Infant Growth and Stroke in Adult Life
The Helsinki Birth Cohort Study

Clive Osmond, PhD; Eero Kajantie, MD; Tom J. Forsén, MD; Johan G. Eriksson, MD; David J.P. Barker, FRS

Background and Purpose—People who had low birth weight are at increased risk of stroke. Little is known about the effects of early postnatal growth on stroke risk.

Methods—We followed-up 12 439 people born in Helsinki during 1934 to 1944. Their body size was measured at birth and, on average, 9 times between birth and age 2 years; 507 of them were hospitalized with stroke or died from the disease.

Results—Hazard ratios for stroke declined progressively with increasing gain in weight between birth and age 2 years. The hazard ratio was 0.85 (95% CI, 0.78 to 0.93; \( P = 0.0004 \)) per standard deviation increase in the difference between the weight attained at age 2 years and that predicted from birth weight. A 1-standard deviation increase in body mass index at 2 years of age was associated with a hazard ratio for stroke of 0.84 (95% CI, 0.77 to 0.92; \( P = 0.0002 \)). This association was little changed by adjustment for measures of socio-economic status. Change in body size after the age of 2 years had little effect on the risk of later stroke. People whose mothers had a small external conjugate diameter of the pelvis had an increased risk of stroke. The hazard ratio associated with a diameter of \( \leq 18 \) cm was 1.62 (95% CI, 1.30 to 2.02; \( P < 0.0001 \)).

Conclusion—Thinness during infancy is associated with an increased risk of stroke in later life. This association may be the result of maternal influences which originated in the mother’s infancy when her pelvic shape was established. (Stroke. 2007;38:264-270.)

Key Words: infant low birth weight stroke pelvimetry

Studies in the United States and Europe have shown that low birth weight is associated with an increased risk of stroke in adult life. The association with birth weight remains after adjustment for gestational age, which suggests that it results from slow fetal growth. A recent study concluded that there was an additional increase in risk associated with premature birth.

Little is known about the effects of early postnatal growth on the later risk of stroke. We report here on a cohort of 12 439 men and women for whom there are data on size at birth, length of gestation, and postnatal growth. We focus on growth rates between birth and age 2 years, which we refer to as infancy. In a previous study we found that slow growth during this period was closely associated with the later development of coronary heart disease, a disorder that has some of the same biological risk factors as stroke.

Infant growth is affected by maternal influences and by living conditions. Two previous studies have suggested that stroke is more common among the offspring of mothers who had a “flat” bony pelvis. In the past, the dimensions of the bony pelvis were often recorded during pregnancy as women with flat pelvises, the result of childhood malnutrition, were at increased risk of obstructed labor. Our data allow us to examine the effects of maternal pelvic size and of living conditions after birth on the later risk of stroke.

Methods

Study Cohort
The study cohort comprised men and women born in Helsinki, Finland, between 1934 and 1944. They were born at 1 of the 2 public maternity hospitals in the city and attended infant welfare clinics. Details of the birth records at Helsinki University Central Hospital have been described before; those at the Helsinki City Maternity Hospital were similar. Details of the records from infant welfare clinics and the school health service have also been described before. We identified 8760 men and women born in the Helsinki University Central Hospital and 4585 born at the Maternity Hospital, who were living in Finland in 1971, when a unique personal identification number was allocated to each member of the Finnish population. We restrict attention to the 12 439 subjects (93% of the total, 6489 men, 5950 women) for whom gestational age at delivery could be estimated from the date of the last menstrual period, so that we could examine the effect of gestational age at birth on risk of...
stroke. The ethics committee at the National Public Health Institute in Helsinki approved the study.

The mother’s height, weight, age, parity, and 3 pelvic diameters (the external conjugate, intercrisel, and interspinous) were taken from the birth records. We used a 9- category classification made by Statistics Finland to assign father’s occupation, recorded at birth, into 1 of 3 social classes. Through Statistics Finland we obtained data on the subject’s own occupation, grouped into 4 categories, and household income, grouped into 5 categories, from the 1980 census.

Definition of Stroke

Using the personal identification number, we identified all hospital admissions and deaths from stroke among men and women during 1971 to 2003. All hospital discharges in Finland are recorded in the national hospital discharge register; all deaths are recorded in the national mortality register. Table 1 lists the successive International Classification of Disease Revision codes used to define stroke and its subtypes, hemorrhagic and thrombotic. It also shows how the 507 stroke cases were divided by gender, subtype, ascertainment source, and age.

