Early growth and coronary heart disease and type 2 diabetes: findings from the Helsinki Birth Cohort Study (HBCS)¹–⁴

Johan G Eriksson

ABSTRACT

A slow rate of intrauterine growth is a major risk factor for several common noncommunicable diseases, which include the following: coronary heart disease (CHD), hypertension, and type 2 diabetes. Likewise, growth patterns in infancy and childhood have been identified as important factors linked to the pathogenesis of these disorders. In this overview, patterns of growth associated with CHD, type 2 diabetes, and related metabolic traits in adult life are presented on the basis of findings from the Helsinki Birth Cohort Study (HBCS) 1934–1944. Later risk of CHD was associated with small body size at birth and during infancy, followed by an increase in body size later in childhood. This pattern of growth has been associated with dyslipidemia in later life, which offers an explanation for the observed findings. Type 2 diabetes and CHD share several risk factors. The early growth of persons who later develop type 2 diabetes includes a small body size at birth as well as a small body size during infancy. An early age at adiposity rebound was associated with a markedly increased risk of type 2 diabetes in adulthood. The patterns of growth associated with type 2 diabetes are also associated with alterations in body composition, which predisposes to insulin resistance and the metabolic syndrome. The presented findings suggest that to be able to understand the pathogenesis of several noncommunicable diseases, the diseases need to be studied from a life-course perspective, and prenatal and childhood growth as well as adult characteristics need to be taken into account. *Am J Clin Nutr* 2011;94 (suppl):1799S–802S.

INTRODUCTION

It is well established that a slow rate of intrauterine growth is a major risk factor for several noncommunicable diseases, which include the following: coronary heart disease (CHD), hypertension, and type 2 diabetes. However, growth patterns in infancy and childhood have also been identified as important factors linked to the pathogenesis of these disorders (1–6). To be able to quantify the importance of the early developmental processes associated with the genesis and pathogenesis of cardiovascular disease and type 2 diabetes, we need to study the effect of prenatal, infant, and childhood growth on the major pathologic events in later life. Focusing on risk factors only will not necessarily provide the correct answers (7). Therefore, the examination and understanding of disease risk attributable to early life development requires information and data on prenatal, infant, and childhood growth in addition to information obtained from adult life. In other words a life course perspective is needed for an optimal understanding of adult health and disease. In this overview, patterns of growth associated with CHD, type 2 diabetes, and related metabolic traits in adult life are presented on the basis of findings from the Helsinki Birth Cohort Study (HBCS) 1934–1944.

SUBJECTS AND METHODS

The HBCS 1934–1944 included 13,345 subjects born at Helsinki University Central Hospital or at the Midwives’ Hospital in Helsinki, Finland. Information on prenatal and childhood growth was collected from hospital birth records, child welfare clinics, and school health care records. These records included information on health and growth during childhood, but also information on socioeconomic factors. The hospital birth records included data on birth weight, length at birth, gestational age, and maternal characteristics. Serial measurements of body size throughout childhood were available and the subjects had, on average, 17 measurements of height and weight from birth to 11 y of age. The cohort was followed up by register linkage to national Finnish registers, which provided information on both morbidity and mortality, suitable for the study of epidemiologic outcomes.

A clinical examination that included >2000 individuals provided more detailed information on metabolic and genetic aspects and their associations with growth and adult health outcomes. The clinical examination included a 75-g oral-glucose-tolerance test and measurements of height, weight, waist circumference, blood pressure, and body composition. Blood was drawn for measurements of blood lipids, inflammatory markers, and adipokines.

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Dietary and exercise habits were assessed by validated questionnaires.

Coronary heart disease

The original study that reported an association between low birth weight, low weight in infancy, and CHD in adult life was based on findings and data from Hertfordshire, United Kingdom (1). By now a large number of studies show that people who were small or thin at birth as a consequence of slow prenatal growth have increased rates of CHD and its risk factors later in life (2, 4, 8–13). However, one important question is whether childhood growth modifies the risk that seems to be already established in utero. The effect of early growth and CHD risk in adulthood has not been assessed in many birth cohorts; the HBCS has provided data focusing on this important aspect.

In the HBCS, deaths from CHD were associated with low birth weight as well as with thinness at birth among men. Men with a birth weight <2500 g had hazard ratios for CHD of 3.63 (95% CI: 2.02, 6.51) compared with the baseline group set at a birth weight >4000 g. Not only a small body size at birth but also slow growth during infancy increased the risk of CHD in later life. Low weight at 1 y added to the CHD risk independently of body size at birth (4).

The simultaneous effect of birth weight and body mass index (BMI; in kg/m²) at 2 y of age for the hazard ratios for CHD in adulthood is shown in Table 1. The highest hazard ratios were observed among those men with a birth weight in the lowest third and a BMI at 2 y in the lowest third.

Another important question was whether the increased risk of CHD associated with a small birth and infant size was modified by later childhood growth. The simultaneous effect of BMI at 2 y and BMI at 11 y is shown in Table 2. The highest hazard ratios for CHD were observed in individuals with the lowest BMI at 2 y of age and the highest BMI at 11 y of age. These findings suggest that CHD is predicted by the tempo of weight gain during childhood rather than body size at any specific time point.

