Chapter 3. Early Origins of Cardiometabolic Disease

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Abstract

Low birth and infant weight, followed by rapid weight gain in later childhood, are associated with an increased risk of cardiovascular disease mortality, morbidity, and risk factors, including high blood pressure, diabetes, and metabolic syndrome. The developmental origins of health and disease (DOHaD) hypothesis suggests that early undernutrition permanently programs the body's structure and metabolism and leaves an increased vulnerability to the adverse effects of excess nutrition in later life. High birth weight has also been associated with an increased risk of diabetes. The DOHaD concepts offer a primordial preventive strategy to reduce the risk in future generations by improving development in early life. Some evidence suggests that early life interventions may be both effective and cost-effective, but interventions focused solely on increasing birth weight may not be appropriate. Interventions to reduce the burden of low birth weight; promotion of a holistic approach before and during pregnancy to improve the health of young women and mothers; and further research on understanding optimum growth patterns during fetal life, infancy, and childhood to target interventions are recommended.

Introduction: Link between Birth Weight and Adult Cardiovascular Disease

This chapter discusses the associations between growth in early life and adult cardiometabolic health. We summarize the evidence 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. We set out the concept of the developmental origins of health and disease (DOHaD) and consider alternative explanations for birth weight associations. We then evaluate the effects of interventions in pregnancy, infancy and childhood on later coronary heart disease, or cardiovascular (coronary heart disease and stroke) risk. We conclude with the public health implications and potential economic benefits of early life interventions.

In 1977, Forsdahl discovered that Norwegian counties with the highest infant mortality in 1896-1925 experienced the highest death rates from coronary heart disease (Forsdahl 1977). He suggested that poverty in childhood caused permanent damage, perhaps due to a nutritional deficit, that resulted in life-long vulnerability to an affluent adult lifestyle and high fat intakes. A decade later David Barker showed a similar phenomenon in the UK (Barker 1986). Using archived birth records from the county of Hertfordshire, Barker further showed that lower birth weight and lower weight at the age one year were associated with an increased risk of death in adult life from coronary heart disease and stroke (Barker 1989; Osmond 1993). There was an approximate doubling of mortality from the highest to the lowest extremes of birth weight or infant weight (figure 3.1). Barker concluded that the processes linked to growth and active in prenatal or early postnatal life strongly influence the risk of coronary heart disease.

Figure _.1

The association of lower birth weight with an increased risk of coronary heart disease has been replicated in many different populations (Andersen 2010; Forsen 1999; Huxley and others 2007; Leon 1998; Stein 1996) (figure 3.2). It is linear and graded across the whole range of birth weight, with an upturn at extreme high birth weight (figure 3.1). The association is independent of adult socioeconomic status, making confounding an unlikely explanation (Leon 1998). Studies with gestational age data indicate that it is restricted fetal growth rather than pre-term delivery that is associated with coronary heart disease (Leon 1998). Most studies are limited to birth weight as a measure of fetal growth, but some have shown strong associations with low ponderal index (weight/length^3) at birth (Eriksson 1999).

These epidemiological studies led to a new area of science: the developmental origins of health and disease (DOHaD).

Figure 3.2

Risk Factors for Cardiovascular Disease

Associations were subsequently shown between small size at birth and coronary heart disease, as well as some of major risk factors, including impaired glucose tolerance (IGT) and type 2 diabetes (T2DM) (Hales 1991), **high blood pressure** (Fall 1995), insulin resistance (Phillips 1995), and the metabolic syndrome (Barker 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 2008). The relationship is particularly strong for birth weights under 3 kilograms. For every kilogram increase in birth weight, the odds of diabetes is 0.75 (95% CI 0.70-0.81). The inverse relationship between birth weight and blood pressure has been demonstrated consistently across different populations in both high-income countries (HICs) and low- and middle-income countries (LMICs), in childhood and adulthood (Barker 2000; Huxley 2000, 2002; Law 1996). The association is stronger for systolic than diastolic blood pressure and is amplified with increasing age (Davies 2006). The size of the effect is debated, ranging from an estimated fall in systolic blood pressure of 0.6 mmHg per kg increase in birth weight (Huxley 2002), to 2-3 mmHg (Huxley 2000; Law 1996). A recent review (Mu 2012) comparing low birth weight (less than 2.5 kilograms) to birth weights more than 2.5 kilograms suggest that adult systolic blood pressure is higher by approximately 2 mm Hg in the low birth weight group.