Statistical Methods

The children had a median of 9 (quartiles 5,15) measurements of height and weight from birth to 2 years of age, and 7 (2,9) measurements from 2 to 11 years of age. We estimated height, weight, and body mass index (weight/height²) for each child at birthdays from age 1 to 11 years,5 whenever a measurement had been recorded within 2 years of the particular age. Fewer measurements were made between ages 2 years and enrolment at school than were made before age 2 years, when most visits to infant welfare clinics occurred. We examined how body size at each age compared with size at an earlier age by using the residual deviation difference in each predictor. We tested for proportionality of the hazards according to gender and age. We also calculated hazard ratios for stroke according to maternal and socio-economic variables. In multivariate Cox models we determined whether associations between early growth and stroke were modified by allowance for maternal and socio-economic factors.

Results

Of the 507 cases of stroke, 333 were in men and 174 were in women. Using the standard European population the directly standardized rates for stroke at ages older than 35 years were 343 per 100 000 in men and 197 per 100 000 in women. The hazard ratio for stroke for women compared with men was 0.55 (95% CI, 0.46 to 0.66). The corresponding figures for hemorrhagic stroke, thrombotic stroke, and death from stroke were 0.65 (0.47 to 0.89), 0.51 (0.40 to 0.64), and 0.61 (0.41 to 0.93), respectively. All subsequent analyses are adjusted for sex. Table 2 shows the mean and standard deviation of the height, weight, and body mass index measurements according to age and sex.

Incidence of Stroke in Relation to Early Growth

Table 3 shows the hazard ratios for stroke for a unit standard deviation increase in body size measurements at different ages. The figure shows hazard ratios at each year of age from birth to 11 years, according to height, weight, and body mass index.

Birth Size and Gestational Age

A 1-standard deviation increase in birth weight was associated with a hazard ratio for stroke of 0.91 (95% CI, 0.83 to 0.99; P=0.03). There was no association with either gestational age (hazard ratio 0.97 [0.89 to 1.06] per standard deviation) or with birth before 37 weeks gestation (hazard ratio, 0.75 [0.43 to 1.30]). Adjustment for gestational age had little effect on the association with birth weight (hazard ratio 0.91 [0.83 to 1.00]). Stroke was also associated with low body mass index at birth (Table 3), but not with length, head circumference, or placental weight.

Infant Growth

The association between stroke and low weight was stronger at age 1 year than at birth, and stronger still at age 2 years. Associations with low body mass index followed a similar pattern. Associations with short stature were weaker. Table 4 shows the trend with body mass index at two years. It shows also the trend with weight at age 2 years in relation to the weight predicted by birth weight. Risk of stroke fell as each measure increased. Risk of stroke also fell with increasing body mass index at age 2 years in relation to that predicted by body mass index at birth (hazard ratio 0.87 [0.79 to 0.95]).

Childhood Growth

Stroke continued to be associated with low weight and body mass index at age 7 years (Table 3), but by age 11 years this association was no longer statistically significant (Figure). We calculated hazard ratios for body size at age 11 years conditional on body size at age 2 years. They were not statistically significant from 1, with the values being 1.03 (0.93 to 1.14) for height, 1.09 (0.98 to 1.20) for weight, and 1.04 (0.94 to 1.15) for body mass index. There was no
statistically significant interaction with sex in predicting incidence of stroke for any of the measures shown in Table 3. Nor were there differences in hazard ratios in analyses at ages older and younger than 55 years.

### Comparison of Hemorrhagic and Thrombotic Stroke

The associations of hemorrhagic stroke and thrombotic stroke with weight and body mass index were similar at each age.
Osmond et al Infant Growth and Stroke in Adult Life 267

TABLE 4. Hazard Ratios (95% Confidence Intervals) for Stroke According to Body Mass Index at Age 2 Years and Weight in Relation to That Predicted by Birth Weight

