
The Obstetric Origins of Health for a Lifetime

DAVID J.P. BARKER, MD, PhD*
and KENT L. THORNBURG, PhD†

*MRC Lifecourse Epidemiology Unit, University of Southampton,
Southampton, UK; and †Moore Institute and Heart Research
Center, Oregon Health & Science University, Portland, Oregon

Abstract: There is a new “developmental” model for the origins of a wide range of chronic diseases. Under this model the causes to be identified are linked to normal variations in fetoplacental development. These variations are thought to lead to variations in the supply of nutrients to the baby that permanently alter gene expression, a process known as “programming.” According to the developmental model variations in the processes of development program the function of a few key systems that are linked to disease, including the immune system, antioxidant defenses, inflammatory responses, and the number and quality of stem cells.

Key words: fetal programming, maternal nutrition, placenta

Review

FETAL PROGRAMMING

There is now clear evidence that the pace and pathways of early growth and

development are major risk factors for the development of a range of chronic diseases including coronary heart disease and type 2 diabetes, which are the focus of this review. This has led to a new “developmental” model for the origins of disease that proposes that nutrition during fetal life, infancy, and early childhood establish gene expression and thereby permanently set functional capacity, metabolic competence, and responses to the later environment, a phenomenon known as “programming.”^{1,2}

Studies in the county of Hertfordshire, UK, were the first to show that rates of coronary heart disease and type 2 diabetes among people in their later lives fall steeply with increasing birthweight across the normal range.^{3,4} These associations have now been extensively replicated among men and women in Europe, the United States, India, and China.^{5–8} The associations between low birthweight and later disease depend on slow fetal growth rather than premature birth. Among the different cohorts that have been assembled around the world to study

Correspondence: David J.P. Barker, MD, PhD, MRC Lifecourse Epidemiology Unit, University of Southampton, Mail Point 95, Southampton General Hospital, SO16 6YD, UK. E-mail: djpbarker@gmail.com

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programming the Helsinki Birth Cohort has some of the most detailed information.⁹ The cohort comprises 20,000 men and women who were born in Helsinki, Finland, during 1924 to 1944 and have been followed up to the present day.

DEVELOPMENTAL PLASTICITY

Like other living creatures in their early life, human beings are “plastic” during development and respond to their environment.¹⁰ Each system and organ has a critical period when it is sensitive to the environment and during which it has to grow and mature. Critical periods are often brief and for most organs and systems they occur in utero. Among the major organs only the brain, liver, and immune system remain plastic after birth. Developmental plasticity enables the production of phenotypes that are better matched to their environment than would be possible if the same phenotype was produced in all environments. It is defined as the phenomenon by which one genotype can give rise to a range of different physiological or morphologic states in response to different environmental conditions during development.¹⁰ A baby’s responses to malnutrition include slowing of growth and altered metabolism, which enable it to survive.

Until recently we have overlooked a growing body of evidence that systems of the body that are closely related to adult disease, such as the regulation of blood pressure, are plastic during early development. In animals it is surprisingly easy to produce lifelong changes in the physiology and metabolism of a fetus by minor modifications to the diet of the mother before and during pregnancy.¹¹

SMALL SIZE AT BIRTH AND LATER DISEASE

There is now clear evidence that a range of chronic diseases, including cardiovascular disease, type 2 diabetes, certain cancers,

and chronic infections, originate through developmental plasticity, in response to malnutrition during fetal life and infancy.¹ Why should fetal responses to malnutrition lead to disease in later life? The general answer is clear: “life history theory,” which embraces all living things, states that during development there is never enough resource to perfect every trait. If a plant in your yard seeks more moisture by growing deeper roots it will do so at the expense of its stem and leaves. In humans, increased allocation of energy to one trait, such as brain growth, necessarily reduces allocation to one or more other traits, such as tissue repair processes. The human fetus has a developmental hierarchy. At the top of this is the brain. Toward the lower end are organs such as the lung and kidney: these do not function in utero and their development may be “traded off” to protect higher priority systems. The costs of trading off include, it seems, disease in later life.

