

ORIGINAL ARTICLE

# Trajectories of Growth among Children Who Have Coronary Events as Adults

David J.P. Barker, F.R.S., Clive Osmond, Ph.D., Tom J. Forsén, M.D.,  
Eero Kajantie, M.D., and Johan G. Eriksson, M.D.

## ABSTRACT

### BACKGROUND

Low birth weight is a risk factor for coronary heart disease. It is uncertain how postnatal growth affects disease risk.

### METHODS

We studied 8760 people born in Helsinki from 1934 through 1944. Childhood growth had been recorded. A total of 357 men and 87 women had been admitted to the hospital with coronary heart disease or had died from the disease. Coronary risk factors were measured in a subset of 2003 people.

### RESULTS

The mean body size of children who had coronary events as adults was below average at birth. At two years of age the children were thin; subsequently, their body-mass index (BMI) increased relative to that of other children and had reached average values by 11 years of age. In simultaneous regressions, the hazard ratios associated with a 1 SD increase in BMI were 0.76 (95 percent confidence interval, 0.66 to 0.87;  $P < 0.001$ ) at 2 years and 1.14 (95 percent confidence interval, 1.00 to 1.31;  $P = 0.05$ ) at 11 years among the boys. The corresponding figures for the girls were 0.62 (95 percent confidence interval, 0.46 to 0.82;  $P = 0.001$ ) and 1.35 (95 percent confidence interval, 1.02 to 1.78;  $P = 0.04$ ). Low BMI at 2 years of age and increased BMI from 2 to 11 years of age were also associated with raised fasting insulin concentrations ( $P < 0.001$  for both).

### CONCLUSIONS

On average, adults who had a coronary event had been small at birth and thin at two years of age and thereafter put on weight rapidly. This pattern of growth during childhood was associated with insulin resistance in later life. The risk of coronary events was more strongly related to the tempo of childhood gain in BMI than to the BMI attained at any particular age.

From the Developmental Origins of Health and Disease Division (D.J.P.B.) and the Medical Research Council Epidemiology Resource Center (C.O.), University of Southampton, Southampton General Hospital, Southampton, United Kingdom; and the National Public Health Institute, Helsinki (T.J.F., E.K., J.G.E.). Address reprint requests to Professor Barker at the DOHaD Division, Level F (887), Princess Anne Hospital, Coxford Rd., Southampton SO16 5YA, United Kingdom, or at [djpb@mrc.soton.ac.uk](mailto:djpb@mrc.soton.ac.uk).

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PEOPLE WITH A LOW BIRTH WEIGHT ARE at increased risk for the development of coronary heart disease.<sup>1-6</sup> There is uncertainty about the effects of growth during early childhood, a time when rapid weight gain may predispose to later overweight.<sup>7</sup> We used data from a cohort of subjects in Helsinki to examine associations between growth in early childhood and later coronary events. We have previously analyzed this cohort for the association between annual changes in body size up to 11 years of age and subsequent coronary events.<sup>5,8</sup> We found that rapid weight gain after two years of age increased the risk of disease. In the present study, we have analyzed how monthly changes in body size from birth to 2 years of age, as well as annual changes through 11 years of age, relate to the subsequent development of coronary risk factors and coronary events.

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## METHODS

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### STUDY POPULATION

The study cohort consisted of men and women who were born at Helsinki University Central Hospital from 1934 through 1944 and attended child-welfare clinics in the city. Details of the birth records, records from the child-welfare clinics, and school health records have been described previously.<sup>5</sup> We identified 4630 men and 4130 women who were living in Finland in 1971, when a unique identification number was allocated to each member of the Finnish population. The ethics committee at the National Public Health Institute in Helsinki approved the study.

### ANALYSIS OF CORONARY EVENTS

With the use of the unique identification number, we identified hospital admissions for coronary heart disease and deaths from coronary heart disease among the men and women in the cohort from 1971 to 1998.<sup>5,8</sup> All hospital admissions in Finland are recorded in the national hospital discharge register. All deaths are recorded in the national mortality register. Through Statistics Finland we obtained data on occupation and taxable household income recorded in the 1980 census.

