Pathways of Infant and Childhood Growth That Lead to Type 2 Diabetes

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OBJECTIVE — Although a link between small body size at birth and later type 2 diabetes has been repeatedly documented, less is known about the associations between the disease and growth during infancy. The aim of this study was to explore the pathways of infant and early growth that lead to type 2 diabetes in adult life.

RESEARCH DESIGN AND METHODS — We carried out a longitudinal study of 8,760 subjects born in Helsinki from 1934 to 1944. On average, they had 8 measurements of height and weight between birth and 1 year of age and another 10 measurements between 1 and 12 years of age. We identified people with type 2 diabetes using a national register.

RESULTS — Among babies whose birth weights were ≤3.5 kg, the rate of infant growth was unrelated to later type 2 diabetes. Among babies with birth weights >3.5 kg, slow growth in length between birth and 3 months of age predicted later disease. Rapid gain in BMI after age 2 years increased the risk of later disease in both groups of babies, but this effect was greatest among children who had slow growth in length between birth and 3 months of age. In children whose Z-scores for length decreased, an SD increase in BMI at age 12 years was associated with an odds ratio (OR) for type 2 diabetes of 1.77 (95% CI 1.50–2.09). The corresponding OR in subjects whose Z-scores for length increased was 1.42 (95% CI 1.20–1.69). Rapid gain in childhood BMI was associated with high maternal BMI and socioeconomic factors (fewer people in the home and lower social class).

CONCLUSIONS — Babies with above-average birth weights may develop type 2 diabetes later in life if poor living conditions lead to faltering growth in length in the first few months after birth. We speculate that growth faltering at this time is associated with lifelong impairment of insulin metabolism and inability to meet the challenge of rapid childhood increase in BMI.

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Though a link between low birth weight and later type 2 diabetes has been repeatedly documented, less is known about the associations between the disease and growth during infancy (1,2). In the Hertfordshire study (1), which first showed the association between low birth weight and type 2 diabetes, the disease was also associated with low weight at 1 year of age. This has also recently been shown to be the case in the Helsinki birth cohort study (3).

In this study of 8,760 men and women born in Helsinki from 1934 to 1944, we explore the pathways of infant growth that lead to type 2 diabetes in adult life. In the Helsinki birth cohort study there is an average of eight measurements of height and weight recorded between birth and 1 year of age for each member of the cohort, thereby providing important information on the association between growth in infancy and type 2 diabetes in adult life.

RESEARCH DESIGN AND METHODS

The cohort of 8,760 men and women were born at Helsinki University Central Hospital from 1934 to 1944, attended child welfare clinics in the city of Helsinki, and were still residents of Finland in 1971. The majority (77%) also went to school in Helsinki. Details of the birth, child welfare clinic, and school health records have been described previously (3,4). The child welfare clinic records include information about duration of breast-feeding, the number of people in the home, and the number of rooms in the home. Using the father's occupation, we grouped the subjects according to a social classification used by Statistics Finland. Overall, 67% of the fathers were laborers and were classified as lower social class. On average, each person had 18 measurements of height and weight between birth and 12 years of age, 8 of which were made between birth and 1 year of age.

Using the unique personal identification number, we were able to link the records to a national database of all people receiving medication for type 2 diabetes. Antidiabetic drugs are free of charge in Finland, subject to the approval of a physician who reviews each case history and confirms the diagnosis of diabetes. In this way we identified 290 individuals in the cohort who received diabetes medication at any time between 1964 and 1997 and whose diabetes was diagnosed at >40 years of age. The register does not distinguish between patients with type 1 and type 2 diabetes. We have previously compared the national medication database with the national hospital discharge register and shown that ~90% of those diagnosed after age 40 years and receiving antidiabetic medication have type 2 diabetes (5). We therefore use the incidence of diabetes diagnosed after 40 years as an indicator of type 2 diabetes. The ethical committee of the National Public Health Institute, Helsinki, approved the study.

