
The Developmental Origins of Insulin Resistance

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Key Words

Fetal growth · Childhood growth · Insulin resistance · Type 2 diabetes mellitus · Body mass index

Abstract

Until recently, the principal causes of degenerative disease were thought to act in adult life and to accelerate destructive processes, such as the formation of atheroma and rise in blood pressure. Recent observations that people who develop coronary heart disease grow differently to other people during fetal life and childhood have, however, led to a new 'developmental' model for the disease. Low birthweight has been shown to be associated with increased rates of coronary heart disease, type 2 diabetes mellitus and altered glucose tolerance. These associations with low birthweight extend across the normal range of birthweight and reflect slow fetal growth rather than premature birth. The associations are thought to be consequences of developmental plasticity, the phenomenon by which one genotype can give rise to a range of different physiological or morphological states in response to different environmental conditions during development. Recent observations suggest that low birthweight, thinness at 2 years of age and an increase in body mass index (BMI) after the age of 2 years are each associated with the development of insulin resistance in later

life. The prevention of a substantial proportion of type 2 diabetes and other disorders linked to insulin resistance may, therefore, depend on interventions during development. These include protecting the growth of babies during the first 2 years after birth by good infant feeding practices and preventing a rapid increase in BMI after the age of 2 years. Improving fetal nutrition remains an important long-term goal.

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Introduction

Until recently, the search for the causes of degenerative diseases, and ways to prevent them, has been guided by a 'destructive' model. The principal causes to be identified were thought to act in adult life and to accelerate destructive processes, such as the formation of atheroma and rise in blood pressure. This model, however, has had limited success. The effects of modifying adult lifestyle, when formally tested in randomized trials, have been disappointingly small [1]. Recent observations that people who develop coronary heart disease grow differently from other people during fetal life and childhood have led to a new 'developmental' model for the disease [2]. To explore the developmental origins of chronic disease required studies of a kind that had not hitherto been carried out.

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Table 1. Premature death from coronary heart disease (aged <65 years) according to birthweight in 10,636 men born in Hertfordshire between 1911 and 1930 [3, 4]

Birth weight, kg (pounds)	Hazard ratios (95% confidence interval)
≤ 2.5 (5.5)	1.37 (1.00–1.87)
–2.95 (6.5)	1.30 (1.01–1.67)
–3.4 (7.5)	1.17 (0.92–1.47)
–3.85 (8.5)	1.11 (0.88–1.41)
–4.3 (9.5)	0.90 (0.69–1.18)
≥ 4.55 (10)	1.00
p for trend	<0.001

It was necessary to identify groups of men and women, now in middle-to-late life, whose size at birth had been recorded at the time. Their birthweight could then be related to the later occurrence of disease. Table 1 shows the findings among 10,636 men born in Hertfordshire, UK, during 1911–1930, for whom weight at birth was known. This study showed for the first time that the risk of coronary heart disease falls with increasing birthweight [3, 4]. This finding of an association between low birthweight and risk of coronary heart disease has now been replicated among men and women in Europe, the USA and India [4–11]. Low birthweight has also been shown to predict the later development of type 2 diabetes mellitus and altered glucose tolerance in studies around the world [12–16].

These associations with low birthweight reflect slow fetal growth rather than premature birth. They suggest that influences linked to fetal growth have an important effect on the risk of coronary heart disease and type 2 diabetes. As the association between birthweight and later disease extends across the whole range of what are regarded as normal birthweights (table 1), an implication is that normal variations in the delivery of nutrients to the fetus have profound consequences for its long-term health. It has been argued, however, that people whose growth was impaired in utero may continue to be exposed to an adverse environment in childhood and adult life, and it is this later environment that produces the effects attributed to intrauterine influences. There is now strong evidence that this argument cannot be sustained. In a number of studies, data on lifestyle including smoking habits, employment, alcohol consumption and exercise were collected. In the Nurses' Health Study, in the USA, allowance for these influences had little effect on the association between birthweight and risk for coronary heart dis-

ease [6]. Similar results came from studies in Sweden and the UK [5, 8]. Adult lifestyle, however, adds to the effects of early life: for example, the prevalence of type 2 diabetes is highest in people whose weight at birth was low but who were obese as adults [12, 17].

Biological Basis

Like other living creatures, in their early life human beings are 'plastic' and able to adapt to their environment. The essence of developmental plasticity is a critical period when a system is plastic and sensitive to the environment; this is followed by loss of plasticity and a fixed functional capacity. For most organs and systems the critical period occurs in utero. *Developmental plasticity* is formally defined as the phenomenon by which one genotype can give rise to a range of different physiological or morphological states in response to different environmental conditions during development [18, 19]. From studies using animal models, we are beginning to understand the biological processes that are initiated by the early environment [20]. As in humans, such processes can operate within the normal range of fetal growth and birthweight [21].