### ANALYSIS OF CORONARY RISK FACTORS

For the analysis of risk factors, we used random-number tables to select a subset of people in the initial study group who were still alive and living in Finland. In order to achieve a sample size in excess

of 2000 people for this subset, we selected 2691 subjects for evaluation. Of these subjects, 2003 attended a clinic at the institute after an overnight fast. Plasma glucose concentrations were measured according to the hexokinase method, whereas plasma insulin and proinsulin concentrations were determined by two-site immunometric assay.<sup>9,10</sup> Serum total cholesterol and triglyceride concentrations were measured with the use of standard enzymatic methods.<sup>11,12</sup> Height was measured with a Kawi stadiometer. Weight was measured on a Seca Alpha 770 scale. Blood pressure was measured from the right arm while the subject was in the sitting position and was recorded as the mean of two successive readings from a standard sphygmomanometer. Written informed consent was obtained from each subject participating in the analysis of risk factors before any procedures were carried out.

### STATISTICAL ANALYSES

We examined height, weight, and body-mass index (BMI; the weight in kilograms divided by the square of the height in meters) for each child every month from birth to 2 years of age and at each birthday thereafter until 11 years of age. We converted each measurement to a z score.<sup>13</sup> A z score represents the difference from the mean value for the whole cohort and is expressed in standard deviations.

The end point for the analysis of coronary events was hospitalization or death due to coronary heart disease. We examined trends in hazard ratios for this end point with neonatal and childhood measurements of body size with the use of a Cox proportional-hazards model.

Data on coronary risk factors were analyzed by tabulating means and multiple linear regression. Significance refers to analysis of continuous variables. Plasma glucose, insulin, and proinsulin concentrations and serum triglyceride concentrations had skewed distributions and were log-transformed for analysis. We adjusted the clinical measurements for age, sex, and BMI with the use of linear regression.

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## RESULTS

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### CORONARY EVENTS

The body measurements of the 4630 boys and 4130 girls are shown in Table 1. The children had an average ( $\pm$ SD) of  $11\pm 8$  measurements of height and weight from birth to 2 years of age, and  $6\pm 4$  measurements from 2 to 11 years of age. A total of 357

**Table 1. Characteristics of 4630 Boys and 4130 Girls Born in Helsinki from 1934 to 1944.\***

Characteristic	Boys			Girls		
	Mean $\pm$ SD	Range	No. of Missing Values	Mean $\pm$ SD	Range	No. of Missing Values
<b>At birth</b>						
Length (cm)	50.6 $\pm$ 2.0	41–59	56	49.9 $\pm$ 1.8	41–59	55
Weight (g)	3456 $\pm$ 490	1290–5180	0	3327 $\pm$ 458	1260–5400	0
BMI	13.4 $\pm$ 1.2	7.8–21.4	56	13.3 $\pm$ 1.2	8.6–17.5	55
Ponderal index	26.5 $\pm$ 2.2	16.8–50.3	56	26.7 $\pm$ 2.2	16.2–34.4	55
<b>During childhood</b>						
2 Yr						
Height (cm)	86.5 $\pm$ 3.1	75.0–98.0	7	85.4 $\pm$ 3.1	74.0–96.8	6
Weight (kg)	12.3 $\pm$ 1.2	8.7–17.3	1	11.8 $\pm$ 1.2	8.2–16.9	1
BMI	16.7 $\pm$ 1.2	12.7–21.7	6	16.4 $\pm$ 1.2	12.4–21.4	4
11 Yr						
Height (cm)	141.3 $\pm$ 5.9	120.2–162.3	1237	141.4 $\pm$ 6.4	118.5–164.2	1150
Weight (kg)	33.6 $\pm$ 4.5	20.5–53.8	1239	34.2 $\pm$ 5.7	18.7–60.9	1151
BMI	16.8 $\pm$ 1.5	12.2–23.1	1242	17.1 $\pm$ 2.0	11.3–25.4	1156

\* Plus–minus values are means  $\pm$ SD. The ponderal index is equal to the weight in kilograms divided by the cube of the length in centimeters.

men and 87 women either had been hospitalized with coronary heart disease or had died from the disease.

Figure 1A shows the growth of those boys who later had coronary events, including mean height, weight, and BMI at each month from birth to 2 years of age, and at each year from 2 to 11 years of age. The mean value for each measurement among all the boys is set at zero, with deviations from the mean expressed as standard deviations (z scores). A boy maintaining a steady position as tall or short and fat or thin in relation to other boys would follow a horizontal path on the figure. The mean birth weight of the 357 boys who later had coronary events was approximately 0.2 SD below the average. Low BMI at birth predicted later coronary events ( $P < 0.001$ ), as did low ponderal index (equal to the birth weight in kilograms divided by the cube of the length in centimeters) ( $P < 0.001$ ), which is the more usual measure of neonatal thinness. Short length at birth did not predict coronary events. Between birth and one year of age, mean z scores for each measurement fell. At one and two years of age, both low BMI and short stature predicted later coronary events ( $P < 0.001$  for BMI at each age;  $P = 0.007$  for height at one year of age and  $P = 0.02$  for height at two years of age).