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A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

Table 1—*Cumulative incidence of type 2 diabetes according to birth weight and BMI at age 12 years*

Birth weight (kg)	BMI at age 12 years (kg/m^2)			
	<16	16–17	17–18	≥18
<3.0	3.9 (14/369)	3.5 (10/286)	4.4 (10/226)	4.9 (15/309)
3.0–3.5	1.5 (9/594)	3.3 (20/602)	3.8 (19/502)	5.9 (43/727)
>3.5	1.8 (7/392)	1.0 (6/577)	2.4 (15/618)	5.5 (18/873)

Data are % (*n* cases/*n* subjects).

Statistical analyses

Tests for trend were based on multivariate logistic regression using continuous variables, which included sex and year of birth, to adjust for the effects of age. The occurrence of type 2 diabetes was the dependent variable. We converted each measurement of height, weight, and BMI for each individual to a Z-score. We interpolated between successive Z-scores with a piecewise linear function and so obtained a Z-score at each month from 1 to 11 months and at each birthday from ages 1 to 12 years. We did not assign a Z-score at a particular age if the individual had not been measured within 2 years of that age. We back transformed Z-scores to obtain the corresponding height, weight, and BMI. The mean Z-score for the cohort is set at zero, and the SD is set as unity. A child maintaining a steady position as large or small in relation to other children would maintain the same Z-score above or below zero.

RESULTS — Both low birth weight and low weight at age 1 year were associated with an increased incidence of type 2 diabetes ($P = 0.009$ and 0.05, respectively). The disease was also associated with high weight and high BMI in later childhood ($P < 0.001$ for both at age 12 years). Table 1 shows the combined effects of birth weight and BMI at age 12 years on the incidence of type 2 diabetes. BMI at 12 years of age is shown for consistency with our previous publications; the results for other ages around 12 years are similar to these. The incidence of type 2 diabetes falls with increasing birth weight (P for trend = 0.004) and rises with increasing BMI at 12 years of age ($P < 0.001$). The trend with BMI, however, is greatest in people who had higher birth weights. This interaction between the effects of birth weight and BMI is statistically significant (P for interaction = 0.005).

Table 1 suggests that there may be two different pathways of growth that lead to type 2 diabetes, one among children who were small at birth and the other among children who had above-average birth weight and developed above-average BMIs in childhood. We therefore divided the subjects into two groups around a birth weight of 3.5 kg, which is close to the median birth weight (3.4 kg) for the cohort. Of the 290 children who later developed type 2 diabetes, 192 had birth weights ≤3.5 kg, giving a cumulative incidence of 3.7% in that group, while 98 had birth weights >3.5 kg, giving a cumulative incidence of 2.8% (P for differences = 0.01).

Children with birth weights <3.5 kg

Figure 1 shows changes in heights, weights, and BMIs between birth and 12 years of age in the two groups. The measurements are expressed as Z-scores, with the Z-score for the whole cohort being set at zero. The group of children with birth weights ≤3.5 kg tended to "catch up" toward the zero line in height, weight, and BMI. Those among them who later developed type 2 diabetes had lower birth weight, though this was not statistically significant; they also "caught up". Their heights, weights, and BMIs, however, remained below those of the other children until age 7 years. After this age they became larger than the other children and the difference, especially in weight and BMI, progressively increased. In this group of children the later incidence of

