

## Towards a new developmental synthesis: adaptive developmental plasticity and human disease

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*The Lancet* has rightly drawn attention to the goals of reducing the burden of maternal and childhood undernutrition,<sup>1</sup> focusing mainly on short-term outcomes such as infant survival and stunting.<sup>2</sup> However, the longer term effects on adult health<sup>3</sup> of a poor start to life suggest a further perspective. Developmental effects have been viewed traditionally in the context of major disruptions such as caused by teratogens, prematurity and growth retardation, but there is increasing appreciation of the role of developmental plasticity, which provides individuals with the flexibility to adjust their trajectory of development to match their environment. Plasticity operates across the entire range of environment, from undernutrition to excessive nutritional environments associated with gestational diabetes or maternal obesity,<sup>4,5</sup> leading to multi-generational cycles of disease.<sup>6</sup> Intervention strategies need to take account of these complexities.

The potential for health improvement throughout the life-course can be realised by integration of knowledge from several disciplines. In December, 2006, an interdisciplinary meeting—representing clinicians and public-health specialists from high-income and low-income countries, developmental and evolutionary biologists, geneticists, anthropologists, and economists—was held in Bellagio, Italy. The starting point was the question: how might adoption of a developmental perspective on the human life-course inform efforts to reduce the burden of non-communicable disease, particularly for populations in rapid nutritional transition? In this Viewpoint, we summarise conclusions from the ensuing dialogue.

Nowadays, people live in evolutionarily novel environments, and mismatch between our evolved physiological capabilities and contemporary exposures can lead to ill-health.<sup>7,8</sup> This mismatch is especially relevant to food preferences and consumption and to energy expenditure, which have changed greatly over several decades in affluent societies and in recent times in low-income countries undergoing socioeconomic improvement. Substantial variations in disease risk exist between individuals, even in the same environment,<sup>9</sup> and between populations.<sup>10</sup> This disparity could have a genetic component,<sup>11,12</sup> but findings of experimental work undertaken in the 1970s, and data of retrospective epidemiological cohort studies, have indicated additional non-genetic developmental contributions to risk for later disease. Although caution must be exercised when extrapolating from historical cohorts to current conditions, results from various experimental, clinical, and prospective

epidemiological studies show that changes in maternal or infant nutrition can produce heritable effects on risk for chronic disease.<sup>13</sup>

Organisms respond to challenges over a range of timescales (figure). At one extreme, rapid and reversible homeostatic mechanisms counter an immediate challenge. Then, stressors or exposures during critical developmental periods can affect growth, tissue differentiation, and physiological set-points, affecting responses to environmental challenges for life. Such adaptive plasticity, mediated in part by epigenetic processes,<sup>14,15</sup> gives advantage in environments that change over several generations. Fidelity of cues inducing adaptive plasticity might be enhanced by integration of the experience of recent generations, and new evidence suggests that epigenetic mechanisms could contribute to such non-genomic transgenerational inheritance.<sup>16,17</sup> On a long timescale, the genomes of populations can change over many generations as a result of selection or drift, and there are many examples of responses to environmental change becoming integrated into the human genome.<sup>18,19</sup> Clinical medicine and public health research have focused largely on causation and intervention at the short-term end of this spectrum. Consideration of the outcomes of developmental plasticity acting over the intermediate timescale is now important.<sup>20</sup>

Developmental plasticity evolved because it is adaptive, promoting Darwinian fitness by enhancement of survival and reproductive success.<sup>21</sup> Plasticity uses environmental cues (which in mammals are transduced and buffered by the mother) to optimise the life-course strategy for maximum fitness, both making the best of present conditions and being well prepared for the future environment.<sup>22</sup> Hormones and nutrients that cross the placenta can be affected by the mother's body composition, metabolism, and long-term lifestyle and by her immediate diet and stress levels. Thus, environmental cues affecting development provide historical information that offspring use to predict the future.<sup>23</sup>

However, this anticipatory strategy has limitations, especially for long-lived species such as human beings, with the result that challenges during development can induce responses that have short-term benefits for the mother or the fetus but then longer term costs in terms of reduced fitness.<sup>24,25</sup> When environmental conditions change strikingly between conception and adulthood, as has happened in most current human populations, the potential for a substantial mismatch is especially

great, and this difference contributes to disease risk. Shifts in environmental conditions between generations might also exceed evolved capacity for intergenerational transmission of information. In developed societies, we now live on average twice as long as did our Palaeolithic ancestors; therefore, the detrimental effects of inaccurate predictions are more likely to be apparent.

