

Chapter 3

Early Origins of Cardiometabolic Disease

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INTRODUCTION: BIRTH WEIGHT AND ADULT CARDIOVASCULAR DISEASE

This chapter discusses the developmental origins of health and disease (DOHaD) and their implications for public health. It summarizes the epidemiological evidence in humans linking low birth weight, infant and childhood growth, adult body mass index (BMI), and maternal weight and nutrition to cardiometabolic risk factors in later life. It describes what is meant by developmental programming and considers alternative explanations for the epidemiological associations. It then evaluates the effects of interventions in pregnancy, infancy, and childhood on later cardiovascular risk and concludes with the public health implications and potential economic benefits of early life interventions.

Forsdahl (1977) discovered that Norwegian counties with the highest infant mortality in 1896–1925 experienced the highest death rates from coronary heart disease in the mid to late twentieth century. He suggested that poverty in childhood caused permanent damage, perhaps due to a nutritional deficit, that resulted in lifelong vulnerability to an affluent lifestyle and high fat intake. A decade later, Barker and Osmond (1986) found a similar phenomenon in the United Kingdom. Using archived birth records from the county of Hertfordshire, they found that lower birth weight and lower weight at age one year were associated with an increased risk of death from coronary heart disease and

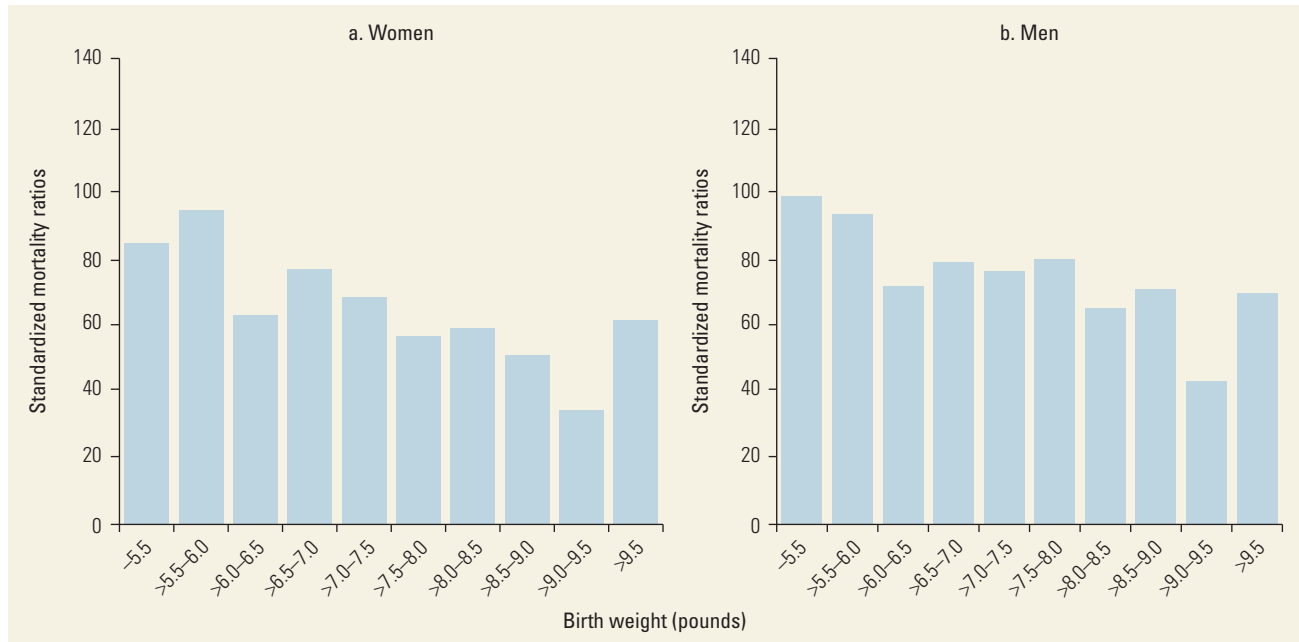
stroke in adulthood (Barker and others 1989; Osmond and others 1993). Mortality approximately doubled from the highest to the lowest extremes of birth weight or infant weight (figure 3.1). Barker and others (1989) concluded that processes linked to growth and active in prenatal or early postnatal life strongly influence the risk of adult coronary heart disease.

The association between lower birth weight and increased risk of coronary heart disease has been replicated in many different populations (Andersen and others 2010; Forsen and others 1999; Huxley and others 2007; Leon and others 1998; Stein and others 1996) (figure 3.2). The association is linear and graded across the whole range of birth weight, with an upturn at extremely high birth weight (figure 3.1). The association is independent of adult socioeconomic status, making confounding an unlikely explanation (Leon and others 1998). Studies that include gestational age data indicate that restricted fetal growth, rather than preterm delivery, is associated with coronary heart disease (Leon and others 1998).

RISK FACTORS FOR CARDIOVASCULAR DISEASE

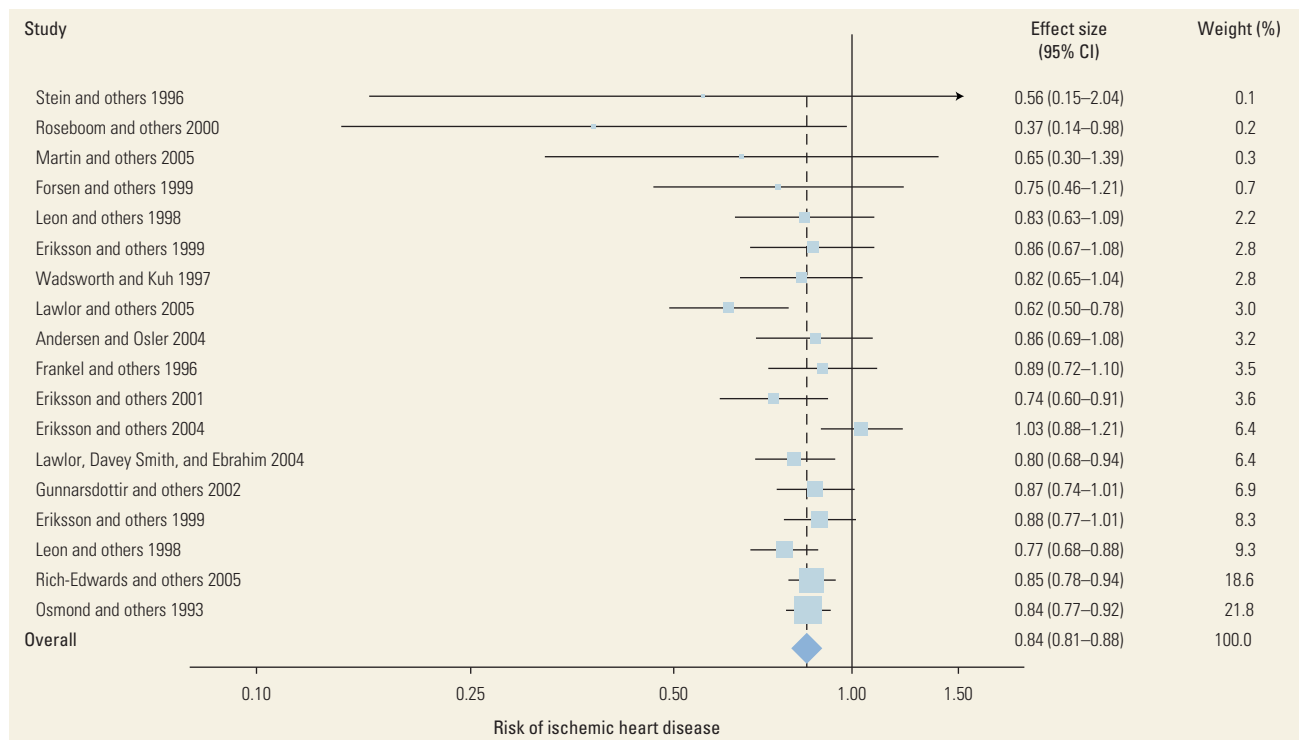
Associations were subsequently found between small size at birth and some of the major risk factors for coronary heart disease, including impaired glucose tolerance

Figure 3.1 Standardized Mortality Ratios for Cardiovascular Disease in Women and Men Younger than Age 65 Years (up to 1992) in Hertfordshire, United Kingdom, by Category of Birth Weight



Source: Osmond and others 1993.