Developmental Origins Hypothesis

This hypothesis proposes that coronary heart disease, type 2 diabetes, stroke and hypertension originate through developmental plasticity, in response to under-nutrition during fetal life and infancy [22, 23]. People who were small at birth may be vulnerable to later disease through three kinds of process. First, they have fewer cells in key organs, such as the kidney. One theory holds that hypertension is initiated by the reduced number of glomeruli found in people who were small at birth [24, 25], which necessarily leads to increased blood flow through each glomerulus, and ultimately to glomerulosclerosis and glomerular loss. Animal studies provide support for this theory [26]. Another process by which slow fetal growth may be linked to later disease is in the setting of hormones and metabolism. An undernourished baby may establish a 'thrifty' way of handling food, one manifestation of which is insulin resistance, which becomes disadaptive if under-nutrition is followed by over-nutrition [27].

A third link between low birthweight and later disease is that people who were small at birth have enhanced stress responses [28]. Figure 1 shows the effects of low

Fig. 1. Hazard ratios for coronary heart disease (hospital admission or death) in 3,676 Finnish men according to income in 1980 and ponderal index at birth. Data from Barker et al. [28].

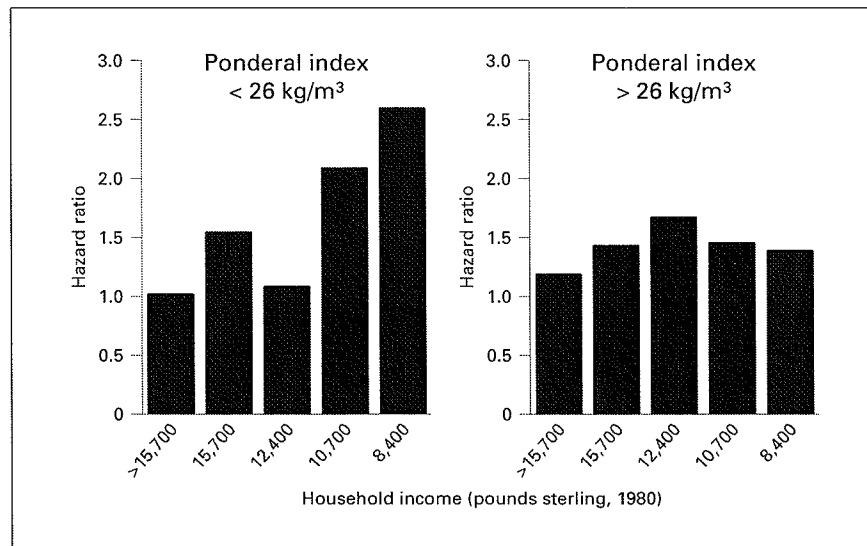
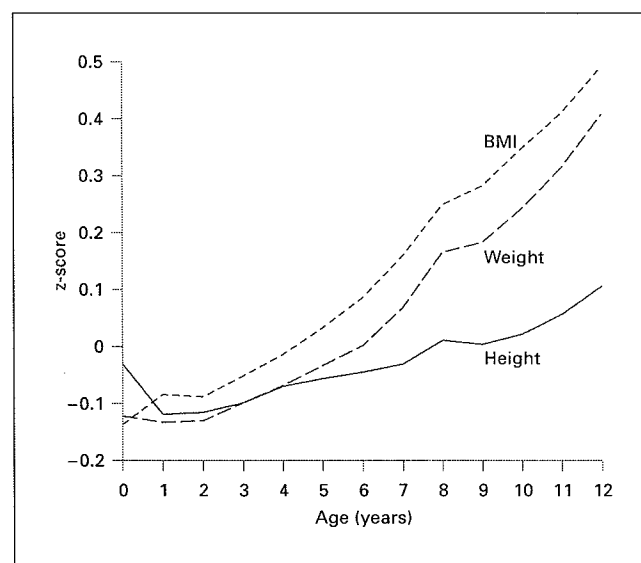


Fig. 2. Mean SDS (z-scores) for height, weight and BMI during childhood in 290 people who later developed type 2 diabetes within the Helsinki cohort of 8,760 men and women. At any age, the mean z-score for the cohort is set at zero while the standard deviation is set at 1 [30].



income, which may be linked to psychosocial stress [29], on the risk of coronary heart disease among men in Helsinki, Finland. As expected, men with low household incomes had higher rates of the disease, but this was confined to men who had slow fetal growth and were thin at birth, defined by a ponderal index (birthweight/length³) of less than 26 kg/m³ [28].

Figure 2 shows the infant and childhood growth of 290 men and women who later developed type 2 diabetes within a cohort of 8,760 men and women who were born in Helsinki between 1934 and 1944, and for whom serial data on weight are available from birth [30]. The average

height, weight and body mass index (BMI) for the cohort are set at zero, and deviations from it are expressed as standard deviation scores (SDS; z-scores). A child maintaining a steady position as large or small in relation to other children would follow a horizontal path on figure 2. Children who later developed type 2 diabetes, however, had below average body size at birth and at 1 year, after which their weight and body mass indices rose progressively to exceed the average.

