Pregnancy, programming, and predisposition

Published Online
February 21, 2019
http://dx.doi.org/10.1016/S2214-109X(19)30051-8

See Articles page e523

Epidemiological studies from numerous populations and animal models have shown that low birthweight is associated with an increased risk of non-communicable diseases (NCDs) later in life, including diabetes, hypertension, cardiovascular disease, and neurological disorders.[1] Moreover, the associations between low birthweight and NCDs can be transmitted across generations, even in the absence of further adverse exposures, such as maternal malnutrition.[2] Therefore, birthweight is a measure of newborn health and a key indicator of later disease risk.

Mechanisms underlying birthweight and adult disease remain to be fully elucidated, but have been conceptualised as the Developmental Origins of Health and Disease (DOHaD) hypothesis. This concept suggests that adverse environmental factors might induce changes in fetal growth and metabolism to match the environment; however, in environments that subsequently change this process could become maladaptive and lead to disease in later life.[1] There are other powerful mechanisms through which these intergenerational effects might be mediated, for example, via transmission of genes associated with both birthweight and specific diseases.[3] Additionally, similar associations might merely reflect persistence of adverse extrinsic factors, such as malnutrition and poverty, across generations.

Generally, genetic factors are considered to govern less than 50% of variation in birthweight; most of the variation appears to be dependent on maternal factors such as physical constraints and metabolic environments during pregnancy.[4] However, even within this so-called maternal compartment, the relative contributions of programmed maternal factors, such as a mother's own birthweight, versus extrinsic environmental factors during pregnancy, are not fully understood.

In *The Lancet Global Health*, Alison Gibberd and colleagues[5] present important new evidence on the consequences of low birthweight in an Australian Aboriginal population. Australia's Aboriginal population has been well documented to be chronically disadvantaged, with a large health gap compared with non-Indigenous Australians in terms of many health indicators.[6] This study[5] found a strong association between maternal behavioural factors and health status during pregnancy in terms of children's birthweight. For instance, smoking and drug misuse were associated with a mean decrease in offspring birthweight Z score of 0·39 (95% CI −0·45 to −0·34) and 0·31 (−0·43 to −0·20), respectively, and diabetes with an increase of 0·58 (0·39 to 0·77). However, analyses did not support any appreciable association between maternal fetal programming and birthweight. Maternal and paternal factors had similar influences on birthweight, and no association between maternal and child birthweight was found in a substudy of cousins with shared maternal grandparents. Since this sub-analysis controlled for genetic and environmental factors shared by related mothers, this suggests that fetal programming played little or no part in birthweight. Therefore, the effects of environmental insults in this population did not appear to have intergenerational consequences.

However, data from other populations are less reassuring. In a large cohort in California, the probability of a child having low birthweight was nearly 50% higher if the mother herself had low birthweight. This association was maintained in a comparison of sisters sharing similar genetic material and some environmental factors, and after controlling for intergenerational changes in socioeconomic status.[7] The acute insult of the Dutch famine in 1944–45 caused various intergenerational consequences for health, although not specifically for birthweight.[8]

These discrepant findings might reflect the complexities around processes such as fetal growth, in which several factors, originating from both nature and nurture, are involved. The relative effect size of each factor probably varies between populations. Furthermore, within the concept of DOHaD, birthweight is only a surrogate marker of adverse intrauterine environment, and is not necessarily a mediator of later risk of disease. Disease risk might occur via other processes, such as epigenetic modification, changes in cell numbers, organ structure, or altered hormonal axes. Indeed, some studies have shown that other indicators, such as thinness at birth or other body composition indices (particularly if associated with rapid catch-up growth in early childhood) have stronger associations with later disease than birthweight itself. Therefore, we cannot assume that the insufficient evidence of

maternal fetal programming of birthweight as described by Gibberd and colleagues[5] excludes transgenerational risks of disease transmission. More long-term research in a range of settings is required to fully assess these risks.

From the DOHaD concept, intergenerationally transmissible adaptations that occur following perturbation of the environment would only be advantageous to population survival when environmental conditions are consistent over several generations. Any rapid change in the environment appears to put the programmed offspring at risk of NCDs, such as hypertension and diabetes. This explanation might, at least in part, account for the increasing epidemic of NCDs in low-income and middle income countries (LMICs),[9] where populations are rapidly undergoing urbanisation, migration, and the adoption of Western lifestyles associated with nutritional changes and reduced physical activity. Demographic and nutrition transitions can create mismatching between programmed biological systems and prevailing environmental conditions, as happened in the Dutch famine, but is perhaps less true of the chronic health gap for the Australian Aboriginal population. Therefore, DOHaD research has relevance in LMICs and other populations in rapid transition, for whom there is a paucity of data. In this respect, it is encouraging that the DOHaD Society is expanding its interest to LMICs, including the recent launch of its Africa Chapter,[10] which will help promote this science globally.

*Moffat J Nyirenda, Peter Byass
Medical Research Council/Uganda Virus Research Institute and London School of Hygiene & Tropical Medicine Uganda Research Unit, London School of Hygiene & Tropical Medicine, London WC1E 7HT, UK (MJN); and Department of Epidemiology and Global Health, Umeå University, Umeå, Sweden (PB)
moffat.nyirenda@lshtm.ac.uk

We declare no competing interests.

1 Hanson MA, Gluckman PD. Early developmental conditioning of later health and disease: physiology or pathophysiology? *Physiol Rev* 2014; **94:** 1027–76.
2 Drake AJ, Walker BR. The intergenerational effects of fetal programming: non-genomic mechanisms for the inheritance of low birth weight and cardiovascular risk. *J Endocrinol* 2004; **180:** 1–16.
3 Hattersley AT, Beards F, Ballantyne E, Appleton M, Harvey R, Ellard S. Mutations in the glucokinase gene of the fetus result in reduced birth weight. *Nat Genet* 1998; **19:** 268–70.
4 Fleming TP, Watkins AJ, Velazquez MA, et al. Origins of lifetime health around the time of conception: causes and consequences. *Lancet* 2018; **391:** 1842–52.
5 Gibberd AJ, Simpson JM, McNamara BJ, Eades SJ. Maternal fetal programming of birthweight among Australian Aboriginal infants: a population-based data linkage study. *Lancet Glob Health* 2019; published online Feb 21. http://dx.doi.org/10.1016/S2214-109X(18)30561-8.
6 Australian Institute of Health and Welfare. Australia's Health 2018. Canberra: Australian Institute of Health and Welfare, 2018.
7 Currie J, Moretti E. Biology as destiny? Short- and long-run determinants of intergenerational transmission of birth weight. *J Labor Econ* 2007; **25:** 231–64.
8 Painter RC, Osmond C, Gluckman P, Hanson M, Phillips DI, Roseboom TJ. Transgenerational effects of prenatal exposure to the Dutch famine on neonatal adiposity and health in later life. *BJOG* 2008; **115:** 1243–49.
9 GBD 2017 Mortality Collaborators. Global, regional, and national age-sex-specific mortality and life expectancy, 1950–2017: a systematic analysis for the Global Burden of Disease Study 2017. *Lancet* 2018; **392:** 1684–735.
10 Norris SA, Daar A, Balasubramanian D, et al. Understanding and acting on the developmental origins of health and disease in Africa would improve health across generations. *Glob Health Action* 2017; **10:** 1334985.