Developmental origins of noncommunicable disease: population and public health implications1–4

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ABSTRACT
Noncommunicable diseases (NCDs), including cardiovascular disease, diabetes, chronic lung disease, allergy, some forms of cancer, cognitive decline, osteoporosis, sarcopenia, and affective disorders, are the world’s biggest killers. Eighty percent of these deaths occur in low- and middle-income countries, especially as these countries undergo socioeconomic improvement after reductions in infectious disease. The World Health Organization predicts a global increase of 17% in NCDs over the next decade. NCDs are preventable, but new initiatives are needed to institute such prevention, especially in early life. In this article, we emphasize that all children are affected by their early developmental conditions, not just children exposed to a very deficient environment, and that this has long-term consequences for their predisposition to NCDs. We highlight the biomedical implications of this developmental origins of health and disease (DOHaD) concept of NCDs and discuss the implications for health policy.

INTRODUCTION
Noncommunicable diseases (NCDs), including 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 account for 35 million deaths per year, which is 60% of all deaths globally. Although the focus of much preventative strategy is on NCD in developed countries, the World Health Organization (WHO) statistics suggest that 80% of these deaths occur in low- and middle-income countries (1). This is especially true as developing countries undergo socioeconomic improvements after reductions in infectious disease. Worse still, the WHO predicts an increase of 17% in NCD over the next decade globally. NCDs are preventable, but such a prevention strategy is absent from the millennium development goals. However, the UN General Assembly recently agreed that an international summit should be held to address the challenge of NCD, especially in low- and middle-income countries.

In this review, we address 3 points. First, we emphasize that all children are affected by their early developmental conditions, not just children exposed to a very deficient environment, and that this has long-term consequences for their predisposition to NCD. Second, we highlight the biomedical implications of the developmental origins of health and disease (DOHaD) concept of NCD. Last, we emphasize the policy implications of these issues.

THE NORMAL NATURE OF DOHaD PHENOMENA
Epidemiologic studies across a wide range of countries and over many years have confirmed the observation that early human development affects risk of NCD in later life. Importantly, it has been shown that risk is graded across the normal range of development, at least as measured by proxy measures such as birth weight (2). Specific aspects of the developmental environment, such as the mother’s diet or her body composition, have also been shown to affect risk factors for later disease. For example, Gale et al (3) showed that a mother’s energy intake in late pregnancy was related to the carotid intima-media thickness (which is an early marker of vascular disease) in 9-y-old children, which is an effect amplified by the child’s weight at age 9 y. Because these studies were conducted in an unselected population in a European city, they clearly showed how risk was graded within the spectrum of normal human development.

Understanding why human development may influence a predisposition to NCD even under normal circumstances can be assisted by taking an evolutionary perspective. Fundamentally to this is the concept that Darwinian fitness (ie, reproductive success), longevity, and health are not the same, and processes that influence fitness, such as natural and sexual selection, may not affect health but can affect longevity. In the context of these fundamental evolutionary processes, we can consider the changes that have occurred in human societies, particularly in developed societies, over the last few decades. Infant mortality and child mortality have fallen dramatically (4), and human longevity has also increased substantially; it is estimated that the average human life span increases by ∼6 h/d (5). In addition, many aspects of fitness are affected by life history traits (eg, age at puberty), and these change along with changes in our reproductive behavior.

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We now live in evolutionary novel environments. These environments include energy-dense nutrition, unbalanced macronutrient diets, decreased energy expenditure, new physical environments (e.g., artificial light), new social pressures, and even changes in the symbiotic environment. Thus, humans in many situations are mismatched (6) because we are challenged by environmental conditions that extend beyond our evolved capacity to adapt or indeed to new environments or challenges not met before in our evolution. Demographic and social changes mean that this mismatch is exaggerated in many societies. Fetal developmental constraint is greater in primigravida pregnancies, with higher maternal age, multiple births, and teenage pregnancy, and in women who diet before or during pregnancy. All of these circumstances are becoming more common globally, with pressure to reduce family size, changes in reproductive behavior, and lifestyles. In addition, as the balance between energy intake and expenditure becomes more obesogenic, children are more likely to be mismatched even if their prenatal development was not greatly constrained (7, 8).