In the HBCS, deaths from CHD were associated with a small birth and infant size followed by an above-average BMI during later childhood. These findings show that if one becomes relatively overweight in childhood in relation to one’s birth size, the consequences are largely conditioned and modified by growth in utero. In other words a mismatch between birth size and later childhood body size seems to predispose to CHD (13).

Infant and childhood growth of the men who later developed CHD is shown in Figure 1 (4). Growth was expressed as SD or z scores. The z score for the whole study cohort was set at zero. An individual who maintained a steady position as either large or small in relation to other individuals followed a horizontal path on the graph. Those men who later developed CHD had a small body size at birth and during infancy. Thereafter they experienced accelerated gain in weight and BMI; however, their heights remained below average. In a simultaneous regression, low BMI at birth, low BMI at 2 y, and high BMI at 11 y were each associated with later CHD (all P values < 0.001). Based on these findings we suggest that rapid weight gain in infancy is associated with a decreased risk of CHD among men born small, whereas an accelerated growth later in childhood seems to increase the risk of CHD. These described associations are principally similar for girls and women, although among women shortness at birth seemed to be more important than thinness at birth (11, 12).

What could be the underlying mechanisms that explain the association between a low birth weight and low BMI in infancy and CHD later in life? We have been able to test the hypothesis that this pattern of early growth is associated with an atherogenic lipid profile in adulthood. Liver regulates lipid metabolism, and altered liver growth during early life may alter cholesterol metabolism. People born small who experience a slow growth in infancy have poor liver growth, which predisposes to dyslipidemia (a major risk factor for CHD) in later life. Support for the hypothesis comes from the Hertfordshire study, where low weight

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**TABLE 1**

Hazard ratios and 95% CIs for coronary heart disease in adult life according to birth weight and BMI at 2 y of age in 4630 persons born between 1934 and 1944 included in the Helsinki Birth Cohort Study

<table>
<thead>
<tr>
<th>BMI (in kg/m²) at age 2 y</th>
<th>&lt;16</th>
<th>16–17</th>
<th>&gt;17</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;3.0 kg</td>
<td>1.9 (1.3, 2.8)</td>
<td>1.9 (1.2, 3.0)</td>
<td>1.3 (0.7, 2.2)</td>
</tr>
<tr>
<td>3.0–3.5 kg</td>
<td>1.5 (1.0, 2.1)</td>
<td>1.6 (1.1, 2.2)</td>
<td>1.2 (0.8, 1.8)</td>
</tr>
<tr>
<td>&gt;3.5 kg</td>
<td>1.7 (1.2, 2.5)</td>
<td>1.5 (1.1, 2.2)</td>
<td>1.0</td>
</tr>
</tbody>
</table>

**TABLE 2**

Hazard ratios and 95% CIs for coronary heart disease in adult life according to BMI at 2 y and 11 y of age in 4630 persons born between 1934 and 1944 included in the Helsinki Birth Cohort Study

<table>
<thead>
<tr>
<th>BMI (in kg/m²) at age 11 y</th>
<th>&lt;16</th>
<th>16–17.5</th>
<th>&gt;17.5</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;16 kg/m²</td>
<td>1.6 (0.8, 3.3)</td>
<td>2.4 (1.2, 4.9)</td>
<td>3.0 (1.4, 6.3)</td>
</tr>
<tr>
<td>16–17 kg/m²</td>
<td>1.4 (0.7, 3.1)</td>
<td>1.6 (0.8, 3.3)</td>
<td>1.9 (0.9, 3.9)</td>
</tr>
<tr>
<td>&gt;17 kg/m²</td>
<td>1.0</td>
<td>1.3 (0.6, 2.7)</td>
<td>1.1 (0.5, 2.3)</td>
</tr>
</tbody>
</table>

**FIGURE 1.** Growth in BMI, height, and weight of 357 men who developed coronary heart disease in relation to the growth of the whole cohort (n = 4630), expressed as z scores. Reproduced with permission from reference 4.
at 1 y was associated with an atherogenic lipid profile in adult life (14, 15). Animal studies also give strong support to the hypothesis about early programming of lipid metabolism (16, 17).

Similar observations were made in the HBCS. At a mean age of 62 y those 18% of the subjects who participated in the clinical study and took lipid-lowering drugs had significantly lower BMI at birth and at 2 y (18). The exclusion of these subjects from further analyses showed that a low birth BMI was associated with higher non-HDL cholesterol and apolipoprotein B concentrations. Likewise, lower BMI at 2 y of age was associated with lower HDL cholesterol and higher non-HDL cholesterol and apolipoprotein B concentrations. The early growth patterns that predisposed to an adverse lipid profile were a slow increase in BMI between birth and 6 mo and slow linear growth between 6 and 24 mo—in other words, growth patterns similar to those described for CHD.