There is little evidence that obesity, as measured by BMI, in later life is associated with lower birth weight. On the contrary, those who were small at birth also tend to be thinner adults

(Oken 2003). Evidence indicates that the lower adult BMI associated with lower birth weight reflects lower lean body mass rather than less adiposity (Wells 2007). Some evidence suggests that small size at birth is associated with central obesity, as measured by waist circumference, waist-hip ratio, or subscapular to triceps skinfold ratio, in later life (Barker 1997; Oken 2003). Further studies are needed, with detailed and serial measurements of lean and fat mass.

No consistent associations have been identified between small size at birth and adverse plasma lipids and clotting factors. A systematic review concluded that there was only a weak inverse association between birth weight and total cholesterol (Huxley 2004). However, total and LDL-cholesterol and fibrinogen were inversely associated with abdominal circumference at birth , and with weight at one year (Barker 1993, Barker 1992), although these associations have not been replicated.

Small size at birth has been shown to predict structural and functional cardiovascular measures (Vijayakumar 1995, Martyn 1995), although results from LMICs have been inconsistent (Kumaran 2000, Norman 2008, Vijayakumar 1995).

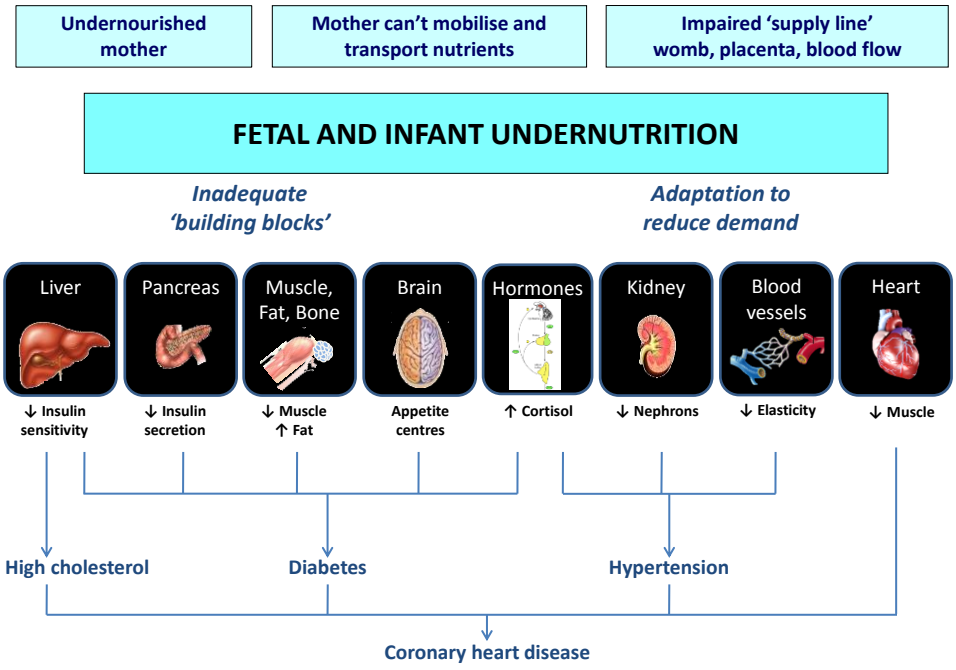
Lower birth weight has also been associated with poorer lung function in HICs and LMICs (Lawlor 2005; Barker 1991; Stein 1997). The associations are independent of smoking, socioeconomic class, or later body size.

