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Relationship between Childhood Growth and Later Outcomes

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Abstract

Many studies in different settings and times provided us with enough evidence of the association between environmental exposures (mainly nutrition) during pregnancy/infancy and later health outcomes, such as adult non-communicable diseases (NCDs). An individual with a given susceptibility will continue to experience new environmental challenges (e.g. growth), and these later experiences will modulate the early ones. Children that are thin in infancy and then become larger are at greater risk for later NCD. Studies demonstrated that rapid weight gain is a strong predictor of later NCD, independently of the birthweight. But which periods imply a greater risk for developing NCD? Two periods in the first years of life have been linked to the early obesity onset: the first 6 months and between 2 and 5 years of age. And when do these later health outcomes appear? The literature suggests that they start long before adulthood. Children with rapid weight gain have greater risk for hypertension and cardiovascular disease in the first years of life. These lines of evidence suggest that future research should be committed with educational programs and preventive actions focusing on better life behavior in childhood, adolescence and pregnancy.

Many observational epidemiological studies in different settings and times, as well as many intervention studies in animals and some in humans provided us with enough evidence of the association between environmental exposures (mainly nutrition) during pregnancy/infancy and later health outcomes, such as adult non-communicable diseases (NCDs). The existence of critical developmental windows has been postulated to explain these long-lasting effects on organs or tissues. During these critical periods, body structure and/or function

would adapt themselves to cope with non-adequate conditions, and this adaptation could have high costs depending on the future life circumstances [1].

An individual with a given susceptibility, in fact, will continue to experience new environmental challenges, and these later experiences – such as nutritional status, infections and social conditions – will modulate the early ones. For instance, thinness at birth has been found to be related to cardiovascular disease (CVD) in adulthood, but mostly among those who were poorer in childhood [1]. Likewise, there is substantial evidence telling us that the incidence of NCD in adulthood depends greatly on the growth experience during childhood [1, 2]. This means that the growth pattern interacts with the individual susceptibility increasing or diminishing the risk of disease. This last subject is the one on which we want to focus our attention.

It has been known for some decades that the risk of CVD is related to adult height in different populations [3]. Adult height is a good proxy of child growth. Although confounding factors could explain part of this association, it seems that the effect remains after adjustments. Because of potential recall bias and lack of information, these associations are better studied in longitudinal studies. These are expensive and need a long time to start producing results. Nevertheless, the literature offers us a good amount of them, like the Finnish Helsinki Birth Cohort Study (individuals born in 1924–1933 and in 1934–1944) [1], the Brazilian birth cohorts of Ribeirao Preto (born in 1982) [4] and Pelotas (born in 1982–1993–2004) [5], the INTV study in Guatemala (younger than 7 years in 1969 and born in 1969–1977) [6], in Philippines the Cebu cohort (born in 1983–1984) [7], in India the New Delhi cohort (born in 1969–1972) [2] and in South Africa the Soweto cohort (born in 1990) [8]. The adult outcomes that have been studied are CVD, hypertension, diabetes, and obesity among others.

Changes in weight patterns are normally analyzed in these studies. For instance, in a follow-up study with 1,094 subjects from Ribeirao Preto, we have found that diastolic adult pre-hypertension and hypertension were independently associated with lower ponderal index at birth and higher body mass index (BMI) at school age [unpubl. data]. On the other hand, the Consortium of Health-Orientated Research in Transitioning Societies found that weight gain at any age during childhood is associated with elevated adult blood pressure [9].

Similar findings were replicated in different settings and with different outcomes. It seems that children that are thin in infancy and then become larger are at greater risk for later NCD. Coronary heart disease (CHD) risk, for instance, was associated with smaller babies at birth followed by an above-average BMI during later childhood [1] (table 1). The highest probability of having CHD is among those that were larger at 12 years but thinner at 2 years (hazard ratio = 3.0).

The same patterns have been described for children that later developed diabetes mellitus (DM). In the New Delhi cohort, the highest prevalence of

Table 1. Hazard ratios for CHD according to birthweight and BMI at 2 years of age (upper) and according to BMI at 2 and 11 years of age among 8,760 men and women born 1934–1944 in Helsinki (adjusted for sex)

Birthweight g	BMI at 2 years		
	–16	–17	>17
–3,000	1.9 (1.3–2.8)	1.9 (1.2–3.0)	1.3 (0.7–2.2)
–3,500	1.5 (1.0–2.1)	1.6 (1.1–2.2)	1.2 (0.8–1.8)
>3,500	1.7 (1.2–2.5)	1.5 (1.1–2.2)	1.0
BMI at 2 years	**BMI at 11 years**		
	–16	–17.5	>17.5
–16	1.6 (0.8–3.3)	2.4 (1.2–4.9)	3.0 (1.4–6.3)
–17	1.4 (0.7–3.1)	1.6 (0.8–3.3)	1.9 (0.9–3.9)
>17	1.0	1.3 (0.6–2.7)	1.1 (0.5–2.3)

Adapted from Eriksson [1].

impaired glucose tolerance and diabetes was among subjects who were in the lowest third of the group with respect to body mass index at the age of 2 years and the highest at the age of 12 years [2]. It is important to underline that not necessarily the larger size at childhood means obesity. The rapid weight gain is more important than the anthropometric diagnosis itself.