Figure 3.2 Forest Plot from a Meta-Analysis of the Relative Risk for a Fatal or Nonfatal Cardiovascular Event per Kilogram Increase in Birth Weight across 18 Studies



Source: Huxley and others 2007.

Note: CI = confidence interval. Weight (%) refers to the relative weighting of each study in the meta-analysis, based on the study sample size.

and type 2 diabetes mellitus (T2DM) (Hales and others 1991), hypertension (Fall and others 1995), insulin resistance (Phillips 1995), and metabolic syndrome (Barker and others 1993). A systematic review confirmed that the relationship between birth weight and T2DM is inverse, graded, and independent of current body size and socioeconomic class (Whincup and others 2008). The relationship is particularly strong for birth weight under 3 kilograms. For every kilogram increase in birth weight, the odds of diabetes are 0.75 (95 percent confidence interval [CI], 0.70 to 0.81). The inverse relationship between birth weight and blood pressure has also been demonstrated consistently across different populations in both high-income countries (HICs) and low- and middle-income countries (LMICs) and in both childhood and adulthood (Huxley, Neil, and Collins 2002; Huxley, Shiell, and Law 2000; Law and Shiell 1996). The size of the effect is debated, ranging from an estimated fall in systolic blood pressure of 0.6 millimeter of mercury (mmHg) per kilogram increase in birth weight (Huxley, Neil, and Collins 2002) to 2–3 mmHg (Huxley, Shiell, and Law 2000; Law and Shiell 1996). A review (Mu and others 2012) comparing low birth weight (less than 2,500 grams) to high birth weight (more than 2,500 grams) suggested that adult systolic blood pressure is higher by approximately 2 mmHg in the low–birth weight group.

Obesity, as measured by BMI, is not associated with lower birth weight. On the contrary, persons who were small at birth also tend to be thinner as adults (Fall 2011). Evidence indicates that the lower adult BMI associated with lower birth weight reflects lower lean body mass rather than less adiposity (Wells, Chomtho, and Fewtrell 2007). Some evidence suggests that small size at birth is associated with central obesity in later life, as measured by waist circumference, waist-hip ratio, or subscapular-to-triceps skinfold ratio (Fall 2011).

Small size at birth has been shown to predict structural and functional cardiovascular measures such as increased left ventricular size and dysfunction and reduced arterial compliance (Lamont and others 2000; Martyn and others 1995; Vijayakumar and others 1995), although results from LMICs have been inconsistent (Kumaran and others 2000; Norman 2008). Associations between small size at birth and adverse concentrations of plasma lipid or clotting factor have been reported, but they are inconsistent across populations (Lauren and others 2003).

In summary, poor fetal growth resulting in small size at birth is associated with an increased risk of adult coronary heart disease and some of its risk factors. The findings potentially have significance in the context of LMICs, where the prevalence of low birth weight is high.

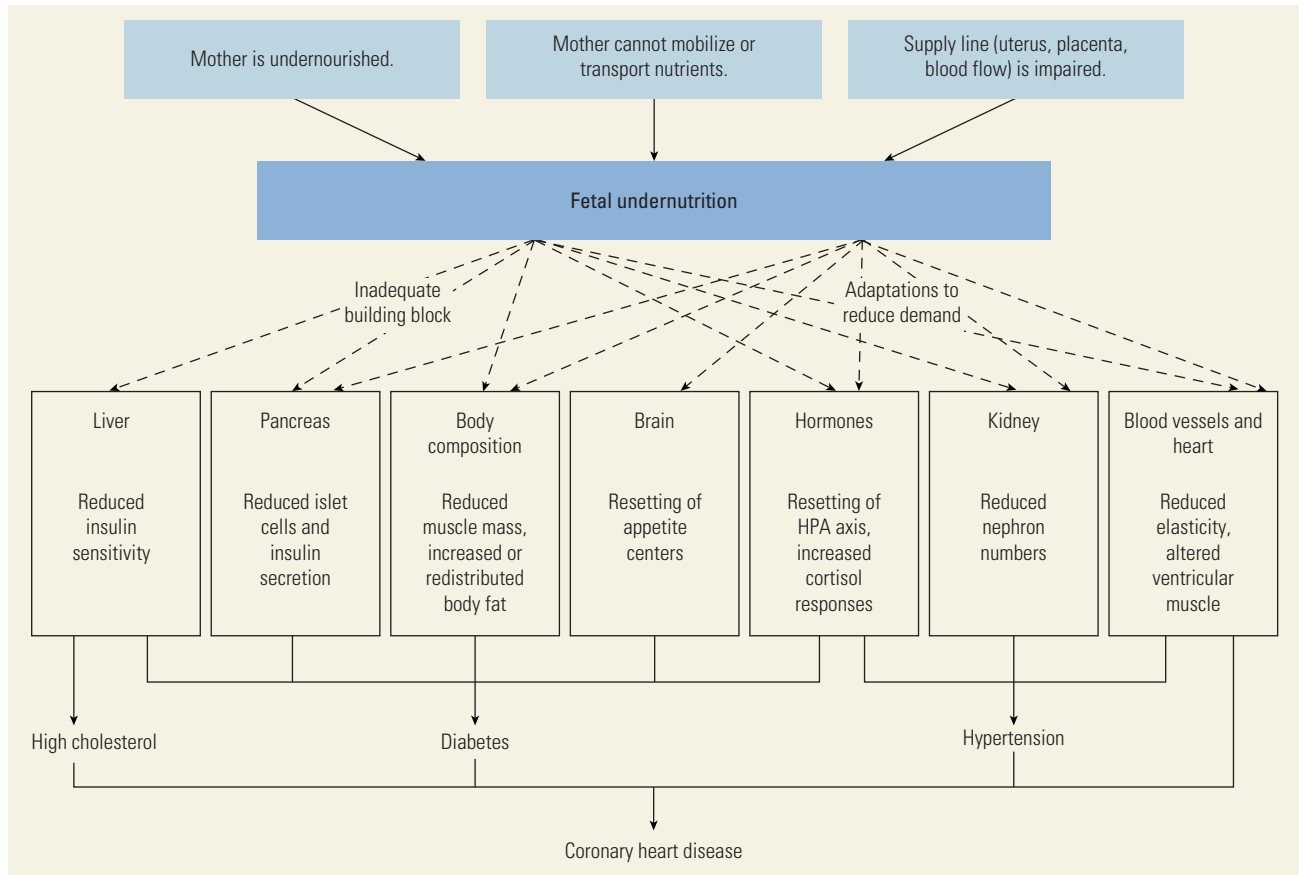
Approximately one in four newborns in South Asia weighs less than 2,500 grams, and 10 countries account for more than 50 percent of the global burden of low birth weight; India alone accounts for more than 30 percent.¹