Developmental plasticity evolved to make the most of an organism's Darwinian fitness, not necessarily its health, and life-course strategies ensure survival to reproduce rather than longevity. Anthropological and clinical data support this idea. Women throughout hunter-gatherer societies show an inverse relation between age at menarche and anticipated lifespan,<sup>26</sup> and in high-income countries, lower birthweight individuals have earlier menarche, an effect exaggerated by prepubertal weight gain.<sup>27</sup> Although being a small (but healthy) individual might not be a disease outcome, it incurs costs (in lower reproductive fitness, earnings, or social status).<sup>28</sup> These costs might be viewed—biologically if not ethically—as trade-offs for gains in survival through better match of metabolic requirements to energy availability.

Manipulation of developmental cues might be used to shift the adaptive capacity of the organism to cope in a later environment. This approach is possible experimentally (eg, metabolic disease induced by prenatal undernutrition can be prevented by postnatal hormonal manipulation),<sup>29</sup> but recommendation of prenatal diets with a view to promotion of human offspring health would be premature. The effect of multiple micronutrients on fetal growth<sup>30</sup> and birth outcomes<sup>31</sup> suggests that factors additional to energy and protein intake in pregnancy might be important. Postnatal plasticity can account for the beneficial outcomes—metabolic and cognitive—conferred by breastfeeding.<sup>32,33</sup>

Enhanced understanding of adaptive developmental plasticity has three important implications for public health. First, interventions to augment adult health might need to start early in life and take a cross-generational perspective, a challenging strategy for policy makers and funders. Approaches starting in adult life need to take account of developmental history—eg, attempts to change health behaviours in adults might be less effective in populations that have, through adaptive responses to past environments of food insecurity, developed tendencies to excessive fat storage. Second, interventions in early life aimed at essential short-term gain, such as infant survival, could also have longer term effects on individuals throughout their life-course, and such outcomes might not always be beneficial. Programmes aimed at increasing birthweight might raise risk for later diabetes, amplified by accelerated fat gain in childhood, a possible result of universal supplementation programmes.<sup>34</sup> Third, initiatives for development of a uniform standard for human growth<sup>35</sup> use the assumption that optimum health across the

life-course will be achieved through comparable growth in various settings, irrespective of factors such as maternal diet, body composition, or physical activity. The best outcome measure for postnatal growth remains uncertain; Black and colleagues<sup>36</sup> proposed stunting (height-for-age) as a better indicator of undernutrition than being underweight (weight-for-age), but, in turn, this measure assumes that the only outcome associated with inappropriate undernutrition is impaired growth. Design of interventions to promote growth requires consideration of the variance of risk for later disease across the whole distribution of growth and size, not solely that associated with shifting the population mean in what seems to be a healthy direction in the short term.<sup>37</sup>

Approaches to interventions for enhancement of maternal and child health have focused largely on issues of survival, in consonance with the Millennium Development Goals for reduction of maternal and child mortality substantially by the year 2015.<sup>38</sup> Focusing on early survival might not capture outcomes that have longer term implications for adult health, life expectancy, quality of life, and accumulation of human capital. Further, recommendations for nutritional interventions are frequently based on raising birthweight, focusing on gains in stature or micronutrient status in the short term.<sup>39</sup> Longer term follow-up data confirm the existence of a window of opportunity for intervention in early childhood, younger than 24 months of age, and only limited benefit, or even harm, of feeding strategies thereafter.<sup>3,40</sup>

Health is usually not included in calculations of human capital other than in terms of health expenditure, although a healthier population is an economically more productive one. Estimates of the true accumulation of human capital embodied in an individual should include more than the conventional economic measure of educational attainment: ideally, calculations should incorporate the effect of events from conception or earlier, perhaps even extending to measures of intergenerational accrual of biological benefit.

