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FETAL ORIGINS

Fetal origins of adult disease: strength of effects and biological basis

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Background	Low birthweight has been consistently shown to be associated with coronary heart disease (CHD) and its biological risk factors. The effects of low birthweight are increased by slow infant growth and rapid weight gain in childhood. To quantify the importance of developmental processes in the genesis of CHD it is necessary to establish the impact of fetal, infant and childhood growth on major pathological events in later life—death, hospital treatment and the need for medication.
Methods	Longitudinal study of 13 517 men and women who were born in Helsinki University Hospital during 1924–1944, whose body sizes at birth and during childhood were recorded, and in whom deaths, hospital admissions, and prescription of medication for chronic disease are documented.
Results	The combination of small size at birth and during infancy, followed by accelerated weight gain from age 3 to 11 years, predicts large differences in the cumulative incidence of CHD, type 2 diabetes and hypertension.
Conclusions	Coronary heart disease and type 2 diabetes may originate through two widespread biological phenomena—developmental plasticity and compensatory growth.

Keywords	Fetal growth, childhood growth, type 2 diabetes, hypertension, coronary heart disease
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Associations between small body size at birth and during infancy and later cardiovascular disease and its biological risk factors have been found consistently.[1–4] For different risk factors the magnitude of the effects varies. For example, while birthweight is associated with large variations in indices of insulin resistance,[5,6] it is associated with small variations in blood pressure.[7] A possible explanation for this is that, following an intra-uterine lesion regulatory mechanisms may maintain homeostasis for many years until further damage, due to age, obesity or other influences, initiates a self-perpetuating cycle of progressive functional loss.[8] Brenner has proposed such a model for the development of hypertension following reduced nephron numbers at birth, a known correlate of low birthweight.[8] In order to quantify the importance of developmental processes in the genesis of cardiovascular disease and type 2 diabetes we need to establish the impact of fetal and infant growth on major pathological events in later life rather than risk factors.

Recent studies have shown that the effect of small body size at birth on later cardiovascular disease and type 2 diabetes is modified by the path of childhood growth.[9–12] In particular, rapid childhood weight gain increases the risk of disease associated with small body size at birth and during infancy. Examination of the risk of disease attributable to early development therefore requires data on fetal, infant and childhood growth. The Hertfordshire studies showed, for the first time, that people who had low birthweight and low weight at age one year were at increased risk of developing coronary heart disease (CHD) and type 2 diabetes;[1,13] but the data did not include measurements of height or weight beyond 1 year of age. We have examined the combined effects of fetal, infant and childhood growth in the Helsinki cohort and present data on the magnitude of the effects together with their possible biological interpretation.

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Methods

The Helsinki cohort comprises a group of men and women, born 1924–1933, for whom there are data on size at birth and serial measurements of height and weight through school years; together with another, younger group of men and women born 1934–1944, for whom there are serial measurements of height and weight from birth.[12] The total cohort comprises 15 846 individuals: we present here data for 13 517 men and women, for whom there are measurements of body size both at birth and at age 11 years. In Finland there are national registers of hospital discharges by cause, and registers of people receiving medication for chronic illness, including type 2 diabetes and hypertension, in addition to registers of deaths by cause.[9–12] The registers of people receiving medication are maintained because the costs of medication are reimbursed to the patients. This is subject to the approval of a physician who reviews each case history. The diagnosis of type 2 diabetes is based on World Health Organization criteria.[14] Of the estimated 150 000 patients with diagnosed diabetes in Finland 113 000 (75%) are treated with medication.[15] It is therefore possible to relate fetal and childhood growth to type 2 diabetes and hypertension defined by prescription of medication,[11,12] and to CHD defined by hospital admission or death.[9] We identified all people receiving medication for type 2 diabetes and hypertension at any time from 1964 to 1997 and all hospital discharges or deaths from CHD during 1971 to 1997.

We calculated odds ratios for type 2 diabetes and hypertension in the cohort according to birthweight and body mass index (BMI) (weight/height^2) at age 11 years. We selected 11 years for comparability with previous studies,[11] but the results for adjacent years are similar. In the past boys and girls of these ages in Finland would not yet have reached puberty. The average age of menarche at that time was around 14 years.[16] We calculated the odds ratios for men and women combined and adjusted them for year of birth and sex.