After two years of age, the z scores for the BMI

of the boys who later had coronary events began to increase and continued to do so. The z scores for height were little changed. BMI at 11 years of age did not, on its own, predict coronary events, but in a simultaneous regression, both low BMI at 2 years of age and high BMI at 11 years of age were associated with later coronary events ( $P < 0.001$  and  $P = 0.05$ , respectively). The hazard ratios associated with an increase in BMI of 1 SD were 0.76 (95 percent confidence interval, 0.66 to 0.87) at 2 years of age and 1.14 (95 percent confidence interval, 1.00 to 1.31) at 11 years. When BMI at birth was added to the model, the measurements of BMI at each of the three ages were associated with later coronary events ( $P = 0.04$  for low BMI at birth,  $P = 0.001$  for low BMI at 2 years of age, and  $P = 0.03$  for high BMI at 11 years of age).

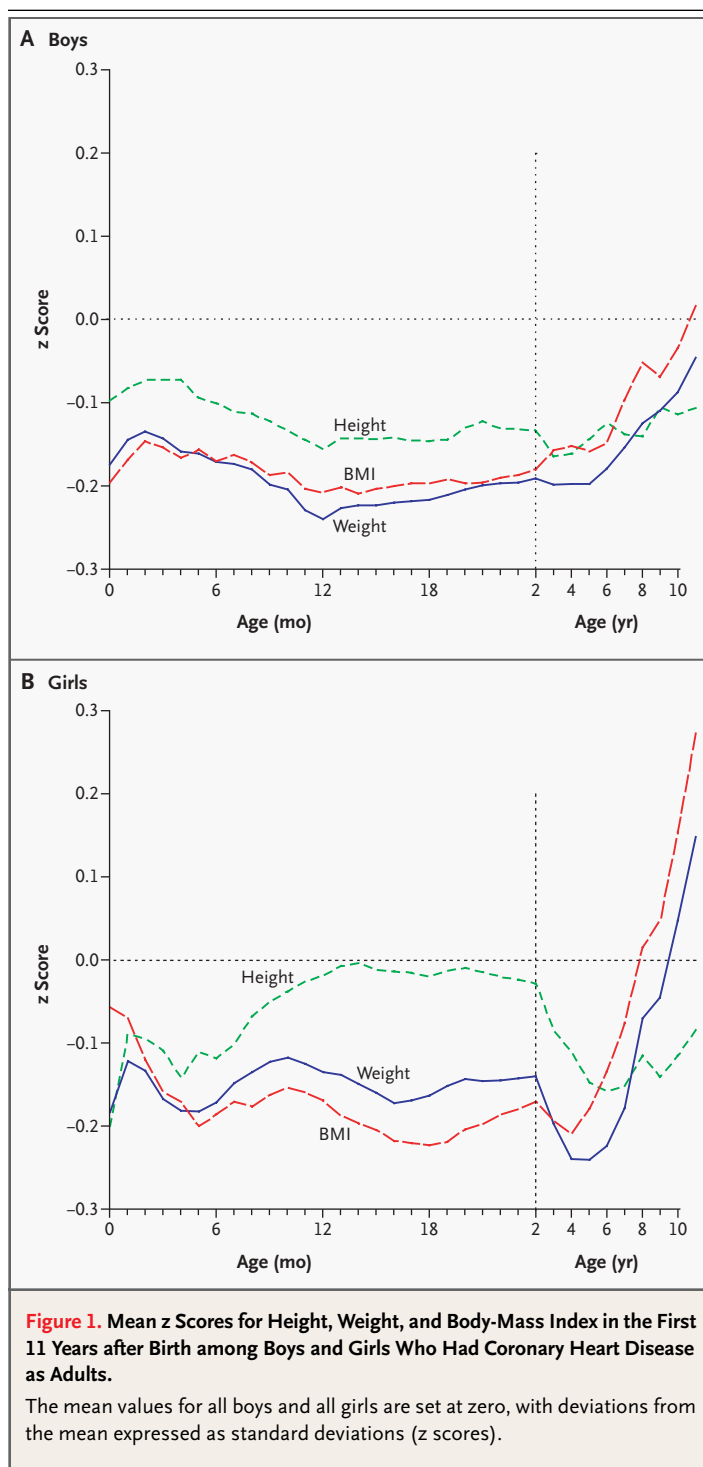
As with the boys, the mean birth weight of the girls who later had coronary events was below the average (Fig. 1B). They tended to be short rather than thin, although this association was not statistically significant ( $P = 0.10$  for birth length). At approximately four months of age, the z scores for height of the girls who later had coronary events began to rise, and height at one and two years of age did not predict later coronary events. The mean z scores for BMI fell progressively in the first six months after birth and remained low at two years

