished or endocrinologically challenged during pregnancy could be prevented by neonatal dietary or endocrine intervention during a critical window of developmental plasticity [39, 40]. Strikingly, such a preventative treatment could also reverse the epigenetic changes induced by perturbed maternal diet [41].

Epigenetic processes are involved in matching fetal growth to mother’s stature, body composition and lifestyle [42]. In adolescent pregnancies or pregnancies where the woman consumes an unbalanced diet, the conflict between allocation of nutrients to the woman or her fetus is resolved in favour of the mother, which makes good evolutionary sense but puts the offspring at greater risk of later disease. Thus, educational and social initiatives aimed at delaying the age of first pregnancy until about 4 years after menarche, to allow young women to complete their growth and the pelvis to reach its maximal dimensions, would not only empower them but impact on the health of the next generation. The cultural and political

It is therefore questionable whether the efficacy of interventions that currently form the mainstay of NCD risk reduction in adults could be greater than that obtained from interventions made earlier in life.

issues preventing implementation of such a strategy need to be confronted.

Similar considerations apply to maternal diet and body composition at conception. Animal studies demonstrate compelling long-term effects of altered nutrition in this period on metabolic and cardiovascular control in the offspring [reviewed in ref. 43], and human data reveal similar effects [44, 45]. Studies in the UK show that less than 3% of pregnant women (irrespective of whether the

Fig. 4. Summary of possible strategies to reverse developmentally induced phenotypes, particularly those leading to NCD in later life.

Table 2. Factors negatively affecting pregnancy outcome

Maternal obesity
Inadequate weight gain in pregnancy
GDM
Smoking
Drug and alcohol abuse
HIV/AIDS
Malaria

Table 3. Beneficial effects of breastfeeding

Optimal growth
Resistance to infection
Cardiovascular health ↑
Neurocognitive development ↑

pregnancy was planned or not) adhered to guidelines on a healthy diet and lifestyle (fig. 4) [46]. The strongest correlate with unbalanced maternal diet is low educational achievement. This strongly suggests that interventions to improve the nutrition and lifestyle of all women of childbearing age – and their partners – would have a major impact on NCD risk.

The maternal condition during pregnancy is in need of greater attention in both the developed and the developing world. We also need to consider the full range of such factors: maternal obesity and GDM both leave lasting effects on the offspring; on the opposite end of the spectrum, in Japan, birthweight has been falling in recent years due to inadequate weight gain in pregnancy, sometimes following ill-conceived medical advice [47]. Smoking, drug and alcohol abuse, HIV/AIDS and malaria still

complicate far too many pregnancies (table 2). Human development is far from complete at birth, and recent data confirm the importance of exclusive breastfeeding for at least 6 months in promoting optimal growth, resistance to infection, cardiovascular health and neurocognitive development (table 3) [48, 49]. Yet, breastfeeding rates are low, even in developed countries such as the UK, so clearly public education is urgently needed.

None of these solutions seems sophisticated, although it may have taken the recent insights into the underlying developmental epigenetic mechanisms of soft inheritance to endorse them. We are not in a good place to prevent NCD in today's adults, particularly if efforts are directed towards palliative and not preventative interventions. But perhaps, after a glance back to our developmental past, we can aim to help the next generation. Eradicating the hardness of past biomedical concepts about development in favour of a softer, integrative, new synthesis may be difficult. However, if we persist in thinking deterministically about chronic disease, we will continually be surprised when, perhaps because interventions are made too late, they turn out to be relatively ineffective.

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