The data of Ramachandran et al (9) showed how economic progress amplified this mismatch. In India, China, and Malaysia, the rise in the prevalence of diabetes parallels the increasing gross domestic product since 1981. Risk of NCD from mismatch is amplified further by conditions such as gestational diabetes (10) and maternal obesity (11, 12). The prevalence of these conditions is increasing worldwide and is associated with high morbidity in the mother and her offspring (13). The biology of these processes is not fully understood, although several pathways may be involved (14). Maternal hyperinsulinaemia and hyperglycemia may promote greater fetal growth and adiposity, but in some cases, maternal obesity is associated with smaller offspring size at birth (15). It is not known whether the effects of gestational diabetes and maternal obesity are always toxic or whether there is a range over which the effects on the fetus of greater nutrition provision are potentially adaptive (16). There is a need for more clinical and experimental studies in this area.

As with the effects of undernutrition, the effects of maternal adiposity appear to operate within the normal range because increasing maternal body mass index (in kg/m²) from <18.5 to >40 was associated with increasing obesity in children at age 4 y, but the process appeared to be graded across this range (17). Last, the effects of maternal constraint and obesity in pregnancy interact. For example, Reynolds and Godfrey (18) showed that a mother’s in early pregnancy was related to the percentage of body fat in her offspring at ages 28–31 y, but this effect was substantially greater in primiparous pregnancies than in multiparous pregnancies. In this regard, the rapid fall in family size associated with socioeconomic progress that leads to proportionately more primiparous pregnancies may be an important factor and even more so in China where NCD is now a very major issue. Thus, we envisage overlapping multigenerational cycles of chronic disease. Chronic undernutrition leads to stunting and low pregnancy weight gain and is associated with unbalanced nutrition in pregnancy. However, in some individuals the subsequent increased risk of obesity, insulin resistance, and gestational diabetes can lead to a further elevated risk of NCD in the next generation, which perpetuates the cycle of risk (19). Therefore, the incidence of NCD is expected to increase for several generations unless effective interventions can be found in the near future.

**BIOMEDICAL IMPLICATIONS**

DOHaD does not fit conventional models of disease because its cause and demography conflict with several underlying assumptions inherent in such models. Unlike models of infectious disease, in which individuals remain healthy until they catch a disease, NCD develops gradually over the life course. Moreover, underlying most conventional models is the assumption that genetic variants are the most important determinants of the variation in predisposition to disease between individuals. However, genome-wide association studies have not identified common fixed genetic variants, such as single nucleotide polymorphisms, that are linked to a substantial component of NCD risk, despite multiple studies of very large cohorts (20). In addition, it is assumed that adult lifestyle interventions are the most likely effective intervention, and thus, efforts should be focused on screening for risk in young adult people. Such arguments ignore the fact that responses to similar environmental challenges vary substantially between individuals, even in individuals who are genetically identical. Bouchard and Tremblay (21) showed that the effects of imposing either a positive or negative energy balance for a prolonged period produced dramatically disparate changes in body weight in homozygous twins. It is now more appropriate to think of a life-course model of NCD, where risk increases because of the sequential effects of the developmental induction in early life of different metabolic trajectories, the age-dependent decline in plasticity, and the subsequent differential responses to subsequent challenges (22). The exponentially rising risk of NCD (Figure 1) means that the greatest leverage in terms of reduction of risk can be achieved through a timely intervention in the developmentally plastic phase. Recent data (23) confirmed that such exponentially rising chronic-disease patterns occur with age, and the trajectory in early life is associated with social conditions such as the level of deprivation and the well-described influences of prenatal and infant nutritional and other experiences (24). Thus, although the modeling studies of Khan et al (25) revealed that the earlier screening for a disease such as type II diabetes is instituted after

![Figure 1](https://example.com/figure1.png)

**FIGURE 1.** Risk of noncommunicable disease increases along a trajectory through the life course, contrasting with models on the basis of infectious disease. The inherited, fixed genetic variation makes only a small contribution to later risk. In addition, because they occur too late, adult lifestyle interventions reduce risk to only a small degree or transiently. The maximum effect will be gained from timely interventions in early life when plasticity permits a sustained reduction in the trajectory of risk to be attained.
the age of 30 y, the more effective the capture of individuals suffering from the disease will be, this does not constitute a preventative intervention strategy. Last, current models of disease privilege the targeted golden-bullet approach to treatment or prophylaxis, usually via a pharmaceutical agent. However, as risk of NCD is graded across normal human development, it seems unlikely that a drug-based strategy could be widely applied.

