Pre-Eclampsia Is Associated With Increased Risk of Stroke in the Adult Offspring
The Helsinki Birth Cohort Study

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

Background and Purpose—Women who develop pre-eclampsia in pregnancy are at increased risk of cardiovascular disease. The offspring from pregnancies complicated by pre-eclampsia have higher blood pressures during childhood, but little is known about their long-term health. We hypothesized that pre-eclampsia would lead to an increased risk of cardiovascular disease in the offspring.

Methods—We traced 6410 babies born in Helsinki, Finland, from 1934 to 1944. We used the mothers’ blood pressure levels and the presence of proteinuria during pregnancy to define pre-eclampsia and gestational hypertension without proteinuria according to modern criteria.

Results—Two hundred eighty-four of the pregnancies were complicated by pre-eclampsia (120 with nonsevere and 164 with severe disease) and 1592 by gestational hypertension. The crude hazard ratio for all forms of stroke among people whose mothers had pre-eclampsia was 1.9 (1.2 to 3.0; \( P=0.01 \)); among people whose mothers had gestational hypertension, it was 1.4 (1.0 to 1.8; \( P=0.03 \)). There was no evidence that these pregnancy disorders were associated with coronary heart disease in the offspring. Pre-eclampsia, in particular severe disease, was associated with a reduced mean head circumference at birth, whereas gestational hypertension was associated with an increased head circumference in relation to body length.

Conclusions—People born after pregnancies complicated by pre-eclampsia or gestational hypertension are at increased risk of stroke. The underlying processes may include a local disorder of the blood vessels of the brain as a consequence of either reduced brain growth or impaired brain growth leading to “brain-sparing” responses in utero. \( \text{(Stroke. 2009;40:1176-1180.)} \)

Key Words: coronary artery disease ¦ pre-eclampsia ¦ pregnancy ¦ pregnancy complications ¦ stroke

Women who develop pre-eclampsia in pregnancy have higher levels of cardiovascular risk factors, including raised blood pressures, serum cholesterol concentrations, and hyperinsulinemia, and are at increased risk of cardiovascular disease in later life. The offspring from pregnancies complicated by pre-eclampsia have higher blood pressures during childhood, but little is known about their long-term health. We hypothesized that pre-eclampsia would lead to an increased risk of cardiovascular disease in the offspring.

Methods
The Helsinki Birth Cohort Study includes 13 345 men and women who were born as singletons from 1934 through 1944 in one of 2 maternity hospitals in Helsinki, the University Central Hospital and the City Maternity Hospital, who attended child welfare clinics in the city and who were still living in Finland in 1971, by which time a unique personal identification number had been assigned to each resident of the country. Details of the birth records have been described. They include the mother’s height, weight on admission to the birth hospital, age, and parity. Duration of gestation was estimated from the date of the last menstrual period. After birth, the babies visited child welfare clinics where their heights and weights were recorded. The birth, child welfare clinic, and school health-care records included in addition data on the fathers’ occupations, which were grouped into upper and lower middle class and manual workers based on a classification from Statistics Finland. We used father’s occupation as a marker of the family’s socioeconomic status.

In 6410 of the pregnancies, the mothers’ blood pressures and the results of urinary protein tests were recorded after 20 weeks of pregnancy at antenatal clinics or at the birth hospital. There were an average 2.0 blood pressure and 2.5 urinary protein measurements recorded in each pregnancy. All pregnant women were encouraged to attend the antenatal clinics, which were introduced in Helsinki in...
1928.14 We used the blood pressure levels and urinary protein results to define pre-eclampsia and defined 4 groups of mothers: (1) those who had severe pre-eclampsia, with proteinuria + and a systolic blood pressure of 160 mm Hg or more or a diastolic pressure of 110 mm Hg or more; (2) those who had none severe pre-eclampsia, with proteinuria+ and a systolic pressure of ≥140 mm Hg or a diastolic pressure of ≥90 mm Hg but no proteinuria; and (4) those who were normotensive, with neither systolic pressure attaining ≥140 mm Hg nor diastolic pressure attaining ≥90 mm Hg. The 263 women (4.1%) who had recorded a systolic pressure of ≥140 mm Hg or a diastolic pressure of ≥90 mm Hg before 20 weeks of pregnancy were excluded from the analyses. These definitions are consistent with the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy (NHBPEP) 2000 criteria15 with 2 exceptions; first, we considered one high blood pressure measurement to be sufficient for diagnosis because our data did not allow us to require 2 separate measurements as the NHBPEP criteria do; second, our data included only a qualitative protein measurement; proteinuria+ approximates to 1 mg/mL of albumin.14 Compared with 6935 members of the cohort who did not have maternal blood pressure and urinary protein recorded after 20 weeks of gestation, those 6410 with records had similar body size at birth and maternal weight, but their mothers were 0.5 cm shorter and 0.4 years younger. Fifty percent of them were primiparous compared with 46% of those with no data available. Seventy-two percent of them were of low socioeconomic status, defined by the father being a manual worker, compared with 60%.