Another important aspect to be considered is the age at which the adiposity rebound (AR) occurs. AR is the lowest point on the BMI curve. In normal children with future normal BMI, it occurs around 6 years of age [10]. Early AR can be associated with excessive adipocyte multiplication [11] that is linked to later obesity. It has been seen that AR occurring before 5 years is highly associated with future type 2 DM (fig. 1). The commutative incidence of type 2 DM was more than 4 times higher among those Finnish children that had AR before 4 years of age when compared with those who had it after 8 years [1].

The individual growth pattern is essential to assess risk for adult NCD. In the New Delhi study, it was seen that future adults with impaired glucose tolerance and diabetes had a BMI drop between birth and 2 years of age, and after that they had an accelerated increase in BMI. Again, only 3.3% of them were overweight at the age of 12 years, and none were obese [2].

Weight gain is associated with other adult outcomes: osteoporosis, final schooling, and some biomarkers as well. For instance, C-reactive protein (CRP) is a mediator of atherosclerosis and chronically elevated levels predict cardiovascular outcomes. It has been found that males who were stunted at 2 years and centrally obese at 23 years had the highest CRP levels [12].

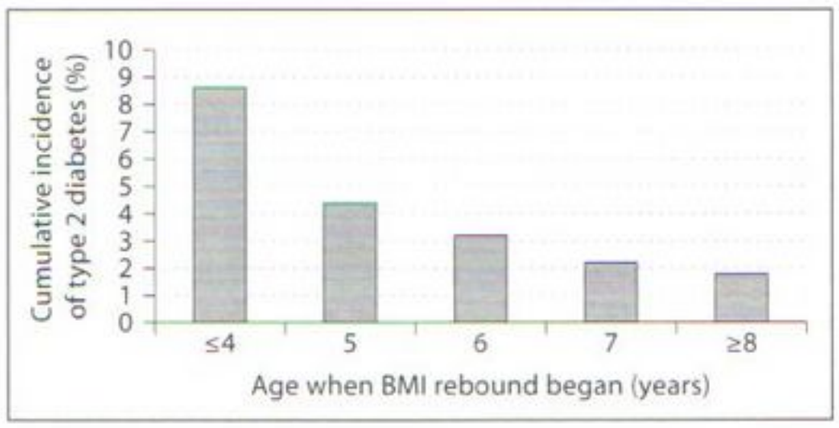

Fig. 1. Cumulative incidence of type 2 diabetes in adult life in Finland in relation to age at AR. Adapted from Eriksson [1].

In summary, a rapid weight gain is a strong predictor of later NCD, independently of the birthweight [13]. But which periods imply a greater risk for developing NCD?

Two periods in the first years of life have been linked to the early obesity onset: the first 6 months [14] and between 2 and 5 years of age [15, 16].

Different countries found similar results. The US Project Viva, a cohort study that followed up 1,401 children, found out that a rapid increase in weight for length in the first months of life was an important risk for obesity at 3 years of age [14]. The French Fleurbaix-Laventie Ville Santé study (FLVS II) that followed the growth of 468 children up to the age of 12 years observed two critical periods for the development of adolescence obesity: the first semester and from 2 years onwards [16]. The English Avon Longitudinal Study of Parents and Children has collected data from birth up to15 years of age of 625 children, and found the age range of 7–9 years as the one with greatest weight gains [17] – in contrast to previous UK studies [18]. In Brazil, the Pelotas cohort failed to show any evidence of a specific period with a greater contribution, but demonstrated that the fat mass:lean mass ratio was strongly associated with weight gain from 4 years onwards [19]. And finally, in a study we conducted among slum children in the city of Sao Paulo, we found that obesity at age 10 was linked with rapid weight gain in the first semester of life and at 2–5 years of age, after adjustments – odds ratio of changing quartiles of weight gain was 4.51 and 4.22, respectively [20].

For other outcomes different from obesity, some lines of evidence suggest another age range. A Chilean study analyzed a population representative sample of 314 children which were born within the normal birthweight range. It was found that changes in BMI, particularly from 6 to 24 months, predicted a higher prevalence of CVD risk at age 4 years. The authors recognized that the presence of CVD biomarkers could either be due to rapid weight gain or obesity (13% of them were obese and 10% presented central obesity). Both explanations would explain the results [20–22].