We used the cumulative incidence of type 2 diabetes and hypertension to examine the proportion of cases attributable to low birthweight and rapid childhood gain in BMI. We examined change in BMI between age 3 years and age 11 years because type 2 diabetes is associated with low rates of growth up to age 2 years. Age 3–11 years broadly corresponds to the juvenile phase of growth.[16] Use of age 2 or 4 years as the starting point has little effect on the results. The analysis of cumulative incidence was restricted to the people who were born 1934–1944, for whom growth data were available from birth, through infancy and early childhood and into school years. As described previously,[9–12] we used standard deviation scores to describe growth and divided the subjects into those whose standard deviation score for BMI increased or decreased between the ages of 3 and 11 years.

To correspond with our analyses of type 2 diabetes and hypertension we calculated hazard ratios, adjusted for sex and year of birth, for death and for hospital discharge or death from CHD. We examined the associations with birthweight and BMI at age 11 years in the total cohort of 13 517 men and women. We again used cumulative incidence to examine the associations with birth size and change in BMI between age 3 and 11 years in younger subjects, born 1934–1944. Among men in the total cohort, ponderal index at birth (birthweight/birth length^3) predicted CHD more strongly than birthweight,[9] while among women birth length was the strongest predictor.[10] We therefore analysed men and women separately using these two different measures of body size at birth.

Results

Type 2 diabetes and hypertension

Table 1 is based on 698 patients being treated for type 2 diabetes and 2997 patients being treated for hypertension in people born 1924–1944. It shows odds ratios according to birthweight and fourths of BMI at age 11 years. The risks for each disease fell with increasing birthweight and rose with increasing BMI. The odds ratio for type 2 diabetes was 0.67 (95% CI: 0.58–0.79) for each kilogram increase in birthweight and 1.18 (95% CI: 1.13–1.23) for each kg/m^2 increase in BMI at age 11 years. The corresponding figures for hypertension were 0.77 (95% CI: 0.71–0.84) and 1.07 (95% CI: 1.04–1.09).

Table 2 is based on 227 patients being treated for type 2 diabetes and 1036 patients being treated for hypertension in people born 1934–1944. Subjects are divided into six groups according to thirds of birthweight and whether their standard deviation score for BMI decreased or increased between age 3 and 11 years. For both diseases there were independent effects of birthweight and change in BMI score. In the group with the highest birthweight and a subsequent decrease in BMI score, the cumulative incidence of type 2 diabetes was 1.5% (95% CI: 0.9–2.4%). This was less than half the incidence in the other five groups combined, 4.0% (95% CI: 3.5–4.5%, P for difference < 0.001). The corresponding figures for hypertension were 12.0% (95% CI: 10.2–13.9%) and 17.1% (95% CI: 16.0–18.1%, $P < 0.001$). The patterns of odds ratios and incidence shown in Tables 1 and 2 were similar in the two sexes.

Coronary heart disease

Table 3 is based on 1235 patients who were admitted to hospital or died from CHD, and 480 patients who died from the disease

Table 1 Odds ratios[a] (95% CI) for type 2 diabetes and hypertension according to birthweight and body mass index at 11 years: 13 517 men and women born 1924–1944

Birthweight (kg)	Body mass index at 11 years (kg/m^2)			
	–15.7	–16.6	–17.6	>17.6
No. of men and women				
–3.0	991	719	581	560
–3.5	1394	1422	1264	1246
–4.0	827	984	1122	1110
>4.0	167	254	413	463
Type 2 diabetes (698 cases)				
–3.0	1.3 (0.6–2.8)	1.3 (0.6–2.8)	1.5 (0.7–3.4)	2.5 (1.2–5.5)
–3.5	1.0 (0.5–2.1)	1.0 (0.5–2.1)	1.5 (0.7–3.2)	1.7 (0.8–3.5)
–4.0	1.0 (0.5–2.2)	0.9 (0.4–1.9)	0.9 (0.4–2.0)	1.7 (0.8–3.6)
>4.0	1.0	1.1 (0.4–2.7)	0.7 (0.3–1.7)	1.2 (0.5–2.7)
Hypertension (2997 cases)				
–3.0	2.0 (1.3–3.2)	1.9 (1.2–3.1)	1.9 (1.2–3.0)	2.3 (1.5–3.8)
–3.5	1.7 (1.1–2.6)	1.9 (1.2–2.9)	1.9 (1.2–3.0)	2.2 (1.4–3.4)
–4.0	1.7 (1.0–2.6)	1.7 (1.1–2.6)	1.5 (1.0–2.4)	1.9 (1.2–2.9)
>4.0	1.0	1.9 (1.1–3.1)	1.0 (0.6–1.7)	1.7 (1.1–2.8)