DEVELOPMENTAL ORIGINS OF HEALTH AND DISEASE

Barker proposed that the association between small size at birth and disease in later life reflects the permanent effects of fetal undernutrition (Barker 1998; Barker and others 1993). Fetal undernutrition could occur because the mother is undernourished or because the materno-fetal supply line (uterine blood flow, placenta) is suboptimal. The fetus depends on the transfer of nutrients from the mother and adapts to an inadequate supply of nutrients in various ways: prioritization of brain growth at the expense of other tissues, such as the abdominal viscera; reduction in the secretion of and sensitivity to the fetal growth hormones (for example, insulin); and upregulation of the hypothalamo-pituitary-adrenal (stress) axis. Barker (1998) proposed that, although they occur in response to a transient phenomenon of fetal undernutrition, these changes become permanent or *programmed* because they occur during critical periods of early plasticity. Programmed changes may include different tissues, producing a variety of metabolic effects (figure 3.3), which could lead directly to adult cardiovascular disease or render the individual more susceptible to the adverse cardiometabolic effects of environmental stressors, such as smoking and obesity in later life. Subsequent research in experimental animals has confirmed that it is possible to program high blood pressure and diabetes by manipulating the nutrition of the mother during pregnancy (Duque-Guimaraes and Ozanne 2013).

Research in humans and further studies in experimental animals suggest that environmental influences other than undernutrition can program later disease. These influences include fetal overnutrition (as in maternal diabetes or obesity), maternal smoking, and exposure to environmental pollutants. Many of the body's tissues and organs and its endocrine system may be affected, leading not only to cardiovascular disease and diabetes, but also to renal disease, lung disease, osteoporosis, and impaired mental health (Luyckx and others 2013; Victora and others 2008). While the fetal period may be particularly important because of the rapid growth and development of organs and tissues at this time, evidence suggests that exposures during infancy and childhood also have programming effects. It has become clear that changes in body size, such as low

Figure 3.3 Developmental Origins of Health and Disease Hypothesis



Note: HPA = hypothalamo-pituitary-adrenal (stress) axis.

birth weight, do not *cause* later disease. Birth weight is a convenient, frequently measured summary of the *effect* on the fetus of multiple maternal factors, including size, nutritional status, metabolism, pregnancy complications, physical activity, and lifestyle. The effects of these factors on developing fetal organs, resulting in permanently altered structure and function, are thought to be responsible for later disease risk. This new understanding led to what was initially known as the Barker hypothesis or the fetal programming hypothesis, later renamed the DOHaD hypothesis.

A challenge facing DOHaD research is the long lag between early life exposures (such as fetal undernutrition) and the emergence of hard disease outcomes in adult life. This lag means that much of the evidence in humans comes from observational data and from associations between early life factors (usually birth weight) and adult outcomes. However, associations between lower birth weight and higher risk markers for cardiovascular disease, such as blood pressure, glucose, and insulin concentrations,

can be found even in children (Bavdekar and others 1999) and young adults, long before disease becomes apparent, suggesting that the effects of programming and the potential benefit of interventions may be detectable at relatively young ages.

GESTATIONAL DIABETES, MATERNAL OBESITY, AND FUEL-MEDIATED TERATOGENESIS

Fetal overnutrition attributable to maternal hyperglycemia or obesity is thought to program the offspring for obesity and T2DM, strong risk factors for cardiovascular disease. Pedersen (1954) proposed that the transfer to the fetus of excess maternal glucose in gestational diabetes mellitus (GDM) stimulates fetal pancreatic islets to produce fetal hyperinsulinemia, which leads to macrosomia (Pedersen 1954). Freinkel (1980) suggested that a mixture of maternal nutrients (glucose, lipids, and

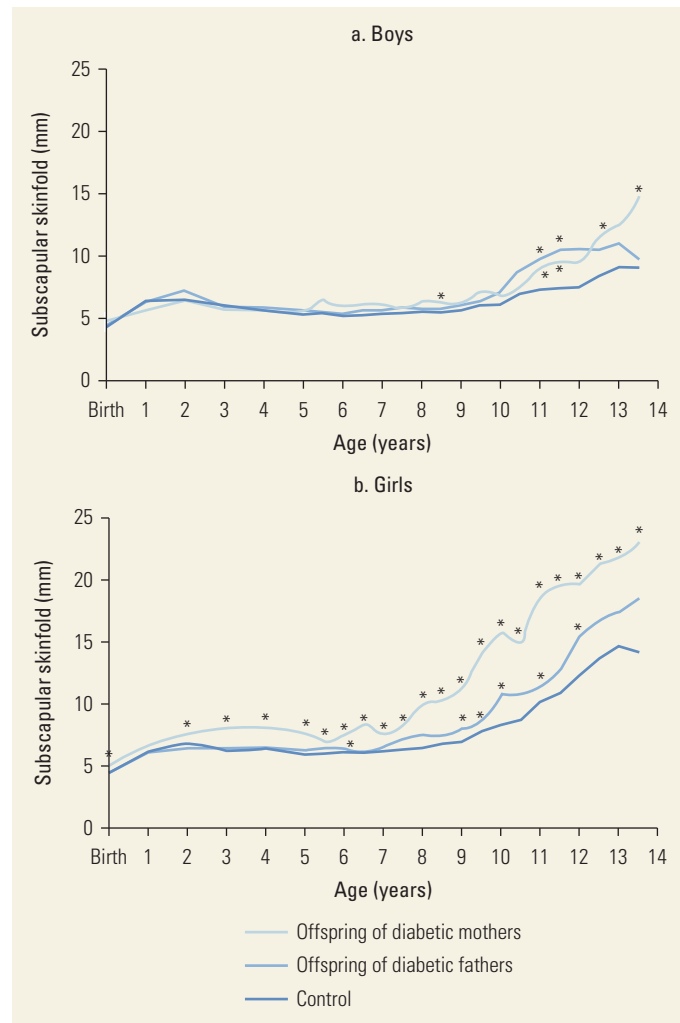
amino acids) affects not only the growth of the fetus, but also its risk of future obesity, diabetes, and neurocognitive development (fuel-mediated teratogenesis). Infants of mothers with GDM are born larger and develop early obesity, central obesity, higher insulin resistance, and impaired glucose tolerance and T2DM (Dabelea and Pettitt 2001). The inheritance of genes responsible for both obesity and GDM could cause such an effect. However, offspring of diabetic mothers have higher rates of obesity and T2DM than do siblings born before the mother developed diabetes (Dabelea and others 2000), suggesting that these higher rates are an effect of the intrauterine diabetic environment.

These findings have been replicated in India, where children born to mothers with GDM were larger at birth and had higher subcutaneous adiposity compared with the newborns of non-GDM mothers (Hill and others 2005). The difference in adiposity in girls continued to increase throughout childhood (figure 3.4). At age nine years, the children of GDM mothers had higher glucose concentrations and insulin resistance (Krishnaveni and others 2010).