Type 2 diabetes

In several studies a small body size at birth was associated with increased rates of impaired glucose tolerance and type 2 diabetes in adult life (5, 19–21). Findings from the HBCS showed that a small body size at birth was associated with both insulin resistance and impaired insulin secretion among nondiabetic individuals in later life (Figure 2) (22).

Type 2 diabetes and CHD share several risk factors, and the early growth of individuals who later in life develop type 2 diabetes greatly resembles the growth of those who develop CHD. The Hertfordshire study showed that the disease was also associated with a low weight at 1 y of age (14). This was later confirmed in the HBCS (23). Characteristics that predispose to type 2 diabetes in later life included a small body size at birth and during infancy and an increase in weight and BMI (23).

Obesity is a major risk factor for type 2 diabetes. In the HBCS those individuals who developed type 2 diabetes were not overweight at birth or during infancy in general. Furthermore, one has to keep in mind that childhood obesity was extremely uncommon in those days in Finland. At what time point does the increased risk of obesity and type 2 diabetes become evident in the growth patterns? After 2 y of age the adiposity of young children, as measured by BMI, decreases to a minimum at ≈6 y of age before increasing again. This new rise in BMI has been called the adiposity or BMI rebound (24). An early rise in BMI in young children has been associated with later obesity. Within the HBCS we explored whether an early age at BMI rebound was also associated with an increased risk of type 2 diabetes in adulthood. Those children who had a BMI rebound at an early age had the highest cumulative incidence of type 2 diabetes in adult life. The cumulative incidence of type 2 diabetes was 8.6% in those in whom a BMI rebound occurred before 5 y of age but was only 1.8% in those in whom it occurred after 7 y of age (23). An early age at adiposity rebound was preceded by thinness at birth and during infancy and an above-average BMI at 11 y of age.

Interestingly, a population-based longitudinal study of children born in Delhi, India, about 30 y ago, showed results similar to those presented from the HBCS. Those who showed impaired glucose regulation in young adult life had a low BMI up to 2 y of age followed by an early age at BMI rebound and an accelerated increase in BMI until adult life (25).

The processes that link low weight gain in infancy with an early BMI rebound are unknown. They could reflect a postweaning infant diet low in fat but high in protein followed by a childhood diet high in fat. An early BMI rebound could be associated with lifelong settings of hormones and growth factors that facilitate the deposition of fat and thereby cause a predisposition to obesity and type 2 diabetes.

Early growth and body composition

Numerous studies support the importance of events during critical periods of growth and development in the pathogenesis of CHD and type 2 diabetes (1, 2, 4, 5, 8–21). There are a number of possible mechanisms by which a nonoptimal early growth combined with accelerated weight gain later in childhood could predispose to CHD and type 2 diabetes. One possible underlying mechanism is through alterations in body composition. BMI denotes both lean and fat mass and is consequently not the optimal proxy for obesity. Research around body composition has shown that low birth weight and low weight in infancy are associated with reduced lean body mass (26–30). This nonoptimal body composition seems to track into adulthood. If a baby born thin develops a relatively high BMI in childhood, this might lead to an unfavorable body composition that includes a disproportionately high fat mass (30, 31). This again may be associated with a lower metabolic rate, insulin resistance, and alterations in inflammatory markers and adipokines.

In both men and women birth weight has been strongly correlated with lean body mass in adult life. A 1-kg increase in birth weight among men was associated with a 4.1-kg increase in lean

![FIGURE 2. Insulin sensitivity (ISI) and insulin secretion (DI) according to birth weight in nondiabetic individuals from the Helsinki Birth Cohort Study (n = 1692 men and women) on the basis of measurements during a 75-g oral-glucose-tolerance test. Ter, tertile.](image-url)
mass in later life; the lean mass increase in women was 2.9 kg.
The association was not attenuated by adjustments for adult body size, physical activity, social class, and smoking status (29). Muscle tissue is an important site for glucose metabolism, and a low muscle mass may lead to disturbances in glucose and insulin metabolism, especially in subjects born with a low birth weight. Later accumulation of fat mass may initiate this process. Fat mass and fat distribution were not consistently related to birth weight. However, in both men and women a higher fat percentage was predicted by lower birth weight when adult BMI was taken into account.

Adult lean body mass was also positively associated with more rapid gain in BMI from birth to 11 y of age. Rapid gain in BMI before 2 y of age increased adult lean mass without excess fat accumulation. Rapid gain in BMI later in childhood, despite concurrent rise in lean mass, resulted in relatively larger increases in fat mass.

CONCLUSIONS

We are beginning to understand that adult noncommunicable diseases are associated with different patterns of early growth. Yet it is not clear what optimal growth is and how it can be achieved. Most data suggest that the development of many noncommunicable diseases involves a number of interactions, which include genetic ones. Therefore, these diseases can best be focused on from a life-cycle perspective. The presented results are based on findings in subjects born between 1934 and 1944 in the HBCS. These findings need to be replicated in younger contemporary cohorts before public health initiatives can be proposed.

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REFERENCES