[a] Odds ratios adjusted for sex and year of birth.

Table 2 Cumulative incidence (%) of type 2 diabetes and hypertension according to birthweight and change in standard deviation score for body mass index between 3 and 11 years of age: 6424 men and women born 1934–1944

	Change in standard deviation score for body mass index 3–11 years	
Birthweight (kg)	Decrease	Increase
Type 2 diabetes (227 cases)		
–3.2	3.1 (1075)	5.5 (1080)
–3.6	2.4 (1274)	4.3 (950)
>3.6	1.5 (1190)	5.4 (855)
Hypertension (1036 cases)		
–3.2	15.9 (1075)	21.3 (1080)
–3.6	14.8 (1274)	19.4 (950)
>3.6	12.0 (1190)	13.9 (855)

Figures in parentheses are numbers of subjects.

Table 3 Hazard ratios[a] (95% CI) for coronary heart disease according to birthweight and body mass index at 11 years: 13 517 men and women born 1924–1944

Birthweight (kg)	Body mass index at 11 years (kg/m^2)			
	–15.7	–16.6	–17.6	>17.6
Hospital admissions and deaths (1235 cases)				
–3.0	1.4 (0.8–2.4)	1.6 (0.9–2.8)	1.8 (1.0–3.2)	2.1 (1.1–3.8)
–3.5	1.3 (0.7–2.2)	1.5 (0.9–2.7)	1.5 (0.8–2.6)	1.6 (0.9–2.9)
–4.0	1.3 (0.7–2.3)	1.4 (0.8–2.4)	1.3 (0.8–2.4)	1.4 (0.8–2.6)
>4.0	1.0	1.2 (0.6–2.3)	1.1 (0.6–2.1)	1.0 (0.5–1.8)
Deaths (480 cases)				
–3.0	1.4 (0.5–4.0)	1.8 (0.6–5.1)	2.1 (0.7–6.2)	3.0 (1.0–8.6)
–3.5	1.4 (0.5–3.9)	1.9 (0.7–5.2)	2.2 (0.8–6.1)	2.7 (1.0–7.6)
–4.0	1.9 (0.7–5.3)	1.8 (0.7–5.2)	1.7 (0.6–4.8)	1.6 (0.6–4.5)
>4.0	1.0	1.4 (0.4–4.6)	1.6 (0.5–4.7)	1.3 (0.4–4.0)

[a] Hazard ratios adjusted for sex and year of birth.

Table 4 Cumulative incidence (%) of coronary heart disease (hospital admissions and deaths) according to body size at birth and change in standard deviation score for body mass index between 3 and 11 years: 3387 men and 2958 women born 1934–1944

	Change in standard deviation score for body mass index 3–11 years	
Birth size	Decrease	Increase
Men (279 cases)		
Birthweight (kg)		
–3.2	8.8 (512)	9.0 (476)
–3.6	6.9 (662)	11.3 (512)
>3.6	5.9 (740)	8.6 (521)
Birth length (cm)		
–49	8.1 (431)	9.6 (353)
–50	6.9 (433)	9.0 (344)
>50	6.7 (1034)	10.1 (792)
Ponderal index (kg/m^3)		
–25	8.0 (411)	11.7 (394)
–27	7.6 (649)	10.8 (556)
>27	6.2 (838)	7.2 (539)
Women (66 cases)		
Birthweight (kg)		
–3.2	1.6 (563)	3.8 (604)
–3.6	1.5 (612)	2.5 (438)
>3.6	0.7 (450)	3.6 (334)
Birth length (cm)		
–49	1.5 (543)	4.2 (520)
–50	1.5 (452)	3.3 (338)
>50	0.8 (609)	2.6 (496)
Ponderal index (kg/m^3)		
–25	1.6 (313)	4.3 (350)
–27	1.5 (543)	2.4 (467)
>27	0.9 (748)	3.7 (537)

