This paper highlights evidence that the development of cardiovascular disease risk is affected by prenatal nutrition as well as feeding mode and diet during infancy. Although the strong evidence for long-term effects of prenatal nutrition comes from experimental animal studies, there is a growing body of epidermiologic studies that relate size at birth to adult blood pressure, insulin resistance, and other cardiovascular disease risk factors. Studies of the long-term effects of breast-feeding and specific components of the infant diet are inconclusive, largely because of methodological limitations.

In light of recent evidence supporting the notion that prenatal nutrition affects adult chronic disease risk, the old adage “you are what you eat” may need to be revised to also say “you are what your mother ate.” In the past several decades, research into the early life or developmental origins of adult health and disease has burgeoned. Maternal diet and nutritional status during pregnancy and early infant diet are thought to play an important role. Here, we highlight some of the animal and human epidemiologic evidence for long-term effects of nutrition in early life on cardiovascular disease (CVD) and related risk factors in 2 contexts: the prenatal nutrition environment and infant diet in the first year of life.

Prenatal Nutrition

Prenatal nutritional sufficiency is affected by the nutritional status of the mother before conception (her weight status, fat stores, and micronutrient status), by her diet and nutritional status during pregnancy, and by placental function. Insufficient oxygen and nutrients can impair fetal growth and development, affect body composition, and trigger metabolic alterations that have both short-term and long-term health effects.

Animal studies provide strong evidence that increased blood pressure and other CVD-related risk factors are raised in offspring born to mothers exposed to diet restriction during pregnancy.

The strongest evidence for the long-term effect of maternal nutrition on offspring health comes from laboratory animal studies that experimentally manipulate maternal diet. In the classic experiment, the mother is fed a low-protein or globally restricted diet, and her offspring are compared with those born to mothers with adequate diets. For example, several studies by a New Zealand research group nicely demonstrate how prenatal maternal diet restriction influences offspring food intake, physical activity, and weight gain (see Figure 1). Wistar rat mothers were fed a normal diet or 30% restricted diet throughout pregnancy. In one set of experiments, the offspring were fed either normal or hypercaloric diets after weaning. In another set, the voluntary locomotor activity of similar groups was observed. Rats whose mothers were nutritionally restricted were smaller at birth but consumed more energy, particularly when offered a high-fat diet. In addition, they had less voluntary physical activity. This “couch potato syndrome” of increased energy intake and decreased activity persisted throughout adulthood and resulted in obesity. A history of prenatal nutrient restriction also resulted in increased blood pressure and altered glucose tolerance.
A key question concerns how information on the maternal diet or the status of the mother’s nutritional stores is communicated to the offspring and how it is acted upon. Several types of evidence can be brought to bear on these questions.

First, there is evidence from in vitro fertilization studies that the composition of the preimplantation incubation medium can affect both the short-term and long-term health of the developing individual. For example, differences in the chemical composition of the incubation medium have been linked to restricted fetal growth in rodents, excess somatic and organ growth in ruminants, and preterm delivery and/or low birth weight in humans. Although we know very little about the microenvironment where very early development occurs in vivo, proteins such as leptin have been suggested as possible signals reflecting maternal nutrition.

Second, there is fascinating evidence that gene expression can be altered by the maternal diet during pregnancy. Maternal diet is hypothesized to affect gene expression principally through DNA methylation (the addition of single carbon methyl groups to DNA bases). Dietary intake of methyl donors or cofactors, including folate, vitamin B₁₂, and methionine, affects DNA methylation patterns, which in turn affect offspring phenotype. In one study, researchers fed agouti strain mice either a standard diet or a diet supplemented with folate, vitamin B₁₂, and methionine for 2 weeks before mating and throughout lactation. Offspring coat color, which is affected by the expression of the agouti gene, varied according to the maternal diet: offspring of mothers fed the diet low in methyl donors were more likely to have yellow coats and were more likely to be obese as adults (Figure 2). More recently, the agouti mouse model was used to test the effects of maternal dietary genistein intake. Pregnant mice given genistein in levels similar to what would be consumed by humans with a high-soy diet had offspring that were less likely to express the agouti gene (few had the yellow coat color) and less likely to become obese as adults.