In conclusion, small size at birth is associated with coronary heart disease, as well as with its risk factors, and to lung function. The findings may have even greater significance for LMICs, where the burden of low birth weight is greater. Approximately one in four newborns in South Asia weighs less than 2,500 grams, and where 10 countries account for more than 50 percent of the burden of low birth weight; India alone accounts for more than 30 percent (http://data.unicef.org/nutrition/low-birthweight).

Developmental Origins of Health and Disease

Barker proposed that the association between small size at birth and disease in later life reflected permanent effects of fetal undernutrition (Barker 1998; Barker 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 is dependent on the transfer of nutrients from the mother and adapts to an inadequate nutrient supply in a number of ways: prioritization of brain growth at the expense of other tissues, such as the abdominal viscera; reduced secretion of and sensitivity to the fetal growth hormones (for example, insulin); and upregulation of the hypothalamo-pituitary-adrenal (stress) axis. The DOHaD hypothesis suggests 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.

Figure 3.3 Developmental Origins of Health and Disease Hypothesis



Source: Authors

Gestational Diabetes and Fuel-Mediated Teratogenesis

It was soon apparent that birth weight itself was unlikely to be on the causal pathway, and that both low and high birth weight were associated with subsequent T2DM, producing a U-shaped relationship between birth weight and adult T2DM in some populations (Whincup 2008). Birth weight is likely to be a marker of a multitude of exposures during fetal life, rather than an exposure per se. Fetal overnutrition, due to maternal obesity or hyperglycemia, may also program the offspring for T2DM. Pedersen proposed that the transfer of excess maternal glucose in a diabetic pregnancy stimulates fetal islets to produce fetal hyperinsulinemia, which leads to macrosomia (Pedersen 1954). Freinkel suggested that a mixture of maternal nutrients (glucose, lipids, and amino acids) affects not only fetal growth and development but also the risk of future obesity, diabetes, and neurocognitive development (*fuel-mediated teratogenesis*) (Freinkel 1980). Infants of gestationally diabetic mothers are born larger, and develop early obesity, central obesity, higher insulin resistance, and impaired glucose tolerance and T2DM, similar to the offspring of undernourished mothers (Dabelea 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 siblings born before the mother developed diabetes (Dabalea 2000), suggesting that it is an effect of the intrauterine diabetic environment.

These findings have been replicated in India, where children born to GDM mothers were larger at birth and had higher subcutaneous adiposity compared to the newborns of non-GDM

mothers (Hill 2005). The difference in adiposity continued to increase throughout childhood; and at age nine years, the children of GDM mothers had greater adiposity (figure 3.4), higher glucose and insulin concentrations, and higher insulin resistance (Krishnaveni 2010). Although these women had gestational diabetes and tended to have a higher BMI than women without diabetes, they were deficient in micronutrients. Maternal B12 deficiency was also associated with an increased risk of gestational diabetes and subsequent T2DM in the mother (Krishnaveni 2009). A recent study from Scotland showed that offspring of obese mothers have an increased risk of premature cardiovascular mortality in middle age (Reynolds 2013). With rates of obesity and gestational diabetes increasing in rapidly transitioning LMICs, there exists a dual burden of undernutrition and overnutrition that could cause intergenerational programming of disease.

Figure 3.4

Childhood Weight Gain and Growth

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

Weight and Body Mass Index 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 1989), less type 2 diabetes (Hales 1991), and lower fibrinogen concentrations (Barker 1992). 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 2001 and 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 2004) (figure 3.5). However, data from the COHORTS collaboration, combining adult birth cohorts in five LMICs, showed no association between weight or BMI in infancy and later blood pressure or diabetes (Adair 2013).

