

# Papers

## Recurrence of pre-eclampsia across generations: exploring fetal and maternal genetic components in a population based cohort

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### Abstract

**Objectives** To assess the impact on risk of pre-eclampsia of genes that work through the mother, and genes of paternal origin that work through the fetus.

**Design** Population based cohort study.

**Setting** Registry data from Norway.

**Participants** Linked generational data from the medical birth registry of Norway (1967-2003): 438 597 mother-offspring units and 286 945 father-offspring units.

**Main outcome measures** Pre-eclampsia in the second generation.

**Results** The daughters of women who had pre-eclampsia during pregnancy had more than twice the risk of pre-eclampsia themselves (odds ratio 2.2, 95% confidence interval 2.0 to 2.4) compared with other women. Men born after a pregnancy complicated by pre-eclampsia had a moderately increased risk of fathering a pre-eclamptic pregnancy (1.5, 1.3 to 1.7). Sisters of affected men or women, who were themselves born after pregnancies not complicated by pre-eclampsia, also had an increased risk (2.0, 1.7 to 2.3). Women and men born after pre-eclamptic pregnancies were more likely to trigger severe pre-eclampsia in their own (or their partner's) pregnancy (3.0, 2.4 to 3.7, for mothers and 1.9, 1.4 to 2.5, for fathers).

**Conclusions** Maternal genes and fetal genes from either the mother or father may trigger pre-eclampsia. The maternal association is stronger than the fetal association. The familial association predicts more severe pre-eclampsia.

### Introduction

The heritable aspects of pre-eclampsia, which occurs in 3-5% of pregnancies, are complex.<sup>1</sup> The first pattern to be identified was the tendency for the risk of pre-eclampsia to be passed from mother to daughter. Specifically, women who were born after a pregnancy affected by pre-eclampsia are themselves at increased risk of pre-eclampsia in their own pregnancies.<sup>2-4</sup> This risk could reflect at least two genetic pathways: transmission to the daughter of genes that enhance maternal susceptibility to pre-eclampsia, or transmission from the daughter to her fetus of fetal genes that are capable of triggering pre-eclampsia.

Recent studies have shown that an increased risk of pre-eclampsia could also be transmitted through the father. One study showed that men who had fathered a pre-eclamptic pregnancy in one woman had an increased risk of fathering a pre-eclamptic pregnancy in another woman.<sup>5</sup> In another study, men who themselves were born after a pre-eclamptic pregnancy conveyed an increased risk of pre-eclampsia in pregnancies they

subsequently fathered.<sup>6</sup> These findings support the hypothesis that the father's genes can be passed to the fetus and increase the risk of pre-eclampsia.

We explored these two pathways of genetic transmission of risk of pre-eclampsia using linked birth data between family members as recorded in the medical birth registry of Norway.

### Methods

#### Population based generational data

We used data from the medical birth registry of Norway, a population based registry of all births in Norway since 1967 (more than 2.2 million births).<sup>7</sup> Up to 2003, 238 617 women born in Norway in 1967 or later (and therefore registered in the medical birth registry) had given birth to 438 597 singleton infants. Similarly, 158 340 men born in 1967 or later had fathered 286 945 singleton infants. The number of mothers is considerably higher because mothers are generally younger than fathers and 4.4% of fathers were unknown and could not be identified. Fifty eight per cent of the mothers were born during 1967-71 and 89% during 1967-76. For the fathers the figures were 65% and 94%, respectively.

We used these data to study whether women and men who themselves were born after a pregnancy complicated by pre-eclampsia have a higher risk of parenting a pre-eclamptic pregnancy, compared with those who had no family history of pre-eclampsia. We estimated risk related to their first pregnancy or to the second pregnancy if pre-eclampsia had not occurred in the first pregnancy.

We also assessed the risk of pre-eclampsia in any siblings who were born after an unaffected pregnancy to study whether such offspring with a family history of pre-eclampsia could none the less pass on an increased risk to the next generation. We identified families with at least two siblings (male or female) born since 1967 who later became parents. We identified 105 525 pairs of siblings (45.6% of these were first and second births), and then excluded the 185 pairs where both siblings from the first generation were born after a pregnancy complicated by pre-eclampsia.