Maternal glycemia and insulin resistance are closely linked to maternal adiposity, and there is growing interest in whether maternal obesity, greater pregnancy weight gain, or both also program obesity and increased cardiometabolic risk in children through their effect on fetal nutrition. Studies in HICs have shown that, like diabetic mothers, obese mothers have altered lipid and glucose metabolism, have increased insulin resistance and circulating pro-inflammatory factors (Huda, Brodie, and Sattar 2010), and potentially expose the fetus to fuel-mediated teratogenesis. Newborns of obese women in the United States have increased body fat (Catalano and others 2009), and higher maternal BMI or adiposity during pregnancy is associated with a greater risk of overweight and obesity in children (Oken 2009). Another U.S. study has shown that children of mothers who are obese but do not have GDM are at increased risk of developing metabolic syndrome (Boney and others 2005). Population-based studies in the United Kingdom have shown that children of women who gained excess weight during pregnancy had higher blood pressure, lipids, and body fat percentage (Fraser and others 2010) and that offspring of obese mothers had an increased risk of death from cardiovascular disease in middle age (Reynolds and others 2013).

It is not yet certain that these associations reflect fetal programming by maternal obesity, but the evidence for programming by GDM is strong, with important implications for public health as the world gets fatter. Upward trends in maternal BMI and GDM

Figure 3.4 Median Subscapular Skinfold Thickness for Offspring of Diabetic Mothers, Offspring of Diabetic Fathers, and Controls Ages 0–9.5 Years, in Mysore, India



Source: Krishnaveni and others 2010; personal communication.
 Note: mm = millimeter.
 * = values that were significantly different ($p < 0.05$) from those of control children.

could accelerate the diabetes and obesity epidemics across generations, making young women key targets within strategies to prevent obesity. GDM and obesity are not only a problem in HICs; the prevalence of both conditions is also rising rapidly in LMICs.² In Indian cities the prevalence of GDM is now as high as 15 percent to 20 percent (Seshiah and others 2004).

CHILDHOOD WEIGHT GAIN AND GROWTH

Numerous studies have shown that changes in weight or BMI after birth are related to adult cardiovascular disease and its risk factors.

Weight and BMI in Infancy

Greater weight or BMI gain in infancy initially appeared to be protective. In Hertfordshire, men with higher weight at age one year had lower cardiovascular disease mortality (Barker and others 1989) and less T2DM (Hales and others 1991). Higher weight and BMI at age one year were also associated with a lower risk of coronary heart disease and T2DM in both men and women in Finland (Eriksson and others 2001; Eriksson and others 2003). Because there are relatively few adult cohorts with infant data and adult follow-up, the consistency of these findings in other populations is unclear. In India, lower weight or BMI at age one year was associated with a higher risk of diabetes (Bhargava and others 2004) (figure 3.5). However, data from the Consortium of Health-Orientated Research in Transitioning Societies collaboration, combining adult birth cohorts in five LMICs, showed no association between weight or BMI in infancy and later blood pressure or diabetes (Adair and others 2013).

BMI in Childhood and Adolescence

In contrast, greater childhood or adolescent BMI gain is consistently and strongly associated with an increased risk of later cardiovascular disease. In all populations studied—both LMICs and HICs—accelerated childhood or adolescent BMI or weight gain (upward crossing of centiles or rising Z-scores) was associated with an increased risk of coronary heart disease (Eriksson and others 2001; Forsen and others 1999), higher blood pressure (Adair and others 2013), and T2DM (Adair and others 2013; Bhargava and others 2004; Eriksson and others 2003). However, upward crossing of BMI centiles during childhood does not necessarily mean an abnormally high childhood BMI. In Delhi, the children who later developed T2DM had a mean BMI at age 10 years that was similar to the rest of the cohort (figure 3.5) (Bhargava and others 2004).³ They were on an upward trajectory, becoming “obese relative to themselves,” but were not obese in absolute terms. There are no data indicating how many children in LMICs are following this

Figure 3.5 Childhood SD Scores for Height and BMI for Members of the New Delhi Birth Cohort Who Developed Impaired Glucose Tolerance or Diabetes in Young Adulthood



Source: Bhargava and others 2004.

Note: BMI = body mass index; SD = standard deviation. The solid lines indicate mean within-cohort SD scores at each age from birth to age 30 years for height and BMI among the cohort members who developed impaired glucose tolerance or type 2 diabetes mellitus. The dotted lines indicate 95 percent confidence intervals. The dashed line indicates a period between ages 21 years and 30 years in which there was no follow-up. The SD score for the cohort as a whole was set at zero (solid horizontal line).

growth pattern. However, childhood overweight and obesity are certainly rising; of the estimated 42 million children under age five years who were overweight in 2013, 31 million lived in LMICs.⁴

Childhood weight or BMI sometimes interacts with birth weight in the prediction of adult disease. In Finland, an increase in BMI from birth to age seven years was only associated with an increased risk of death from coronary heart disease in persons who were small at birth (figure 3.6).

BMI in Adulthood

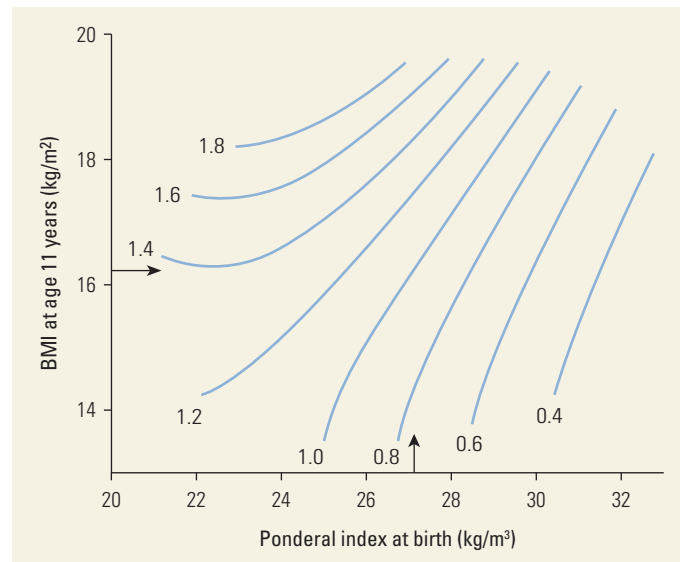
Adult obesity adds to, and may interact with, the effects of low birth weight. The most adverse cardiovascular disease risk profile is consistently found across countries and populations in men and women who were small at birth but obese as adults. The effects of adult BMI on coronary heart disease, hypertension, T2DM, and insulin resistance are greater in individuals with low birth weight (Frankel and others 1996; Hales and others 1991). Similar interactive effects have been described between size at birth and other aspects of adult lifestyle—for example, between ponderal index at birth and adult socioeconomic status on coronary heart disease (Barker and others 2001) and between weight in infancy and the effects of smoking on fibrinogen concentrations (Barker and others 1992).

BMI gain in childhood combined with a background of impaired fetal development might be associated with disease for several reasons. Growth-restricted newborns tend to catch up (compensatory weight gain), and the rapidity of postnatal weight gain may indicate greater severity of fetal growth restriction in relation to potential (Leon and others 1996). Alternatively, the catch-up process itself may be disadvantageous. It may place excessive demand on organs that are not capable of compensatory hyperplasia, such as the pancreas or kidneys. It may alter body composition; fat maintains its capacity for growth throughout life, unlike muscle, which develops earlier and loses the capacity for cell division. Several studies have shown that, while lower birth weight and infant weight are associated with reduced adult lean body mass, accelerated BMI gain after infancy is associated with greater gain in fat mass relative to lean mass (Fall 2011). Another possibility is that the hormones driving compensatory weight gain (for example, insulin and insulin-like growth factors) have adverse long-term cardiovascular and metabolic effects.

