Original Contribution

Maternal Effects for Preterm Birth: A Genetic Epidemiologic Study of 630,000 Families

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This study was undertaken to disentangle the maternal genetic from the fetal genetic effects for preterm birth and to study the possibility of these effects being explained by known risk factors. By cross-linking of the population-based Swedish Multigeneration and Medical Birth registers, 989,027 births between 1992 and 2004 were identified. Alternating logistic regression was applied to model the familial clustering with pairwise odds ratios (PORs), and covariates were included to evaluate if the familial aggregation was explained by exposure to shared risk factors. Generalized linear mixed models were used to estimate the contribution of genetic and environmental effects. Sisters of women who had a preterm delivery had themselves an increased odds of having a preterm delivery (POR = 1.8, 95% confidence interval: 1.5, 2.1), while there was no corresponding increase in odds in families joined by brothers (POR = 1.1, 95% confidence interval: 0.9, 1.4). Twenty-five percent of the variation in preterm birth was explained by maternal genetic factors, whereas fetal genetic factors only marginally influenced the variation in liability. The increased odds ratio between offspring of sisters was independent of maternal risk factors for preterm birth, suggesting that the relative importance of maternal effects is not explained by these well-known risk factors.

components of variance; family; logistic regression; mixed linear model; premature birth; risk factors

Abbreviations: CI, confidence interval; POR, pairwise odds ratio.

Editor's note: Related articles appear on pages 1358 and 1373, an invited commentary on the 3 articles is published on page 1382, and a response by Svensson et al. to the commentary is on page 1386. In accordance with Journal policy, the authors of the first and third articles were asked whether they wanted to respond to the commentary but chose not to do so.

Preterm birth represents a major source of neonatal and infant morbidity and mortality and has long-term consequences also for diseases in adulthood (1–3). There is a familial aggregation of preterm birth (4–11), and twin (12, 13) and family (14) studies provide evidence that at least part of this familiality is due to genetic effects. In a Norwegian study of gestational age (rather than preterm birth), Lunde et al. (15) found that fetal genes explained 11% of the variance, whereas maternal genes explained an additional 14%. Whether fetal effects are of importance for preterm birth is not known.

Further, it is unclear how the familial effects for preterm birth are mediated. Early onset preeclampsia, a common reason for induced preterm birth, is a potential genetic contributor to preterm delivery (16). Several sociodemographic risk factors, such as ethnicity, teenage or older mothers, low socioeconomic status, cigarette smoking, and not living with a partner (17, 18), have been identified, and they are all likely candidates for mediating the familial effects.

To disentangle the maternal genetic from the fetal genetic effects for preterm birth and to study the possibility of these effects being explained by known risk factors, we have analyzed a large sample of siblings and their offspring using...
a register linkage between the population-based Swedish Multigeneration and Medical Birth registers.

MATERIALS AND METHODS

Data sources

The Swedish Multigeneration Register includes children (index persons) born since 1932, linked to their parents. The register comprises 9 million children and 11 million unique individuals (19). The same individual can exist in the register both as a child and later as a parent.

Since 1973, data on all births in Sweden are recorded in the Medical Birth Register. By the end of 2004, there were 2.9 million births recorded, covering more than 99% of the births in Sweden (20).

We linked the registers, using the unique national registration number. The linkage identified 989,027 singleton live offspring to siblings who gave birth in Sweden between 1992 and 2004. The choice of birth cohort was decided by the availability of baseline data, for instance, prepregnancy weight included in 1992.

Study populations

In the analysis of familial aggregation, births with missing data on any of the covariates (n = 316,679) and births above second order (n = 135,711) were excluded. Thus, the final data set comprised 536,637 births.

In the evaluation of the genetic and environmental effects, we analyzed a cohort of parents of at least 2 offspring born from 1992 onward. There was a total of 93,087 sibling pairs (24,398 sister pairs, 23,701 brother pairs, and 44,988 brother-sister pairs). All analyses were limited to pregnancies where both the parents and at least 1 pair of the grandparents could be identified (Figure 1).