Figure 3.5

Body Mass Index 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, accelerated childhood or adolescent BMI or weight gain (upward crossing of centiles, or rising Z-scores) is associated with an increased risk of **coronary heart disease** (Eriksson, 2001; Forsen **1999**), higher blood pressure (Adair 2013; Law 2012), and T2DM (Adair 2013; Bhargava 2004; Eriksson 2003). It is important to point out that 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 10 years that was similar to the rest of the cohort (Bhargava 2004). They were becoming obese relative to themselves but were not obese in absolute terms (Sachdev 2009). These findings have significant implications for places where childhood obesity rates are rising, especially urban areas. Of the estimated 42 million children under age five years who were overweight in 2013, 31 million lived in LMICs (http://www.who.int/dietphysicalactivity/childhood/en/).

BMI tends to steadily decrease after birth in early childhood and then starts increasing again

at ages four to six years. This phenomenon of increase in BMI after it reaches its lowest point is termed *adiposity rebound* and is a normal pattern of growth in all children. Earlier onset **a**diposity rebound is associated with an increased risk of adult obesity and diabetes. The cumulative incidence of T2DM was 8.6 percent in men and women where adiposity rebound occurred before age five years, compared with 1.8 percent where it occurred after age seven years (Eriksson 2003). Although the determinants of adiposity rebound are unknown, it was associated with lower weight at age one year in Finland (Eriksson 2003). Further research on the determinants of adiposity rebound, and a breakdown of the higher BMI into fat mass versus lean mass or bone, would be useful.

Childhood weight or BMI sometimes interacts with birth weight in the prediction of adult disease. In Finland, an increase in BMI from birth to seven years was only associated with an increased risk of adult **coronary heart disease** in those who were small at birth (figure 6).

Figure 3.6

Adult Body Mass Index

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 became obese adults. The effects of adult BMI on **coronary heart disease**, hypertension, T2DM, and insulin resistance are greater in individuals of low birth weight (Frankel 1996; Hales 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 2001), and between weight in infancy and the effects of smoking on fibrinogen concentrations (Barker 1992).

BMI gain in childhood, with a background of impaired fetal development, might be associated with disease for several reasons. Low birth weight babies 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 1996). Alternatively, the process of catch-up may be disadvantageous in itself. It may place excessive demand on organs that are not capable of compensatory hyperplasia, such as the pancreas or kidney. 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 BMI gain (for example, insulin and insulin-like growth factors) have adverse long-term cardiovascular and metabolic effects.

Height

Greater height growth in childhood has been associated with a higher risk of later **coronary heart disease,** higher blood pressure, T2DM, and insulin resistance (**Bavdekar 1999**;

Eriksson 2001; Forsen 1999, Leon 1996). In contrast, taller adult height has consistently been associated with a lower risk of **coronary heart disease**. Although the reasons for the association between height and **coronary heart disease** remain unclear, it is interesting that 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 shows no relationships (Lawlor 2002, 2004; Schooling 2007). Leg length may reflect fetal and infant health and nutrition (Gunnell 2001; Wadsworth 2002), while trunk height is thought to be determined during puberty (Gunnell 2001; Wadsworth 2002), although the evidence is poor.

One possible reason for the direct relationship between taller childhood height and cardiovascular risk factors is that it is difficult to disentangle the effects of linear growth from weight gain when using conventional measures of height and weight in statistical analyses. Recent statistical modeling techniques using conditional variables have been able 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 2013). However, it was not associated with any adverse disease in later life. Understanding optimal patterns of growth in early life will elucidate the relationship between linear growth and disease outcomes, and help to target interventions.

Other Early Life Exposures

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

Breastfeeding

Breastfeeding has many well-documented benefits for infants and mothers, but there is debate as to whether it protects against later obesity and cardiometabolic disease. Compared with formula feeding, breastfeeding has been associated with less obesity and T2DM, and lower adult blood pressure and lipids in later life (Owen 2005, 2006, 2011), but the effects appear to be modest. A meta-analysis examining breast feeding and later blood pressures suggested that those who were breastfed had a lower mean systolic blood pressure of 1.4 mm Hg, compared to those who were bottle fed (Martin 2005). The review raised the possibility of publication bias. Most of the evidence on long-term effects of breastfeeding is from observational studies in HICs; 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 2011b). The few randomized controlled trials of breastfeeding interventions have been similarly negative, although none has followed the children into adult life (Fewtrell 2011; Kramer 2007; Martin 2014).

