OBJECTIVE: Knowledge about the causes of placental dysfunction disorders is limited. We performed an intergenerational study, focusing on the risks of placental dysfunction disorders in mothers and fathers who had been born small for gestational age (SGA).

STUDY DESIGN: Using linked generational data from the Swedish Medical Birth Register from 1973-2006, we identified 321,383 mother-offspring units and 135,637 mother-father-offspring units.

RESULTS: Compared with mothers who had not been born SGA, mothers who had been born SGA had the following adjusted odds ratios: late preeclampsia, 1.41 (95% confidence interval [CI], 1.26–1.57); early preeclampsia, 1.87 (95% CI, 1.38–2.35); placental abruption, 1.60 (95% CI, 1.23–2.09); spontaneous preterm birth, 1.11 (95% CI, 1.00-1.23); and stillbirth, 1.24 (95% CI, 0.84–1.82). Compared with parents who had not been born SGA, the risk of preeclampsia was more than 3-fold increased if both parents had been born SGA, whereas if only the mother had been born SGA, the corresponding risk was increased by only 50%.

CONCLUSION: There is an intergenerational recurrence of placental dysfunction disorders on the maternal side and most likely also on the paternal side.

Key words: intergeneration, placental abruption, preeclampsia, small for gestational age, stillbirth


Abnormal placentation is associated with the birth of a small-for-gestational-age (SGA) infant, preeclampsia, placental abruption, spontaneous preterm birth, and stillbirth.1-5 Each outcome has a recurrence risk in successive births to the same woman, and there are recent reports that these adverse outcomes predispose to each other.6-10 The underlying reason for this may be that abnormal placentalization also tends to recur in subsequent pregnancies.

Recurrence of adverse pregnancy outcomes across generations has not been extensively investigated. There are studies that support the fact that women or men who had been born SGA, born preterm, or born in pregnancies that were affected by preeclampsia are at increased risks of the corresponding complication when she or his partner get pregnant.11-16 There are also a few studies that suggest that disorders that are associated with abnormal placentation may predispose to each other through generations, at least from mother to daughter, with increased risks of preterm birth and preeclampsia in mothers who had been born SGA.13,17,18

Intergenerational studies may increase our knowledge about the causes of placental dysfunction disorders and their potential correlations. Associations that occur across generations may reflect a family lifestyle or shared genetic causes. Fetal genes, which are inherited from both the mother and father, may be of importance for successful placentation.19,20 A genetic predisposition for placental dysfunction disorders may be of further interest, because placental dysfunction disorders have been associated with mother and offspring risks of cardiovascular diseases; genetic factors could be underlying these associations.21

Knowledge concerning recurrence of placental dysfunction disorders across generations is limited. Previous studies have investigated only specific single outcomes and assessed recurrence in either mother and offspring or father and offspring.11-18,22 Information on both parents’ birth characteristics in the same analysis might provide new knowledge concerning the maternal and paternal genetic contribution to the cause of placental dysfunction disorders.
To test our hypothesis that placental dysfunction disorders are inherited across generations, we performed a population-based study that included 324,383 mother-offspring units and investigated associations between mothers who had been born SGA and risks of early and late pre-eclampsia, placental abruption, spontaneous preterm birth, and stillbirth. To further explore the maternal and paternal influence on placental dysfunction disorders, we created 135,637 mother-father-offspring units and estimated the effect of mother, father, or both parents being born SGA on the risks of pre-eclampsia, placental abruption, and spontaneous preterm birth.

MATERIALS AND METHODS
The Swedish National Board of Health and Welfare gave access to information from the Swedish Medical Birth Register; Statistics Sweden provided data from the Multi-Generation Register and the Education Register. Individual record linkage between the registries was possible through each individual’s unique personal registration number, which is assigned to Swedish residents at birth or immigration.23 The Swedish Medical Birth Register contains data on >98% of all births in Sweden since 1973 and includes demographic data, information on reproductive history and complications during pregnancy, delivery, and the neonatal period.24 In Sweden, antenatal care is standardized and free of charge. During the first antenatal visit, usually taking place at the end of the first trimester, the mother is interviewed about her medical and obstetric history, including height, weight, and smoking habits.25 Complications during pregnancy and delivery are classified according to the International Classification of Diseases (ICD), as noted by the responsible doctor at discharge from hospital. Information on each pregnancy and delivery is forwarded to the Birth Register through copies of standardized antenatal, obstetric, and pediatric records.