Measures

Preterm birth. Preterm delivery was defined as live birth at less than 37 completed weeks of gestation. When available, ultrasound performed during the second trimester was used to estimate gestational age; otherwise, gestational age was estimated from the date of the last menstrual period. Since 1990, routine ultrasound screening no later than at 18 weeks of gestation has been offered to all pregnant women in Sweden, and more than 95% accept this offer (21). Previous investigations have demonstrated that data on gestational age are accurately recorded in the Birth Register (22).

Information about onset of delivery is routinely recorded in a standardized manner in the obstetric record by the midwife at the delivery ward and is categorized into spontaneous onset, induced vaginal onset, and cesarean delivery before the onset of labor (20). In this study, onset of delivery was dichotomized into spontaneous and induced onset.

Maternal risk factors. Maternal age was defined as completed years at the time of delivery. At the first visit for antenatal care, the woman was classified as to whether or not she was born in a Nordic country (Sweden, Norway, Denmark, Iceland, and Finland), was a daily smoker, and was living with the infant’s father, and self-reported records were taken of height (centimeters) and prepregnancy weight (kilograms). Body mass index was calculated as weight (kg)/height (m)² (23). Information about highest achieved maternal education completed by 2004 was obtained through linkage to the Education Register, and information about the mother’s country of birth was retrieved from the Total Population Register (24). We also retrieved information about maternal hypertension, including gestational hypertension, preeclampsia, or eclampsia recorded according to the International Classification of Diseases, Ninth Revision (codes 642 E–G) or Tenth Revision (codes O14–15), diagnosed by the obstetrician at the time of discharge from the hospital. Variables were categorized as shown in Table 2.
Statistical analyses

Familial aggregation. The familial aggregation of preterm birth was analyzed with alternating logistic regression (25). An alternating logistic regression model consists of 2 parts: 1 model for the population mean where the effect of covariates on preterm birth is estimated (corresponding to a standard logistic regression model) and 1 model for the clustering (i.e., the association between and within the pairs of subjects analyzed). Alternating logistic regressions model the clustering with pairwise odds ratios (PORs). Because we analyzed the oldest 2 siblings in each family and included a maximum of 2 births per sibling, we have 6 PORs in the model(s): 2 within-sibling PORs and 4 between-sibling PORs (Figure 1). Formally testing the magnitude of the PORs by chi-square tests, we found neither a statistically significant difference between the 2 within-sibling PORs nor a statistically significant difference among the 4 between-sibling PORs. Thus, we could simplify the model structure of the familial associations to 1 POR within each sibling (together with his/her partner) and 1 POR between the siblings, without restricting the model.

As the outcome was measured on the offspring, the POR between offspring of siblings describes the correlations of preterm birth between cousins, and the within-sibling POR describes the correlations of preterm birth between full siblings. Statistically significant differences were assumed when $P < 0.05$ (2 sided). The alternating logistic regression was fitted by use of the SAS/IML and SAS, version 9.2, GENMOD procedure (SAS Institute, Inc., Cary, North Carolina). For a more in-depth description of the alternating logistic regression model, refer to Web Appendix 1. (This information is described in the first of 3 supplementary appendixes; each is referred to as “Web Appendix” in the text and is posted on the Journal’s website (http://aje.oxfordjournals.org/).

Mediation of the familial effects. The estimated familial aggregation may be explained by exposure to shared environmental and/or genetic risk factors common to the siblings and/or their offspring. We included different covariates in the mean model of the alternating logistic regression model described above and tested whether the inclusion of the covariates changed the familial risks.