Height in Childhood

Greater growth in height in childhood has been associated with a higher risk of later coronary heart

Figure 3.6 Hazard Ratios for Death from Coronary Heart Disease of Men Born in Helsinki, 1924–33, According to Ponderal Index at Birth and BMI at Age 11 Years



Source: Eriksson and others 1999.

Note: BMI = body mass index; kg/m^2 = kilograms per square meter; kg/m^3 = kilograms per cubic meter. Arrows indicate average values. Ponderal index is a ratio of birth weight to birth length; a lower ponderal index at birth implies a higher degree of thinness.

disease, higher blood pressure, T2DM, and insulin resistance (Bavdekar and others 1999; Eriksson and others 2001; Forsen and others 1999; Leon and others 1996). In contrast, taller height in adulthood has consistently been associated with a lower risk of coronary heart disease. The reasons are unclear. The components of height (leg length and trunk height) show opposite relationships with cardiovascular risk. Longer leg length appears protective, while greater trunk height is associated with an adverse risk profile or with no relationship (Lawlor, Ebrahim, and Davey Smith 2002; Lawlor and others 2004; Schooling and others 2007). Leg length may reflect fetal and infant health and nutrition, while trunk height is thought to be determined during puberty (Gunnell 2001; Wadsworth and others 2002), although the evidence is poor.

Recent statistical modeling techniques using conditional variables have been used to examine separate effects of linear growth and relative weight gain—that is, weight gain independent of linear growth. In five cohorts in LMICs, faster linear growth between birth and mid-childhood was associated with higher adult blood pressure and BMI (mostly lean mass) (Adair and others 2013). It was not associated with T2DM in later life.

OTHER EARLY LIFE EXPOSURES

Other maternal and offspring factors may influence the future risk of cardiometabolic disease. The best studied exposures are diet in infancy, including breastfeeding, and maternal smoking.

Breastfeeding

Compared with formula feeding, breastfeeding has been associated with less obesity and T2DM and lower blood pressure and lipids in later life (Owen and others 2005; Owen and others 2006; Owen, Whincup, and Cook 2011), but the effects appear to be modest. Meta-analyses have shown that mean cholesterol levels in adulthood were 0.04 nanomole per liter lower and systolic blood pressure was 1.4 mmHg lower in persons who were breastfed as infants, compared with those who were bottle fed (Martin, Gunnell, and Davey Smith 2005; Owen and others 2008). The reviews raised the possibility of publication bias. Studies of duration and exclusivity of breastfeeding have shown no evidence that these factors influence later obesity or blood pressure. Most of the evidence on long-term effects of breastfeeding is from observational studies in HICs, and because breastfeeding is strongly associated with higher maternal socioeconomic status and education in these countries, residual confounding is a major issue. Data from five LMICs showed no evidence that breastfeeding is protective against hypertension, diabetes, or obesity (Fall and others 2011). The few randomized controlled trials of breastfeeding interventions have been similarly negative, although none has followed the children into adult life (Fewtrell 2011; Kramer and others 2007; Martin and others 2014).

Maternal Smoking

Maternal smoking has been associated with childhood obesity and behavioral disorders (Swanson and others 2009). In a meta-analysis, the odds ratio for maternal smoking was 1.5 in persons who were obese in later life compared with controls who were not obese (Oken, Levitan, and Gillman 2008). Confounding is an issue because smoking is strongly associated with lower maternal socioeconomic status, which is also strongly related to childhood obesity in HICs. However, it is plausible that maternal smoking could permanently affect fetal development through decreased utero-placental blood flow, hypoxia, direct effects of harmful substances in cigarette smoke, or maternal appetite suppression. Interventions to prevent or stop smoking in pregnancy are effective (Lumley and others 2013), but there are no data on long-term outcomes in the children.

Other Exposures

Prenatal exposure to common environmental pollutants, especially those that have endocrine activity (endocrine disruptors), has been shown to increase adiposity in animals in later life (Heindel, Newbold, and Schug 2015). Chemicals shown to have this effect include estrogenic compounds such as bisphenol A (a weak estrogenic component of polycarbonate plastics used in food containers), polychlorinated biphenyls (used in electrical equipment), dichlorodiphenyl dichloroethene (a breakdown product of the pesticide DDT [dichlorodiphenyltrichloroethane]), and phytoestrogens (derived from soya products). There are few human studies, but prenatal exposure to some of these pollutants has been associated with increased adiposity or weight for height in children in HICs (Vafeiadi and others 2016). More research on this topic is needed in LMICs, where environmental pollution is often poorly regulated and people (especially in low-income groups) are poorly protected.

Stressful experiences in early life may have a role in the programming of adult disease. Although the evidence in humans is limited, children born in Helsinki between 1934 and 1944 who were separated (evacuated) from their parents had higher systolic and diastolic blood pressure and were more likely to be on medication for coronary heart disease than children who were not separated (Alastalo and others 2012, 2013). The age and duration of separation were related to blood pressure levels, suggesting that these early life influences can have lasting effects, perhaps via stress-mediated metabolic or hormonal alterations.

ALTERNATIVE EXPLANATIONS FOR ASSOCIATIONS BETWEEN SIZE IN EARLY LIFE AND LATER HEALTH

Much of the evidence for the early life programming of cardiometabolic disease in humans still rests on observational studies and on associations with crude proxy measures of adverse early life exposures. Such associations could have other explanations, some of which are reviewed briefly here, using birth weight as an example.

Statistical Issues

Selection Effects

Participants recruited into studies in late life may not be representative, either in their early growth and development or in their adult disease, of the original population from which they came. For example, persons with extremely low birth weight may have died earlier. However, bias arises only when the sampling

processes for exposures and outcomes are linked—for example, if the selection of persons with low birth weight was based on whether they had adult coronary heart disease. Moreover, comparisons in these studies were made within the cohort, further reducing the possibility of selection bias.

Measurement Errors

Measurement errors, especially in historical data, may be a source of bias. For example, in the Hertfordshire birth cohort, newborns were measured with agricultural weighing scales to the nearest quarter or even half pound, which could cause misclassification of birth weight. However, such random measurement errors tend to weaken associations rather than create spurious ones.

Confounding

An association between an exposure and an outcome may be induced because of a third variable (known as a confounder) that is related to both exposure and outcome but is not on the causal pathway. For example, confounding by socioeconomic status could induce an association between low birth weight and adult coronary heart disease, because poorer socioeconomic conditions are associated with lower birth weight, poorer childhood and adult diets, and fewer life opportunities, all of which could predispose individuals to adult disease. It is important, therefore, to identify confounders and adjust for them in the analysis. The association between low birth weight and adult coronary heart disease persists even after adjusting for socioeconomic status, although it is possible that some residual confounding remains.

Socioeconomic factors may also operate through behaviors such as differences in maternal diet and stress. Socioeconomic status may be not just a confounder, but also an effect modifier, in that early life effects may have associations with adult disease that differ according to socioeconomic status.