Study population and parental exposures at birth
By means of the personal registration number, we identified women who had been born in 1973 and later who were included in the Birth Register both as infants and mothers. From data recorded from 1973-2006, we identified a cohort of 326,547 births, with data also on births of the mothers (mother-offspring units). Only single births in both generations were included.

Mothers were classified as being born SGA or not. SGA was defined as a birthweight of 2 SDs or more below the mean birthweight for gestational age according to the sex-specific Swedish fetal growth curve.26 Gestational age at birth of the mothers was calculated from the last menstrual period. We defined births with a birthweight for gestational age ≥5 SDs above or below the mean for a given gestational age as being misclassified. We excluded 2164 births in which the mother’s birthweight and/or gestational age were missing or misclassified.

The fathers were identified through linkage of the Birth Register to the Multi-Generation Register. If the fathers had been born in Sweden in 1973 or later, we obtained information on their births from the Birth Register. The fathers were classified as being born SGA or not in the same way as the mothers. Fathers to stillborn infants could not be identified in the Multi-Generation Register; therefore, analyses within the mother-father-offspring cohort were restricted to live births.

To assess the parental influence on risks of adverse pregnancy outcomes that are associated with abnormal placentation, we established a mother-offspring cohort and a mother-father-offspring cohort. The mother-offspring units (n = 324,383) were categorized into births with a mother who was born SGA (n = 12,237) or not born SGA (n = 312,146). The mother-father-offspring units (n = 135,637) were categorized into 4 groups: births with no parent who was born SGA (n = 126,326); births with a mother, but not a father, who was born SGA (n = 4885); births with a father, but not a mother, who was born SGA (n = 4240); and births with both parents who had been born SGA (n = 186).

We used the ICD-8 and -9 revisions to identify complications during pregnancy and delivery when the mothers and fathers had been born. Preeclampsia was defined as ICD-8 code 637 and ICD-9 codes 642E-G; placental abruption was defined by ICD-8 code 641.4 and ICD-9 code 641C. In the mother-offspring cohort, we identified 3128 mothers who had been born in pregnancies complicated by preeclampsia and 1085 mothers who had been born after placental abruption. In the mother-father-offspring cohort, we identified 1345 mothers and 1244 fathers who had been born in pregnancies that were complicated by preeclampsia and 482 mothers and 427 fathers who had been born in pregnancies that were complicated by placental abruption. We did not have information on onset of delivery in births before 1990 and were not able to identify spontaneously preterm-born mothers and fathers. Therefore, among the mothers and fathers, preterm births (<37 gestational weeks) included births with both spontaneous and induced onsets of delivery. In the mother-offspring cohort, we identified 13,166 preterm-born mothers; in the mother-father-offspring cohort, there were 6382 and 5481 preterm-born mothers and fathers, respectively.

Exposures at offspring birth
From the data that were collected at the first antenatal visit, we used information about the mother’s height, prepregnancy weight, and smoking habits. We calculated the mother’s body mass index (BMI) as the weight in kilograms divided by the square of height in meters. Information about maternal age and parity was collected at delivery. Information on maternal diseases included chronic hypertension (ICD-9 codes 642A-C, 642H; ICD-10 codes O10-11) and pregnancy-induced diabetes mellitus (ICD-9 codes 250, 648A; ICD-10 codes O24-O43). Information on the mother’s education was obtained by linkage with the Education Register as of December 31, 2005. Variables were categorized according to Table 1.