Maternal Smoking

Maternal smoking has been associated with adverse offspring outcomes, including birth defects, prematurity, intrauterine growth, childhood obesity, and behavioral disorders (Swanson 2009). A meta-analysis has shown that the odds ratio for maternal smoking was 1.5

in those who were obese in later life, compared to non-obese controls (Oken 2008). Confounding is an issue because smoking is strongly associated with lower maternal socioeconomic status, which is also strongly related to childhood obesity. 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 2013**), but there are no data on long-term outcomes in the children.

Stress in early life may have a role in programming of adult disease. Although the evidence in humans is limited, children born in Helsinki between 1934-44 and who were separated (evacuated) from their parents had higher systolic and diastolic blood pressures, and were more likely to be on medication for **coronary heart disease**, compared to those who were not separated (Alastalo 2012, 2013). The age and duration of separation were related to blood pressure levels. This suggests that these early life influences can have lasting effects, perhaps via stress mediated metabolic or hormonal alterations.

In summary, other factors in addition to maternal nutrition may play roles in the development of disease, either independently or by interaction.

Alternative Explanations for Associations between Size in Early Life and Later Health

The associations between size in early life and later health may be due to statistical issues or genetic reasons; we briefly review alternative explanations.

Statistical Issues

Selection Effects

From the original population from which participants might have been recruited, it is possible that those finally studied will not be representative in early size or in adult disease. For example, those of extreme 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 those with low birth weight was based on whether they had adult **coronary heart disease**. Moreover, comparisons are made within the cohort and this would also minimize the possibility of selection bias.

Measurement Errors

Measurement errors, especially in historical data, may be a source of bias. However, random measurement errors tend to weaken associations rather than create spurious ones.

Confounding

Confounding by socioeconomic status could induce an association between low birth weight and adult **coronary heart disease**. Poorer socioeconomic conditions are associated with lower birth weight, poorer childhood and adult diets, and fewer life opportunities, all of which could predispose to adult disease. However, the association between low birth weight

and adult **coronary heart disease** persists even after adjustment 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 not just be a confounder, but also an effect modifier, in that early life effects may have associations with adult disease that differ according to socioeconomic status.

Inappropriate 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 in the prediction of an adult outcome captures the net effect of these two processes; a model that includes adult size isolates the direct programming effect. These models address different questions, and so they give different answers. This disparity has caused confusion (Tu 2005). It is important to look for interactions between the effects of early and adult size on adult disease. It is likely that the effects of low birth weight have greater adverse consequences on those who become bigger adults. Figure 3.6 showing hazard ratios for CHD for men in Helsinki illustrates this concept; although those with lower birth weight have a higher risk, the risk is greater in those with higher adult BMI than those with lower BMI. However, those with higher birth weight have a smaller risk, and the risk is similar irrespective of their adult size.

Critical Periods

Theoretically, it is very challenging to separate the influences of early size, adult size, and the growth that led from the one to the other (Lucas 1999); only two independent observations lead to these three variables. Studies that include intermediate time-points may be more able to identify the windows of growth that are critical for adult disease (Adair 2013).

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 production, such as the glucokinase gene, could cause lower birth weight, insulin resistance, and later T2DM (Hattersley 1999). A large genome-wide association study (GWAS) recently identified seven loci significantly associated with birth weight, of which two were also related to T2DM and one to blood pressure (Horikoshi 2013). However, these would not explain the findings from epidemiological studies. A study comparing associations between birth weight and glucose tolerance in monozygous and dizygous twins suggested that shared genetic determinants of birth weight and glucose tolerance were neither prevalent nor powerful (Baird 2001).