#### Definition of pre-eclampsia

We included pregnancies with a specified diagnosis of pre-eclampsia and pregnancies with a combination of pregnancy induced hypertension and proteinuria. Obstetric guidelines in Norway define pre-eclampsia as an increase in blood pressure to at least 140/90 mm Hg after the 20th week of gestation.<sup>8,9</sup> Compared with measures before the 20th week, either the diastolic blood pressure has to be at least 15 mm Hg higher or the systolic blood pressure has to be at least 30 mm Hg higher. Proteinuria (protein excretion at least 0.3 g per 24 hours) also

**Table 1** Risk of pregnancy\* affected by pre-eclampsia in women and men† who themselves were born after a pregnancy complicated by pre-eclampsia, Norway, 1967-2003

	Birth order	No of offspring	No (%) of affected pregnancies	Odds ratio (95% CI)‡
<b>Women</b>				
Maternal pre-eclampsia:				
Yes	First	2 768	299 (10.8)	2.2 (1.9 to 2.5)
No	First	91 338	4794 (5.2)	1.0§
Yes	Subsequent	1 977	200 (10.1)	2.1 (1.8 to 2.4)
No	Subsequent	142 288	7261 (5.1)	1.0§
<b>Men</b>				
Maternal pre-eclampsia:				
Yes	First	1 908	146 (7.7)	1.4 (1.2 to 1.7)
No	First	60 137	3274 (5.4)	1.0§
Yes	Subsequent	1 270	101 (8.0)	1.5 (1.2 to 1.8)
No	Subsequent	94 917	5154 (5.4)	1.0§

\*Confined to first pregnancies of women and men.

†For men this is No (%) in their partners.

‡Pooled odds ratios (Mantel-Haenszel): 2.2 (2.0 to 2.4) for women and 1.5 (1.3 to 1.7) for men.

§Reference category.

has to be present. We further divided pre-eclampsia according to gestational age at delivery, as either term (37-42 weeks) or preterm (before 37 weeks) pre-eclampsia.

Since 1999, clinical severity, divided into mild or severe and according to whether clinical signs were evident early (<34 weeks) in pregnancy, has been added to the registration of pre-eclampsia. This information allowed us to explore the main results in greater detail in a subgroup of the population.

### Statistical analysis

For women born after a pre-eclamptic pregnancy, we estimated their own risk of pre-eclampsia in subsequent pregnancies compared with the risk in women who were not born after a pregnancy complicated by pre-eclampsia. We compared the risk of fathering a pre-eclamptic pregnancy in men who were born after a pre-eclamptic pregnancy and men who were not. For sisters and brothers who were born after another pregnancy without pre-eclampsia, we also estimated the risk of pre-eclampsia compared with the risk in women and men with no family history.

We used SPSS for Windows (release 12.0), Stata (version 8), and StatXact (version 6), with logistic regression and multinomial logistic regression analysis to estimate odds ratios and 95% confidence intervals.

## Results

### Pre-eclampsia related to first and second birth

Women who were born after a pre-eclamptic pregnancy had more than twice the risk of having pre-eclampsia in their first pregnancy compared with other women (odds ratio 2.2, 95% confidence interval 2.0 to 2.4, table 1). For men who were born after a pregnancy complicated by pre-eclampsia, the risk of pre-eclampsia in the first pregnancy of their partner was moderately increased compared with men who were born after a pregnancy not complicated by pre-eclampsia (1.5, 1.3 to 1.7, table 1). For both men and women, these associations were remarkably stable, regardless of their own birth order.

We also estimated the familial risk of pre-eclampsia related to the second birth, provided that the first pregnancy was not affected by pre-eclampsia. Although the baseline risk of pre-eclampsia for the second birth was lower than for the first (1.5%), we found that women who themselves were born after a pre-eclamptic pregnancy still had more than twice the risk (2.3, 1.8 to 2.9) of pre-eclampsia related to their second birth

compared with other women (data not shown). The results were similar for men (1.5, 1.1 to 2.1). The combination of both parents having been born after an affected pregnancy did not occur more often than expected so simultaneous estimation, with logistic regression, gave similar odds ratio estimates: 2.1 (2.0 to 2.4) and 1.5 (1.3 to 1.7), respectively.

