Fetal Malnutrition and Long-Term Outcomes
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Recent epidemiological studies have shown that lower birthweight is associated with a wide range of adverse outcomes in later life, including poorer ‘human capital’ (shorter stature, lower cognitive performance), increased risk factors for later disease (higher blood pressure and reduced glucose tolerance, and lung, kidney and immune function), clinical disease (diabetes, coronary heart disease, CHD), chronic lung and kidney disease) and increased all-cause and cardiovascular mortality [1]. Higher birthweight is associated with an increased risk of cancer, and (if caused by gestational diabetes) obesity and diabetes. The ‘developmental origins of health and disease’ hypothesis proposes that fetal nutrition has permanent effects on growth, structure and metabolism (‘programming’, fig. 1). This hypothesis is supported by studies in animals showing that maternal undernutrition (global diet restriction, low protein diet) and overnutrition (obesity, high-fat diet) before and during pregnancy can produce similar abnormalities in the adult offspring. These studies have shown that long-term cardiometabolic programming can occur in the absence of an effect on birthweight.

Animal studies have shown that the epigenome is sensitive to the nutritional environment during early embryogenesis and gestation, and that this may be an important mechanism underlying programming. A number of animal studies have shown that levels of protein and methyl donor nutrients in the mother’s diet (for example vitamin B_{12}, folic acid, choline and betaine) alter methylation of the offspring genome, change the expression of genes related to energy metabolism, and influence insulin resistance and adiposity in adult life. Several human studies have now related maternal vitamin B_{12} and/or folate status in pregnancy to insulin resistance and adiposity in the children [2]. A complete sequence linking maternal nutrition to epigenetic changes in children and the later development of cardiometabolic disturbances and disease has not yet been demonstrated in humans.
Postnatal weight gain and growth also influence long-term capacity and health. Poor nutrition and stunting during infancy are associated with reduced human capital outcomes such as achieved education and adult income. The risk of adult chronic cardiometabolic diseases such as diabetes and CHD is highest in men and women who showed evidence of intrauterine undernutrition (e.g. low birthweight) and poor weight gain during infancy, but had accelerated body mass index (BMI) gain in late childhood or adolescence and became overweight adults [3]. These phenomena may explain the rapid rise in adult chronic disease occurring in low- and middle-income countries, where intrauterine growth restriction and infant stunting remain widespread, and where upward crossing of BMI centiles in adolescence and adulthood are increasing with economic transition (fig. 2). In women, poor early-life nutrition and adult overweight combine to increase risk of gestational diabetes, which leads to a form of fetal overnutrition and ‘fuel-mediated teratogenesis’, which also contributes to diabetes risk in the next generation (fig. 2).
Common chronic diseases could potentially be prevented by achieving optimal fetal nutrition, and this could have additional benefits for survival and human capital. Recent opportunistic follow-up of children born after randomized nutritional interventions started in mid-pregnancy provides some evidence of beneficial effects on growth, vascular function, lipid concentrations, glucose tolerance and insulin resistance, but results are inconsistent [4, 5]. If epigenetic phenomena underlie programming, these interventions missed the periconceptional period, and may have started too late in pregnancy to influence long-term outcomes. Intervention studies are required that cover the whole ‘first 1,000 days’ of life (the periconceptional period until the end of infancy) and achieve adequate and balanced maternal nutrition by the time of conception in order to test the programming hypothesis fully.

References

Fig. 2. Intergenerational effects of fetal nutrition on diabetes risk.