Outcomes
Using the mother-offspring and mother-father-offspring cohorts, we studied whether being born SGA influenced preg-
### TABLE 1

Rates of the adverse pregnancy outcomes

<table>
<thead>
<tr>
<th>Maternal characteristics</th>
<th>n</th>
<th>Preeclampsia (n = 11,631)</th>
<th>Placental abruption (n = 1281)</th>
<th>Spontaneous preterm birth* (n = 14,779)</th>
<th>Stillbirth* (n = 795)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤24</td>
<td>122,974</td>
<td>41.1</td>
<td>4.0</td>
<td>50.0</td>
<td>2.6</td>
</tr>
<tr>
<td>25-29</td>
<td>148,841</td>
<td>33.6</td>
<td>4.0</td>
<td>44.9</td>
<td>2.3</td>
</tr>
<tr>
<td>≥30</td>
<td>52,568</td>
<td>29.8</td>
<td>3.6</td>
<td>41.8</td>
<td>2.4</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤19</td>
<td>32,401</td>
<td>21.2</td>
<td>4.2</td>
<td>51.6</td>
<td>1.9</td>
</tr>
<tr>
<td>20-24</td>
<td>151,812</td>
<td>28.2</td>
<td>3.9</td>
<td>43.4</td>
<td>2.1</td>
</tr>
<tr>
<td>≥25</td>
<td>98,654</td>
<td>51.2</td>
<td>3.6</td>
<td>43.6</td>
<td>3.5</td>
</tr>
<tr>
<td>Missing</td>
<td>41,516</td>
<td>38.9</td>
<td>4.8</td>
<td>59.1</td>
<td>1.8</td>
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<td>Height, cm</td>
<td></td>
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<td>≤163</td>
<td>89,537</td>
<td>38.3</td>
<td>4.4</td>
<td>52.9</td>
<td>2.9</td>
</tr>
<tr>
<td>164-172</td>
<td>160,472</td>
<td>34.7</td>
<td>3.6</td>
<td>42.7</td>
<td>2.5</td>
</tr>
<tr>
<td>≥173</td>
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<td>3.7</td>
<td>36.7</td>
<td>2.3</td>
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<td>38.8</td>
<td>5.1</td>
<td>70.0</td>
<td>1.0</td>
</tr>
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<td>Parity</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>1</td>
<td>198,013</td>
<td>46.5</td>
<td>3.8</td>
<td>49.8</td>
<td>3.3</td>
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<tr>
<td>≥2</td>
<td>126,370</td>
<td>19.3</td>
<td>4.2</td>
<td>40.9</td>
<td>1.2</td>
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<td>Smoking habits</td>
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<td></td>
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<tr>
<td>Nonsmoker</td>
<td>260,587</td>
<td>37.4</td>
<td>3.4</td>
<td>43.6</td>
<td>2.3</td>
</tr>
<tr>
<td>Daily smoker</td>
<td>43,792</td>
<td>25.9</td>
<td>6.6</td>
<td>52.2</td>
<td>3.9</td>
</tr>
<tr>
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<td>5.3</td>
<td>69.1</td>
<td>1.6</td>
</tr>
<tr>
<td>Education, y</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤12</td>
<td>215,242</td>
<td>37.4</td>
<td>4.1</td>
<td>46.7</td>
<td>2.3</td>
</tr>
<tr>
<td>≥13</td>
<td>107,600</td>
<td>32.9</td>
<td>3.5</td>
<td>45.2</td>
<td>1.6</td>
</tr>
<tr>
<td>Missing</td>
<td>1541</td>
<td>24.5</td>
<td>9.7</td>
<td>61.1</td>
<td>92.5</td>
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<tr>
<td>Chronic hypertension</td>
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<tr>
<td>Yes</td>
<td>1301</td>
<td>154.5</td>
<td>8.5</td>
<td>42.2</td>
<td>5.4</td>
</tr>
<tr>
<td>No</td>
<td>323,082</td>
<td>35.4</td>
<td>3.9</td>
<td>46.3</td>
<td>2.4</td>
</tr>
<tr>
<td>Pregestational diabetes mellitus</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1929</td>
<td>146.2</td>
<td>9.8</td>
<td>105.2</td>
<td>9.4</td>
</tr>
<tr>
<td>No</td>
<td>322,454</td>
<td>35.2</td>
<td>3.9</td>
<td>46.0</td>
<td>2.4</td>
</tr>
<tr>
<td>Year of birth</td>
<td></td>
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<tr>
<td>1987-1996</td>
<td>24,407</td>
<td>43.6</td>
<td>4.8</td>
<td>57.1</td>
<td>2.3</td>
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<tr>
<td>1997-2001</td>
<td>84,630</td>
<td>39.2</td>
<td>4.2</td>
<td>46.4</td>
<td>2.7</td>
</tr>
<tr>
<td>2002-2006</td>
<td>215,346</td>
<td>33.7</td>
<td>3.7</td>
<td>45.1</td>
<td>2.4</td>
</tr>
<tr>
<td>Total no/rates</td>
<td>324,383</td>
<td>35.9</td>
<td>3.9</td>
<td>46.3</td>
<td>2.5</td>
</tr>
</tbody>
</table>