Birth weight is only partly determined by genetic factors, and the relative importance of genes and environment has been an active area of research over the past two decades. It is likely that interactions between genetic and environmental factors influence not only fetal growth but also the development of adult disease. Recent research suggests these effects may act through epigenetic mechanisms that alter expression of genes without altering the base

sequence (Tarry-Adkins 2011).

Evidence from Intervention Studies

We are only beginning to see the developmental hypothesis tested definitively in humans by following up children born during randomized controlled trials of different nutritional exposures in utero, infancy, or childhood (Hawkesworth 2009). Rather than the immediate effects on birth weight and survival, the focus is on the long-term cardiometabolic effects, which necessarily require prolonged follow-up.

Nutritional Interventions in Pregnancy

Protein and Energy

The trial with the longest follow-up is the cluster-randomized Institute of Nutrition of Central America and Panama **(INCAP)** trial in Guatemala, in which pregnant mothers and children up to age seven years received either Atole (a high-energy, high-protein drink) or Fresco (lower energy, no protein) as a daily supplement. Both drinks contained micronutrients. Several studies that have investigated cardiometabolic outcomes in the young adult offspring have shown beneficial effects of prenatal supplementation with Atole on HDL-cholesterol and triglyceride concentrations (Stein 2006) and on plasma glucose concentrations in women (Conlisk 2004), but no effect on blood pressure (Webb 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. There was a small increase in birth weight of approximately 61 grams in offspring born to women in the intervention villages (Kinra 2013). Insulin resistance and arterial stiffness were reduced, but not blood pressure, in the adolescent children of women in the intervention villages, compared to controls (Kinra 2008). These children were also taller by approximately 14 mm. A more recent follow-up concluded there were no differences in lean body mass and grip strength between the groups (Kulkarni 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 **2008, 2009b**, **2011).** There were 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 mmol/l) and unlikely to be clinically significant.

Micronutrients

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 with folic acid; folic acid + iron; folic acid + iron + zinc; or a multiple micronutrients, from early pregnancy until three months postpartum. The children were followed up to six to eight years of age. None of the micronutrient combinations influenced blood pressure, cholesterol, triglycerides, glucose or insulin concentrations, or insulin resistance (Stewart 2009). There

was a lower risk of microalbuminuria in the folic acid [odds ratio (OR), 0.56; 95%CI, 0.33-0.93; P = 0.02) and folic acid + iron + zinc (OR, 0.53; CI, 0.32-0.89; P = 0.02) groups and a reduced risk of metabolic syndrome in the folic acid group (OR, 0.63; CI, 0.41-0.97; P = 0.03). Maternal supplementation with folic acid + iron + zinc resulted in a reduction in triceps and subscapular skinfold thickness (- 0.25 mm; 95% CI: - 0.44, - 0.06; - 0.20 mm; 95% CI: - 0.33, -0.06), and arm fat area (- 0.18 cm (2); - 0.34, - 0.01) (Stewart 2009b).

Follow-up data from another multiple micronutrient trial for pregnant women in Nepal showed lower systolic blood pressure in the children (N=917) at age two years (- 2.5 mmHg, 95% CI –4.55 to –0.47), compared with children whose mothers received standard iron/folate tablets (Vaidya 2008). Triceps skinfold thickness was increased in the multiple micronutrient group (2.0 mm [0.0-0.4]).

Several studies have followed up children born to mothers who took part in calcium supplementation trials (Hawkesworth 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 trial (MINIMAT) in Bangladesh randomized pregnant women to supplementation with either iron and folic acid or multiple micronutrients combined in a factorial design with randomized food-based energy supplementation (608 kcal six days per week), starting either at nine weeks or 20 weeks gestation. Follow-up of the children at 4.5 years showed no effect of either early energy supplementation or multiple micronutrients on body composition (Khan 2012). Early pregnancy energy supplementation was associated with a 0.72 mm Hg [(95% CI: 0.16, 1.28); P = 0.01] lower childhood diastolic blood pressure; multiple micronutrient supplementation was associated with a higher childhood diastolic blood pressure [0.87 mm Hg (95% CI: 0.18, 1.56); P = 0.01] (Hawkesworth 2013).