Genetic and environmental effects. To estimate the genetic and environmental effects for preterm birth, we fitted a generalized linear mixed model (26). The model allows the total variance to be separated into maternal ($M$) and fetal ($F$) genetic effects, couple effects ($C$), sibling environment ($S$), and a nonshared environment ($E$) component. The probability ($Pr$) of preterm birth was modeled as follows:

$$Pr(\text{preterm birth}) = \beta_1 I_1 + \beta_2 I_2 + M + F + C + S,$$

where $\beta_1$ and $\beta_2$ are fixed effects associated with preterm birth in primiparous and multiparous women. $I_1$ and $I_2$ are indicators of first and later pregnancies. The random effects $M$, $F$, $C$, and $S$ are assumed normal with mean zero and variances $\sigma^2_m$, $\sigma^2_f$, $\sigma^2_c$, and $\sigma^2_s$, respectively. The expected contributions of genetic and environmental correlations in liability to preterm birth are presented in Table 1.

Mothers can genetically influence the growth of their offspring by genes influencing the intrauterine environment ($M$). In families joined by sisters, similarity in preterm birth may indicate a maternal genetic effect, as the maternal genetic correlation between full sisters is 0.5 (Table 1). Successive pregnancies also provide information on maternal genetic effects, because the maternal genes are constant over pregnancies. Both mothers and fathers affect their offspring’s potential for growth through their genes transmitted to the fetus ($F$). Thus, within all 3 types of sibling pairs, familial aggregation of preterm births may be due to the fetal genes from the mother and the father (the genetic correlation between cousins is 0.125, whereas full siblings have a genetic correlation of 0.5).

The model also identifies couple, sibling, and nonshared environmental components (26). The couple effects reflect conditions caused by the couple that contribute to the within-sibling effect in Figure 1. This effect might be due to external environmental factors, such as nutrition and lifestyle, but it could also be due to interactions between maternal and paternal genes. Information about successive pregnancies in couples (Table 1) is thus used to estimate the couple effect and to improve the precision of the genetic effects. A large sibling environmental effect would indicate that the common childhood and adolescent environments experienced by the siblings are important. The residual effect comprises all other unexplained effects, including effects from the nonshared environment ($E$). These factors do not contribute to the familial clustering; hence, the expected correlation is zero for all relationships (Table 1).

The variance accounted for by fetal genetic effects, maternal genetic effects, couple effects, sibling environment,
The alternating logistic regression model was fitted by use of the statistical software R, version 1.9.1. Interaction between familial effects and maternal covariates. The alternating logistic regression model is very flexible and can be extended. For example, it is possible that specific individuals or groups of individuals may be strongly affected by an exposure (i.e., interaction). In a heterogeneous population mixed with many exposures, this effect may show up only as a very small effect. Calculating PORs among exposed and nonexposed families (e.g., smokers vs. nonsmokers) offers an alternative description of the effect of a covariate. We fitted alternating logistic regression models allowing for different magnitudes of familial clustering for different groups of individuals homogeneous with respect to some exposures. Only 1 covariate at a time was considered, although in theory it is possible to adjust for other covariates, as well as to study change between levels of a covariate.

RESULTS

Table 2 presents the prevalence of preterm birth by maternal factors and the corresponding odds ratios from the mean model (model 1) and the multivariate model (model 2), adjusting for all covariates. In model 2, the odds of preterm birth were statistically significantly increased by primiparity, preeclampsia, height less than 175 cm, body mass index below 18.5 or above 30 kg/m², Nordic country of birth, smoking, age at birth younger than 20 years or 35 years or more, and lower than university studies.

Familial aggregation

Table 3 presents the number of pairs concordant and discordant for preterm birth among the siblings and the correlations expressed as PORs (model 1). Women whose sisters had a preterm birth had a 90% increased odds of giving birth to a preterm offspring (POR = 1.9, 95% confidence interval (CI): 1.6, 2.2) compared with women whose sisters had not had a preterm birth, an increase which could be due to both fetal and maternal genetic effects or environmental influences. However, there were no statistically significant increased odds for brothers and mixed sibling pairs, which suggests that neither fetal genetic effects nor effects from a shared sibling environment influence the risk of preterm birth. As expected, there was a strong tendency for repeated preterm births (Table 3).