Third, Gluckman and Hanson and Gluckman et al suggested that observations of long-term effects of early

Specific components of the maternal diet during pregnancy can influence gene expression in the offspring.
environments can be understood in an evolutionary context by considering predictive adaptive responses. For example, in small mammals, seasonal day length during pregnancy influences offspring coat growth, with those born nearest to winter months developing thicker coats. It is hypothesized that poor nutritional quality while in the prenatal environment will induce structural changes (e.g., reduced number of nephrons) or metabolic adaptations, leading to enhanced survival in a similarly poor postnatal environment. However, in an environment with adequate or excessive nutrition, such changes increase susceptibility to disease. Although this hypothesis is difficult to test, it is consistent with the observation that risk of adult disease (e.g., hypertension or type 2 diabetes) occurs in individuals who were relatively small at birth but relatively large (in a state of positive energy balance) as adults.

Birth Weight and Later CVD Risk

Controlled experiments, which impose dietary restriction during pregnancy, are not possible in humans for obvious ethical reasons. Human studies therefore rely heavily on observational data from “natural experiments,” retrospective studies, and data collected prospectively for other purposes. Because fetal nutrition is difficult to assess directly, most epidemiologic studies use proxy measures of fetal nutrition, the most common of which is birth weight. Although favored for simplicity of measurement, birth weight is an inadequate proxy. Small size may reflect prematurity or growth restriction. Growth restriction may occur across a range of birth weights and may reflect causes other than nutrition. However, despite its limitations, a vast literature describes associations of birth weight to later CVD risk.

The most widely studied CVD-related outcome is blood pressure. Numerous studies, reviews, and meta-analyses document an inverse association of birth weight with childhood and adult blood pressure and risk of hypertension. The effects on blood pressure are generally small (on the order of 2 mm Hg per 1 kg difference in birth weight) but are considered to be biologically important when weighed in the context of CVD mortality. Huxley et al. conducted a meta-analysis summarizing the results of many studies. They examined the magnitude of coefficients derived from regressing systolic blood pressure on birth weight according to the sample size of the study on which they are based. Among the results from 55 studies, nearly all of the coefficients were negative, but smaller coefficients tend to be found in larger studies.

The relationship of birth weight to blood lipids is less well studied, and there is a lack of consistency across studies. In a meta-analysis, Huxley et al. summarized coefficients from a regression of total cholesterol on birth weight. They found no consistent pattern of associations either in relation to study size or age of participants. However, most studies have focused on total cholesterol, possibly obscuring important relationships with lipoprotein subtypes or atherogenic lipid profiles. In general, researchers have concluded that there is no medically important association of birth weight with later cholesterol levels.

Effects of Maternal Diet on CVD Risk

Although the experimental animal literature shows strong effects of maternal diet during pregnancy on offspring health, the evidence from human studies on maternal diet is much less convincing. Inconsistencies and confusion result from the wide range of variation in the nature and quality of available dietary data and also the degree and nature of dietary deficiencies found in observational studies. Available data come largely from studies that followed the offspring of mothers who experienced food restriction during pregnancy as a result of war, natural disaster, following specific dietary recommendations, or natural variation in dietary intake related to socioeconomic circumstances.

Several studies have followed offspring born to mothers exposed to severe wartime food rationing during the 1941–1944 Siege of Leningrad and the 1943–1945 Dutch hunger winter. In each case, assumptions about maternal diet are made from records of daily food rations rather than documentation of individual food intake. Nonetheless, the studies are informative because they allow researchers to determine not only the effects of severe food restriction but also of the timing of most severe nutritional deprivation. The work of Ravelli et al. suggests that maternal exposure to famine conditions

Multiple studies demonstrate an inverse relationship of birth weight to adult cardiovascular mortality. In studies that mark the beginning of the expansion of research on developmental origins of adult health and disease, Barker and colleagues observed that ischemic heart disease mortality increased steadily as birth weight declined from 9.5 to 5.5 lb in a cohort born in Herfordshire, England, from 1911 to 1930. Similar work in other European samples confirms this early observation.
during the Dutch hunger winter resulted in altered glucose tolerance in adult offspring. However, data from the Leningrad Siege found no effects of maternal exposure to food restriction on offspring glucose intolerance, lipid profiles, hypertension, or CVD. A study in Britain used biochemical and clinical assessments to learn whether wartime rations were adequate to prevent nutritional deficiencies. Forty years later, researchers found no association of maternal nutritional status during pregnancy to glucose tolerance, blood pressure, or lipid profiles.