Accordingly, we make two specific recommendations for measurement of economic benefits of intervention programmes. First, use of linear discount rates for assessment of benefit undervalues early-life

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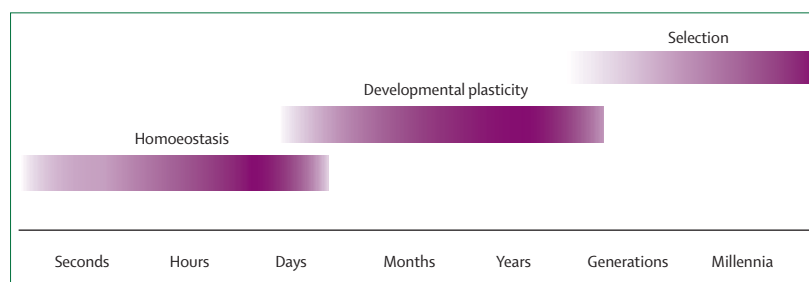


Figure: Modes of human adaptability

**Panel: Research agenda for adaptive plasticity and human health****Basic research**

- What are the mechanisms by which early-life events have long-term effects, and can the pathway be altered or reversed?
- What is best fetal development? How can it be defined in relation to later risk?
- What are the indicators of best pregnancy outcome—eg, birth size, duration of pregnancy—and what levels of risk do they represent?
- To what extent could markers of specific nutrient status before or during pregnancy inform us about the likely outcomes of the pregnancy?
- To what extent could postnatal epigenetic markers inform us about the likely life-course of the offspring?
- What are the postnatal windows of plasticity and, therefore, intervention?
- What is the extent and mechanism of intergenerational transmission of disease risk?

**Applied research**

- What is the importance of developmental processes in generating the burden of disease in different populations?
- What approaches are possible to intervene in individuals and in populations during different stages of the life-course (preconception, pregnancy, lactation, childhood, adult, parent)?
- How can developmental interventions be made context-specific, balancing prevention of undernutrition against the later-life consequences of rapid postnatal weight gain?
- What level of developmental risk of later chronic disease is acceptable?
- How can the various levels of intervention (societal to individual) be designed appropriately within the cultural context?
- What are the societal costs of less than optimum development, measured with more appropriate models than simple discounting?
- What are the short-term and long-term economic benefits of optimising early-life development?
- What is the cost-benefit ratio of early intervention?
- Which interventions are most likely to be cost effective?

interventions<sup>41</sup> and has limitations when considering intergenerational equity.<sup>42</sup> Second, although utility-based measures of disease burden (such as disability-adjusted life-years) enable comparison of intervention programmes<sup>2</sup> they fail to capture intergenerational benefit or the monetary value of ensuing savings in health care or increases in labour productivity. More elaborate composite measures of outcome are needed to show the true cost-benefit ratio of early-life interventions.

The growing prevalence of metabolic disease worldwide, with its large current and projected costs, challenges many disciplines to provide an explanation for the underlying human biology and to define the best ways to intervene (panel). Merely focusing on genetic predisposition or improving adult lifestyle is inadequate. Disease risk from mismatch is exacerbated by a relatively small change in nutritional conditions in societies starting from a low baseline level, and the resulting increased susceptibility to obesity and gestational diabetes passes risk on to the next generation. Because early growth and development is a time in human life when substantial biological stock is transferred to future generations,<sup>3,43</sup> ignoring the processes by which this transfer takes place risks erosion of future human capital in both health and economic terms. Since developmental plasticity results in variation in human phenotype and life-course strategy, adoption of a “one size fits all” approach to intervention will not be effective for a proportion of the population, and might put some individuals at greater risk of later poor health.

**Contributors**

All authors participated in the Bellagio workshop, contributed to subsequent discussions, and have seen and approved the final version. PDG, MAH, PB, ASB, CML, and ZAB wrote the report. PDG had final responsibility to submit this paper for publication.

**Conflicts of interest**

We declare that we have no conflicts of interest.

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