In DOHaD research, there has been relatively little attention paid to the effects of development on human reproduction and behavior. However, the recent publication from the Centre for Global Development stressed the importance of a focus on adolescence in addressing a range of widespread problems including NCD (26). We previously pointed out that puberty and adolescence are good examples of life history plasticity, evolutionary mismatch and its adverse consequences (22, 6). Tanner (27) showed the secular trend in the falling age at menarche in many Western countries since 1850. The data of Sloboda et al (28) emphasized the role of pre- and postnatal environments on age at menarche with girls larger at birth and smaller at 8 y of age entering menarche $\sim$1.5 y later than those who were smaller at birth and larger at 8 y of age. Cooper et al (29) made similar observations in the 1946 UK birth cohort study. These observations raised issues about the sexualization of girls in their early teenage years, or before, which precedes by many years the full maturation of the brain. Lebell et al (30) showed that the fronto-thalamic pathways involved in decision-making processes do not mature fully until substantially after the age of 25 y. Kalitälä-Heino et al (31) related age at menarche to risk of psychosocial adjustment problems in girls and showed an exponential increase in depression, anxiety, substance abuse, bullying, and truancy as menarche commenced before the age of 11. In a large study, Michaud et al (32) showed that girls and boys entering puberty early were more likely to have early sexual experiences and mental health problems than were their peers: in the data of Michaud et al (32), boys were 5 times more likely to attempt suicide if they went into puberty earlier.

POLICY IMPLICATIONS

Arguably the major achievements in public health over the last century have largely been in the reduction of the incidence of communicable diseases. While this is projected to decrease still further in the next decade, the incidence of NCD will increase. To calculate the cost of such problems, we need to estimate what populations will spend on health care and the value of individual lives and their human capital (eg, resources, knowledge, and health), and we will have to accept that the investment in human capital will have long-term effects on several generations because susceptibility to NCD is heritable through a variety of potential intergenerational mechanisms, including genetic, direct, and indirect epigenetic inheritance and cultural transmission (33). It is recognized that the first economic analysis of the costs of low birth weight (defined as $<$2500 g) (34) gave an underestimate of such cost. New models need to take account of other developmental factors not reflected in such a dichotomous low compared with normal birth-weight classification, including effects operating at both high and low ends of the developmental spectrum, a wider range of socioeconomic and health consequences, effects that pass to more than just the next generation, and factors that influence health that do not have an effect on birth weight. The analysis of Stuckler et al (35) showed that the WHO’s budgetary allocations did not match the burden of disease when comparisons were made between Africa and the Western Pacific. While in Africa, the WHO funding for infectious disease reduction was disproportionate to the mortality and disability-adjusted life-year burden, which in the Western Pacific region was disproportionately large. In contrast, in Africa and, to an even greater extent, in the Western Pacific, funding is inadequate in relation to the disease burden for NCD. The analysis of Heckman (36) showed that family-income gradients in child-health status emerged early and widened with age; thus, investment in early life pays very substantial dividends. Such investment could be very effective if focused on young girls, as emphasized in the Centre for Global Development’s publication Start With a Girl (26). This publication emphasized the global health goals that can be achieved through preventative strategies targeted on young girls and why they will provide a substantial lever for economic and social development. Similarly, the WHO technical report on Optimizing the Outcomes of Pregnancy (37) reached similar conclusions with respect to the effects across the life course on the offspring’s health. Both reports pointed out that, eg, child marriage is still common in many regions of the world and younger mothers are more likely to have unhealthy babies. The problem is compounded by the fact that girls who marry young are less likely to continue attending school. Promoting access to education is Millennium Development Goal 3 (38), an area where some progress is being made but which will fall short of the target in many countries (39).