Another study followed the offspring of women in Motherwell, Scotland—women who had been advised to eat a pound of meat per day and to avoid carbohydrate-rich foods during pregnancy. Different degrees of adherence to the recommendation resulted in variation in dietary intake, which was then related to offspring health. Systolic blood pressure of adult offspring (aged 27–30 years) was positively related to their mothers’ meat consumption in late pregnancy, but this association was attenuated among women consuming 7 or more portions of vegetables per week (see Figure 3). The interaction of diet components was demonstrated in another study that found different effects of maternal carbohydrate intake according to the mother’s level of protein intake on offspring blood pressure. The highest adult systolic blood pressure in offspring was associated with high maternal protein but low carbohydrate intake.

Our own work in a Cebu, Philippines, birth cohort showed opposite effects, with a higher percentage of maternal dietary energy from protein during late pregnancy being associated with lower systolic blood pressure in adolescent male offspring. It is important to note that mean dietary protein intakes varied substantially between the Philippine and British studies. However, the Cebu study found that a composite indicator of maternal nutritional status at 30 weeks of gestation, composed of height, mid-arm circumference, triceps skinfold, and energy intake, predicted systolic blood pressure of adolescent male offspring, independent of their birth weight (see Figure 4).

**The Role of Maternal Hypercholesterolemia**

Animal studies provide evidence that maternal cholesterol levels during pregnancy affect the development of atherosclerosis in the offspring. Rabbits were fed a normal diet or diets that raised their plasma cholesterol during pregnancy. Although plasma cholesterol levels of the newborn offspring did not differ by maternal diet, those with hypercholesterolemic mothers had raised levels of markers of lipid peroxidation and a dramatic increase in the size of atherosclerotic lesions that had developed in utero.

In humans, autopsy studies were performed on fetal aortas from spontaneous abortions and premature newborns who died within 12 hours of birth. The aortas of offspring of hypercholesterolemic mothers had significantly more lesions and larger atherosclerotic lesions. The extent to which these findings were affected by maternal diet versus common genetic factors is not known.

**Summary of Prenatal Influences**

Animal studies provide strong evidence supporting the biological plausibility of an effect of early nutritional exposures. However, most evidence in humans relates to birth weight, not to specific aspects of the maternal diet. Studies of birth weight have shown consistent, small inverse associations of birth weight with adult
blood pressure, coronary heart disease mortality, and type 2 diabetes, although no consistent association has been shown between birth weight and serum lipids. Studies of maternal diet have not shown consistent relationships and are confusing because of large variations in timing and nature of diet assessments and degree of variation in diet exposures. Creative and ethical prospective studies designed to test long-term effects of maternal diet are needed.

Infant Nutrition

Most studies on infant nutrition and later CVD risk have compared those who received human milk with those fed breast milk substitutes. The most common CVD-related outcomes examined in recent studies are blood pressure, serum lipids, and insulin levels. Research has focused on differences in milk composition, notably protein, total fat, and fatty acid composition, as the most likely causes of cardiovascular effects. However, formula milk is also devoid of many hormones and growth factors present in breast milk, and its role has not been evaluated. Cardiovascular effects may also be caused by differential regulation of hunger and satiety related to feeding mode, but few studies have examined this or other possible causes.

Challenges in Research

Studies of infant diet and later disease risk must confront a number of challenges. Randomized studies (where experimental and control diets only differ on the component of interest) are best suited to test hypotheses about the causal effects of diet, but randomization is only ethical among infants whose mothers choose not to breast-feed. Retrospective studies suffer from bias related to inaccurate recall of breast-feeding duration and poor quantification of mixed feeding. Comparison of results across observational studies is difficult for several reasons.

First, breast milk substitutes have changed substantially over time in attempts to mimic breast milk composition. Before the mid-1970s, infants were often given unmodified cow’s milk preparations or formulas made from evaporated milk. Infant formula has also differed in composition over time and across brands. The most recent differences reflect the addition of long-chain fatty acids. As substitutes have come to more closely resemble breast milk, developmental differences between breast-fed versus formula-fed infants have likely been reduced to some extent. Second, dietary exposure variables are defined in many different ways across studies. Exposure to breast-feeding may be recorded as dichotomous (ever/never) or, in more detail, reflecting exclusivity and/or duration. Timing of measurements is also important, with the best data coming from studies where measurements of breast-feeding are taken in infancy rather than recalled. Third, studies also struggle with many confounding factors. Breast-feeding does not have equal social desirability in all populations. In most industrialized countries, mothers who choose to breast-feed tend to be better educated and may have other unmeasured health-promoting behaviors (eg, more exercise and better diet) that would also affect offspring CVD risk. It becomes difficult to distinguish the effects of breast milk composition, the physical act of breast-feeding, and other associated behaviors. Because randomization to breast versus formula feeding is unethical in most contexts, the effects of confounding can only be addressed through careful study design and prudent use of statistical methods. Finally, studies considering CVD outcomes in adulthood must also deal with the many factors that have influenced individuals’ risk since birth. Lifestyle in later childhood and adulthood may modify the effects of early feeding.