<table>
<thead>
<tr>
<th>BMI at age 2 years, kg/m²</th>
<th>No. of Subjects</th>
<th>No. of Cases (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>No. of Cases (%)</th>
<th>Hazard Ratio (95% CI)</th>
<th>No. of Cases (%)</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>1225</td>
<td>66 (5.4)</td>
<td>1.7 (1.2 to 2.4)</td>
<td>21 (1.7)</td>
<td>1.6 (0.8 to 2.9)</td>
<td>39 (3.2)</td>
<td>1.6 (1.0 to 2.5)</td>
</tr>
<tr>
<td>16</td>
<td>2959</td>
<td>125 (4.2)</td>
<td>1.2 (0.9 to 1.7)</td>
<td>41 (1.4)</td>
<td>1.2 (0.7 to 2.1)</td>
<td>77 (2.6)</td>
<td>1.2 (0.8 to 1.8)</td>
</tr>
<tr>
<td>17</td>
<td>3939</td>
<td>174 (4.4)</td>
<td>1.2 (0.9 to 1.7)</td>
<td>57 (1.4)</td>
<td>1.2 (0.7 to 2.1)</td>
<td>105 (2.7)</td>
<td>1.2 (0.8 to 1.7)</td>
</tr>
<tr>
<td>18</td>
<td>2809</td>
<td>87 (3.1)</td>
<td>0.9 (0.6 to 1.2)</td>
<td>22 (0.8)</td>
<td>0.7 (0.4 to 1.2)</td>
<td>58 (2.1)</td>
<td>0.9 (0.6 to 1.4)</td>
</tr>
<tr>
<td>&gt;18</td>
<td>1500</td>
<td>54 (3.6)</td>
<td>1.0 (baseline)</td>
<td>18 (1.2)</td>
<td>1.0 (baseline)</td>
<td>34 (2.3)</td>
<td>1.0 (baseline)</td>
</tr>
</tbody>
</table>

HR per SD (95% CI) 0.84 (0.77 to 0.92) 0.81 (0.69 to 0.95) 0.87 (0.78 to 0.98)

P for trend 0.0002 0.009 0.02

Weight at age 2 years minus predicted weight, kg

<table>
<thead>
<tr>
<th>HR per SD (95% CI)</th>
<th>0.85 (0.78 to 0.93)</th>
<th>0.87 (0.74 to 1.02)</th>
<th>0.84 (0.75 to 0.94)</th>
</tr>
</thead>
<tbody>
<tr>
<td>P for trend</td>
<td>0.0004</td>
<td>0.08</td>
<td>0.003</td>
</tr>
</tbody>
</table>

Hazard ratios are adjusted for sex.

HR indicates hazard ratio.

(The Table 3). The effect of height growth was different. Thrombotic stroke was associated with short stature at age 2 years, whereas hemorrhagic stroke was not (Table 3). For thrombotic stroke the hazard ratio for height at age 2 years conditional on birth length was 0.90 (0.80 to 1.00). The corresponding figure for height at age 3 years was 0.83 (0.72 to 0.96).

Death From Stroke

The pattern of hazard ratios for death from stroke followed closely that for incidence of the disease. The hazard ratios were 0.82 (0.67 to 0.99) for weight and 0.81 (0.66 to 0.99) for body mass index at age 2 years. The ratios for size at 2 years conditional on birth size were 0.80 (0.65 to 0.98) for weight and 0.79 (0.64 to 0.98) for body mass index.

Maternal Influences

The incidence of stroke was not related to mother’s height, weight, body mass index, parity, or age. The external conjugate diameter of the pelvis, the distance between the spine of the fifth lumbar vertebra and the front of the pubic bone, was measured in 64% of the mothers, who were similar in height and body mass index to those without measurements. The external conjugate diameter was more often measured in primiparous mothers, in those of low social class and in those giving birth in the early part of 1934 to 1944. Twenty-five percent of mothers had diameters of ≤18 cm. The hazard ratio for incidence of stroke among their offspring was 1.62 (1.30 to 2.02) compared with the offspring of other mothers. Findings were similar for hemorrhagic and thrombotic stroke (hazard ratios 1.63 and 1.51, respectively). In a simultaneous analysis with body mass index at age 2 years, the effect of external conjugate on stroke was changed very little (hazard ratio 1.60 [1.29 to 2.00]).

Mothers with diameters of ≤18 cm were on average 4.1 cm shorter, 8.0 kg lighter, and had a 1.8 kg/m² lower body mass index than mothers with larger diameters. The association between external conjugate diameter and stroke remained after adjustment for maternal height. The offspring of women who had conjugate diameters of ≤18 cm were 0.4 cm shorter, 146 g lighter, and 0.3 kg/m² lower in body mass index at birth (P<0.001 for each). Conditional on size at birth they were 0.8 cm shorter, 257 g lighter, and 0.1 kg/m² lower in body mass index at age 2 years (P<0.001 for height and weight; P=0.006 for body mass index). Simultaneous analysis showed that the effect of external conjugate diameter on body mass index at age 2 years was largely mediated by body mass index at birth. The correlation between body mass index at birth and at age 2 years was 0.27 (P<0.0001).