* Only live births were included; 4416 births were excluded because of missing data on start of delivery or gestational length at birth; ** Only births in gestational week ≥28 were included (n = 323,589).

nancy and birth outcomes in the next generation. We included preeclampsia, placental abruption, and spontaneous preterm birth as pregnancy and birth outcomes. In the mother-offspring units, we also studied stillbirth.

Preeclampsia in offspring pregnancies was identified by the ICD-9 codes 642E-G and ICD-10 codes O14 and O15. In Sweden, preeclampsia is defined as a blood pressure above 140/90 mm Hg combined with proteinuria (>0.3 g/24 h) that occurs at >20 weeks of gestation. In the mother-offspring cohort, preeclampsia was categorized into early preeclampsia, which included women with preeclampsia who gave birth at <34 gestational weeks, and late preeclampsia, which included women with preeclampsia who gave birth at ≥34 gestational weeks. The onset of disease is not recorded in the birth register. In the analyses of early and late preeclampsia, we excluded 1003 births with missing data on gestational length (50 women had preeclampsia). Gestational age, since the early 1990s, has been assessed by ultrasound scans in 95% of women, usually at approximately week 17 of gestation.7 If no early second-trimester ultrasound scan was available, the last menstrual period was used to calculate gestational age at delivery. Placental abruption was identified by ICD-9 code 641C and ICD-10 code O45.

We included all live births at <37 weeks of gestation that were recorded in the Birth Register with a spontaneous onset of labor and all preterm births with a diagnosis of premature rupture of the membranes (ICD-9 code 658B and ICD-10 code O42). From this analysis, we excluded births without information on the onset of birth or gestational length at birth (n = 4416). Stillbirth was defined as a fetal death that occurred at ≥28 weeks of gestation.

Statistical analyses
SAS PROC GENMOD software (SAS Institute, Cary, NC) was used to estimate the risks of early and late preeclampsia, placental abruption, spontaneous preterm birth, and stillbirth in pregnancies in which the mother had been born SGA; mothers who had not been born SGA were the reference. Risks were calculated as odds ratios by unconditional logistic regression analysis and are presented with 95% CIs before and after adjustments for maternal age, early pregnancy BMI, smoking, maternal height, parity, mother’s formal education, year of birth, and presence of chronic hypertension or pregestational diabetes mellitus. There is a tendency to repeat outcomes across generations,11-16 and our outcomes are also more common in SGA pregnancies.5,28-30 We wanted to isolate associations between being born SGA and risks of other placental dysfunction disorders in offspring pregnancies from the risk of repeating a specific placental dysfunction disorder across generations. In analysis of each outcome, we therefore excluded births in which the mother or father was born in a pregnancy that had been complicated by the outcome under study. Thus, when estimating risks of early and late preeclampsia, we excluded pregnancies in which the mother or father was exposed prenatally to preeclampsia. Likewise, in the analyses of placental abruption, we excluded pregnancies in which the mother or father was exposed prenatally to placental abruption; in the study of spontaneous preterm birth, we excluded pregnancies to mothers or fathers who had been born preterm.