of age. After four years of age, the z scores began to increase and continued to do so, reaching the average at approximately eight years of age. BMIs at 2 and 11 years of age, when analyzed separately, were not associated with later coronary events. Similar to the boys, however, BMIs at 2 and 11 years of age were associated with later coronary events in a simultaneous regression ( $P=0.001$  and  $P=0.04$ , respectively). The hazard ratios associated with an increase in BMI of 1 SD were 0.62 (95 percent confidence interval, 0.46 to 0.82) at 2 years of age and 1.35 (95 percent confidence interval, 1.02 to 1.78) at 11 years. When length at birth was added to the model, body size at each of the three ages was associated with later coronary events ( $P=0.02$  for short length at birth,  $P=0.002$  for low BMI at 2 years of age, and  $P=0.02$  for high BMI at 11 years of age).

In Table 2, findings for boys and girls have been combined to show the simultaneous effect of birth weight and BMI at two years of age, divided into thirds, on hazard ratios for coronary events. The highest hazard ratios were among subjects with birth weights below 3.0 kg and BMIs of 17 or less at two years of age. We have previously shown that, among the men in this cohort, low occupational status and low household income are associated with increased rates of coronary heart disease.<sup>14</sup> There was a similar trend with household income among women, although it was not statistically significant.<sup>8</sup> Therefore, we adjusted the hazard ratios for coronary events in Table 2 according to occupational status and income during adulthood. The trends were little changed.

Table 3 shows the simultaneous effects of BMI at 2 and 11 years of age for all study subjects. BMI at each age is divided into thirds. The highest hazard ratios were among people with BMIs in the lowest third at 2 years of age and in the highest third at 11 years of age. The trends were little changed by adjustment for occupational status and income during adulthood.

We analyzed the simultaneous effects on coronary events of the combined mean z score for BMI at 2 and 11 years of age and the change in z scores for BMI from 2 to 11 years of age. A low mean BMI was associated with coronary events. The hazard ratio associated with a decrease in BMI of 1 SD was 1.16 (95 percent confidence interval, 1.02 to 1.33;  $P=0.02$ ). Changes in z scores had a stronger effect. The lowest hazard ratios were for people whose z scores fell by more than 1 SD, whereas the highest values were for those whose z scores rose by



more than 1 SD. The hazard ratio associated with an increase in BMI of 1 SD was 1.28 (95 percent confidence interval, 1.15 to 1.42;  $P<0.001$ ).

We examined the effect of early postnatal weight gain (before two years of age) in babies who were

**Table 2. Hazard Ratios for Coronary Heart Disease According to Birth Weight and BMI at Two Years of Age for Boys and Girls Combined.\***

Birth Weight (kg)	Hazard Ratio (95% CI)		
	BMI at Two Years of Age		
	<16	16–17	>17
	<i>adjusted for sex/adjusted for sex, adult occupational status, and household income</i>		
<3.0	1.9 (1.3–2.8)/1.9 (1.3–2.9)	1.9 (1.2–3.0)/1.9 (1.2–3.1)	1.3 (0.7–2.2)/1.1 (0.6–2.1)
3.0–3.5	1.5 (1.0–2.1)/1.3 (0.9–2.0)	1.6 (1.1–2.2)/1.4 (1.0–2.1)	1.2 (0.8–1.8)/1.2 (0.8–1.8)
>3.5	1.7 (1.2–2.5)/1.3 (0.9–2.1)	1.5 (1.1–2.2)/1.4 (0.9–2.0)	1.0/1.0†

\* Values for birth weight and body-mass index were divided into three groups of equal size. CI denotes confidence interval.  
 † This group served as the reference group.