Neither of the 2 other maternal pelvic measurements, the intercristal and interspinous diameters, which measure the maximal and anterior distances between the iliac crests, was related to the incidence of stroke, nor neither was the difference between these measurements. This difference, in combination with an external conjugate diameter of ≤18 cm, was once used in obstetric practice to define a “flat” pelvis.10

Living Conditions

Infants whose fathers worked as laborers, the lowest of the 3 social class groups, were on average 0.5 cm shorter and 141 grams lighter at the age of 2 years (P<0.001 for both). Body mass index at age 2 years, however, was not related to father’s social class. Whereas hemorrhagic stroke was not
related to social class, the hazard ratio in the children of laborers being 0.94 (0.67 to 1.31), thrombotic stroke was associated with low social class, with the hazard ratio in the children of laborers being 1.67 (1.28 to 2.18). The effect of mother’s external conjugate diameter on stroke was changed little by adjustment for childhood social class.

Because incidence of stroke may affect income and occupational status in adult life, we restricted our further analyses to strokes that occurred after income and occupational status were recorded in 1980. The incidence of stroke was higher in people with low income (hazard ratio per standard deviation 0.85 [0.79 to 0.92]) and low socio-economic status (hazard ratio 1.26 [1.15 to 1.39]). These associations were similar for hemorrhagic and thrombotic stroke. We adjusted the effects of low body mass index at age 2 years for social class in childhood and for social class and income in adult life. The effects remained statistically significant (hazard ratio 0.83 [0.75 to 0.92]).

Discussion
This study of 12,439 men and women born in Helsinki, Finland, during 1934 to 1944 confirms previous observations that low birth weight is associated with increased risk of stroke.1–6 This association is independent of the length of gestation and therefore reflects slow fetal growth. Low body mass index at birth was also associated with later stroke. The disorder was not associated with small head circumference at birth, which is consistent with previous reports of relative sparing of brain growth during the slow fetal growth that precedes stroke.8 We were not able to confirm the association between thrombotic stroke and preterm birth reported from Sweden.7 One difficulty in interpreting this is that large numbers of babies born prematurely 60 or more years ago would have failed to survive infancy.

We have been able to examine, for the first time to our knowledge, the associations between growth in the first 2 years after birth and later stroke. We have previously shown that slow growth during this period predicts later coronary heart disease.9 Both thrombotic and hemorrhagic stroke were associated with low weight gain between birth and 2 years of age and a relative decline in body mass index during this period. If each person had been in the highest of 5 categories of weight gain between birth and 2 years (Table 4), the incidence of stroke would have been reduced by 21% and the death rate by 28%. These findings are consistent with the observation that men in Hertfordshire, UK, who had low weight at 1 year of age were at increased risk of stroke;10 in that study, there were no data on height, or on body size at other ages. We found that between the ages of 2 and 11 years, children in whom stroke developed later remained thin. Changes in their body size during this period were not related to the risk of later stroke.

The rates of all types of stroke in our study were comparable to those in Finland as a whole.14–16 We ascertained the occurrence of stroke through the national mortality and hospital discharge registers, which have been validated against individual hospital records.15 Use of these 2 registers slightly underestimates the total occurrence of stroke. This is especially true for thrombotic stroke. Nevertheless, there was 90% agreement between the diagnosis of stroke on the national hospital register and the diagnosis in the records.15 For subarachnoid hemorrhage, the agreement was only 79%. For all deaths from stroke, the agreement was 97%. In Finland >97% of stroke diagnoses are verified by CT scan, MRI imaging, or necropsy.16 We divided stroke into 3 categories, thrombotic, hemorrhagic, and other, based on groupings in the international classification of disease that have been used in previous analyses.5–7 The number of cases in our study was insufficient for examination of smaller diagnostic groupings, such as subarachnoid hemorrhage.