There are three processes through which people whose birthweights were toward the lower end of the normal range have worse health through life than larger babies. First, they have less functional capacity in key organs, such as the kidney.¹² Second, they have different settings of hormones and metabolism.¹³ Third, they are more vulnerable to adverse environmental influences in later life.¹⁴

INFANT AND CHILDHOOD GROWTH

Figure 1 shows the early growth of men and women, born in Helsinki, who were either admitted to hospital with coronary heart disease or died from it.⁹ Their mean height, weight, and body mass index (BMI, weight/height²) at each month from birth to 2 years of age, and at each year from 2 to 11 years of age, are expressed as SDs (*z* scores). The mean *z* score for the cohort is set at 0 and a child maintaining a steady position as tall or short, or fat or thin, in relation to other children would follow a horizontal path

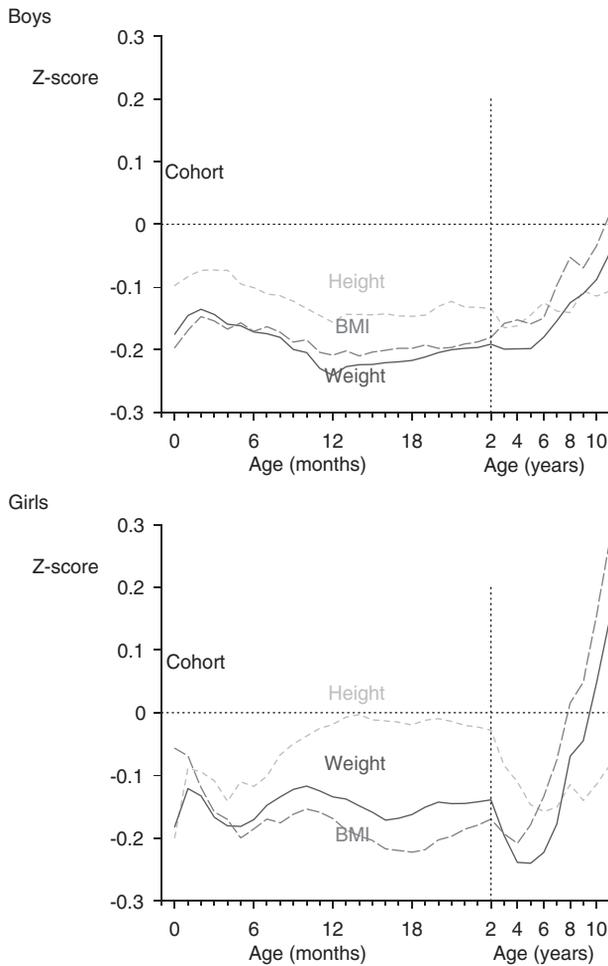


FIGURE 1. Mean z scores for height, weight, and body mass index (BMI) in the first 11 years after birth among boys and girls who had coronary heart disease as adults. The mean values for all boys and all girls are set at 0, with deviations from the mean expressed as SDs (z scores).

on the Figure. At birth the mean body size of the boys who developed coronary heart disease in their later lives was approximately 0.2 SDs below the average and they were thin. Between birth and 2 years of age, mean z scores for each measurement fell, so that at 2 years the boys were thin and short. After 2 years of age their z scores for BMI began to increase and continued to do so. Similarly to the boys, the mean body size of the girls who later had coronary events was below the average at birth (Fig. 1). At 2 years of age they

were thin but after that their z scores for BMI began to increase and continued to do so.

COMPENSATORY GROWTH

The rapid weight gain after the age of 2 years, that characterizes the growth of children who later develop coronary heart disease (Fig. 1) is thought to reflect “compensatory” growth. If the growth of a fetus, infant, or child falters because of malnutrition or other adversity it has the

TABLE 1. Odds Ratios (95% Confidence Intervals) for Type 2 Diabetes and Hypertension According to Birthweight and Body Mass Index (BMI) at Age 11 Years