Using the personal identification number of each of the 6410 offspring, we identified deaths and hospital discharges for cardiovascular disease among them from 1971 to 2003. All deaths in Finland are recorded in the national mortality register. All hospital discharges are recorded in the national hospital discharge register. We have previously analyzed deaths and hospital discharges for coronary heart disease and stroke within the cohort.16,17 Causes of death and hospital treatment were recorded according to the International Classification of Diseases (ICD). The codes for coronary heart disease were 410 to 414 in ICD-8 and 9 and I21 to I25 in ICD-10.16 The codes for thrombotic stroke were 432 to 436 in ICD-8, 433 to 436 in ICD-9, and I62 to I66 in ICD-10. Those for hemorrhagic stroke were 430 to 431 in ICD-8, 430 to 432 in ICD-9, and 160 to I60 in ICD-10. All strokes included in addition other forms of stroke (437 to 439 and I67 to I69, respectively).17 We ascertained the occurrence of hypertension in the offspring using the Social Insurance Institution’s Register of people on medication for chronic disease.18 In Finland, the costs of antihypertensive drugs are partly reimbursed by the state subject to the approval of a physician who reviews each case history.

The ethics committee at the National Public Health Institute in Helsinki approved the study.

Statistical Methods
We used 2-sample t tests and χ2 tests to compare the characteristics of mothers and babies in pregnancies affected by pre-eclampsia or hypertension with those of mothers and babies in normotensive pregnancies. We adjusted these analyses birth and childhood measurements and gestational age by multiple linear regression. We used a Cox proportional hazards model to calculate the hazard ratios for coronary heart disease and stroke in the offspring. Each Cox model was stratified for year of birth and included sex as a covariate. People were censored in the analysis when they migrated from Finland, died, were admitted to hospital with coronary heart disease or stroke, or reached the end of 2003. Mean age at the start of follow-up in 1971 was 30.0 years (SD, 2.9), and mean duration of follow-up was 28.8 years (SD, 8.9). We used multiple logistic regression analysis to calculate ORs for hypertension among the offspring in later life. Each logistic regression model included age and sex as a covariate.

Results
Two hundred eighty-four (4.4%) of the 6410 pregnancies were complicated by pre-eclampsia; 160 of these had severe pre-eclampsia, whereas 124 had none severe disease. A total of 1592 mothers had gestational hypertension.

Maternal Characteristics
Table 1 shows that mothers who had gestational hypertension or who had either mild or severe pre-eclampsia had higher mean body mass indices during late pregnancy than the normotensive mothers. More of them were primiparous. There was a higher percent of primiparous mothers in those who had pre-eclampsia compared with those who had gestational hypertension.

Body Size and Gestational Age at Birth
Table 1 shows that the babies of mothers who had pre-eclampsia had on average lower birth weight and length, head circumference, and ponderal indices (birth weight/length3) compared with the babies of normotensive mothers. They were in addition born at an earlier gestational age. Differences in birth measurements remained statistically significant after adjustment for gestational age, except the lower head circumference in babies of mothers with none severe pre-eclampsia, which became nonsignificant. All of these measurements were smaller in babies of mothers who had severe pre-eclampsia than in babies whose mothers had none severe disease. Also, this difference remained statistically significant after adjustment for gestational age.

Babies whose mothers had gestational hypertension had a lower birth weight and ponderal index at birth than babies from normotensive mothers. However, they had a higher mean head circumference and a higher ratio of head circumference to length (P=0.0002).

Body Size at Age 2 Years
Table 1 shows that at the age of 2 years, children whose mothers had severe pre-eclampsia were on average shorter and thinner in comparison to children whose mothers were normotensive. Children whose mothers had none severe pre-eclampsia or gestational hypertension were thinner at age 2 years than those whose mothers were normotensive.