### Pre-eclampsia in brothers and sisters

Sisters who were not themselves born after a pregnancy complicated by pre-eclampsia were none the less at increased risk of pre-eclampsia compared with women with no family history of pre-eclampsia (2.0, 1.7 to 2.3, table 2). For brothers not themselves born after a pre-eclamptic pregnancy, the risk of fathering a pre-eclamptic pregnancy was similar to that in men with no family history (1.1, 0.9 to 1.4). Birth order did not influence these results. The figure illustrates the results shown in tables 1 and 2.

**Table 2** Risk of pregnancy\* affected by pre-eclampsia in sisters and brothers† who were born after a pregnancy not complicated by pre-eclampsia, Norway, 1967-2003

	No of siblings	No (%) with pre-eclampsia	Odds ratio (95% CI)‡
<b>Younger sisters</b>			
Mother had pre-eclampsia in first pregnancy:			
Yes	1 146	117 (10.2)	2.1 (1.7 to 2.5)
No	63 736	3327 (5.2)	1.0§
<b>Younger brothers</b>			
Mother had pre-eclampsia in first pregnancy:			
Yes	728	48 (6.6)	1.2 (0.9 to 1.5)
No	38 754	2251 (5.8)	1.0§
<b>Older sisters</b>			
Mother had pre-eclampsia in second pregnancy:			
Yes	580	54 (9.3)	1.9 (1.4 to 2.5)
No	59 205	3116 (5.3)	1.0§
<b>Older brothers</b>			
Mother had pre-eclampsia in second pregnancy:			
Yes	396	23 (5.8)	1.0 (0.7 to 1.6)
No	43 285	2461 (5.7)	1.0§

\*Confined to first pregnancies of both siblings in first generation. Excludes families with recurrent pre-eclampsia in first generation.

†For brothers, this is No (%) in their partners.

‡Pooled odds ratios (Mantel-Haenszel): 2.0 (1.7 to 2.3) for sisters and 1.1 (0.9 to 1.4) for brothers.

§Reference category.

**Table 3** Severity of pre-eclampsia in women and in men's partners, by maternal history of pre-eclampsia, Norway, 1999-2003

	No of pregnancies	No (%) of mothers with pre-eclampsia*	Odds ratio (95% CI)†
<b>Women's pregnancy</b>			
No pre-eclampsia	131 805	2357 (1.8)	1.0‡
Type of pre-eclampsia:			
Mild	3 839	136 (3.5)	2.1 (1.8 to 2.4)
Severe/early	1 792	90 (5.0)	3.0 (2.4 to 3.7)
<b>Pregnancy in men's partners</b>			
No pre-eclampsia	96 405	1905 (2.0)	1.0‡
Type of pre-eclampsia:			
Mild	3 014	67 (2.2)	1.2 (1.0 to 1.5)
Severe/early	1 340	40 (3.0)	1.9 (1.4 to 2.5)

\*For pregnancy in men's partners, this was man's mother.

†Estimated with multinomial logistic regression.

‡Reference category.

### Clinical severity of pre-eclampsia

In the subgroup of women who had given birth since 1999, those who had clinically severe or early onset pre-eclampsia were much more likely to have been born after a pre-eclamptic pregnancy themselves compared with women born after an unaffected pregnancy (3.0, 2.4 to 3.7, table 3). Men who had fathered a pregnancy with severe or early pre-eclampsia were also more likely to have been born after a pre-eclamptic pregnancy themselves compared with men who had not fathered an affected pregnancy (1.9, 1.4 to 2.5).

### Discussion

Men born after a pre-eclamptic pregnancy are apparently more likely to carry fetal alleles capable of triggering pre-eclampsia. These men then pass the fetal risk alleles to their offspring, increasing their partner's risk of pre-eclampsia. The same presumably occurs for women born after pre-eclamptic pregnancies who can then pass susceptibility alleles to their own fetuses. In addition, women born after pre-eclamptic pregnancies may inherit from their mother genes that confer maternal susceptibility to pre-eclampsia. This maternal susceptibility can pass from mother to daughter but not from mother to son.