Adjustments

Early size may be associated with adult outcomes in two ways: a direct programming effect and an indirect effect that arises because early size is associated with adult size, which has its own association with adult outcome. A model that only includes early size captures the net effect of these two processes; a model that also includes adult size isolates the direct programming effect. These models address different questions; therefore, they give different answers. This disparity has caused confusion (Tu and others 2005). Theoretically, it is impossible to separate the influences of early size, adult size, and the growth that led from the one to the other (Lucas, Fewtrell, and

Cole 1999) because only two independent observations led to these three variables. Studies that include intermediate time points may be better able to identify the windows of growth that are critical for adult disease (Adair and others 2013). It is important to look for interactions between the effects of early and later size on adult disease (figure 3.6). Data from Finland showed that persons with a lower ponderal index at birth had a higher risk of coronary heart disease and that the risk was greatest in those with higher BMI at age 11 years. Those with a higher ponderal index at birth had a lower risk, and the risk was similar irrespective of their size at age 11 years.

Genetic Effects

The fetal insulin hypothesis suggests a genetic explanation for associations between birth size and adult disease. For example, mutations or polymorphisms in fetal genes influencing insulin secretion, such as the glucokinase gene, could cause lower birth weight, insulin resistance, and later T2DM (Hattersley and Tooke 1999). A large genome-wide association study identified seven loci significantly associated with birth weight, of which two were also related to T2DM and one to blood pressure (Horikoshi and others 2013). However, these loci would not explain the findings from epidemiological studies.

Birth weight is only partly determined by genetic factors, and the relative importance of genes and environment has been an active area of research for the past two decades. It is likely that interactions between genetic and environmental factors influence not only fetal development but also the risk of adult disease. Research suggests that these effects may additionally act through epigenetic mechanisms, which alter the expression of genes without altering the base sequence (Tarry-Adkins and Ozanne 2011).

Randomized controlled trials will provide the best tests of causative links between early life factors and later disease and lead to evidence-based interventions. However, not all interventions are amenable to trials, for ethical and other reasons; even if trials are possible, lengthy follow-up may be needed to see effects. The next section presents what is currently known from intervention studies in early life. Recently developed techniques can strengthen causal inference from observational studies, overcome some of the statistical issues, and lead to new insights into potentially modifiable early life exposures (reviewed in Gage, Munafo, and Davey Smith 2016; Richmond and others 2014). These techniques include the use of cross-cohort comparisons, sibling comparisons, negative control approaches, and instrumental variables (which can be genetic markers, as in the technique known as Mendelian randomization).

EVIDENCE FROM INTERVENTION STUDIES

The DOHaD hypothesis has been tested definitively in humans only recently in studies following up children born during randomized controlled trials of different exposures in utero, in infancy, or in childhood (Hawkesworth 2009). Rather than the immediate effects on birth weight and survival, the focus here is on long-term cardiometabolic effects, which necessarily require prolonged follow-up and for which data are still sparse.

Nutritional Interventions in Pregnancy

Protein and Energy

The trial with the longest follow-up is the cluster randomized trial conducted by the Institute of Nutrition of Central America and Panama in Guatemala, in which pregnant mothers and children up to age seven years received either Atole (a high-energy, high-protein drink) or Fresco (a lower-energy, no-protein drink) as a daily supplement. Both drinks contained micronutrients. Several studies investigating cardiometabolic outcomes in the young adult offspring have shown beneficial effects of prenatal supplementation with Atole on concentrations of high-density lipoprotein cholesterol and triglycerides (Stein and others 2006) and on concentrations of plasma glucose in women (Conlisk and others 2004), but no effect on blood pressure (Webb and others 2005).

In a cluster randomized trial in India, pregnant mothers in intervention villages received food-based energy and protein supplements as part of a package of public health interventions, while those in control villages received standard care. A small increase in birth weight of approximately 61 grams occurred in offspring born to women in the intervention villages, suggesting an effect on fetal development (Kinra and others 2014). Insulin resistance and arterial stiffness were reduced, but not blood pressure, in the adolescent children of women in the intervention villages compared with controls (Kinra and others 2008). These children were also taller by approximately 14 millimeters. A later follow-up found no differences in lean body mass and grip strength between the groups (Kulkarni and others 2014).

Hawkesworth and others have followed up adolescents whose mothers took part in a randomized controlled trial of protein-energy supplementation during pregnancy in The Gambia (Hawkesworth and others 2008, 2009; Hawkesworth and others 2011). They found no differences in blood pressure, body composition, or serum cholesterol concentrations between the intervention and control groups. Plasma glucose was lower in the offspring of mothers who received the

protein-energy intervention, but the effect was very small (0.05 millimoles/liter) and unlikely to be clinically significant.

Micronutrients

Micronutrient deficiencies are common among pregnant women in LMICs, and because micronutrient requirements are higher during periods of rapid growth, these deficiencies may impair fetal development. Between 1999 and 2001, 4,926 pregnant women in rural Nepal were cluster randomized to receive daily micronutrient supplements containing vitamin A alone (control) or in combination with folic acid, folic acid plus iron, folic acid plus iron plus zinc, or multiple micronutrients from early pregnancy until three months postpartum. The children were followed up to between ages six and eight years. None of the micronutrient combinations influenced blood pressure, concentrations of cholesterol, triglycerides, glucose, or insulin, or insulin resistance (Stewart, Christian, Schulze, and others 2009). There was a lower risk of microalbuminuria in the folic acid (odds ratio [OR], 0.56; 95 percent CI, 0.33 to 0.93; $p = 0.02$) and folic acid plus iron plus zinc (OR, 0.53; 95 percent CI, 0.32 to 0.89; $p = 0.02$) groups and a reduced risk of metabolic syndrome in the folic acid (OR, 0.63; 95 percent CI, 0.41 to 0.97; $p = 0.03$) group. Maternal supplementation with folic acid plus iron plus zinc resulted in a reduction in triceps thickness (-0.25 millimeter [mm]; 95 percent CI, -0.44 to -0.06), subscapular skinfold thickness (-0.20 mm; 95 percent CI, -0.33 to -0.06), and arm fat area (-0.18 square centimeter [cm²]; 95 percent CI, -0.34 to -0.01) (Stewart, Christian, Leclercq, and others 2009).

Follow-up data from another multiple micronutrient trial for pregnant women in Nepal showed lower systolic blood pressure in children ($N = 917$) at age two years (-2.5 mmHg; 95 percent CI, -4.55 to -0.47) compared with children whose mothers received standard iron plus folate tablets (Vaidya and others 2008), and triceps skinfold thickness was increased in the group who received multiple micronutrients (2.0 mm; 95 percent CI, 0.0 to 0.4). However, these differences were not maintained when the children were studied again at age eight years (Devakumar and others 2014).

Several studies have followed up children born to mothers who took part in calcium supplementation trials. Calcium supplementation is a common clinical intervention to prevent pregnancy-induced hypertension (Hawkesworth and others 2009). Overall, there is little evidence of a significant effect on blood pressure.

Combined Protein-Energy and Micronutrients

The Maternal and Infant Nutrition Interventions in Matlab (MINIMat) trial in Bangladesh randomized

pregnant women to receive supplementation with either iron and folic acid or multiple micronutrients combined in a factorial design with randomized food-based energy supplementation (608 kilocalories for six days a week), starting either at 9 weeks or at 20 weeks gestation. Follow-up of the children at age 4.5 years showed no effect on body composition of either early energy supplementation or multiple micronutrients (Khan and others 2012). Early pregnancy energy supplementation was associated with a 0.72 mmHg (95 percent CI, 0.16 to 1.28; $p = 0.01$) lower childhood diastolic blood pressure; multiple micronutrient supplementation was associated with higher childhood diastolic blood pressure (0.87 mmHg; 95 percent CI, 0.18 to 1.56; $p = 0.01$) (Hawkesworth and others 2013).