In mother-father-offspring units, we estimated the risks of preeclampsia, placental abruption, and spontaneous preterm birth. We used births in which none of the parents had been born SGA as reference and calculated risks in births with a mother (but not a father) who had been born SGA, a father (but not a mother) who had been born SGA, and both the mother and father had been born SGA. As for the mother-infant cohort, we excluded births in which one of the parents had been born in a pregnancy that was complicated by the estimated complication. All analyses were performed using the Statistical Analysis Software (version 9.1; SAS Institute, Inc).

Ethics committee approval
The study was approved by one of the Regional Ethical Review Boards at Karolinska Institutet, Stockholm.

Results
Table 1 presents associations between maternal characteristics and rates of preeclampsia, placental abruption, spontaneous preterm birth, and stillbirth in the mother-offspring cohort. The rates of all adverse outcomes decreased with maternal age, height, and years of formal education. The oldest mothers in the cohort were 33 years. Mothers with the lowest BMI had the highest rates of placental abruption and spontaneous preterm birth, whereas mothers with the highest BMI had the highest rates of preeclampsia and stillbirth. Primiparous women had, except for placental abruption, higher rates of all adverse outcomes than did multiparous women. Smoking during pregnancy increased the rates of all outcomes, except preeclampsia, where the rate decreased. Women with chronic hypertension had 2-4 times higher rates of all adverse outcomes, except for spontaneous preterm birth. Pregestational diabetes mellitus had a strong positive association with the adverse outcomes, especially preeclampsia and stillbirth. With the exception of stillbirth, the adverse outcomes were slightly more common during the first years of follow up.

Table 2 shows risks of adverse outcomes that were associated with abnormal placentation in mothers who had been born SGA. Compared with mothers who had not been born SGA, mothers who had been born SGA had a higher risk of preeclampsia, especially early preeclampsia. Mothers who had been born SGA also had a 60% increased risk of placental abruption, but essentially no increased risk of spontaneous preterm birth. The risk of stillbirth in mothers who had been born SGA did not reach statistical significance in the adjusted analysis.

Table 3 shows risks of adverse outcomes in births in which one or both of the parents had been born SGA, compared with pregnancies in which none of the parents had been born SGA. Compared with pregnancies to parents who had not been born SGA, the risk of preeclampsia was increased 1.5-fold in pregnancies in which only the mothers had been born SGA, but not significantly in-
creased when only the father had been born SGA. If both parents had been born SGA, the risk of the development of pre-eclampsia was increased >3-fold. The increased risks of placental abruption in pregnancies in which 1 or both parents had been born SGA were not statistically significant. However, there was a tendency for a slightly increased risk of placental abruption if one parent had been born SGA and a further increase if both parents had been born SGA. The risks of spontaneous preterm birth were not affected in pregnancies in which the mother or both parents had been born SGA, whereas the risk was slightly decreased when the father had been born SGA.

**Comment**

In this large nation-wide study, women who had been born SGA were found to have increased risks of preeclampsia, placental abruption, and stillbirth. If the father also had been born SGA, the risk of preeclampsia, and possibly also the risk of placental abruption, was further increased. These findings support our hypothesis of a hereditary trait in placental dysfunction disorders mainly channelled through the mother but possibly also through the father. Considering the modest risk increases, our findings might have greater implications for the understanding of the pathophysiologic finding of placental dysfunction disorders rather than for clinical practice.