After around 2 years of age, the body mass of all young children falls, reaching a minimum around 6 years of age, before increasing again – the so-called adiposity rebound

Table 2. Age at adiposity rebound in relation to later incidence of type 2 diabetes in 8,760 boys and girls in the Helsinki cohort. Data from Eriksson et al. [30]

Age at adiposity rebound, years	Cumulative incidence of diabetes, %	Change in z-score for weight from birth to 1 year	BMI at 1 year kg/m ²
≤ 4	8.6	-0.20	16.9
5	4.4	-0.27	16.9
6	3.2	+0.06	17.7
7	2.2	+0.16	18.2
≥ 8	1.8	+0.25	18.4
p for trend	<0.001	<0.001	<0.001

[31]. In the Helsinki cohort, the age at adiposity rebound ranged from 4 years or less to 8 years or more [30]. Early age at adiposity rebound was found to be a strong predictor of later type 2 diabetes [30]. Table 2 shows that the cumulative incidence of the disease fell progressively from 8.6% in people whose adiposity rebound occurred at 4 years or less to 1.8% in those in whom it occurred at 8 years or more. This large trend shows how important the speed of childhood weight gain is in determining the risk of later disease. Table 2 also shows that adiposity rebound at an early age was associated with low weight gain between birth and 1 year of age, and consequent low body mass at that age. It was not, therefore, the overweight preschool child who developed type 2 diabetes, but the child who was thin up to the age of around 2 years and began to put on weight rapidly thereafter.

New findings based on examination of 2,003 men and women in the Helsinki cohort show that low birthweight, thinness at 2 years of age and an increase in z-scores for BMI after the age of 2 years are each associated with the development of insulin resistance in later life [32].

Pathways of Development

We are beginning to see that adult degenerative diseases are associated with different paths of fetal and infant growth, and that the same disease may originate in more than one path. Studies on the Helsinki cohort suggest that type 2 diabetes is associated with three paths of growth. One begins with slow fetal growth; another begins with normal fetal growth followed by slow infant growth [33]; a third path begins with gestational diabetes and the birth of a macrosomic baby with high birthweight [14].

Compensatory Growth

When under-nutrition during early development is followed by improved nutrition, many animals and plants stage accelerated or 'compensatory' growth [34]. Compensatory growth has costs, however, which in animals include reduced life-span. There are a number of processes by which, in humans, under-nutrition and small size at birth followed by rapid childhood weight gain could lead to cardiovascular disease and type 2 diabetes in later life [11, 16]. Rapid growth may be associated with persisting hormonal and metabolic changes; it may increase the demand on functional capacity that has been reduced by slow early growth; it may lead to an unfavourable body composition. Babies that are small and thin at birth lack muscle, a deficiency that will persist because the critical period for muscle growth occurs in utero and there is little cell replication after birth [35]. If they develop a high body mass during later childhood they may have a disproportionately high fat mass in relation to lean body mass, which will lead to insulin resistance [32, 36].

Gene-Nutrient Interactions during Development

New studies, especially the Helsinki study with its detailed information on child growth and socio-economic circumstances, increasingly suggest that the pathogenesis of degenerative diseases depends on a series of interactions occurring at different stages of development. To begin with, the effects of the genes acquired at conception may be conditioned by the early environment. For example, the Pro12Pro polymorphism of the PPAR- γ (peroxisome proliferator-activated receptor) gene is known to be associated with insulin resistance. In the Helsinki cohort, this effect occurred only among men and women who had low birthweight [37]. Conversely, low birthweight has been consistently linked to later insulin resistance [27], but this effect occurred only among people with the Pro12Pro polymorphism. As birthweight serves as a marker of fetal nutrition [38], this gene-birthweight interaction may reflect a gene-nutrient interaction during development. Many such interactions are likely to be found in the future. The effects of the intrauterine environment on later disease are conditioned not only by the genes acquired at conception, but by events after birth, including childhood gain in BMI.

Table 3. Cumulative incidence (%) of type 2 diabetes according to birthweight and change in standard deviation score for BMI between 3 and 11 years of age in men and women from the Helsinki cohort. Reproduced from Barker et al. [39] with permission from Oxford University Press

Birthweight, kg (pounds)	Change in SDS for BMI 3–11 years	
	decrease	increase
–3.2 (7.1)	3.1	5.5
–3.6 (7.9)	2.4	4.3
>3.6 (7.9)	1.5	5.4

Strength of Effects

When men and women from the Helsinki cohort were divided into six groups according to thirds of birthweight and whether their SDS for BMI decreased or increased between the ages of 3 and 11 years, birthweight and

change in BMI both had independent effects on the cumulative incidence of type 2 diabetes (table 3) [39]. In the group with the highest birthweight and a subsequent decrease in BMI score the cumulative incidence of type 2 diabetes was 1.5%. This was less than half the incidence in the other five groups combined (4.0%).

Summary

Prevention of a substantial proportion of type 2 diabetes, and other disorders linked to insulin resistance, may depend on interventions during development. Improving fetal nutrition remains an important long-term goal. More immediate benefit may come from (a) protecting the growth of babies during the first 2 years after birth by good infant feeding practices and the avoidance of recurrent illness, and (b) preventing a rapid increase in BMI after the age of 2 years, especially in those who were small or thin at birth and at 2 years.

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