Summary

These results provide little evidence of long-term benefits from supplementing undernourished mothers for their offspring's cardiometabolic risk and little support for the DOHaD hypothesis. More evidence is needed, however, because these trials suffer from limitations related to sample size, losses to follow-up, and age at follow-up (Hawkesworth 2009). Follow-up in childhood or adolescence may be too early. It may be necessary to intervene earlier in pregnancy or even preconceptionally to influence processes such as placentation, organogenesis, and periconceptional epigenetic changes, which may be important for programming later disease.

Interventions to Prevent or Treat Gestational Diabetes

Evidence relating to the efficacy of interventions to prevent gestational diabetes is limited. Recent reviews have concluded that, although dietary counseling and increased exercise may provide some benefits, the quality of evidence is poor and no firm conclusions can be drawn (Han, Middleton, and Crowther 2012; Oostdam and others 2011; Skouteris and others 2014). Evidence suggests that more intensive treatment of gestational diabetes reduces macrosomia and pregnancy complications (Han, Crowther, and Middleton 2012); however, on follow-up, there were no differences in BMI between children at ages four to five years (Gillman and others 2010). Large, well-designed randomized controlled trials are needed to assess the benefits of various interventions on gestational diabetes as well as on downstream outcomes, including newborn size, perinatal complications, and the cardiometabolic health of offspring.

Lifestyle Interventions in Obese Pregnant Women

Several large randomized controlled trials, either recently completed or currently in progress, have studied lifestyle

interventions among obese pregnant women (Poston and others 2015). Most of these trials are or have been conducted in HICs. There is little information yet as to whether these interventions alter cardiometabolic outcomes in children. The Lifestyle in Pregnancy and Offspring study in Denmark found no differences in blood pressure, plasma glucose, insulin, lipids, or body composition in children at ages two to three years of obese women who participated in a diet counseling and exercise program compared with controls, but this age may be too young for effects to be observable (Tanvig and others 2014, 2015).

Breastfeeding Interventions

It is clearly unethical to randomize infants to different durations of breastfeeding or to breastfeeding versus formula feeding. However, two large studies have randomized mother-infant pairs to receive additional encouragement to breastfeed, compared with standard care, and have follow-up data on the children. The Promotion of Breastfeeding Intervention Trial in Belarus recruited mother-infant pairs who were cluster randomized to an intervention designed to encourage exclusive breastfeeding for six months or to standard care. Although the intervention increased exclusive breastfeeding compared with controls, it showed no differences between the groups at ages 6 and 11 years in adiposity, blood pressure, plasma glucose, insulin, adiponectin or apolipoprotein A1 concentrations, or prevalence of metabolic syndrome (Kramer and others 2007, 2009; Martin and others 2014). In the MINIMat trial in Bangladesh, 4,436 pregnant women were randomized to six equal-size food and micronutrient groups; 3,214 were randomized during the last trimester of pregnancy to receive either breastfeeding counseling or common health messages. There were no differences in these groups in the growth trajectory or body composition of their children at age five years (Khan and others 2013).

Interventions to Reduce Childhood Obesity and Adiposity

Evidence suggests that BMI and obesity track through childhood and into adulthood. Reversing obesity is difficult, and studies attempting to reduce or prevent childhood obesity have shown varying results; some of these are reviewed in chapter 7 on weight management in this volume (Malik and Hu 2017). Although behavioral changes relating to diet and physical activity are major features of intervention strategies, it is important to consider the wider obesogenic environment and its impact on children. A Cochrane review found evidence that child obesity prevention programs result in reduced

BMI (Waters and others 2011), particularly programs for children ages 6–12 years. These studies used a broad range of components; the authors concluded that it was difficult to disentangle which aspects contributed the most. Overall, school-based interventions that influenced the curriculum, provided support to teachers, and improved the nutritional quality of school food; interventions that provided support to parents; and home activities that encouraged healthy behaviors were effective. No evidence was found to suggest that any of these interventions had adverse effects. Further robust studies with long-term follow-up and cost-effectiveness analysis are needed.

PUBLIC HEALTH IMPLICATIONS

Alternative Preventive Strategy

Current preventive strategies to reduce the burden of cardiovascular disease focus on middle-age individuals with preexisting disease or risk factors but do not address the impact of the disease on future generations. The DOHaD findings have substantial public health implications because they suggest the potential for an alternative primary prevention strategy of optimizing early development to control and prevent the rising burden of cardiovascular disease and break the cycle of intergenerational transmission of susceptibility. Potential interventions include improving the lifestyle, health, and nutrition of future mothers and pregnant women; preventing and reducing exposure to cigarette smoke and other toxins during pregnancy; and optimizing childhood nutrition. The DOHaD findings are likely to have particular significance in LMICs undergoing rapid economic and demographic changes. These transitions include increasing availability of cheap energy-dense but nutrient-poor “fast foods,” leading to upward trends in maternal and child BMI, frequently combined with intrauterine and infant undernutrition. Urban environments are often polluted and stressful. Rapid urban development is associated with loss of green spaces and traffic congestion, which militate against healthy physical activity—an important requirement for maintaining a healthy body weight.

Current evidence of long-term benefits to cardiometabolic health of interventions in pregnant women and children is scant. Most of the evidence comes from nutritional interventions, and although these interventions have shown effects on short-term outcomes such as birth weight, they do not suggest significant long-term benefits to the cardiometabolic risk profile in childhood. Longer periods of follow-up are required to assess the effects of these trials. Current knowledge

suggests that unless interventions are targeted before conception, it may be difficult to influence programming because key processes such as placentation and organogenesis occur in the first trimester of pregnancy and major epigenetic changes occur around the time of conception.

Potential Size of Effect

Attempts have been made to calculate the potential benefits of improving early life development. Because better markers of adverse intrauterine programming are not available, these attempts focus mainly on birth weight, a major limitation. It has been suggested that the population attributable fraction of diabetes and hypertension due to low birth weight is small compared with adult lifestyle and heredity, respectively (Boyko 2000; Mogren and others 2001). However, these calculations treat birth weight as a dichotomous outcome and do not consider the potential benefit of shifting the birth weight distribution to the right (Ben-Shlomo 2001).

The calculations often ignore combined effects of birth weight and childhood growth. Findings from Finland suggest that if every individual in the cohort had been in the highest third of birth weight and reduced their standard deviation score for BMI between ages 3 and 11 years, the incidence of diabetes would have been reduced by 50 percent and the incidence of hypertension by 25 percent. If each man had been in the highest third of BMI at age 1 year and reduced the standard deviation score for BMI between ages 3 and 11 years, the incidence of coronary heart disease would have been reduced by approximately 40 percent (Barker and others 2002). In an analysis using data from Hertfordshire, United Kingdom, where birth weights were rounded to the nearest 0.5 pound, Joseph and Kramer (1997) showed that if all newborns weighed between 9.0 and 9.5 pounds at birth, 26 percent and 33 percent of deaths from coronary heart disease would be prevented in men and women, respectively. If people within any birth weight category attained birth weights in the next higher category, the decrease in coronary heart disease would be 9 percent, assuming a mean birth weight increase of one pound. It is, however, difficult to identify interventions that can change birth weight by such a large amount.

