

# The Fetal and Childhood Growth of Persons Who Develop Type 2 Diabetes

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**Background:** Type 2 diabetes is associated with low birthweight followed by obesity in adulthood. Persons who develop the disease may therefore have a particular pattern of growth from birth through childhood.

**Objective:** To examine the relation of type 2 diabetes to size at birth and childhood growth.

**Design:** Cohort study.

**Setting:** Helsinki, Finland.

**Participants:** Men ( $n = 3639$ ) and women ( $n = 3447$ ) who were born at the Helsinki University Central Hospital between 1924 and 1933, who went to school in Helsinki, and who still lived in Finland in 1971. Detailed birth and school health records were available for all 7086 participants. We identified 471 men and women who developed type 2 diabetes by using the national Social Insurance Institution's register of all persons in Finland who are receiving long-term therapy with medication.

**Measurements:** Incidence of diabetes ascertained from a national register. The main explanatory measurements were size at birth and childhood growth in terms of height, weight, and body mass index.

**Results:** The cumulative incidence of type 2 diabetes was 7.9%

( $n = 286$ ) in men and 5.4% ( $n = 185$ ) in women. The incidence increased with decreasing birthweight, birth length, ponderal index (birthweight/length<sup>3</sup>), and placental weight. The odds ratio for type 2 diabetes was 1.38 (95% CI, 1.15 to 1.66;  $P < 0.001$ ) for each 1-kg decrease in birthweight. The mean weights and heights of the children at 7 years of age who later developed type 2 diabetes were about average. Thereafter, their growth in weight and height was accelerated until 15 years of age. The odds ratio for development of type 2 diabetes was 1.39 (CI, 1.21 to 1.61;  $P < 0.001$ ) for each standard deviation increase in weight between 7 and 15 years of age. The odds ratio became 1.83 (CI, 1.37 to 2.45;  $P < 0.001$ ) in an analysis restricted to persons whose birthweights were below 3000 g. Children of both sexes whose mothers had a high body mass index in pregnancy had more rapid growth during childhood and an increased incidence of type 2 diabetes.

**Conclusions:** These findings are consistent with the hypothesis that type 2 diabetes is programmed in utero in association with low rates of fetal growth. The increased risk for type 2 diabetes associated with small size at birth is further increased by high growth rates after 7 years of age.

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Men and women who had low birthweight as a result of slow fetal growth have increased rates of type 2 diabetes and the metabolic syndrome (1–4). This finding has led to the hypothesis that diabetes is one of a group of related disorders, including coronary heart disease and hypertension, that originate through adaptations that occur when the fetus is undernourished. These adaptations include reduced growth (5, 6). Insulin plays a central role in the regulation of fetal growth, and one fetal adaptation to undernutrition is alteration of insulin and glucose metabolism. Both insulin resistance and insulin deficiency are found in patients with type 2 diabetes and may be initiated by fetal adaptations (7).

Adult obesity adds to the effects of low birthweight in increasing the risk for type 2 diabetes (2, 3). A recent study has shown that obesity established in childhood has a greater effect on the development of the metabolic syndrome than does obesity that occurs in adulthood (8). We

do not yet know whether, or to what extent, the increased risk for type 2 diabetes associated with reduced prenatal growth is modified by particular patterns of growth throughout childhood.

We recently reported the occurrence of coronary heart disease in a cohort of 7086 men and women who were born in Helsinki, Finland, for whom detailed records of body size at birth and height and weight throughout childhood are available (9–11). We describe here the associations between body size at birth, childhood growth, and the risk for type 2 diabetes.

## Methods

### Study Cohort

The study cohort consisted of 7086 persons who were born between 1924 and 1933 at the Helsinki University Central Hospital, went to school in Helsinki, resided in

Finland in 1971, and remained in Finland thereafter. Each member of the study cohort had both a detailed birth record and a school health record. The details of these records have been described previously (9–11). Data on the mothers included age, parity, height, date of the last menstrual period, and body weight measured on admission for labor. Data on the newborn babies included birthweight, length, head circumference, and placental weight. The school health records include a mean ( $\pm$ SD) of  $10 \pm 4$  measurements of height and weight between the ages of 6 and 16 years. These records also include the number of persons living in the child's home, recorded at the time of the first examination, and the number of rooms. Using the father's occupation, which was recorded on the birth records, we grouped the men and women according to a social classification used by the Central Statistical Office. Overall, 78% of the fathers were laborers and 10% were classified as lower middle class. These groups constituted the lower social class. The upper social class was subdivided into upper middle class (2%) and self-employed (2%). Eight percent of the cohort was unclassified.