Figures in parentheses are numbers of subjects. Seventy-nine subjects had unknown birth length.

in people born 1924–1944. It shows hazard ratios according to birthweight and fourths of BMI at age 11 years. Similarly to type 2 diabetes and hypertension (Table 1), the risks of disease fell with increasing birthweight and rose with increasing BMI. The pattern was similar in the two sexes. The hazard ratios for admissions and deaths were 0.80 (95% CI: 0.72–0.90) for each kilogram increase in birthweight and 1.06 (95% CI: 1.03–1.10) for each kg/m^2 increase in BMI at age 11 years. The hazard ratios for deaths alone were 0.83 (95% CI: 0.69–0.99) and 1.10 (95% CI: 1.04–1.16).

Table 4 is based on 279 hospital admissions or deaths from CHD among men and 66 among women in people born 1934–1944. Similarly to type 2 diabetes and hypertension (Table 2), there were independent effects of birth size and change in BMI score. Among men ponderal index at birth was more strongly related to CHD than birthweight: among women length at birth was stronger. Among men with the highest ponderal index at birth and a subsequent decrease in standard deviation score for BMI the cumulative incidence of CHD was 6.2% (95% CI: 4.7–8.1%) compared with 8.9% (95% CI: 7.8–10.1%, $P = 0.03$) in the other five groups. The corresponding figures for birth length and change in BMI score among women were 0.8% (95% CI: 0.3–1.9%) and 2.6% (95% CI: 2.0–3.3%, $P = 0.02$).

Among men, CHD is related to low weight gain in infancy and to low BMI at age 1 year more strongly than to ponderal index at birth.[1,9] Table 5 shows the independent effects of BMI at age one year and change in BMI between age 3 and 11 years in men and women. In men with the highest BMI at age one year and a subsequent decrease in standard deviation score for BMI the cumulative incidence of CHD was 5.4% (95% CI: 4.0–7.2%) compared with 9.2% (95% CI: 8.1–10.3%, $P = 0.001$) in the other five groups. The corresponding figures for women were 1.2 (95% CI: 0.5–2.5) and 2.5 (95% CI: 1.9–3.2, $P = 0.10$).

Discussion

Size of effects

Men and women who had birthweights above 4 kg and whose pre-pubertal BMI was in the lowest fourth had around half the risk of type 2 diabetes and hypertension when compared with people who had birthweights below 3 kg but whose BMI was in

Table 5 Cumulative incidence (%) of coronary heart disease (hospital admissions and deaths) among men and women according to body mass index at one year and change in standard deviation score for body mass index between 3 and 11 years: 3387 men and 2958 women born 1934–1944

Body mass index at one year (kg/m^2)	Change in standard deviation score for body mass index 3–11 years	
	Decrease	Increase
Men (279 cases)		
–17	10.4 (424)	11.2 (716)
–18.3	7.0 (642)	8.0 (461)
>18.3	5.4 (832)	9.0 (312)
Women (66 cases)		
–17	1.5 (482)	3.8 (819)
–18.3	1.1 (552)	3.3 (335)
>18.3	1.2 (570)	2.0 (200)

Figures in parentheses are numbers of subjects.

the highest fourth (Table 1). Disease risk was related to the rate of increase in childhood BMI as well as to the BMI attained at any particular age.[11,12] If each individual in the cohort had been in the highest third of birthweight and had lowered their standard deviation score for BMI between age 3 and 11 years (Table 2) the incidence of type 2 diabetes would have been reduced by 57% and the incidence of hypertension by 25%.