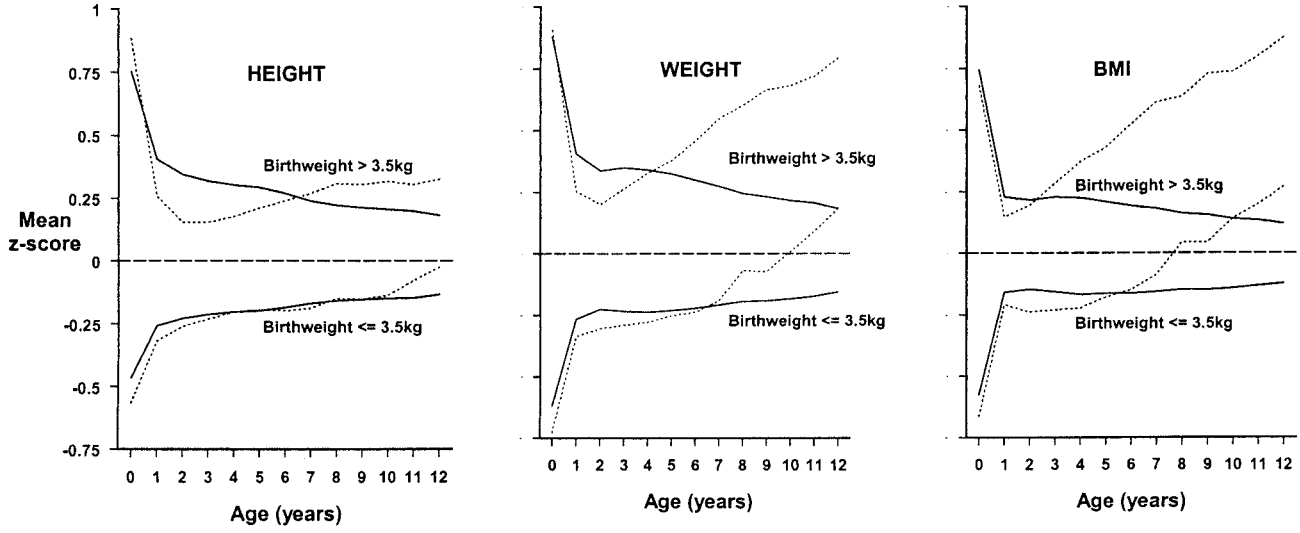

Figure 1—*Growth of 8,760 children in two birth weight groups above or below 3.5 kg. The solid lines represent the growth in height, weight, and BMI of all children in the two birth weight groups. The dotted lines represent the growth in height, weight, and BMI of the 290 children who later developed type 2 diabetes. The Z-scores for the entire cohort are set at zero, represented by the dashed line.*

Table 2—*Cumulative incidence of type 2 diabetes after age 40 years in people with birth weights >3.5 kg according to increase in length between birth and age 3 months*

Increase in length (cm)	Cumulative incidence of diabetes (%)	*n* cases/*n* subjects
≤8	4.0	14/347
8–9	3.3	21/637
9–10	2.4	26/1078
10–11	2.9	26/895
>11	2.1	10/475
	P for trend = 0.004	

type 2 diabetes was unrelated to the rate of growth in height or weight during infancy.

Children with birth weights >3.5 kg

Figure 1 shows that among children with birth weights >3.5 kg, the Z-scores for heights, weights, and BMIs tended to regress toward zero. The mean birth weight of those who later developed type 2 diabetes was similar to that of the other children in this group. Their heights and weights also regressed toward the average but fell more steeply than those of the other children. After age 2 years, however, a steep rise began (in weight especially), so that after age 4 years they were larger in weight and BMI than the other children. This difference progressively increased.

We examined the heights and weights of children with birth weights >3.5 kg at each month between birth and 1 year to identify the time in infancy when the growth of those who later developed type 2 diabetes faltered. We found that their linear growth had faltered before age 3 months. For each child we calculated the growth in length between birth and 3 months. This was inversely related to the cumulative incidence of type 2 diabetes, as shown in Table 2. Linear growth between 3 months and 2 years was unrelated to the incidence of type 2 diabetes. There was no similar trend with change in weight.

