Developmental origins of health and disease: Moving from biological concepts to interventions and policy

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ARTICLE INFO

Keywords:
Development
Diabetes
Interventions
Life-course
Mismatch
Noncommunicable disease
Obesity

ABSTRACT

The rising incidence of noncommunicable diseases (NCDs), especially in young adults, presents great humanitarian and economic challenges to high-resource and, increasingly, to low-resource countries. No longer considered to be diseases of affluence, NCDs are exacerbated by urbanization and changes in social and lifestyle factors such as diet and family size. New research emphasizes the importance of early life factors in establishing the risk of NCDs through inadequate responses to later challenges, such as an obesogenic environment. A new focus on interventions to promote a good start to life in at-risk populations necessitates revision of public health policy, with implications for the health, education, and empowerment of women and children in particular.

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1. Introduction: A changing world

Noncommunicable diseases (NCDs), in particular cardiovascular disease, diabetes, chronic lung disease, and some forms of cancer, are the world’s biggest killers. Far from resulting from the “diseases of affluence,” 80% of these deaths occur in low- and middle-income countries, especially as these countries undergo socioeconomic improvement following reductions in the burden of infectious disease [1]. WHO predicts an increase of 17% in NCDs over the next decade globally—higher in some regions, e.g. parts of Sub-Saharan Africa. The risks of NCDs are exacerbated by sedentary lifestyles and poor diet high in sugar, salt, and fats. This is the concept of “mismatch” between the developmental environment and that experienced in young adulthood [2]—a phenomenon of increasing importance in the lifestyle transitions that have occurred between generations recently. But individual risk in the mismatched environment depends on genetic and developmental factors that affect individual sensitivity to an obesogenic world [3]. Unless this is appreciated there is a risk that the focus of preventative strategies could be misplaced. Alarming, NCDs are increasingly present in young adults, many in their thirties in low-income regions of the world, and in individuals who are not necessarily obese by Western standards.

Other demographic and social changes raise additional concerns in light of recent evidence of their effects on risk factors for NCDs in the next generation. As family size falls, the relative number of first-born children rises and they have a greater risk of developing obesity than subsequent siblings [4]. Such observations raise many concerns, e.g. in relation to China’s one-child policy. Nearly 80 million women worldwide suffer from gestational diabetes, increasing the risk of obesity in their children [5]. Many women consume unbalanced diets before and during pregnancy, and weight gain in pregnancy is often excessive or, in Japan, inadequate [6]. In some societies, pregnant women undertake substantial physical workloads, in industry or agriculture. Pregnancy in adolescent girls compromises fetal development and leads to young mothers dropping out of school. Addressing these problems—for example, in delaying first pregnancy until several years after menarche—necessitates empowerment of young women, but raises culturally sensitive issues such as access to contraception and loss of earnings.

The increasing use of technology associated with reproduction makes matters worse still. There are steady increases in the use of assisted conception services in some societies and alarmingly high rates of birth by cesarean delivery, reaching 80% of deliveries in parts of Brazil, for example [7].

2. The impact of NCDs

The substantial financial and humanitarian costs of NCDs may destabilize the economies of low-income countries, where risk markers become evident early in the process of socioeconomic improvement and well below the level of affluence associated with them in high-income nations [8]. This is the “double burden of poverty,” but the scale of widening global inequalities in health associated with NCDs has only recently been recognized.

The increases in NCDs in low- and middle-income countries in young adults will have substantial effects on productivity and
lifelong healthcare costs. WHO expenditure on communicable diseases is disproportionate to that on NCDs—when considered in relation to mortality and the disability-adjusted life-years burden—especially in the Western Pacific region compared with Africa [9]. The costs of these diseases are of great concern in countries where healthcare resources are low. The true costs are not known because previous attempts to measure such costs focused on the sequelae of low birth weight and a limited range of outcomes. Newer economic modeling approaches aim to include the impact on cognitive and noncognitive abilities and on health capital across generations and the entire range of human early development [10].

NCDs are generally preventable, although promoting such prevention was missing from the Millennium Development Goals (MDGs). Thus, new initiatives are now urgently needed. In high-income countries, current programs aimed at lifestyle alteration in adults have been met with limited and variable success, with the exception of reducing smoking. Progress in understanding the underlying causes of susceptibility to NCD has been slow owing to excessive emphasis on adult lifestyle as the trigger and on fixed genomic variations as determinants of inherited susceptibility [11]. The concepts of path dependency are clearly relevant. Some individual variation in susceptibility to environmental stressors is genetic; for example, polymorphisms have been associated with smoking addiction and the risk of obesity. But fixed genetic variations (for example small mutations and single nucleotide polymorphisms, repeat sequences, etc.) can account for only a small fraction of such risk [11]. Equally, there is some overstatement of the effectiveness of lifestyle interventions in adults [12]. The prevalence of obesity in high-income countries continues to rise and there remains great reliance on medical interventions. Further, these diseases are characterized by subtle prolonged prodrums with subclinical pathophysiology, suggesting an origin much earlier in life. Insulin resistance and abnormal vascular function can be detected in children [13] and considerable data point to prenatal and early life factors affecting later life disease risk [14].