There were similarly strong gradients in risk of CHD, whether defined by death or by hospital admission or death, across groupings of birthweight and BMI at age 11 years (Table 3). Again men and women who had birthweights above 4 kg and whose pre-pubertal BMI was in the lowest fourth had around half the risk of CHD when compared with people who had birthweights below 3 kg but whose BMI was in the highest fourth (Table 3). If each man in the cohort had been in the highest third of ponderal index at birth, and each woman in the highest third of birth length, and if each man or woman had lowered their BMI score between age 3 and 11 years the incidence of CHD would have been reduced by 25% in men and 63% in women (Table 4). The number of cases among women is, however, small. Consistent with findings in Hertfordshire[1] low weight and BMI at age 1 year were more strongly associated with CHD among men than low birthweight or ponderal index at birth.[9] If each man had been in the highest third of BMI at age 1 year, and had lowered his standard deviation score for BMI between age 3 and 11 years the incidence of CHD would have been reduced by 40% (Table 5).

The large reductions in disease incidence that we have shown to be associated with modest alterations in fetal, infant and childhood growth may be underestimates. As Robinson[17] wrote, 'birthweight and ponderal index (as well as body mass index) are crude measures of how fetal nutrition has affected body composition, so the true size of the effect of fetal growth on later disease is hard to measure'.

Biological basis

Since McCance and Widdowson's pioneering observations in Cambridge,[18,19] experimentalists have repeatedly demonstrated that minor alterations to the diets of pregnant animals can produce lasting changes in the offspring's physiology and metabolism.[20,21] That this should be so is unsurprising. So-called 'phenotypic plasticity' enables one genotype to give rise to a range of different physiological or morphological states in response to different environmental conditions during development.[22,23] Such gene-environment interactions are ubiquitous in the development of all living things. The benefit of developmental plasticity is that, in a changing environment, it enables the production of phenotypes that are better matched to their environment than would be possible by the production of the same phenotype in all environments.[23]

The different size of newborn human babies exemplifies plasticity. The growth of babies has to be constrained by the size of the mother, otherwise normal birth could not occur. Small women have small babies:[24] in pregnancies after ovum donation they have small babies even if the woman donating the egg is large.[25] Babies may be small because their growth is constrained in this way or because they lack the nutrients for growth. As McCance wrote long ago, 'The size attained *in utero* depends on the services which the mother is able to supply. These are mainly food and accommodation'.[26] Since mother's height or pelvic dimensions are generally not found to be important predictors of chronic disease in later life,[27,28] research into the fetal origins of disease has focussed on the nutrient supply to the baby. The central concept is that despite current levels of nutrition in Western countries the nutrition of many fetuses and infants remains sub-optimal because the nutrients available are unbalanced or because their delivery is constrained by the long and vulnerable fetal supply line.[29] Size at birth for gestational age serves as a marker of fetal nutrition.[30]

When undernutrition during early development is followed by improved nutrition many animals and plants stage accelerated or 'compensatory' growth.[31] Compensatory growth has costs, however, which in animals include reduced lifespan.[31] One suggestion is that a higher rate of cell division causes more rapid shortening of the protective ends of the chromosomes (telomeres) and hastens cell death and organ degradation.[32] There are a number of other possible processes by which, in humans, undernutrition and small size at birth followed by rapid childhood growth could lead to cardiovascular disease and type 2 diabetes in later life.[9,11,12] The Helsinki cohort has shown that people who were small at birth and had rapid growth thereafter are not only physiologically and morphologically different, but also have altered responses to poor living standards in later life.[33]

Conclusion

Our findings suggest that a substantial part of the risk of CHD, type 2 diabetes and hypertension is established during development. We suggest that this reflects two widespread biological phenomena, developmental plasticity and compensatory growth.

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KEY MESSAGES

- To quantify the importance of developmental processes in the genesis of chronic disease it is necessary to examine the impact of fetal, infant and childhood growth on later death, hospital admission and treatment.
- This has been examined in the Helsinki cohort.
- Small body size at birth and during infancy followed by accelerated weight gain in childhood have large effects on the incidence of coronary heart disease, type 2 diabetes and hypertension.
- These diseases may originate through two biological phenomena, developmental plasticity and compensatory growth.

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