### Study Design

We linked the birth and school records to a national database of all persons receiving medication for type 2 diabetes. Antidiabetic drugs prescribed by a physician are free in Finland, subject to the approval of a physician who reviews each case history. The physician confirms the diagnosis of diabetes on the basis of the World Health Organization criteria (12). All patients receiving free medication (either oral antidiabetic agents or insulin) are entered into a register maintained by the Social Insurance Institute. In 1971, every Finnish citizen was assigned a unique personal identifier. We used this number to ascertain the 513 persons in the cohort who received diabetic medication at any time from 1964 to 1997. The register does not distinguish between patients with type 1 and type 2 diabetes. However, all hospital admissions in Finland are recorded in the national hospital discharge register. We used this register to identify 331 patients who had been admitted to the hospital with a diagnosis of diabetes among the 513 persons who received diabetic medication. We were able to review the records of 291 (88%) of these patients and thereby identified 42 persons who had type 1 diabetes. This is consistent with other studies showing that about 10% of patients

**Table 1. Cumulative Incidence of Type 2 Diabetes according to Size at Birth**

Size at Birth	Men	Women	All
	% (n)		%
Birthweight			
≤2500 g	8.3 (145)	10.0 (190)	9.3
2501–3000 g	10.9 (552)	5.3 (704)	7.7
3001–3500 g	7.7 (1318)	5.1 (1411)	6.4
3501–4000 g	7.5 (1153)	5.2 (879)	6.5
>4000 g	5.9 (444)	4.4 (248)	5.3
<i>P</i> value for trend	0.002	0.08	<0.005
Length at birth			
≤48 cm	10.5 (497)	6.4 (719)	8.1
48.1–49.0 cm	7.9 (518)	4.7 (593)	6.2
49.1–50.0 cm	8.1 (993)	5.4 (1071)	6.7
50.1–51.0 cm	8.1 (749)	5.1 (588)	6.8
>51.0 cm	6.1 (841)	4.9 (449)	5.7
<i>P</i> value for trend	0.009	0.11	0.002
Placental weight			
≤450 g	11.2 (251)	10.1 (257)	10.6
451–550 g	7.7 (845)	5.5 (855)	6.6
551–650 g	8.6 (1181)	4.9 (1106)	6.8
651–750 g	6.7 (836)	4.9 (789)	5.8
>750 g	6.9 (496)	4.5 (418)	5.8
<i>P</i> value for trend	0.05	0.02	0.002

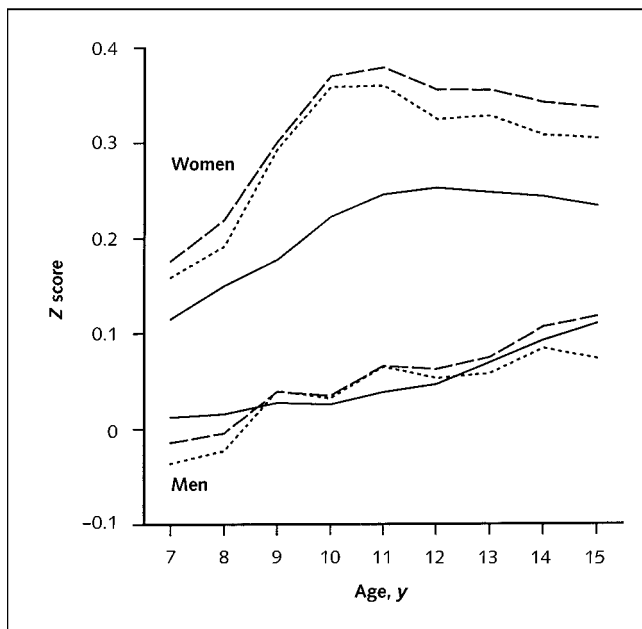
with diabetes have type 1 disease. We excluded these 42 persons, leaving 471 patients with type 2 diabetes, although this number could still include a few patients with type 1 diabetes. Our study did not include patients with type 2 diabetes who do not require medication. Of the estimated 150 000 patients with diagnosed diabetes in Finland, 113 000 (75%) are treated with medication (13).

The study was approved by the Ethical Committee of the National Public Health Institute, Helsinki.