Although interventions to reduce low birth weight (less than 2,500 grams) in LMICs may be appropriate, measures to shift birth weight upward across the range may be inappropriate, because factors that cause both low and high birth weight (if related to maternal diabetes or obesity) are associated with an increased risk of later cardiometabolic disease.

Timing of Interventions

The associations between maternal obesity and adverse cardiometabolic outcomes in children and between rapid childhood weight gain and increased cardiometabolic risk in adulthood have led to concerns about trade-offs. For example, promoting better childhood nutrition to reduce child mortality and improve neurocognitive development may lead to excess childhood weight gain and increase the risk of cardiometabolic disease in adulthood. This line of argument suggests that, to escape undernutrition, LMICs will inevitably pay a price of chronic disease epidemics.

Analyses by the Consortium of Health-Orientated Research in Transitioning Societies collaboration, using data from five birth cohorts in LMICs, allay these fears to some extent. Higher birth weight and faster weight gain and linear growth in the first two years of life were associated with better human capital in adult life, as measured by attained schooling, income, height, and next-generation birth weight (Adair and others 2013; Victora and others 2008). These factors were associated with higher adult BMI, but with lean body mass more than fat mass, and were not associated with increased risk of adult hypertension or diabetes (Adair and others 2013). In contrast, faster weight gain after age two years was clearly associated with an increase in adult obesity, hypertension, and impaired fasting glucose. These data support the concept that intervening to improve nutrition in the first 1,000 days from conception until age two years offers the best chance of preventing the faltering of growth and neurocognitive development that occurs in LMICs (Victora and others 2010), while avoiding the trade-off of more cardiometabolic disease in later life. This concept has yet to be proven. Moreover, it does not preclude interventions at other ages; it does highlight the need to design interventions that avoid weight gain at the expense of linear growth in children and excessive weight gain in young and pregnant women.

A review of evidence-based interventions to improve maternal and child nutrition demonstrated a clear need to introduce evidence-based interventions in adolescence and before conception, especially in countries with a high burden of undernutrition and low age of first pregnancy (Bhutta and others 2013). The review recommended maternal micronutrient and balanced protein-energy supplementation, appropriate breastfeeding and complementary feeding strategies in infants, and micronutrient supplementation in infants and children under age five years as having clear short-term benefits. These interventions were delivered most equitably and cost-effectively in community-based settings. They have not been proven to have long-term

benefits on cardiometabolic health. A holistic approach is recommended for interventions in adolescents and women in LMICs, where large gaps exist in knowledge about reproduction and parenting and where accessing optimal pregnancy care is difficult, but only on the basis of short-term benefits.

The field of DOHaD has moved to preconceptional intervention studies involving food-based and tablet-based micronutrient supplementation of women before and during pregnancy. If successful, these studies will offer, for the first time, a primordial preventive approach to reducing and eventually halting the epidemic of cardiovascular disease. The trials offer an opportunity to investigate the effects of maternal supplementation on offspring health as well as to examine mechanisms such as epigenetic changes in offspring. A preconceptional micronutrient food-based intervention in Mumbai, India, found an absolute risk reduction of 7 percent for low birth weight and approximately 6 percent for gestational diabetes (Potdar and others 2014; Sahariah and others 2016). These findings translate into numbers needed to treat of 15 for low birth weight and 17 for gestational diabetes. The daily cost of the intervention was US\$0.09, which translates into US\$675 to prevent one low birth weight by supplementing 15 women for nine months before conception and throughout pregnancy and US\$765 to prevent one case of gestational diabetes. Given the perinatal and neonatal care required for low-birth weight infants, these costs would seem justifiable even apart from the potential reduced risk of future cardiovascular disease.

An analysis from the World Bank concluded that the economic benefit from reducing low birth weight in low-income countries was approximately US\$580 per infant moved from low to normal birth weight categories (Alderman and Behrman 2004). The interventions considered ranged from provision of micronutrient and food supplements to social interventions to optimize birth spacing and marriage timing. The main economic benefits occurred from improved labor productivity, followed by reduced infant mortality and morbidity, with much smaller gains from reducing chronic disease. The latter outcome was partly due to discounting because gains occur many years after the intervention. However, evidence is limited; better estimates of costs and effects are necessary to obtain more accurate figures. Also, because discounting rates vary, the benefits may also be altered. In conclusion, preconceptional interventions have significant public health potential, not only for health-effectiveness but also for cost-effectiveness.

CONCLUSIONS

Key Policy Issues

Birth weight is not an exposure per se but rather a crude marker of a number of exposures influencing fetal nutrition. Policies to modify birth weight may not be the solution; however, it is reasonable to attempt to reduce the incidence of low birth weight (less than 2,500 grams) in undernourished mothers and of fetal macrosomia resulting from maternal obesity and gestational diabetes.

A holistic approach before and during pregnancy to improve the lifestyles of young women and mothers—incorporating good-quality nutritious diets that have adequate but not excessive calories, moderate physical activity, and measures to reduce smoking—deserves consideration. Although undernutrition is the main issue for most LMICs, rates of overweight and obesity are rising, accompanied by increases in gestational diabetes.

Considerable gaps exist in evidence sufficient to establish causal links between early life exposures and disease outcomes in later life and to develop interventions in early life to prevent disease. It is important that research planners take a long-term view and enable the follow-up of high-quality cohorts and intervention trials for long enough to obtain information on hard disease outcomes in later life. In addition, better surrogate markers of adverse early life programming at younger ages need to be identified; the field of epigenetics offers the potential to develop better biomarkers in the future. Further work is also needed on optimum growth patterns in fetal life, infancy, and childhood so that interventions can be targeted appropriately; these patterns may differ between populations. Longitudinal studies to investigate patterns of linear growth and weight gain and incorporate measurements of body composition and relate them to cardiovascular outcomes should be encouraged. Interventions to reduce childhood obesity should be more nuanced and consider upward crossing of centiles rather than focusing exclusively on obese children.

Main Platforms for Implementation

At the national level, policy makers can revisit recommendations on micronutrients given before and during pregnancy to address common deficiencies in their populations. At the community level, interventions to promote maternal and child health can be developed, implemented, and delivered. Schools can complement curricula with programs to promote healthy lifestyles. To maximize equity, governments should provide funding, at least during the initial stages.

Limitations of the Economic Analysis

The cost-effectiveness data are limited and were not collected explicitly for comprehensive analysis. Appropriate economic data need to be collected to enable cost-effectiveness analyses.

NOTES

World Bank Income Classifications as of July 2014 are as follows, based on estimates of gross national income (GNI) per capita for 2013:

- Low-income countries (LICs) = US\$1,045 or less
- Middle-income countries (MICs) are subdivided:
 - (a) lower-middle-income = US\$1,046 to US\$4,125
 - (b) upper-middle-income (UMICs) = US\$4,126 to US\$12,745
- High-income countries (HICs) = US\$12,746 or more.

1. Based on United Nations Children's Fund data; see <http://data.unicef.org/nutrition/low-birthweight>.
2. Based on data from the International Diabetes Federation Diabetes Atlas 2015 (<http://www.diabetesatlas.org>).
3. See also Centers for Disease Control and Prevention, National Center for Health Statistics, <http://www.cdc.gov/growthcharts>.
4. See World Health Organization, <http://www.who.int/dietphysicalactivity/childhood/en/>.

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