Cardiovascular Disease in Offspring
Four hundred sixty-four of the offspring developed coronary heart disease and 272 developed stroke, among whom 84 had hemorrhagic strokes and 173 had thrombotic strokes, with the type of stroke being unknown for 15 offspring. People whose mothers had pre-eclampsia or gestational hypertension were at increased risk of stroke, but not coronary heart disease. Table 2 shows these associations in offspring born at or after 37 weeks of gestation, the commonly used lower limit of term birth. The hazard ratio for stroke among the offspring whose mothers had either none severe or severe pre-eclampsia was 1.9 (1.2 to 3.0; P=0.01). The separate hazard ratios for hemorrhagic and thrombotic stroke were 2.0 (0.9 to 4.6; P=0.1) and 1.8 (1.0 to 3.2; P=0.06). The hazard ratio of coronary heart disease was 1.4 (0.9 to 2.1; P=0.1). All statistically significant associations remained when subjects born preterm were
included in the analysis. The associations were little changed by adjustment for birth weight or length of gestation.

A total of 1275 of the offspring had received treatment for hypertension. Of these, 356 were born after pregnancies complicated by hypertension. People whose mothers had had severe pre-eclampsia or gestational hypertension were at increased risk of hypertension (Table 2).

### Socioeconomic Status

Mothers with pre-eclampsia tended to be of higher socioeconomic status. Among upper middle class mothers, 3.0% had nonsevere pre-eclampsia and 3.1% had severe pre-eclampsia compared with 2.0% and 2.9% among mothers in lower middle class and 1.7% and 2.4% in manual workers’ families (P for trend = 0.03 and 0.2, respectively). Adjustment for socioeconomic status had little effect on the association between severe pre-eclampsia and stroke in the offspring, the hazard ratio being 2.3 (1.2 to 4.2; P = 0.01). The corresponding figure for gestational hypertension was 1.4 (1.0 to 1.8; P = 0.03). The associations of nonsevere or severe pre-eclampsia or gestational hypertension with coronary heart disease remained nonsignificant after adjustment for socioeconomic status (all P > 0.2).

### Discussion

We have found that people born after pregnancies complicated by pre-eclampsia are at increased risk of stroke in adult life. Pre-eclampsia was also associated with increased risk of hypertension. However, we found no evidence of an increased risk of coronary heart disease in the offspring, although it is not possible to exclude a small increase in risk in a sample of this size.

### Table 1. Mean Value (SD) of Measurements of Mothers and Babies in Pregnancies With Normal Blood Pressure, Gestational Hypertension, or Nonsevere or Severe Pre-Eclampsia

<table>
<thead>
<tr>
<th>Measurement</th>
<th>Normotension (n=4271)</th>
<th>Gestational Hypertension (n=1592)</th>
<th>Nonsevere Pre-Eclampsia (n=120)</th>
<th>Severe Pre-Eclampsia (n=164)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>Mean SD</td>
<td>Mean SD</td>
<td>Mean SD</td>
</tr>
<tr>
<td>Mother</td>
<td>Height, cm</td>
<td>6089 159.5 5.7</td>
<td>159.6 5.7 0.5</td>
<td>160.4 5.8 0.1</td>
</tr>
<tr>
<td></td>
<td>Body mass index in late pregnancy, kg/m²</td>
<td>5995 26.0 2.8</td>
<td>26.8 3.2 &lt; 0.001</td>
<td>26.9 3.4 0.002</td>
</tr>
<tr>
<td></td>
<td>Age, years</td>
<td>6404 27.8 5.2</td>
<td>28.9 5.8 &lt; 0.001</td>
<td>27.7 5.0 0.8</td>
</tr>
<tr>
<td></td>
<td>Parity</td>
<td>6408 1.9 1.3</td>
<td>1.9 1.3 0.06</td>
<td>1.6 1.0 0.005</td>
</tr>
<tr>
<td></td>
<td>Primiparous, %</td>
<td>6408 48.6%</td>
<td>54.4% &lt; 0.001</td>
<td>65.8% 0.002</td>
</tr>
<tr>
<td>Body size at birth</td>
<td>Weight, g</td>
<td>6410 3435 468</td>
<td>3382 500 0.001</td>
<td>3216 545 &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Length, cm</td>
<td>6365 50.3 1.9</td>
<td>50.3 2.0 0.5</td>
<td>49.7 2.2 0.001</td>
</tr>
<tr>
<td></td>
<td>Head circumference, cm</td>
<td>6366 35.0 1.5</td>
<td>35.1 1.6 0.007</td>
<td>34.7 1.5 0.05</td>
</tr>
<tr>
<td></td>
<td>Ponderal index, kg/m³</td>
<td>6365 26.9 2.2</td>
<td>26.5 2.3 &lt; 0.001</td>
<td>25.9 2.2 &lt; 0.001</td>
</tr>
<tr>
<td></td>
<td>Length of gestation, days</td>
<td>6204 280.2 12.9</td>
<td>279.7 13.2 0.2</td>
<td>277.5 14.8 0.02</td>
</tr>
<tr>
<td></td>
<td>Preterm, %</td>
<td>6204 4.7%</td>
<td>5.1% 0.04</td>
<td>6.7% 0.10</td>
</tr>
<tr>
<td>Body size at age 2 years</td>
<td>Weight, kg</td>
<td>6409 12.1 1.2</td>
<td>12.1 1.2 0.9</td>
<td>12.0 1.2 0.5</td>
</tr>
<tr>
<td></td>
<td>Height, cm</td>
<td>6403 86.0 3.2</td>
<td>86.1 3.3 0.2</td>
<td>86.3 3.4 0.4</td>
</tr>
<tr>
<td></td>
<td>Body mass index, kg/m²</td>
<td>6405 16.5 1.2</td>
<td>16.5 1.3 0.08</td>
<td>16.3 1.2 0.03</td>
</tr>
</tbody>
</table>