**Table 3. Hazard Ratios for Coronary Heart Disease According to BMI at 2 and 11 Years of Age for Boys and Girls Combined.\***

BMI at Two Years of Age	Hazard Ratio (95% CI)		
	BMI at 11 Years of Age		
	<16	16–17.5	>17.5
	<i>adjusted for sex/adjusted for sex, adult occupational status, and household income</i>		
<16	1.6 (0.8–3.3)/1.8 (0.8–4.2)	2.4 (1.2–4.9)/2.5 (1.1–6.0)	3.0 (1.4–6.3)/3.1 (1.3–7.8)
16–17	1.4 (0.7–3.1)/1.7 (0.7–4.1)	1.6 (0.8–3.3)/1.8 (0.8–4.4)	1.9 (0.9–3.9)/2.0 (0.8–4.7)
>17	1.0/1.0†	1.3 (0.6–2.7)/1.5 (0.6–3.7)	1.1 (0.5–2.3)/1.2 (0.5–3.0)

\* Values for body-mass index were divided into three groups of equal size. CI denotes confidence interval.  
 † This group served as the reference group.

small at birth. In babies with birth weights below the median of 3.4 kg, weights at 3, 6, and 12 months after birth were all inversely related to coronary events (P=0.1, P=0.005, and P=0.05, respectively). Analyses of babies weighing less than 3.0 kg (20 percent of the total sample) showed similar inverse associations at 3, 6, and 12 months of age, although not all were statistically significant (P=0.15, P=0.05, and P=0.18, respectively).

**CORONARY RISK FACTORS**

The characteristics of the subset of 2003 people seen at the clinic were similar to those of the other men and women in the cohort. The 2003 people were 30 g heavier at birth, and their BMIs were greater by 0.02 at 2 years of age and by 0.04 at 11 years of age. Their mean age was 62 years. We examined the effect on coronary risk factors of birth weight, BMI at two years of age, and change in z score for BMI from 2 to 11 years of age. Table 4 shows that fasting plasma glucose, insulin, and

proinsulin concentrations and serum triglyceride concentrations fell both with increasing birth weight and with increasing BMI at two years of age. There were similar trends with systolic blood pressure. Serum total cholesterol concentrations were unrelated to birth weight or BMI at two years of age. Plasma insulin and proinsulin concentrations were also strongly associated with changes in the z score for BMI (Table 4). The lowest values were in people whose z scores fell by more than 1 SD from 2 to 11 years of age, whereas the highest values were in those whose z scores rose by more than 1 SD. Results in men and women were similar.

**DISCUSSION**

In a retrospective longitudinal study of 8760 subjects, we found that boys and girls who had coronary events as adults had low birth weight and were thin at two years of age. The boys were born thin; the girls became thin during the first six months

**Table 4.** Mean Fasting Plasma Glucose and Insulin Concentrations, Serum Lipid Concentrations, and Blood Pressure Measurements for 2003 Men and Women According to Birth Weight, BMI at 2 Years of Age, and Change in z Score for BMI from 2 to 11 Years of Age.\*

Variable	No. of Subjects†	Plasma Glucose (mmol/liter)	Plasma Insulin (pmol/liter)	Plasma Proinsulin (pmol/liter)	Serum Triglycerides (mmol/liter)	Serum Cholesterol (mmol/liter)	Systolic Blood Pressure (mm Hg)
Birth weight (kg)							
<2.5	72	5.9	8.8	13.8	1.43	5.9	148
2.5–3.0	324	5.8	9.6	12.7	1.39	5.9	148
3.1–3.5	791	5.8	8.6	11.4	1.38	6.0	146
3.6–4.0	612	5.7	8.3	11.1	1.32	5.9	145
>4.0	202	5.6	8.5	10.5	1.23	6.0	142
P for trend		0.004	0.003	<0.001	<0.001	0.7	<0.001
BMI at two years of age							
<15.0	191	5.8	10.0	12.7	1.37	5.92	149
15.0–16.0	486	5.9	9.1	12.7	1.42	6.01	146
16.1–17.0	653	5.7	8.6	11.2	1.37	5.94	146
17.1–18.0	434	5.7	8.3	10.8	1.29	5.86	143
>18.0	235	5.6	7.9	10.5	1.26	5.95	144
P for trend		<0.001	<0.001	<0.001	<0.001	0.3	<0.001
Change in z score for BMI from 2 to 11 years of age							
Decrease of >1.00	314	5.7	7.9	10.4	1.32	6.05	144
Decrease of 0.25 to 1.00	469	5.6	8.3	11.0	1.35	5.85	146
Decrease of <0.25 to increase of <0.25	385	5.8	8.7	11.8	1.35	5.92	146
Increase of 0.25 to 1.00	429	5.8	8.8	11.8	1.35	6.01	146
Increase of >1.00	320	5.8	9.7	12.5	1.37	5.79	145
P for trend		0.06	<0.001	<0.001	0.4	0.04	0.2