Conclusions

These results provide little evidence of long-term benefits from supplementing undernourished mothers on offspring cardiometabolic function and disease risk and little support for the developmental origins hypothesis. More evidence is needed, however, because some of the trials suffer from limitations (Hawkesworth 2009) related to samples size, losses to follow-up, and age at follow-up; childhood or adolescence may be too early. Based on what is known from animal models of fetal programming, it may be necessary to intervene earlier in pregnancy or even preconceptionally to influence processes such as placentation and organogenesis, which occur mainly in the first trimester, and major epigenetic changes that occur around conception.

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 there may be some benefit from dietary counseling and increased exercise, the quality of evidence is poor and no firm conclusions can be drawn (Han 2012; Oostdam 2011; Skouteris 2014). Evidence suggests that more

intensive treatment of gestational diabetes reduces macrosomia and pregnancy complications (Han 2012b); however, on follow-up, there were no differences in BMI between the children at age four to five years (Gillman 2010). There is a need for large well-designed RCTs 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 the offspring.

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 (PROBIT) in Belarus recruited breastfeeding mother-infant pairs who were cluster-randomized to an intervention designed to encourage exclusive breastfeeding for six months or 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 2007, and 2009; Martin 2014).

In the MINIMAT trial in Bangladesh, 4,436 pregnant women were randomized to six equally sized food and micronutrient groups; 3,214 were randomized during the last trimester of pregnancy to receive either breastfeeding counseling or usual health messages. There were no differences in these groups in growth trajectories or body composition at age five years (Khan 2103).

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. Although behavior 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 concluded that there was evidence that child obesity prevention programs result in reduced BMI (Waters 2011), particularly programs for children ages 6 to 12 years. A broad range of components was employed in these studies; the authors concluded it was difficult to disentangle which aspects contributed the most. Overall, effective interventions were the school-based interventions that influenced the curriculum, provided support to teachers, and improved the nutritional quality of school food, as well as those that provided support to parents and home activities that encourage healthy behaviors. 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 analysiss are needed.

Public Health Implications

Alternative preventive strategy

Current preventive strategies to reduce the burden of cardiovascular disease focus on middle-aged 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 an alternative primary prevention strategy of optimizing early development to control and prevent the rising burden of cardiovascular disease and break the intergenerational transmission of susceptibility to cardiovascular disease. Potential interventions include improving the health and nutrition of future mothers and pregnant women, and optimizing childhood nutrition. The DOHaD findings are likely to have particular significance in LMICs undergoing rapid economic and demographic changes, as well as those with coexisting maternal undernutrition and overnutrition, and rapid increases in postnatal weight gain.

However, evidence of any long-term benefits to the cardiometabolic health of children from supplementing mothers is scant. Although longer periods of follow-up are required to assess the effects of trials, present knowledge suggests that unless interventions are targeted preconceptionally, it may be difficult to influence programming; key processes such as placentation, organogenesis, and major epigenetic changes occur around the time of conception. Birth weight has been used as a marker of fetal undernutrition; multiple calculations have been made of the expected benefits of interventions to increase birth weight or modify postnatal weight gain.