P indicates P value for comparison with normotensives; preterm, 36 weeks 6 days of gestation or before.

### Table 2. Hospital Admissions or Deaths From Coronary Heart Disease and Stroke and the Occurrence of Hypertension Among Offspring Born at ≥37 Weeks of Gestation From Pregnancies Complicated by Gestational Hypertension or Pre-Eclampsia

<table>
<thead>
<tr>
<th>Cardiovascular Outcome</th>
<th>All (n=6410)</th>
<th>Gestational Hypertension (n=1592)</th>
<th>Pre-Eclampsia, Nonsevere (n=120)</th>
<th>Severe Pre-Eclampsia (n=164)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N of Cases</td>
<td>Relative Risk* 95% CI P</td>
<td>N of Cases</td>
<td>Relative Risk* 95% CI P</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>464</td>
<td>117 1.0 0.8–1.3 0.8</td>
<td>12 1.3</td>
<td>0.7–2.3 0.4</td>
</tr>
<tr>
<td>Stroke</td>
<td>272</td>
<td>81 1.4 1.0–1.8 0.03</td>
<td>8 1.8</td>
<td>0.9–3.7 0.1</td>
</tr>
<tr>
<td>Hemorrhagic</td>
<td>84</td>
<td>25 1.3 0.8–2.2 0.3</td>
<td>4 3.2</td>
<td>1.1–9.1 0.03</td>
</tr>
<tr>
<td>Thrombotic</td>
<td>173</td>
<td>55 1.5 1.1–2.2 0.02</td>
<td>4 1.4</td>
<td>0.5–3.8 0.5</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1275</td>
<td>356 1.3 1.1–1.5 0.002</td>
<td>24 0.9</td>
<td>0.6–1.5 0.7</td>
</tr>
</tbody>
</table>

*Hazard ratios (adjusted for sex) for coronary heart disease and stroke; ORs (adjusted for sex and age) for hypertension using normotensive pregnancies as the comparison group.
Although there is considerable evidence linking pre-eclampsia with increased risk of coronary heart disease and stroke in the mother,\textsuperscript{1,7} we are unaware of any previous study that has followed up the offspring long enough to attain substantial rates of cardiovascular disease. The detailed maternity clinic and hospital records in the Helsinki Birth Cohort Study allowed us to achieve this. The prevalence of pre-eclampsia in our study was consistent with reported prevalences of 3\% to 5\% of pregnancies.\textsuperscript{2,19} As expected, it was more common among first pregnancies. Consistent with some,\textsuperscript{20} although not all,\textsuperscript{21} observations in European populations, pre-eclampsia was also more common in mothers in families of higher socioeconomic status. There was, however, no evidence of confounding by family socioeconomic status.