\* Values are adjusted for age and sex; values tabulated against the BMI at two years of age are also adjusted for the BMI in adulthood. To convert glucose values to milligrams per deciliter, divide by 0.05551. To convert insulin values to millimoles per liter, divide by 6.0. To convert triglyceride values to milligrams per deciliter, divide by 0.02586.

† Numbers do not sum to 2003 because of missing data.

after birth. After approximately 2 years of age, their BMIs rose progressively as compared with the BMIs of other children, so that by 11 years of age they had reached (or exceeded, in the case of girls) the averages for the cohort. These average BMIs at 11 years of age — 16.8 for boys and 17.1 for girls — are similar to the median values in current U.S. growth charts.<sup>15</sup> We found that an increase in the SD score for BMI after two years of age predicted later coronary events more strongly than did the BMI attained at any particular age. In simultaneous analyses, small size at birth, low BMI at 2 years of age, and high BMI at 11 years of age were each associated with later coronary events in both men and women. These observations demonstrate that coronary events are independently associated with both prenatal and postnatal growth.<sup>16</sup> We found that the effects of body size at these three ages were independent of the effects of socioeconomic status in adulthood.

Raised fasting plasma insulin and proinsulin concentrations, two measures of insulin resistance, were associated with low birth weight, low BMI at 2 years of age, and an increase in SD scores for BMI from 2 to 11 years of age. We therefore conclude that this path of growth may be linked to the development of insulin resistance, a known risk factor for coronary heart disease. Increased serum triglyceride concentrations were also related to low birth weight and low BMI at 2 years of age, but not to changes in SD scores for BMI from 2 to 11 years of age. These observations are consistent with findings in a longitudinal study of 1492 young men and women born in Delhi, India.<sup>17</sup> Thinness at 2 years of age, followed by a rapid increase in BMI, was associated with the development of impaired glucose tolerance and type 2 diabetes at approximately 30 years of age. The cohort is too young for the occurrence of coronary heart disease to be studied.

We found no evidence to support the recent hypothesis that promoting early growth with high intake of nutrients in the first few months after birth will adversely affect cardiovascular health.<sup>18</sup> This hypothesis arose from studies of intermediary outcomes among young people born prematurely. When we restricted our analysis to people with birth weights below the median of 3.4 kg, higher weights at 3, 6, or 12 months were associated with a reduced risk of coronary events. At any birth weight and during any period of infancy, greater

weight gain was associated with a lower incidence of coronary events.

Our study was restricted to people who had attended child-welfare clinics. Although the majority of children attended these clinics, which were free, attendance was voluntary. Therefore, the people in our study may not be representative of all people now living in Helsinki, but at birth the distribution of social class, as indicated by fathers' occupations, was similar to that in the city as a whole, where at that time approximately 60 percent of men were employed as laborers. There were food shortages in Finland before and during the Second World War, and some families were malnourished. These circumstances, which are unusual for most families in the contemporary Western setting, may limit the general application of our results. As expected, many fewer of the women in the study had had coronary events as compared with the men, and the statistical power of our observations on the women is lower than that of our observations on the men.

There is a body of evidence suggesting that the association between slow fetal growth and coronary heart disease is initiated by fetal undernutrition.<sup>19</sup> Among the effects of undernutrition may be "thrifty" metabolic settings that may include resistance of tissues to the effects of insulin.<sup>20</sup> Babies who are thin or short at birth lack muscle,<sup>21</sup> a deficiency that will persist into childhood, since there is little cell replication in muscle after birth.<sup>22</sup> We suggest that rapid weight gain in such children may lead to a disproportionately high fat mass in relation to muscle mass. This may underlie the strong associations between this path of growth and insulin resistance in our study and may offer one explanation of why this pattern of growth leads to later coronary heart disease.

In summary, we have shown that persons who have coronary events as adults tend to have been small at birth and thin at two years of age, after which they tended to increase their BMI rapidly. This pattern of growth is also related to insulin resistance in later life.

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