The finding of an association between mothers who had been SGA and development of preeclampsia is in agreement with 2 earlier studies. In a previous study from the Swedish Birth Register, an association between mothers who had been born SGA and preeclampsia was found in primiparous women; however, after adjustment for occurrence of preeclampsia in the pregnancy in which the mother had been born, the association remained only for severe preeclampsia. In a study from the Norwegian Birth Register, mothers who had been born SGA after a nonpreeclamptic pregnancy had a higher risk of especially early preeclampsia. Our results confirm these earlier findings of a stronger association between placental dysfunction and early, but not late, preeclampsia. In accordance with the findings in the Norwegian study, we found no significantly increased risk of preeclampsia when only the father had been born SGA. On the other hand, we found a substantially higher risk of preeclampsia in pregnancies when both the mother and father had been born SGA than in pregnancies in which only the mother had been born.

**Table 2**

Risks based on mothers who had/had not been born SGA

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Mothers not born SGA (n = 312,146)</th>
<th>Mothers born SGA (n = 12,237)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Rate per 1000</td>
<td>ORb</td>
</tr>
<tr>
<td>Early preeclampsia (&lt;34 wks)</td>
<td>3.0</td>
<td>1.00</td>
</tr>
<tr>
<td>Late preeclampsia (&gt;34 wks)</td>
<td>36.8</td>
<td>1.00</td>
</tr>
<tr>
<td>Placental abruption</td>
<td>3.8</td>
<td>1.00</td>
</tr>
<tr>
<td>Spontaneous preterm birth&lt;36 wks</td>
<td>36.7</td>
<td>1.00</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>2.4</td>
<td>1.00</td>
</tr>
</tbody>
</table>

CI, confidence interval; OR, odds ratio; SGA, small for gestational age.

*Defined as birthweight for gestational age ≤–2 SDs below the sex-specific Swedish fetal growth curve; Reference; Adjusted for maternal age, body mass index, height, parity, smoking habit, year of formal education, year of birth, and presence of chronic hypertension or pregestational diabetes mellitus; Only live births were included; Only births at 26 gestational weeks or later were included.

SGA. These results extend earlier findings and indicate a common hereditary predisposing paternal component to both preeclampsia and SGA.

To our knowledge, this is the first study of recurrence of placental dysfunction across generations with placental abruption as outcome. In the mother-offspring cohort, there was a clearly increased risk of placental abruption if the mother had been born SGA. In the mother-father-offspring cohort, possibly due to the smaller sample size, we could not find any significant associations between one or both parents who had been born SGA and placental abruption. Still, we think that the findings in the mother-father-offspring cohort show interesting trends, with a 35% higher risk of placental abruption if one parent had been born SGA and a 3-fold higher risk if both parents had been born SGA.

We could not find an association between mothers who had been born SGA and a risk of spontaneous preterm birth in the offspring; we found a negative association between fathers who had been born SGA and spontaneous preterm birth. Environmental etiologic factors for preterm birth include infections and possibly uterine distension. Fathers who had been born SGA have increased risk of fathering infants who will be born SGA. The risk of preterm birth seems to increase with paternal birth size, which could explain the protective effect on spontaneous preterm birth of fathers who had been born SGA. We believe that our findings question that spontaneous preterm birth should be regarded as a placental dysfunction disorder.

We also found a slightly, though not statistically significant, increased risk of stillbirth in mothers who had been born SGA. Mothers with an SGA birth in first delivery have an increased risk of stillbirth in the subsequent delivery, which is more pronounced if the SGA birth is preterm. These findings are consistent with the hypothesis that placental dysfunction disorders may be inherited on the maternal side. We lack information on fathers of stillborn infants and therefore could not estimate a possible effect of the father’s birth size on stillbirth risk.

In normal placentation, cytotrophoblasts invade and remodel the spiral arteries to increase the capacity of the uteroplacental circulation. Successful placentation depends on the correct balance of the maternal response of the fetal trophoblasts. Both mothers and fathers pass genes to the fetus, but the maternal response is dependent only on the mother. The maternal predisposition to abnormal placentation may be complex. An adverse maternal response could be a consequence of being born SGA. During the 1990s, the hypothesis of developmental origins of adult health and disease was proposed. This hypothesis states that undernutrition during fetal life may cause permanent damage and lead not only to risks of pregnancy complications but also to increased risks of the development of cardiovascular disease, diabetes mellitus, and hypertension later in life. Children who are born SGA are reported to have impaired endothelial function already at 9 years of age, and the endothelial dysfunction may predispose them to the development of placental dysfunction when they get pregnant.