A limitation of the study is that we have no data on preeclampsia itself, which at that time was a major obstetric challenge complicating 0.6\% of pregnancies at Helsinki University Central Hospital.\textsuperscript{22} Moreover, our data did not allow us to require 2 elevated blood pressure measurements to establish diagnosis,\textsuperscript{15} resulting in a relatively high percentage of mothers with gestational hypertension. Although the number of subjects allowed relatively accurate hazard ratios for the main outcomes, conclusions based on subgroup analyses such as hemorrhagic and thrombotic stroke include a degree of uncertainty. Furthermore, we did not have data on some potential confounders such as family history of cardiovascular disease. We ascertained the occurrence of stroke and coronary heart disease through the national mortality and hospital discharge registers. These registers have been validated against individual hospital records. For stroke, there is a 90\% agreement with the national hospital discharge register and 97\% agreement with the death register.\textsuperscript{23} Corresponding figures for coronary heart disease are 94\% and 95\%.\textsuperscript{24} In Finland, 97\% of stroke diagnoses are verified by CT scan, MRI imaging, or necropsy.\textsuperscript{25} We have previously discussed other limitations of the Helsinki Birth Cohort Study, which comprises 13,345 people who were born in one of 2 public hospitals in the city and attended child welfare clinics.\textsuperscript{16} Although the majority of children attended these clinics, which were free, attendance was voluntary. The distribution of social class, as indicated by fathers’ occupations, was similar, however, to that of the city as a whole. Only half of the cohort had antenatal records after 20 weeks of pregnancy and were therefore eligible for the present study. The body size at birth of people with these records was similar to that of people without records. Their mothers tended to be shorter and younger, although these differences were small. More of the mothers were primiparous, and more were married to manual workers. These differences would, however, introduce bias only if the association between hypertensive disorders in pregnancy and offspring cardiovascular disease were different in people who have antenatal records as compared with those who do not. This seems unlikely but cannot be excluded. Our data on body mass indices were based on the mother’s weight in late pregnancy and do not allow us to distinguish fat mass from retained fluid.

We followed up the offspring for 60 to 70 years after their birth. A number of previous studies have shown that low birth weight\textsuperscript{17,26–31} and short duration of gestation\textsuperscript{32} are associated with an increased risk of stroke in later life. We found that people whose mothers had pre-eclampsia were at increased risk of hemorrhagic or thrombotic stroke. This association was independent of the babies’ birth weights or gestational age at birth and therefore does not simply reflect the association between pre-eclampsia and fetal growth restriction or preterm birth. Babies from pregnancies complicated by pre-eclampsia had reduced head circumferences. We speculate that stroke may originate through reduced brain growth in utero as a consequence of fetal undernutrition. People whose mothers had gestational hypertension were also at increased risk of stroke. Although they had low birth weight indicating a degree of fetal undernutrition, they had a large head circumference in relation to their length. This suggests that growth of the brain had been protected at the expense of growth of the trunk. We have previously suggested that redistribution of cardiac output in favor of the brain, one of the fetal brain-sparing responses, may permanently change the structure of the cerebral arteries.\textsuperscript{26} We now speculate that stroke may originate in 2 ways, either through reduced brain growth or impaired brain growth leading to “brain sparing” responses. Obviously, these suggestions cannot be proved in a birth cohort study but remain to be tested in experimental settings.

In the mother, pre-eclampsia may more clearly be viewed as an early manifestation of an adverse phenotype that leads to cardiovascular disease.\textsuperscript{33,34} This phenotype may in part originate through slow growth in utero because women who had low birth weight are at increased risk of pre-eclampsia,\textsuperscript{15,35} hypertension,\textsuperscript{18} coronary heart disease,\textsuperscript{16,17} and stroke.\textsuperscript{17} This phenotype is associated with impaired implantation.\textsuperscript{19} This initiates pre-eclampsia in the mother and leads to impaired placentation and reduced nutrition in the fetus.

We found that children from pregnancies complicated by severe pre-eclampsia were thin at age 2 years. This is consistent with the reported association between thinness at 2 years of age and later hemorrhagic and thrombotic stroke.\textsuperscript{17} This association was not the result of the children’s living conditions after birth as assessed by the father’s occupation. This led to the suggestion that the association was a consequence of fetal undernutrition leading to thinness at birth that persisted through infancy.\textsuperscript{17} The association between severe pre-eclampsia and thinness at 2 years of age is in agreement with this.

Although we were unable to find evidence of an association between pre-eclampsia and coronary heart disease in the offspring, the point estimates of the relative risk were increased and the CIs did not overlap the null value by a lot. Hence, a small increase in the risk of coronary heart disease is possible, but to confirm it requires a larger study. The associations with stroke were much stronger. This suggests that pre-eclampsia is linked to a local disorder of the blood vessels of the brain rather than, or in addition to, a general vascular lesion. Both pre-eclampsia and gestational hypertension were also associated with hypertension, the major risk factor for hemorrhagic and thrombotic stroke, in the offspring. This is consistent with the observation that the offspring from pregnancies complicated by pre-eclampsia have raised blood pressures during childhood and adolescence.\textsuperscript{10–12}

In conclusion, we have found that people born after pregnancies complicated by pre-eclampsia or gestational...
hypertension are at increased risk of stroke in adult life. We speculate that the underlying processes may include local disorders of the blood vessels of the brain as a consequence of either reduced brain growth or impaired brain growth leading to “brain-sparing” responses.

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Disclosures
None.

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