We examined the influences that were related to slow growth in length between birth and 3 months in babies with birth weight >3.5 kg. In the whole cohort the average maternal height was 160 cm and the average maternal weight was 67.2 kg. The babies of shorter mothers had a smaller increase in length ($P < 0.001$), but growth in length was unrelated to mother's weight. Mother's height was unrelated to the later occurrence of type 2 diabetes. The average number of people in each home was 3.9 (range 2–20), and the average number of rooms in each home was 1.8 (range 1–8). We related the numbers of people to the numbers of rooms to obtain a measure of overcrowding. Neither the number of people nor overcrowding were related to growth in length between birth and 2 months.

All children

We recombined the two groups of children and studied the whole cohort together. We found that the effects of slow growth in length between birth and 3 months interacted with the effect of a high BMI at 12 years of age on the incidence of type 2 diabetes (*P* for interaction = 0.03). The interaction between birth weight and childhood BMI shown in Table 1 ceased to be statistically significant once the interaction between growth in length between birth and 3 months and BMI was taken into account. In children whose Z-scores for length decreased, BMI at 12 years of age had a large effect on diabetes incidence; an SD increase in BMI at 12 years was associated with an odds ratio (OR) for type 2 diabetes of 1.77 (95% CI 1.50–2.09). The corresponding OR in people whose Z-scores for length increased was smaller at 1.42 (95% CI 1.20–1.69).

Childhood gain in BMI

We examined the influences that were linked to rapid gain in weight and BMI during childhood, which was a feature of the pathways of growth that led to later type 2 diabetes in both groups of babies (Fig. 1). A 1-unit increase in Z-score for BMI between 2 and 12 years of age was associated with an OR for type 2 diabetes of 1.56 (95% CI 1.40–1.74). We found that rapid gain in BMI was related to having fewer people in the home ($P < 0.001$), low father's social class ($P = 0.002$), and high maternal BMI recorded on admission in labor ($P < 0.001$). The number of rooms in the home and the mother's height were unrelated to rates of gain in BMI in childhood. There were no differences between children whose birth weights were above and below 3.5 kg in the influences linked to gain in BMI in childhood. We examined the effect of these influences on the occurrence of type 2 diabetes. Low father's social class and high maternal BMI were both related to later diabetes ($P = 0.03$ and 0.001, respectively).

CONCLUSIONS — In a study of 290 people diagnosed with type 2 diabetes within a cohort of 8,760 individuals, we have found that there are two pathways of infant and childhood growth that lead to the disease. We defined these by dividing the cohort into two groups according to whether their birth weights were above or below 3.5 kg. The group with birth weights ≤3.5 kg tended to catch up toward the average in height and weight after birth. Their rate of growth was unrelated to the later occurrence of type 2 diabetes. At ~2 years of age, these children, who later developed type 2 diabetes, began to gain weight and increase BMI more rapidly than the other children. This was sustained through childhood, so they reached weights and BMIs that were above the average for the group. In the other group of children with birth weights >3.5 kg, the linear growth of the 92 children who later developed type 2 diabetes faltered during early infancy. This faltering was associated with short maternal stature. At ~2 years of age their rate of gain in weight and BMI became more rapid than that of the other children in this group, and they also reached weights and BMIs that were above the group average.

We were able to identify 83% of the children through birth and clinic records who were still alive and residents of Finland in 1971. Our study was restricted to men and women who were born in Helsinki University Central Hospital. This would introduce a bias only if the association between early growth and type 2 diabetes differed between those born in the hospital and those born outside it. Our study was further restricted to people who had attended child welfare clinics, which were voluntary. The cohort could therefore be unrepresentative of all peo-

ple living in Helsinki. At the time of the subjects' birth, 67% of their fathers were laborers. We know that at this time in Helsinki ~60% of the men were laborers, and the social class distribution of our sample therefore approximates that of the city as a whole. Although the children in our study grew up in Finland around the time of the second World War, their heights and weights were similar to those of children in Finland in more recent times (6).