### Statistical Analysis

Tests for trends were based on multivariate logistic regression by using continuous variables, which included 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 body mass index (BMI) ( $\text{weight}/\text{height}^2$ ) for each person to a *Z* score by using the method of Royston (14). Interpolation between successive *Z* scores by using a piecewise linear function was performed, and a *Z* score was obtained for each birthday from 7 to 15 years of age. These *Z* scores were back-transformed to obtain the corresponding height, weight, and BMI at these ages. The use of *Z* scores allowed us to make comparisons across ages, across measurements made in childhood, and between boys and girls. At each

**Figure.** Height, weight, and body mass index during childhood in 286 men and 185 women who later developed type 2 diabetes.



A Z score of 0 corresponds to the mean value in the whole cohort; a Z score of 1 corresponds to a value of 1 SD above the mean. Solid line indicates height; dashed line indicates weight; dotted line indicates body mass index.

age, the mean Z score for height or weight or BMI in the 7086 persons in the cohort is set at 0, and the SD is set at 1.

### Role of the Funding Source

This study was funded by British Heart Foundation, Novo Nordisk Foundation, and Finska Läkaresällskapet, which took no part in the collection, analysis, or interpretation of the data or in the decision to submit the paper for publication.

### Results

The maternal, neonatal, and childhood characteristics of the 7086 men and women in the cohort have already been published (9–11). Of this group, 471 persons—286 men and 185 women—were receiving medication for type 2 diabetes. The cumulative incidence of type 2 diabetes was 6.6% (7.9% in men and 5.4% in women).

### Size at Birth

Table 1 shows the associations between the cumulative incidence of type 2 diabetes and size at birth. The inci-

dence increased with decreasing birthweight for both men and women. The odds ratio for type 2 diabetes was 1.38 (95% CI, 1.15 to 1.66;  $P < 0.001$ ) for each 1-kg decrease in birthweight. The trend was stronger in men than in women, in whom it was not statistically significant (Table 1). Type 2 diabetes was not significantly related to the length of gestation; thus, we did not adjust for it in analyses of birth size. The incidence of type 2 diabetes also increased with decreasing birth length, ponderal index (birthweight/length<sup>3</sup>), and placental weight. The odds ratios for type 2 diabetes were 1.07 (CI, 1.03 to 1.12;  $P = 0.002$ ) for each 1-cm decrease in length, 1.04 (CI, 1.01 to 1.09;  $P = 0.03$ ) for each kg/m<sup>3</sup> decrease in ponderal index, and 1.13 (CI, 1.04 to 1.22;  $P = 0.002$ ) for each 100-g decrease in placental weight. On average, the birthweight of men who developed type 2 diabetes was  $-0.17$  SD below that of all the men. They were also 0.15 SD shorter and 0.10 SD lower in ponderal index. The corresponding SDs for the women who developed type 2 diabetes, compared with all the women, were 0.13, 0.12, and 0.10, respectively.

### Growth in Childhood

The Figure shows the childhood growth of men and women with type 2 diabetes by using mean Z scores for height, weight, and BMI at each year from 7 to 15 years of age. The mean values for all persons in the study cohort are 0; the SD is 1. The mean weights and heights of the boys who later developed type 2 diabetes were about average at 7 years of age, whereas the weights and heights of the girls were above average at that age. Thus, body size of both sexes had “caught up” since birth. When we allowed for weight at 7 years, the effects of birthweight on the risk for type 2 diabetes were increased: The odds ratio for type 2 diabetes was 1.48 (CI, 1.23 to 1.79;  $P < 0.001$ ) for each 1-kg decrease in birthweight in a multiple logistic regression that included weight at 7 years. The odds ratio was 1.09 (CI, 1.04 to 1.14;  $P < 0.001$ ) for each 1-cm decrease in birth length in a multiple logistic regression that included height at 7 years.

In comparison with other children, the boys and girls who later developed type 2 diabetes had faster growth rates in height, weight, and BMI between the ages of 7 and 15 years (Figure). We calculated the difference between their Z scores for body size at 7 and 15 years of age. The odds ratio for the subsequent development of type 2 diabetes was 1.44 (CI, 1.20 to 1.72;  $P < 0.001$ ) for each unit in-

crease in height between 7 and 15 years. The corresponding figure was 1.39 (CI, 1.21 to 1.61;  $P < 0.001$ ) for weight and 1.24 (CI, 1.10 to 1.41;  $P < 0.001$ ) for BMI. The findings were similar when we analyzed boys and girls separately.

We evaluated the interaction between childhood growth and size at birth. We found that the effects of childhood weight gain differed between persons whose birthweight was less than 3000 g and those whose birthweight exceeded 3000 g. For each unit increase in SD for weight between 7 and 15 years of age for those with birthweight less than 3000 g, the odds ratio was 1.83 (CI, 1.37 to 2.45;  $P < 0.001$ ); for those with birthweight greater than 3000 g, the odds ratio was 1.25 (CI, 1.06 to 1.48;  $P = 0.008$ ). This difference in odds ratios was statistically significant ( $P = 0.02$ ). Findings for gains in height and BMI were similar.