Mediation of the familial effects

In Table 3 (model 2), we present the familial risks adjusted for maternal parity, preeclampsia, height, body mass index, country of birth, cohabiting with the infant’s father, smoking, age, and education. Compared with model 1, the fully adjusted model only marginally changed the PORs between siblings (e.g., the crude POR for sisters being 1.9 and the adjusted POR being 1.8). The POR of recurrent preterm birth within a family was only slightly attenuated (from 6.9 to 6.2).

GENETIC AND ENVIRONMENTAL EFFECTS

Twenty-five percent (95% CI: 23, 27) of the variance in preterm birth was explained by maternal genetic effects, 5% (95% CI: 0, 23) by fetal genetic effects, 18% (95% CI: 16, 20) by the environment created by the couple, and 52% (95% CI: 41, 58) by unshared environmental effects. There was no indication of sibling environmental effects.

In additional analyses, the familial effects were estimated separately for spontaneous and induced preterm birth. The prevalence of induced and spontaneous preterm birth was 1.4% and 3.1%, respectively. Spontaneous preterm birth showed a similar pattern of familial effects as when grouping all preterm births; 29% (95% CI: 27, 32) of the variance was explained by maternal genetic effects, while there was no indication of fetal genetic effects. For induced preterm birth, the relative importance of maternal genetic effects was lower, 13% (95% CI: 9, 18), and fetal genetic effects explained 14% (95% CI: 0, 36) of the variance. The environmental effects were essentially unchanged.

DISCUSSION

Our results confirm previous findings that familial factors influence the risk of preterm births (4–11). Sisters of women...
Table 2. Distribution of Preterm Births in Sweden (1992–2004) in Relation to Maternal Risk Factors and Corresponding Odds Ratiosa With 95% Confidence Intervals

<table>
<thead>
<tr>
<th>Maternal Characteristics</th>
<th>Total No. of Births</th>
<th>Preterm Birth</th>
<th>Model 1b</th>
<th>Model 2c</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No.</td>
<td>%</td>
<td>Odds Ratio</td>
<td>95% Confidence Interval</td>
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<tr>
<td>Maternal parity</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Primipara</td>
<td>404,405</td>
<td>24,632</td>
<td>6.1</td>
<td>1.8</td>
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<tr>
<td>Multipara&lt;sup&gt;d&lt;/sup&gt;</td>
<td>584,622</td>
<td>22,556</td>
<td>3.9</td>
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</tr>
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<td>Preeclampsia</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>28,288</td>
<td>6,271</td>
<td>22.2</td>
<td>6.0</td>
</tr>
<tr>
<td>No&lt;sup&gt;d&lt;/sup&gt;</td>
<td>960,794</td>
<td>40,917</td>
<td>4.2</td>
<td>1.0</td>
</tr>
<tr>
<td>Height, cm</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;160</td>
<td>93,269</td>
<td>5,577</td>
<td>6.0</td>
<td>1.7</td>
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<td>160–174</td>
<td>729,148</td>
<td>33,376</td>
<td>5.0</td>
<td>1.3</td>
</tr>
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<td>≥175&lt;sup&gt;e&lt;/sup&gt;</td>
<td>90,414</td>
<td>3,365</td>
<td>3.7</td>
<td>1.0</td>
</tr>
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<td></td>
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<tr>
<td>Body mass index, kg/m&lt;sup&gt;2&lt;/sup&gt;</td>
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<td></td>
<td></td>
<td></td>
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<td>≥30</td>
<td>67,943</td>
<td>3,818</td>
<td>5.6</td>
<td>1.2</td>
</tr>
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<td>25–&lt;30</td>
<td>188,111</td>
<td>8,720</td>
<td>4.6</td>
<td>1.1</td>
</tr>
<tr>
<td>18.5–&lt;25&lt;sup&gt;d&lt;/sup&gt;</td>
<td>560,993</td>
<td>24,856</td>
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<td>&lt;18.5</td>
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<td>1,376</td>
<td>6.4</td>
<td>1.3</td>
</tr>
<tr>
<td>Missing</td>
<td>150,473</td>
<td>8,418</td>
<td>5.6</td>
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<tr>
<td>Country of birth</td>
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<td></td>
</tr>
<tr>
<td>Nordic country</td>
<td>950,406</td>
<td>45,239</td>
<td>4.8</td>
<td>1.1</td>
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<tr>
<td>Outside Nordic country&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>1,935</td>
<td>5.0</td>
<td>1.0</td>
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<td>207</td>
<td>14</td>
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<tr>
<td>Living with father</td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>No</td>
<td>33,332</td>
<td>2,020</td>
<td>6.1</td>
<td>1.1</td>
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<tr>
<td>Yes&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>40,940</td>
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<td>Missing</td>
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<td>4,228</td>
<td>6.7</td>
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<td>Smoking</td>
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<tr>
<td>Yes</td>
<td>132,507</td>
<td>7,770</td>
<td>5.9</td>
<td>1.1</td>
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<tr>
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<td>804,767</td>
<td>35,473</td>
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<td>3,945</td>
<td>7.6</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;20</td>
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<td>858</td>
<td>6.4</td>
<td>1.2</td>
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<tr>
<td>20–24</td>
<td>144,190</td>
<td>7,723</td>
<td>5.4</td>
<td>1.2</td>
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<tr>
<td>25–29</td>
<td>369,356</td>
<td>17,083</td>
<td>4.6</td>
<td>1.1</td>
</tr>
<tr>
<td>30–34&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>14,429</td>
<td>4.4</td>
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<td>≥35</td>
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<td>Education</td>
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<td>≤9 years compulsory</td>
<td>76,073</td>
<td>4,606</td>
<td>6.1</td>
<td>1.2</td>
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<tr>
<td>Upper secondary ≤2 years</td>
<td>281,559</td>
<td>14,343</td>
<td>5.1</td>
<td>1.2</td>
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<td>Upper secondary 3 years</td>
<td>226,857</td>
<td>10,674</td>
<td>4.7</td>
<td>1.1</td>
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<td>University education or postgraduate education&lt;sup&gt;d&lt;/sup&gt;</td>
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<td>17,068</td>
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</tr>
<tr>
<td>Missing</td>
<td>9,520</td>
<td>497</td>
<td>5.2</td>
<td></td>
</tr>
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</table>