Birthweight (kg)	BMI at Age 11 (kg/m ²)			
	< 15.7	-16.6	-17.6	> 17.6
Type 2 diabetes (698 cases)				
< 3.0	1.3 (0.6-2.8)	1.3 (0.6-2.8)	1.5 (0.7-3.4)	2.5 (1.2-5.5)
-3.5	1.0 (0.5-2.1)	1.0 (0.5-2.1)	1.5 (0.7-3.2)	1.7 (0.8-3.5)
-4.0	1.0 (0.5-2.2)	0.9 (0.4-1.9)	0.9 (0.4-2.0)	1.7 (0.8-3.6)
> 4.0	1.0	1.1 (0.4-2.7)	0.7 (0.3-1.7)	1.2 (0.5-2.7)
Hypertension (2997 cases)				
< 3.0	2.0 (1.3-3.2)	1.9 (1.2-3.1)	1.9 (1.2-3.0)	2.3 (1.5-3.8)
-3.5	1.7 (1.1-2.6)	1.9 (1.2-2.9)	1.9 (1.2-3.0)	2.2 (1.4-3.4)
-4.0	1.7 (1.0-2.6)	1.7 (1.1-2.6)	1.5 (1.0-2.4)	1.9 (1.2-2.9)
> 4.0	1.0	1.9 (1.1-3.1)	1.0 (0.6-1.7)	1.7 (1.1-2.8)

ability, once the adversity has ceased, to return to its growth trajectory by accelerated growth. The ability to mount rapid “compensatory” growth after growth faltering is common in animals and familiar to farmers. It necessarily has costs. If energy is allocated to rapid growth the allocation to some other developmental activity must be reduced. In animals compensatory growth has a wide range of physiological and metabolic costs that include reduced quality of tissues and organs, such as the bone, heart, kidneys, and premature death. Little is known about these costs in humans.²

One explanation of the associations between coronary heart disease and small body size at birth and thinness at 2 years of age is that babies who are thin or short at birth and during infancy lack muscle, a deficiency that will persist into childhood as there is little cell replication in muscle after around 1 year of age.¹⁵ Rapid weight gain in childhood may lead to a disproportionately high fat mass in relation to muscle mass. This could underlie the strong associations between low birthweight, low BMI at 2 and high BMI at 11, and later insulin resistance, which was found when a subsample of 2003 subjects in the Helsinki cohort were examined at the age of 62 years.⁹

Table 1 shows odds ratios for type 2 diabetes according to birthweight and

fourths of BMI at age 11 years.¹⁶ The 2 disorders are associated with the same general pattern of growth as coronary heart disease.⁹ Risk of disease falls with increasing birthweight and rises with increasing childhood BMI. The Helsinki Birth Cohort allows estimation of the strength of these effects.¹⁶ If each individual in the Helsinki Birth Cohort had been in the highest third of birthweight and had decreased their SD score for BMI between ages 3 and 11 years, the incidence of type 2 diabetes would have been halved. This demonstrates the potential power of interventions during development.

FETAL NUTRITION

The variations in the size and shape of newborn human babies reflects their plasticity in utero. The growth of babies has to be constrained by the size of the mother, otherwise normal birth could not occur. Small women have small babies: in pregnancies after ovum donation they have small babies even if the woman donating the egg is large.¹⁷ Babies may be small because their growth is constrained in this way or because they lack the nutrients for growth. As McCance¹⁸ wrote, “The size attained in utero depends on the services which the mother is able to supply. These are mainly food and accommodation.” Research into the developmental origins

of disease has focussed on the nutrient supply to the baby, while recognizing that other influences, such as hypoxia, stress, and maternal size also influence fetal growth.¹⁹ The availability of nutrients to the fetus is influenced by the mother's nutrient stores and metabolism, as well as by her diet during pregnancy. In developing countries many babies are undernourished because their mothers are chronically malnourished. Despite current levels of nutrition in western countries, the nutrition of many fetuses and infants remains sub-optimal because the nutrients available are unbalanced or because their delivery is constrained by maternal metabolism. Globally, size at birth in relation to gestational age is a marker of fetal nutrition.¹⁹

Size at birth is the product of the fetus's trajectory of growth, which is set at an early stage in development, and the maternoplacental capacity to supply sufficient nutrients to maintain this trajectory. A rapid trajectory of growth increases the fetus's demand for nutrients.¹⁹ This demand is greatest late in pregnancy but the trajectory is thought to be primarily determined by genetic and environmental effects in early gestation. Experiments in animals have shown that alterations in maternal diet around the time of conception can change the fetal growth trajectory.²⁰ The sensitivity of the human embryo to its environment is being increasingly recognized with the development of assisted reproductive technology.²¹ The trajectory of fetal growth is thought to increase with improvements in periconceptional nutrition, and is faster in male fetuses. The consequent greater vulnerability of male fetuses to malnutrition may contribute to the shorter lives of men.²²