The BMI at any age in childhood was not significantly related to the risk for developing type 2 diabetes among men. In contrast, among women, BMI at every age from 7 to 15 years was strongly related to risk for the disease. Table 2 shows the trends in incidence of type 2 diabetes according to BMI at age 11 years, the median age in our study.

### Maternal Characteristics

The cumulative incidence of type 2 diabetes was not related to the mother's height, weight, or BMI during pregnancy. In a simultaneous analysis with birthweight, however, the incidence of diabetes increased with increasing maternal weight and BMI. In a multiple logistic analysis that included birthweight, the odds ratios for type 2 diabetes was 1.17 (CI, 1.04 to 1.31;  $P = 0.007$ ) for every 10-kg increase in the mother's weight during pregnancy and 1.42 (CI, 1.04 to 1.95;  $P = 0.03$ ) for every 10-kg/m<sup>2</sup> increase in the mother's BMI. The mothers' body mass was positively related to the children's heights and weights at all ages. For example, in a multiple linear regression analysis, the children's weight at 7 years of age increased by 80 g (CI, 72 to 87 g;  $P < 0.001$ ) for every 1-kg increase in maternal weight.

### Crowding in the Home and Social Class in Childhood

We examined whether living conditions influenced the children's growth and risk for type 2 diabetes. The average

**Table 2. Cumulative Incidence of Type 2 Diabetes according to Body Mass Index at 11 Years of Age**

Body Mass Index	Men	Women	All
kg/m <sup>2</sup>	% (n)		%
≤15.3	7.7 (675)	4.2 (804)	5.8
15.4–15.9	9.0 (690)	3.9 (571)	6.7
16.0–16.6	7.0 (790)	4.7 (695)	5.9
16.7–17.4	7.8 (798)	5.2 (560)	6.7
>17.4	8.3 (659)	8.4 (802)	8.4
<i>P</i> value for trend	0.2	<0.001	<0.001

number of inhabitants in the homes in which the study participants grew up was 5 (range, 1 to 27), and the average number of rooms in each house was 2 (range, 1 to 14). Forty-seven percent lived in homes with only 1 room. As in previous analyses (9–11), we used the ratio of the number of inhabitants to the number of rooms as an index of crowding. Families living in less crowded homes were of higher social class. Children in less crowded homes were taller and heavier than average at 7 to 15 years of age. However, the incidence of type 2 diabetes was not related to the level of crowding in the household ( $P > 0.2$ ) or social class ( $P > 0.2$ ) during childhood.

### Discussion

We have examined the fetal and childhood growth of men and women who subsequently developed type 2 diabetes. In both sexes, the disease was associated with low weight, short body length, and thinness at birth, followed by catch-up growth after birth and accelerated growth in height and weight during childhood. The association with low birthweight is consistent with findings from previous studies. Low birthweight did not depend on the length of gestation and must therefore reflect slow fetal growth (2–4).

Most studies on the association between size at birth and later impairment in glucose metabolism or type 2 diabetes have used birthweight alone as a marker of fetal growth (2, 4, 15). However, more detailed measurements of birth size have also been found to correlate with future risk for type 2 diabetes. Both a low ponderal index and short body length at birth are associated with impaired glucose tolerance and type 2 diabetes (3, 16). We have confirmed these associations in our study.

We have shown that the growth of persons who develop type 2 diabetes catches up in early childhood so that they are average or above average in height and weight at 7 years of age. Thereafter, their growth in height and weight

is accelerated until 15 years of age. In previous analyses of this cohort, we have shown that catch-up growth between birth and 7 years of age is associated with the development of coronary heart disease (10, 11). The pattern of catch-up growth differed, however, in men and women. Men who developed coronary heart disease were thin at birth and caught up in weight thereafter; women were short at birth and caught up in height. We now find that men and women in this cohort who developed type 2 diabetes caught up in both weight and height. The patterns of growth in men and women who developed type 2 diabetes were similar: They continued to have accelerated growth in weight and height. The women also developed above-average BMI (**Figure**).