<sup>a</sup> Odds ratios were calculated by using alternating logistic regression, adjusting for familial clustering.
<sup>b</sup> Adjustments were made for parity.
<sup>c</sup> Adjustments were made for all the other variables in the table.
<sup>d</sup> Reference category.

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who had a preterm delivery were themselves at increased risk of having a preterm delivery, while there was no corresponding increase in risk in families joined by brothers. We could show that 25% of the variation in preterm birth was explained by maternal genetic factors, whereas fetal genetic factors only marginally influenced the variation in liability. Further, the increase in risk between offspring of sisters was independent of maternal risk factors for preterm birth, suggesting that the effect of maternal genetic effects is not explained by these well-known risk factors.

Consistent with previous reports (6), our report found that a mother whose sister had given birth to a preterm offspring had an 80% increased risk of preterm birth. Similar to a study of inbreeding among the Amish people in Pennsylvania, this study found that preterm delivery was mainly associated with the maternal genotype (14). We estimated that 25% of the variation in preterm births was attributable to maternal genetic effects. This is of the same order of magnitude as the heritability estimates of 27% and 34% from analyses of Australian and Swedish twin data (12, 13), and it also is similar to the 34% heritability of gestational age implied by data from the Netherlands Twin Registry (29).

We found only a weak and statistically nonsignificant indication of preterm birth being inheritable through the father, with an estimate of the fetal genetic effect of 5%. This is lower than the estimated fetal genetic effect of gestational age in 2 register-based Norwegian studies restricted to normal, spontaneous deliveries at term (15, 30). However, it is possible that preterm births are under a different genetic and environmental control than term births. This was highlighted by Lunde et al. (15), who estimated that fetal genetic effects were reduced by 2–3 percentage points when including births from 22 to 34 weeks’ gestation.