Blood Pressure

Several randomized clinical trials provide the best evidence for a causal effect of breast milk on later cardiovascular health. Two studies\textsuperscript{19,20} presented results from a trial on preterm infants who were hospitalized and enterally fed after birth. Infants were randomized to be fed either preterm formula or banked breast milk in addition to any breast milk their mothers provided. The duration of feedings was as little as 2 to 4 weeks. At 13 to 16 years, adolescents randomized to breast milk had a mean arterial blood pressure of 4.2 mm Hg lower (95% confidence interval, −6.0 to −1.6) than those given formula. Cholesterol, measured as the ratio of low-density lipoprotein to high-density lipoprotein, was also lower among infants fed breast milk (see Figure 5).
Another interesting study highlights a potential role for long-chain polyunsaturated fatty acids. Blood pressure was measured in 6-year-old children who had been breast-fed (n = 88) or randomized to be fed formula supplemented with docosahexanoic and arachidonic acid or control formula for 4 months. Mean systolic and diastolic blood pressures were 3 to 4 mm Hg lower in breast-fed children and those supplemented with long-chain polyunsaturated fatty acids than in children fed control formula.

Observational studies provide inconsistent evidence for an association between breast-feeding and later blood pressure. In their meta-analysis of 24 studies, Owen et al found that pooled mean systolic blood pressure was 1.10 mm Hg lower with breast-feeding (95% confidence interval, −1.79 to −0.42), but diastolic blood pressure did not differ. Martin et al conducted a meta-analysis that pooled 15 studies with participants older than 1 year at blood pressure measurement. They estimated a 1.4-mm Hg reduction in systolic blood pressure and a 0.5-mm Hg reduction in diastolic blood pressure with breast-feeding (95% confidence interval: systolic, −2.2 to −0.6; diastolic, −0.9 to −0.04), independent of study size. In both meta-analyses, breast-feeding effects were smaller in studies with a larger sample size, suggesting publication bias (a reluctance to publish except when there are significant findings). Only the effects on diastolic blood pressure found by Martin et al were independent of study size. Table 1 provides some examples of results from several of the larger cohort studies. There are substantial differences in the birth year of participants (and thus, the likely composition of breast milk substitutes), as well as age at follow-up and the extent to which confounders were taken into account.

Other Cardiovascular-Related Outcomes

Several studies have shown an association of breast-feeding history with increased CVD risk. For example, among 45- to 49-year-old men from Caerphilly, South Wales, those who reported having been breast-fed had higher coronary heart disease incidence and mortality than those who were not breast-fed. A study in Hertfordshire, England, found that men breast-fed for more than 1 year had higher rates of ischemic heart disease 60 to 70 years later. Another UK study found that arterial distensibility among 20- to 28-year-old men and women decreased linearly in a dose-dependent manner with durations of breast-feeding ranging from more than 4 months to more than 10 months. In contrast, the large US Nurses Health Study found no association of self-reported breast-feeding in infancy with occurrence of coronary heart disease, stroke, or hypertension among 87,252 female nurses, aged 46 to 71 years, after adjustment for age, birth weight, and smoking.

An association between breast-feeding and serum lipids is thought to reflect the fat composition of breast milk. Breast-feeding related differently to blood lipids depending on age. A recent meta-analysis of 37 studies by Owen et al found that serum cholesterol of breast-fed
versus formula-fed infants differed in infancy, with breast-fed infants having significantly higher total cholesterol. In childhood and adolescence, cholesterol levels did not differ by feeding history, but in adulthood, cholesterol levels were relatively lower among individuals who were breast-fed. However, evidence from adult samples is sparse.