Most of the people with type 2 diabetes in our study had a birth weight ≤3.5 kg. The association between small birth size and later type 2 diabetes has been repeatedly demonstrated (1,2,5). One of the underlying mechanisms in the pathogenesis of type 2 diabetes is insulin resistance, which could be linked to the lower muscle mass of people who were small at birth (7). The association between low weight in infancy and later type 2 diabetes has previously been demonstrated (1,3). We have now shown that it is specifically low rates of linear growth during the first 3 months after birth, in babies >3.5 kg birth weight, that later predict type 2 diabetes. Among these babies, neither linear growth between 3 months and 2 years nor increase in weight predicted the disease.

In babies with birth weight >3.5 kg, slow linear growth between birth and 3 months of age was correlated with short maternal stature. This could be the result of genetic influences. Alternatively, it could reflect the effects of malnutrition mediated through the quantity and quality of breast milk. Maternal BMI was unrelated to this phase of growth, which may argue against postnatal nutritional effects on the infant mediated through breast-feeding. A third possibility is that slow linear growth in early infancy is the result of hormonal resetting and other influences acting prenatally. Type 2 diabetes has previously been reported in babies of above-average birth weight among the Pima Indians and among schoolchildren in Taiwan (8,9). The association between the disease and birth weight was U-shaped in both studies. The increased rates of type 2 diabetes among the Pima Indians who had high birth weight was largely explained by a high incidence of gestational diabetes, which is common among Pima Indians. Among the schoolchildren studied in Taiwan, those with higher birth weight who developed type 2 diabetes were more likely to have a higher BMI and a family history of type 2 diabetes compared with those with a low birth weight and later type 2 diabetes. Adjustment for gestational diabetes did not change the findings. We do not have information on the glucose tolerance of the mothers in our study.

We found that in people with birth weights >3.5 kg a high childhood BMI had a greater impact on the incidence of type 2 diabetes than it did among people with birth weights <3.5 kg. This increased susceptibility to the effects of high childhood BMI was linked to slow linear growth between birth and 3 months. We speculate that this could be mediated through disturbances in insulin metabolism, although there are other possible explanations. Although much of the development of the pancreatic β-cells is completed before birth, development continues during infancy (10). Failure of linear growth during early infancy may be associated with impaired β-cell development and a consequently impaired capacity to secrete insulin.

We found three influences associated with rapid childhood weight gain: fewer people in the home, high maternal BMI, and low social class. An obvious explanation of why fewer people in the home could lead to more rapid gain in weight is that, at a time when food in Finland was relatively scarce, households with fewer people had more food. This could also explain the more rapid growth of children in the homes of mothers who had higher BMIs, though genetic influences offer an alternative explanation. An explanation for the more rapid weight gain in low social class families could be that it reflects the quality of food rather than the quantity, though this is speculative. Both high maternal BMI and low social class predicted later type 2 diabetes.

In babies with birth weight below the median, catch-up growth between birth and 1 year has no effect on the later risk of developing type 2 diabetes. This piece of information is important because promoting the growth of small babies is standard clinical practice. Babies that have above-average birth weight are at risk of type 2 diabetes if their growth in height falters. This may be important to our understanding of the rising epidemics of type 2 diabetes around the world. In India, the origins of the epidemic may lie in the low average birth weight, as a consequence of chronic malnutrition among girls and young women, combined with an increase in the rates of childhood weight gain as a result of increased availability of food over the past 40 years (the Green Revolution). In other third world countries, body size at birth is similar to that in Europe and North America but growth falters during infancy and early childhood (11). In these countries, children become shorter than those in the western world by age 2 years. Thereafter they grow at similar rates so that the deficit is never made up. Our findings suggest that if this pattern of growth is followed by rapid weight gain in childhood, because of the greater availability of food, the second pathway of growth that leads to type 2 diabetes will have become established. The existence of two separate pathways of growth that lead to the disease may explain some of the heterogeneity in its manifestations that are encountered in clinical practice.

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