Potential size of effect

It has been suggested that the population attributable fraction for diabetes and hypertension due to low birth weight is small, compared to adult lifestyle and heredity, respectively (Boyko 2000; Mogren 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 also discount common programming effects on birth weight and adult size. Findings from Finland suggested 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 three 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 one year and reduced the standard deviation score for BMI between ages three and 11 years, the incidence of **coronary heart disease** would have reduced by approximately 40 percent (Barker 2002). In an analysis using data from Hertfordshire, where birth weights were rounded to the nearest 0.5 lb, Joseph and Kramer showed that if all births weighed 9 to 9.5 lb, 26 percent and 33 percent of **CHD** deaths would be prevented in men and women, respectively (Joseph 1997). If people within any birth weight category attained birth weights in the next higher succeeding category, the decrease in **CHD** 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. Moreover, such calculations may be

missing the point, because birth weight and childhood weight are likely to be merely markers, and crude ones, of intrauterine and childhood adversity. 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 both low and high birth weights are associated with increased risk of later diabetes.

Timing of interventions

The associations of maternal obesity with adverse cardiometabolic outcomes in children, and of rapid childhood weight gain with increased later cardiometabolic risk, have led to concerns about tradeoffs. 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 chronic 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 COHORTS collaboration, using data from five birth cohorts in LMICs, allay these fears. 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 2013; Victora 2008). They were associated with higher adult body mass index, but with lean body mass more than fat mass, and were not associated with an increased risk of adult hypertension or diabetes (Adair 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 2010), while avoiding the tradeoff 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 demonstrates a clear need to introduce evidence-based interventions in adolescence and preconceptionally, especially in countries with a high burden of undernutrition and low age of first pregnancy (Bhutta 2013). It recommended maternal micronutrient and balanced protein energy supplementation, appropriate breastfeeding and complementary feeding strategies in infants, and micronutrient supplementation in infants and young children under age five years as having clear short-term benefits; these were **most equitably** and cost-effectivelydelivered in community-based settings. We argue for ensuring long-term follow-up to assess the health effects of such interventions over a life course. We advocate a holistic approach to interventions in adolescents and young men and women in LMICs, where large gaps exist in knowledge about reproduction and parenting, and there are difficulties in accessing optimal pregnancy care.

Based on research findings from India, 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 reduce and eventually halt 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 epigenetic changes in the offspring. Preliminary analyses (Potdar 2014) suggest that a preconceptional micronutrient food-based intervention in Mumbai showed an absolute risk reduction of 7 percent for low birth weight and approximately 6 percent for gestational diabetes. These are potentially important public health results that translate into numbers needed to treat (NNT) 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 preconceptionally and throughout pregnancy, and US$1,305 to prevent one case of gestational diabetes. Given the perinatal and neonatal care required for low birth weight infants, these costs would seem justifiable 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 of the magnitude of US$580 per infant moved from the low birth weight to the normal birth weight category (Alderman 2004). 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 small gains obtained by reducing chronic disease are partly due to discounting because the gains— even though substantial—occur many years after the intervention. However, evidence is limited; better estimates of costs and effects are necessary to obtain more accurate figures. Also, as the discounting rates vary, the benefits may also be altered. The impact of a continuous change in birth weight rather than low birth weight as a dichotomous outcome may also alter the estimates. In conclusion, preconceptional interventions have significant public health potential, not only in terms of effectiveness but also cost-effectiveness.

Conclusions

Key Policy Issues

Birth weight is a marker of fetal nutrition and not an exposure per se. Policies to increase birth weight across the spectrum may not be the solution; however, it is reasonable to attempt to reduce the incidence of low birth weight (less than 2,500 grams).

A holistic approach before and during pregnancy to improve the lifestyle of young women and mothers deserves consideration, incorporating diet, physical activity, and measures to reduce smoking. While undernutrition is the main issue for most LMICs, rates of overweight and obesity are increasing, accompanied by increases in gestational diabetes.

Further work is needed on optimum growth patterns in fetal life, infancy, and childhood so that interventions can be targeted appropriately; these patterns may differ with populations. Longitudinal studies investigating patterns of linear growth and weight gain, and

incorporating measurements of body composition, and relating them to cardiovascular outcomes should be encouraged.

Interventions to reduce childhood obesity should be more nuanced and consider upward crossing of centiles rather than focus exclusively on obese children.

Main Platforms for Implementation

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

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