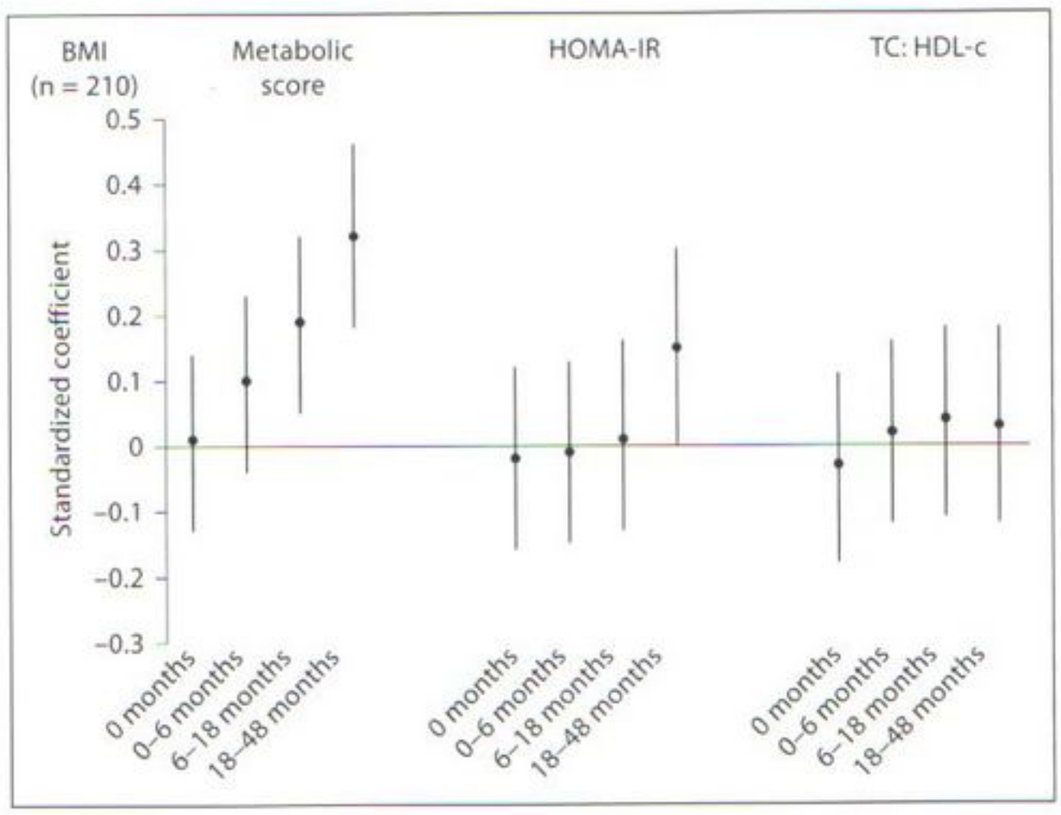

Fig. 2. Standardized regression coefficients (and 95% CIs) for metabolic score, homeostasis model assessment of insulin resistance (HOMA-IR), and the ratio of total to HDL cholesterol (TC:HDL-c) at 4 years per sample-specific 1 SD increments in BMI at birth, and changes in BMI from 0 to 6 months, 6–18 months, and 18–48 months in the Chilean National Nursery School Council Program (2006). Multiple linear regression analyses adjusted for current age, sex, and growth in the previous period. Metabolic score = (waist:height ratio + glucose + insulin + triglycerides – HDL cholesterol z scores)/5. HOMA-IR variables are log-transformed. Sample-specific SDs were as follows: metabolic score = 0.47, HOMA-IR = 0.27, TC:HDL-c = 1.41, BMI 0 months = 1.27, BMI 0–6 months = 1.60, BMI 6–18 months = 1.15, and BMI 18–48 months = 1.39. Differences between growth periods were nonsignificant ($p > 0.05$). Adapted from Corvalán et al. [21].

This last observation raises another question: when do these later health outcomes appear? The literature suggests that they start long before adulthood.

A risk of elevated blood pressure was detected early at age 7 in a biracial US cohort of 29,710 children. In this study, catch-up growth was measured according to change in relative weight compared with other children. The association of birthweight, catch-up growth and blood pressure at 7 years was analyzed. Not the small for gestational age children were at great risk for hypertension, but those who had greater changes in weight. An increase in weight z score of 1 SD above the previous weight z score increased the odds for high systolic pressure by 1.65 (birth to 4 months), 1.79 (4 months to 1 year), 1.71 (1–4 years), and 1.94 (4–7 years) [23]. In this sense, hypertension seems to be associated with rapid weight gain and not to have a critical period, but to increase its risk in a continuous manner.

The rapid weight gain in childhood should become a reason for permanent alertness for pediatricians. A greater concern for doctors and families is normally when the child is located in lower growth percentiles. In this situation,

hypercaloric diets are recommended to provide a quicker catch-up, and reassure all those who take care of the child. We now know the harm of malnutrition, and we are slowly discovering the harm of an excessive weight gain in childhood. We need to find the equilibrium point in the man-environment interaction.

Since Barker's fetal programming theory, a lot of evidence has been added to the initial epidemiological association between fetal growth and NCD (e.g. epigenetics). However, the translation into benefits for the exposed population is still in the beginning. Future research should be committed with educational programs and preventive actions focusing on better life behavior in childhood, adolescence and pregnancy.

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