Recent research has confirmed that formula-fed infants have higher rates of cholesterol synthesis than those breast-fed at 4 months. Infants have high cholesterol needs and compensate for the reduced cholesterol in formula by increased cholesterol synthesis. This pattern has also been seen in baboons, pigs, and rats and is accomplished by altered expression of hepatic enzymes and low-density lipoprotein receptors. In baboons, these changes have been shown to persist into adolescence, suggesting alterations to long-term cholesterol homeostasis. Initial findings in human infants contrast with this—in the study previously mentioned, infants who had different cholesterol synthesis rates at 4 months no longer differed at 18 months of age.

More long-term research is needed to confirm early epidemiologic findings that breast-fed infants have reduced cholesterol in adulthood. However, in one study of carotid-intima thickness, a risk factor related to serum lipids, previously breast-fed adults had lower risk. A very recent study of adults in New Zealand found lower C-reactive protein concentration in women (but not men) with increased breast-feeding duration, suggesting the need to investigate other types of CVD risk factors.30

Conclusions

All studies on the long-term effects of early diet suffer from methodological limitations. The lack of randomized studies, the difficulty of fully characterizing dietary exposures, and the inability to account for numerous other factors that affect risk between infancy and adulthood leave room for a good deal of uncertainty. Animal studies provide clear evidence of the effects of early diet but are not always able to be extrapolated to humans. Human studies, taken together, support a role for early nutrition, but the effects tend to be small. A great deal of more research needs to be done to clarify which cardiovascular effects are truly attributable to early diet, to identify the mechanisms driving these effects, and to determine what health recommendations should be made on the basis of these facts.

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Table 1. Comparison of Large Epidemiologic Studies Considering the Effect of Breast-Feeding on Later Cardiovascular Outcomes

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample</th>
<th>Location</th>
<th>Rates of BF</th>
<th>Results: Effect of BF</th>
</tr>
</thead>
<tbody>
<tr>
<td>European Heart Study</td>
<td>N = 1,557</td>
<td>Denmark</td>
<td>82%–85%</td>
<td>Lower systolic BP, with dose response, no relationship with glucose, insulin, lipids</td>
</tr>
<tr>
<td></td>
<td>Age: 9–15 y</td>
<td>Estonia</td>
<td></td>
<td></td>
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<tr>
<td></td>
<td>Birth year:</td>
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<td></td>
<td></td>
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<tr>
<td></td>
<td>Late 1980s</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Boyd Orr Cohort</td>
<td>N = 339</td>
<td>UK</td>
<td>75%</td>
<td>Lower carotid intima thickness, reduced odds of plaques</td>
</tr>
<tr>
<td></td>
<td>Age: 63–82 y</td>
<td></td>
<td></td>
<td>No relationship with BP, lipids, insulin resistance, or type 2 diabetes</td>
</tr>
<tr>
<td></td>
<td>Birth year:</td>
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</tr>
<tr>
<td></td>
<td>1937–1939</td>
<td></td>
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<tr>
<td>Caerphilly Study</td>
<td>N = 1,580</td>
<td>UK</td>
<td>73%</td>
<td>Positive effect on CHD but no dose response</td>
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<tr>
<td></td>
<td>Men</td>
<td></td>
<td></td>
<td>No relationship with BP, insulin resistance, cholesterol, fibrinogen</td>
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<tr>
<td></td>
<td>Age: 45–59 y</td>
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<tr>
<td></td>
<td>Birth year:</td>
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<tr>
<td></td>
<td>1930s</td>
<td></td>
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<tr>
<td>ALSPAC</td>
<td>N = 7,276</td>
<td>UK</td>
<td>83%</td>
<td>Lower systolic and diastolic BP, no dose response</td>
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<tr>
<td></td>
<td>Age: 7 y</td>
<td></td>
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<tr>
<td></td>
<td>Birth year:</td>
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</tr>
<tr>
<td></td>
<td>1991</td>
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<td></td>
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<tr>
<td>Pelotas birth cohort</td>
<td>N = 4,357</td>
<td>Brazil</td>
<td>82% BF for</td>
<td>No association of BF duration with BP</td>
</tr>
<tr>
<td></td>
<td>Age: adolescents</td>
<td></td>
<td>&gt;1 month</td>
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<tr>
<td></td>
<td>Birth year:</td>
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<tr>
<td></td>
<td>1982</td>
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</table>

BF indicates breast-feeding; BP, blood pressure; CHD, coronary heart disease.
REFERENCES