However, our findings are also consistent with the hypothesis of shared genetic and/or lifestyle factors that predispose the mothers for placental dysfunction disorders and can be passed on to the offspring. Thus, not only genetic but also environmental factors that are shared between generations are possible explanations for intergenerational recurrence of abnormal placentation. Today there is a consensus that women whose pregnancies have been complicated by placental dysfunction disorders are also at increased risks of cardiovascular disease later in life. These increased risks could be attributed not only to factors that originate in pregnancy but also to some common preexisting genetic or environmental factors that predispose to the development of both placental dysfunction disorders and cardiovascular disease. The latter is supported by findings that prepregnancy risk factors for cardiovascular disease in mothers are predisposing to preeclampsia and that adjustments for prepregnancy measurements largely attenuated the differences in cardiovascular risk measurements postpartum between women who have had a preeclamptic pregnancy and those who had not. Potential genetic factors could be associated with thrombophilia or impaired angiogenesis, both of which predispose to placental dysfunction disorders and to cardiovascular diseases.

Fathers can transmit risk of placental dysfunction disorders to the next generation through genetic factors. Normal placentation depends on the correct balance of the maternal response of the fetal trophoblasts; placentation is supposed to be successful if the paternal human lymphocyte antigen–C that is expressed by trophoblasts strongly stimulates the uterine (maternal) immunologic cells. We found no increased risks of preeclampsia in pregnancies fathered by a man who had been born SGA. However, if a man who had been born SGA fathered a pregnancy of a woman also had been born SGA, the preeclampsia risk was substantially higher than if only the mother had been born SGA. This latter finding indicates that there is a paternal genetic component that influences the risk of placental dysfunction. Fetal genes are considered important both for the familial aggregation of preeclampsia and SGA. A possible explanation for the lack of a shown increase in the risk of placental dysfunction in pregnancies when fathers, but not mothers, had been born SGA could be that a maternal predisposition is necessary to the development of abnormal placentation, and, if present, a paternal genetic component has a high penetration. If only the fathers had been born SGA, this paternal genetic risk may have a lower penetration, and a larger cohort of father-offspring units may be needed to detect an increased risk of, for example, preeclampsia.

The strengths and limitations of the present study are constituted in the registry-based study design. The study was nationwide, and data were collected prospectively, which precludes recall biases. However, in a generation study, there is selection by design, because only women and men who are able to reproduce can be included. Another limitation is the fact that we were unable to include mothers and fathers who were >33 years.
old, because the Birth Register started in 1973 and our last year of follow-up evaluation was 2006. This had an impact especially on the numbers in the mother-father-offspring cohort, because most men start to reproduce later than women. High maternal age, and possibly also high paternal age, is associated commonly with increased risks of several adverse pregnancy and birth outcomes, which include preeclampsia, placental abruption, and stillbirth.\textsuperscript{45,46} We therefore believe that the age restriction in our study, if anything, may tend to underestimate our findings. However, our findings are not necessarily exportable to women in older age groups. One major strength of the study was that we had information on adverse outcomes in the pregnancies in which the mothers and fathers had been born, which allowed us to exclude recurrent pregnancy complications of the same type across generations. In this way, we could study the associations between being born SGA and the different outcomes separately from the recurrence risk of a complication in the next generation. In contrast to most previous intergenerational investigations,\textsuperscript{14,17,22} we were able to control for a number of possible confounders, such as BMI and smoking. However, an effect of unmeasured environmental confounding factors cannot be excluded.

In conclusion, we found an association between mothers and fathers who had been born SGA and the risks of placental dysfunction disorders in the next generation. These findings support a related cause of these disorders and the fact that genetic components are involved.

REFERENCES