3. How best to intervene

Greater attention now needs to be paid to how risks are established in early life. Understanding how the developmental environment influences an individual’s responses to their later lifestyle, and thus their risk of NCDs, is now largely focused on processes that involve nongenomic inheritance, especially epigenetic processes [15]. These affect gene expression and development without altering the genes we inherit from our parents.

New evidence demonstrates great opportunities for novel biomarkers of risk to be devised for use in early life. Such studies may point to pathways to target for intervention and may pave the way to much more effective approaches to improving health across the life-course, which can perhaps be customized to individual risk. For example, we recently showed that measurement of an epigenetic change in perinatal tissues at birth can predict a substantial fraction of the variation in body fat in children aged 6–9 years [16]. Further, this epigenetic change is related to the mother’s diet in pregnancy. In experimental studies such epigenetic changes are mechanistically linked to altered metabolic function and, in proof of principle studies, can be reversed by developmental nutritional, pharmacological, or hormonal interventions [17,18].

The specific aspects of the developmental environment, such as the mother’s diet or her body composition, stress levels, her level of physical activity, her age, and whether this is her first pregnancy, have been shown to influence risk factors for later disease in her children. This occurs in part through maternal constraint of fetal development [19], which generates potentially greater mismatch postnatally and may affect the offspring’s behavior and put it at greater risk, for example by altering appetite control [20]. These factors operate in all pregnancies, to a greater or lesser extent, and we are now beginning to understand how aspects of the external environment are transduced by the mother, during both fetal life and nursing, and then act via developmental plasticity to affect the characteristics of the offspring [3]. Paternal factors are also indicated by some recent observations [21].

4. Theoretical considerations

Such “parental effects” appear to have evolved because they confer Darwinian fitness by inducing characteristics appropriate to the environment in which the mother lives and in which the fetus predicts it will grow up: we termed them predictive adaptive responses [22]. The characteristics affect particular aspects of life-course biology such as metabolic homeostasis; numbers of fat, skeletal, and cardiac muscle cells; nephron numbers; and the setting of control systems such as appetite, stress responses, timing of puberty, and so forth. Together they affect the ways in which the adolescent and adult respond to their environment and so the person’s risk of NCD [23]. Because the predictions will be slightly different in each individual, they contribute to the differences in risk of disease between individuals, even if they apparently have very similar lifestyles.

Developmental changes made on the basis of such predictions can turn out to be inappropriate either because the signals sent by the mother to her offspring are inaccurate (for example, as a result of placental dysfunction or because she consumes an unbalanced diet) or because the environment has changed from one generation to the next. The resulting mismatch between the offspring’s characteristics and the environment in which it lives confers a major risk of NCDs [2]. We now know that mismatch processes also operate across the spectrum of environmental signals; for example, an unbalanced maternal diet that is inadequate in a low-income setting can be as potentially harmful as the high glycemic diet consumed in many high-income countries.

Whereas the original focus of attention in developmental origins of disease centered on children born small, even though they might constitute only a small proportion of the population, it is now clear that the developmental environment impacts on the life-course risk trajectory for NCDs of every individual. The story does not end at birth: epigenetic development can be influenced by how the child is nursed, by infection or allergen exposure, and perhaps by how the gut is colonized with commensal bacteria [24].

5. Policy implications

Reductions in child mortality from infectious disease and increased life expectancy are changing the age structure of many populations, and the patterns of disease. The demography of disease is changing quickly around the world, from a pattern dominated by infectious disease to one dominated by NCDs. Ten times as many people now suffer from NCDs as from HIV/AIDS, and according to the World Economic Forum the likely economic impact of NCDs eclipses that of infectious diseases [25]. This is not to imply that investment in infectious disease prevention and treatment should be scaled back, but rather that strategies for both infectious disease and NCDs should be integrated more closely. HIV infection or malaria infestation have detrimental effects on the health of pregnant women and alter placental function and the health of the fetus.

Similar considerations apply to linking NCD prevention to other initiatives in maternal and child health. Programs aimed at reducing maternal and infant mortality and preterm birth and the promotion of breastfeeding are good examples. Such programs have received substantial funding from government, NGOs, and philanthropic sources, and as part of the MDGs there is much infrastructure in place that could be harnessed for NCD prevention. Exclusive
References