MATERNAL NUTRITION

The graded relation between birthweight and later disease implies that variations in the supply of food from normal healthy mothers to normal healthy babies have

major implications for the long-term health of the babies.²³ A baby does not depend on the mother's diet during pregnancy: that would be too dangerous a strategy. Rather it lives off her stored nutrients and the turnover of protein and fat in her tissues.²⁴ These are related to her body composition and therefore reflect her lifetime nutrition. Studies in Europe and India have shown that high maternal weight and adiposity are associated with the development of insulin deficiency, type 2 diabetes, and coronary heart disease in the offspring.²⁵⁻²⁷ There is also evidence that low maternal weight, BMI, and skin fold thickness are associated with insulin resistance and raised blood pressure in the offspring.²⁸⁻³⁴ One of the metabolic links between maternal body composition and birth size is protein turnover. Women with a low lean body mass have low rates of protein turnover in pregnancy.³⁵

Although a mother's diet during pregnancy is not closely linked to the birthweight of her baby it can program the baby. Follow-up studies of people who were in utero during the war-time famine in Holland have shown that, although the babies' birthweights were little affected, the severe maternal caloric restriction at different stages of pregnancy was variously associated with obesity, dyslipidemia, insulin resistance, and coronary heart disease in the offspring.²⁸ In these studies maternal rations with a low protein density were associated with raised blood pressure in the adult offspring.³⁶ This adds to the findings of studies in Aberdeen and Motherwell, UK, which showed that maternal diets with either a low or a high ratio of animal protein to carbohydrate were associated with raised blood pressure in the offspring during adult life.^{29,37} Although it may seem counterintuitive that a high-protein diet should have adverse effects, these findings are consistent with the results of controlled trials of protein supplementation

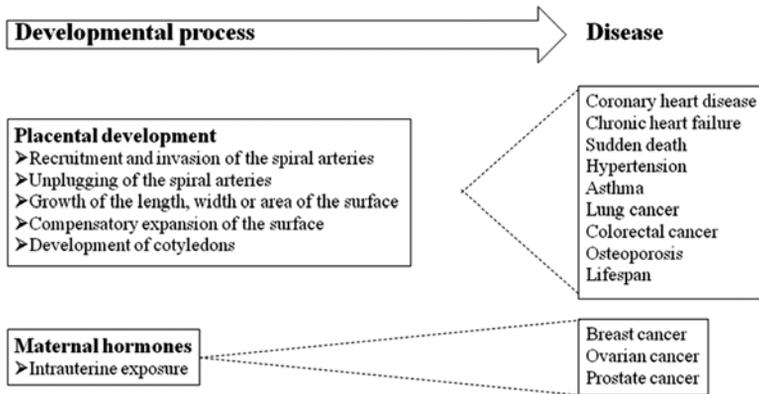


FIGURE 2. Variations in the normal processes of development and later chronic disease.

in pregnancy, which show that high protein intakes are associated with reduced birthweight.³⁸ One possibility is that these adverse effects are a consequence of the metabolic stress imposed on the mother by an unbalanced diet in which high intakes of essential amino acids are not accompanied by the micronutrients required to utilize them.

THE PLACENTA

A baby's birthweight depends on the mother's nutrition and on the placenta's ability to transport nutrients to it from its mother. The placenta seems to act as a nutrient sensor regulating the transfer of nutrients to the fetus according to the mother's ability to deliver them, and the demands of the fetus for them.³⁹ The weight of the placenta, and the size and shape of its surface, reflect its ability to transfer nutrients. The shape and size of the placental surface at birth has become a new marker for chronic disease in later life.⁴⁰ The predictions of later disease depend on combinations of the size and shape of the surface and the mother's body size. Particular combinations have been shown to predict coronary heart disease,⁴¹ hypertension,⁴² chronic heart failure,⁴⁰ and certain forms of cancer.⁴⁰ The placenta is the most varied of all

human organs. Variations in its size and shape reflect variations in the normal processes of its development, including implantation, unplugging of the spiral arteries, and the growth and compensatory expansion of the chorionic plate. (Fig. 2). These variations are accompanied by variations in nutrient delivery to the fetus. Figure 2 also shows potential effects of exposure to maternal hormones during gestation, but this is outside the scope of this review.