The influences of education are not confined to developing countries. Lower educational attainment is associated with the consumption of an unbalance “imprudent” diet in Southampton women (40). In addition, Inskip et al (41) showed that only a small proportion of Southampton women who were planning a pregnancy followed the recommendations for nutrition and lifestyle (ie, folic acid and iron supplements intake, alcohol consumption, smoking, diet, and physical activity). The mother’s diet is also related to the likelihood that she will follow dietary guidelines for her infant (42), and thus, there are transgenerational effects.

These results raise the prospect that a range of interacting factors need to be considered in the complex interventions necessary to prevent NCD. These include individual factors, social environment factors involving peers, parents, and the media, and the promotion of health literacy. Health literacy (43) is the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions. Nutbeam (43) divided health literacy into 3 categories. The first basic or functional health literacy concerns a simple level of knowledge about healthy behavior and risk. The second health literacy is communicative or interactive health literacy, whereby the knowledge is reinforced through contacts with peers. Several studies of interventions have shown that they are much more effective if they operate via peer networks at sites of social interaction. Third, attaining critical health literacy is the ultimate goal (44). At this level, autonomy and personal empowerment to make decisions about health choices is evident. Borzekowski (45) considered the concept of health literacy from a theoretical approach in relation to children and emphasized that health-promotion concepts and behaviors need to be made
culturally relevant and part of the environment of children. How-
ever, capabilities to develop such literacy start earlier than are often
thought, and children themselves can become agents of change in
their families and social groups. Promoting health literacy requires
a focus not so much on the ability to read a health text but on moving
up the stages of health literacy itself, which is a process that can
empower vulnerable and marginalized groups. This process will be
fundamental to reduce NCD.

CONCLUSIONS

DOHaD concepts are slowly beginning to have an effect on
population and public health policy; however, there is still a very
substantial way to go. The new scientific knowledge from DOHaD
research is becoming accepted. This seems to have been a slow
process because it has meant meeting the challenges of genetic
determinism, the focus on lifestyle interventions in adults, and the
failure to recognize the developmental sources of individual var-
ation in vulnerability to NCD. Nonetheless, if the progress to date
is to be capitalized on, it will require a wider acceptance and public
understanding of DOHaD science. At present, the DOHaD ap-
proach looks rather like a “motherhood and apple pie” message to
which few would object but which lacks novelty. In contrast, the
necessary focus on empowerment of women may clash with some
cultural views, and sensitivity to these has to be exercised. There
may also be too much emphasis on women and young girls, but for
pragmatic and ethical reasons, initiatives have to be made in con-
junction with educating men about their importance. If the
result is a culture of blame or shame, the resistance to change
induced will make the battle against NCD even harder.

The incorporation of scientific evidence to public policy is
a complex process. One element is the consideration of the eco-
nomic effect. This consideration requires raising the awareness at
the level of the treasury of the importance of a healthy start to life.
This will raise issues of cost benefit, relative efficacy of early
compared with late interventions, and the problem of discounting in
economic models, which are all aspects about which we have
relatively little hard information. Another element is public ac-
ceptance and opinion, which influence the political agenda, as do
ideological and electoral considerations. The focus on voting cycles
and public opinion can favor spending on treatment in an in-
creasingly ageing population rather than investing in the young.
The more clear the evidence and the better it is communicated, the
more likely will be a policy response that will determine the effect
on population and public health policy.

It must be recognized that the nonspecific nature of current
approaches does not lend itself to changing political minds. Many
politicians think that they already invest adequately in maternal and
infant health. But the scientific evidence and human-capital models
(36, 46) suggest otherwise, and the longer-term outcomes over a
broad range of domains, including adolescent psychosocial
adjustment, cognitive and behavioral development, and NCD risk,
need to be considered. More research is needed, but the evidence is
becoming compelling. It is important that the implications of these
findings are discussed as a matter of urgency. Time is not on our side
for reducing the NCD burden.

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