Our study was restricted to people who were born at either of the 2 public maternity hospitals and who attended infant welfare clinics in Helsinki. Attendance at infant welfare clinics was voluntary, but it was free and all children were encouraged to attend irrespective of their family’s social circumstances. Therefore, the people in our study may not be representative of all people living in Helsinki at that time. At birth, however, the distribution of social class, as indicated by fathers’ occupations, was similar to that in the city as a whole, where ≈60% of men were employed as laborers.
Maternal Physique
We found that stroke incidence was increased among the offspring of mothers who had a small external conjugate diameter of the pelvis. Although the dimensions of the bony pelvis are closely related to height, this association with stroke was unaffected by adjustment for maternal height. An external conjugate <18 cm is one of the measurements that defines a “flat” pelvis, with the other measurement being a reduced difference between the intercristal and interspinous measurements, which we found to be unrelated to stroke. Two previous studies, one in an older Helsinki cohort and the other in Sheffield, UK, have suggested a link between flat pelvis and increased stroke risk in the offspring, although in neither study was there a statistically significant association. Because flat pelvis is a result of malnutrition in early childhood, these observations led to the suggestion that malnutrition among young girls increases stroke risk in the next generation. Our observations support this and point to the importance of nutrition in the first year after birth when pelvic shape is established.

Living Conditions
The association between both forms of stroke and low body mass index at age 2 years was independent of living conditions during childhood, as indicated by father’s low social class. People in whom stroke developed were already thin at birth, and this correlated with thinness at age 2 years. The association between stroke and thinness at age 2 years could therefore reflect intrauterine rather than postnatal influences. The association was not affected by adjusting for adult socio-economic factors.

We found that thrombotic, but not hemorrhagic, stroke was associated with short stature at ∼2 years of age. Short stature was associated with poor living conditions, indicated by low father’s social class. Consistent with this, father’s low social class was associated with increased risk of thrombotic stroke. An association between death from stroke and father’s low social class has been previously described.

Hypertension
Hypertension is a major risk factor for stroke. From clinical examination of 2003 people within this cohort, we have found that slow growth between birth and age 2 years is associated with the later development of hypertension (unpublished data). We therefore conclude that the associations between slow early postnatal growth and stroke may be mediated through hypertension. We do not know the process that links thinness during infancy with both thrombotic and hemorrhagic stroke. We speculate that low birth weight and low body weight gain in infancy may be associated with impaired development of the cerebral vasculature during this period of rapid brain growth.

Liver Growth
The association between slow linear growth after birth and later thrombotic stroke could be mediated through changes in blood coagulation and lipid metabolism. Among men in Hertfordshire, low weight at age 1 year was associated with raised serum concentrations of total and low-density lipoprotein cholesterol and apolipoprotein B. Cholesterol metabolism is regulated by the liver, and one suggestion is that the high concentrations associated with low infant weight gain are persisting responses to impaired liver development during a critical phase in utero and during infancy.

Stroke and Coronary Heart Disease
We have previously reported that, within this cohort, low weight gain between birth and age 2 years and low body mass index at age 2 years are related to increased risk of coronary heart disease. The risk of coronary heart disease was further increased by rapid gain in body mass index after the age of 2 years. Our present study shows that change in body mass index after age 2 years is unrelated to stroke. These observations may be relevant to the wider ecology of these 2 diseases, which have common biological risk factors, including hypertension and dyslipidemia. Coronary heart disease is a disorder of Westernization, one feature of which is improved childhood nutrition and rapid gain in body mass index. Stroke is common in the third world and among poorer communities in the Western world, where failure to thrive after birth may not be followed by compensatory weight gain in later childhood.

Conclusion
We have found that both hemorrhagic and thrombotic stroke are associated with low weight gain between birth and 2 years and low body mass index at 2 years of age. Changes in body size after 2 years had little effect on the risk of stroke. People whose mothers had a small external conjugate diameter of the pelvis had an increased risk of stroke. This suggests that malnutrition among infant girls may initiate stroke in the next generation.

Sources of Funding
The study was supported by grants from the Academy of Finland, British Heart Foundation, Finnish Diabetes Foundation, Finnish Foundation for Cardiovascular Research, Finnish Medical Society Duodecim, Finska Läkaresällskapet, Foundation for Pediatric Research, Jalmari and Rauha Abokas Foundation, Novo Nordisk Foundation, Päiviikki and Sakari Sohlberg Foundation, Signe and Ane Gyllenberg Foundation, The Royal Society of London, and Yrjö Jahnsson Foundation.

References


Infant Growth and Stroke in Adult Life: The Helsinki Birth Cohort Study
Clive Osmond, Eero Kajantie, Tom J. Forsén, Johan G. Eriksson and David J.P. Barker

Stroke. 2007;38:264-270; originally published online January 11, 2007;
doi: 10.1161/01.STR.0000254471.72186.03
Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2007 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the
World Wide Web at:
http://stroke.ahajournals.org/content/38/2/264

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published
in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office.
Once the online version of the published article for which permission is being requested is located, click
Request Permissions in the middle column of the Web page under Services. Further information about this
process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/