Mothers can influence the timing of delivery through the uterine environment, and we hypothesized that preeclampsia or other maternal risk factors would mediate the genetic contribution to preterm delivery. Because of computational challenges, we were unable to include covariates, except for birth order, in our mixed-effects model. Instead, we investigated how sibling risks were affected by adjustment for risk factors. Although the maternal risk factors had an independent effect on preterm birth, the fully adjusted model gave an almost identical pattern of sibling risks as the nonadjusted model. We can only speculate what other effects are mediating the similarity in preterm births between offspring of sisters but not brothers. The uterine environment is regulated by the maternal genotype, and genetic association studies have suggested several functional polymorphisms within immune response genes associated with preterm birth (31–33).

When we investigated interaction effects between risk factors and familial effects, we found that familial risks were stronger among nonsmokers than among smokers. Interestingly, a previous study has described an interaction between maternal smoking and gene polymorphisms (34), where the effect of maternal smoking on preterm birth was significantly increased among women with the high-risk genotypes CYP1A1 and GSTT1.

As already well documented (4–7), our study showed an increased risk for repeated preterm births within couples. In the absence of fetal genetic and shared sibling environmental effects, this indicates influence from the couple environment, and we estimated that the environment created by a couple contributed 18% to the familial clustering. The couple environment includes lifestyle factors, such as smoking and socioeconomic status. However, the tendency for repeated preterm births was only slightly reduced when controlling for maternal smoking and education, suggesting that the effect may be due to other factors. An alternative interpretation is that the couple effect captures the variation due to interaction between maternal and paternal genes (27). Li et al. (35) have demonstrated that transmission of paren tally shared human leukocyte antigen is associated with preterm delivery, providing support for this hypothesis.
There are 2 distinct clinical presentations of preterm birth: spontaneous (onset of labor before or after rupture of membranes) and medically indicated (because of maternal or fetal indications) (36). Little is known about the familial effects of the 2 clinical subtypes, but a study of recurrent spontaneous and medically indicated preterm birth suggested that they may represent similar etiologic entities (7), and most risk factors show homogeneity across spontaneous and medically indicated preterm birth (37). Our results indicate that the genetic effects differ between induced and spontaneous preterm birth. In induced preterm births, fetal genetic effects explained 14% of the variation, whereas the maternal genetic effects were reduced by half. This is in line with previous studies reporting significant fetal genetic effects for both preeclampsia (27) and small-for-gestational-age births (28), 2 important risk factors for preterm birth (38, 39).

To our knowledge, this is the largest study to date that has estimated the relative importance of genes and environmental factors for preterm birth. However, we also note several limitations. Our model cannot distinguish between imprinting and maternal genetic effects (40), although we find it unlikely that imprinting effects would account for a large part of the 25% of the variation in liability estimated in the maternal genetic parameter. Because some covariates were included in the Medical Birth Registry of 1990, the power to estimate interaction effects was limited. Our statistical model for analyzing variance components is still under development, and we were not able to include any covariates (except parity) in the models. Inclusion of covariates will reduce the total variance but, as can be seen from the results from the alternating logistic regression model, this seems to have little effect on the relative proportion of the genetic and environmental effects. Another limitation is that we can only test the parameters we specify. Other specifications of the intergenerational transmission are possible. For example, one hypothesis would be that the social intergenerational transmission to daughters would have been different from that to sons; for example, mothers may impart particular behaviors, such as meal preparation and housekeeping, to their daughters but much less to their sons. This and other hypotheses could in the future be tested with data from the Multigeneration Register (e.g., by including more generations and half-siblings), which offers a multitude of hitherto untapped possibilities.

In conclusion, our results suggest an important role of maternal genes on the risk of preterm birth, which is not affected by well-known risk factors for preterm birth. In contrast, fetal genes explain only a small fraction of the total variation in preterm birth. Fetal genes might be of importance for induced, but not spontaneous, preterm birth. Our results support the use of genetic association studies focusing on the maternal genome and less emphasis on collecting data on paternal and/or fetal genes.

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