The weights and heights of boys and girls in the study were positively associated with their mothers' weights and BMIs, as has been found in other studies (8, 17). Regardless of birthweight, children born to heavier mothers were taller and heavier at 7 years of age and gained weight more rapidly thereafter. We therefore suggest that the "catch-up" growth of persons who develop type 2 diabetes results from high energy intake in childhood. We do not know whether the mothers influenced nutrition through direct effects during lactation or through better availability of food after weaning. We used the level of crowding in the home as an index of living conditions. The level of crowding was not related to development of type 2 diabetes. As would be expected, however, children in less crowded homes were taller and heavier than those in overcrowded homes. Overcrowding reduces childhood growth partly because it is accompanied by increased rates of enteric and respiratory infection (18).

An association between high maternal weight and body mass and type 2 diabetes in the offspring has been found before. In Mysore, South India, the offspring of mothers who were heavier than average during pregnancy had higher rates of type 2 diabetes as adults (19). Those who developed type 2 diabetes had a low insulin increment, suggesting insulin deficiency. In contrast, a study of men and women in China showed that the offspring of women with low BMI during pregnancy had elevated plasma glucose concentrations. These elevated concentrations were associated with increased plasma insulin concentrations, suggesting insulin resistance (19).

Our study was restricted to men and women who were born at Helsinki University Central Hospital (where about 60% of all births in the city occurred), who went to school

in Helsinki, and who were still living in Finland in 1971. The fathers of 78% of the children were classified as laborers. The cohort may not be representative of all persons living in Helsinki, although in the early years of the 20th century about 60% of the men in the city were laborers. This would introduce bias only if the associations between size at birth and childhood growth and type 2 diabetes differed between those born in the hospital and those born elsewhere. We were able to trace 91% of the men and women in a cohort defined by birth and school records and residence in Finland in 1971 (9–11). This is a higher trace rate than has been achieved in studies in the United Kingdom (1, 2). We ascertained type 2 diabetes using the Social Insurance Institution Register for free diabetes medication. We recorded a cumulative incidence of type 2 diabetes of 6.7% in our study cohort, with a higher incidence in men than in women. This corresponds well with another Finnish study in which the cumulative incidence of diabetes ascertained through the register was 6.2% for a sample 65 to 74 years of age (20). In a random sample of Finnish persons 45 to 64 years of age, the age-standardized prevalence of type 2 diabetes, ascertained through standard oral glucose tolerance tests, was 5.7% in men and 4.6% in women (21).

Type 2 diabetes is characterized by both insulin resistance and impaired insulin secretion (7). Thinness at birth, as measured by a low ponderal index, and short body length at birth have been associated with later development of insulin resistance (1, 3, 22, 23). Catch-up growth has also been shown to correlate with insulin resistance. A recent study in India suggested that children who had low birthweight but were heavy at 8 years of age were the most insulin resistant (24). Animal experiments indicate that reduced fetal growth may also be linked to impaired insulin secretion through reduced vascularization of pancreatic islet cells (25, 26). Growth of the human fetus is essentially regulated by the supply of nutrients it receives from the mother (15). The fetal-origin hypothesis proposes that type 2 diabetes originates through fetal undernutrition (5, 6). Fetal nutrition and growth depend on placental function. Animal experiments show that when the mother is undernourished, the placenta may, under some circumstances, enlarge as an adaptive response to protect the fetus (27). Associations between placental enlargement and impaired glucose tolerance in adult life have been described (28). The fetus may also become undernourished because the placenta fails to grow. In the present study, we have found

that type 2 diabetes is associated with reduced placental size, supporting a link with fetal undernutrition. The major risk for type 2 diabetes is obesity in adult life. Not all obese persons develop type 2 diabetes, and the predisposition to do so is familial and commonly inferred to be genetic (29, 30). Familial clustering, however, could result from siblings sharing the same intrauterine environment (31). The role of this environment is supported by recent findings in twins that were discordant for type 2 diabetes or impaired glucose tolerance. The monozygous and dizygous twins with these disorders had lower birthweights (32).

We do not know why postnatal catch-up growth in weight and height are related to coronary heart disease (11). One speculation in relation to type 2 diabetes is that fetal growth restriction leads to reduced cell numbers in the endocrine pancreas and subsequent accelerated growth that continues through childhood and leads to excessive metabolic demand on this limited cell mass. The association between high childhood BMI and type 2 diabetes in the women in our study is consistent with a recent study showing that obesity in children is associated with the metabolic syndrome in adults (8). Overweight in childhood is known to predict overweight in adulthood (33). It is of interest that, in our cohort, high body mass in childhood was associated with coronary heart disease in men and type 2 diabetes in women. Whether these different consequences are mediated by the various paths of growth taken by boys and girls in utero (10) or by sex differences in the endocrine and metabolic correlates of high fat mass in childhood, they emphasize the importance of preventing childhood obesity.

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