Table 2 shows the systolic pressures of a group of men and women who were born at term in Preston, UK.⁴³ They are grouped according to their birthweight and placental weight. As expected systolic pressures falls between those with low and high birthweight; but in addition the pressures increase with increasing placental weight. People with a mean systolic pressure of ≥ 150 mm Hg, a level used to define hypertension, comprise a group who as babies were relatively small in relation to the size of their placentas. In Table 2 the fall in pressures of 10 mm Hg across the range of birthweight is statistically opposed by the rise of 12 mm Hg associated with increasing placental weight. These large trends are concealed when all pressures at a given birthweight are combined, as in the right-hand column. These statistically opposing

TABLE 2. Mean Systolic Blood Pressure (mm Hg) Among Men and Women Aged 50, Born After 38 wk of Completed Gestation, According to Placental Weight and Birthweight

Birthweight [lb (kg)]	Placental Weight [lb (g)]				All
	≤1.0 (454)	–1.25 (568)	–1.5 (681)	> 1.5 (681)	
–6.5 (2.9)	149	152	151	167	152
–7.5 (3.4)	139	148	146	159	148
>7.5 (3.4)	131	143	148	153	149
All	144	148	148	156	149

trends may also explain why some studies have failed to find associations between placental weight and later blood pressure. Animal studies offer a possible explanation of this. In sheep the placenta enlarges in response to moderate undernutrition in midpregnancy.⁴⁴ This is thought to be an adaptive response to extract more nutrients from the mother. It is not, however, a consistent response but occurs only in ewes that were well nourished when they conceived.

PATHWAYS TO DISEASE

The effects of the intrauterine environment on later disease are conditioned not only by the genotype acquired at conception but also by events before and after birth. It seems that the pathogenesis of chronic disease cannot be understood within a model in which risks associated with adverse influences at different stages of life add to each other. Rather, disease is the product of branching paths of development. The environment triggers the branchings. The pathways determine the vulnerability of each individual to what lies ahead. As an example of this we are beginning to understand the processes through which different paths of development initiate hypertension.⁴⁵ The changes occur at different levels and include allocation of stem cells and alteration of gene expression in the embryo, changes in renal growth, and alteration in hemostatic set-points that control blood pressure. These changes can make the affected systems more vulnerable to disruptive influences

in postnatal life, which include rapid weight gain, oxidative stress, environmental stress, and a high salt intake.

Conclusions

Under the new developmental model for the origins of chronic disease, the causes to be identified are linked to normal differences in the processes of development that lead to variations in the supply of nutrients to the baby.⁴⁶ These variations program the function of a few key systems that are linked to chronic disease—the immune system, antioxidant defenses, inflammatory responses, the number and quality of stem cells, neuroendocrine settings, and the balance of the autonomic nervous system. There is not a separate cause for each different disease. Rather one cause can have many different disease manifestations. Which chronic disease originates during development may depend more on timing than on qualitative differences in exposures.

Exploration of the developmental model will illuminate people’s differing responses to the environment through their lives. As René Dubos wrote long ago “The effects of the physical and social environments cannot be understood without knowledge of individual history.”⁴⁷ The model will also illuminate geographical and secular trends in disease. Because human growth has changed over the past 200 years, so different chronic diseases have risen and then fallen, to be replaced by other diseases.^{48,49} Much remains to be

done. We are only at the beginnings of an understanding of the costs of compensatory growth in humans. Our knowledge of the structure and function of the normal human placenta is fragmentary.

Coronary heart disease, type 2 diabetes, breast cancer, and other chronic diseases are unnecessary. Their occurrence is not mandated by genes passed down to us through thousands of years of evolution. Chronic diseases are not the inevitable lot of humankind. They are the result of the ever-changing pattern of human development. We could readily prevent them, had we the will to do so. Prevention of chronic disease, and an increase in healthy aging, require improvement in the nutrition of girls and young women. Many babies in the womb in the western world today are receiving unbalanced and inadequate diets. Many babies in the developing world are malnourished because their mothers are chronically malnourished. Protecting the nutrition and health of girls and young women should be the corner stone of public health. Not only will it prevent chronic disease but it will produce new generations who have better health and well-being through their lives.

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