The purest expression of maternal genes would be among women not themselves born after a pre-eclamptic pregnancy but whose mothers had had pre-eclampsia in another pregnancy. Such women have twice the risk of pre-eclampsia in their own pregnancies compared with other women. The purest expression of fetal genes predisposing to pre-eclampsia would be among the offspring of men who had themselves triggered pre-eclampsia as fetuses. Such men have a 50% increased risk of fathering a pre-eclamptic pregnancy. Women who were born after a pre-eclamptic pregnancy potentially carry both types of

genetic predisposition—maternal and fetal—and seem to be at highest risk (figure).

### Comparisons with other studies

Evidence for maternal predisposition to pre-eclampsia has been reported before.<sup>4 10-13</sup> A population based case-control study from Utah, US, showed that women born after a pregnancy complicated by pre-eclampsia were more likely themselves to have pre-eclampsia.<sup>6</sup>

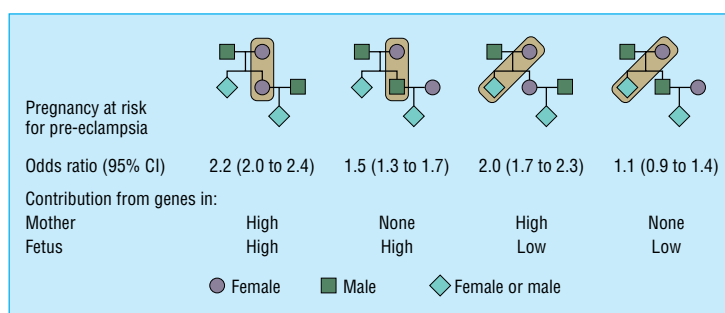
Another population based study in Norway supports the hypothesis that the father's genes also contribute to the risk of pre-eclampsia.<sup>5</sup> In that study, men who fathered a pre-eclamptic pregnancy in one woman were also more likely to father a pre-eclamptic pregnancy in other women. The Utah study also supported a paternal predisposition,<sup>6</sup> with men born of affected pregnancies at increased risk of fathering a pre-eclamptic pregnancy.

### Strength and weaknesses

Among women and men who had a family history of pre-eclampsia, some were first born and others were born second or later. The familial association with pre-eclampsia was independent of birth order. As expected, the absolute risk of pre-eclampsia was reduced with increasing birth order, but the familial association was consistent, strengthening the evidence of an association.

Our cohort data are based on mandatory reporting in a population based registry over a 37 year period. The large study size and the standardised collection of data provide high precision in the estimates of effect. Moreover, the cohort design, comprising a whole population, reduces the possibility that selection bias can explain our findings. However, we cannot exclude potential confounding by other risk factors for pre-eclampsia.<sup>14</sup> For example, obesity before pregnancy may be shared by mothers and daughters and may contribute to their shared risk of pre-eclampsia. In Norway, however, obesity of the degree that increases the risk of pre-eclampsia was relatively uncommon over the time of the study.<sup>15</sup> Also, recent evidence suggests that the association with obesity may be limited to the relatively mild type of pre-eclampsia with term delivery.<sup>16</sup> We found a stronger familial association for clinically severe than for mild pre-eclampsia, which may decrease the likelihood that obesity could have confounded our results.

Other factors, such as interval between births,<sup>9</sup> change of partner between births,<sup>9 17</sup> chronic hypertension,<sup>18</sup> and smoking in pregnancy,<sup>19</sup> have also been associated with the risk of pre-eclampsia. Although confounding by any one of these factors cannot be excluded, it seems unlikely that such factors could produce the specific contrasts within affected families that we see here. In the subgroup of women who had given birth since 1999, we had more detailed information on potentially



Risk of parenting a pregnancy with pre-eclampsia

confounding factors. In a supplementary analysis in this subgroup, we adjusted for length of gestation, diabetes in pregnancy, smoking early in pregnancy, and maternal age and education. This adjustment did not substantially influence the results.

### Maternal or fetal genes

It seems reasonable to attribute the observed patterns of familial predisposition to genetic inheritance. Daughters born after a pre-eclamptic pregnancy may carry their mothers' susceptibility genes, as well as genes from either parent that operate through the fetus.<sup>1 5 6</sup> Their sisters who were born after pregnancies not complicated by pre-eclampsia would be at lower risk as they are less likely to be carrying the genes that operate through the fetus. Still they are just as likely to be carrying their mothers' susceptibility genes. Thus, sisters of affected men and women have about twice the risk of women with no family history of pre-eclampsia.

For men who were born after an affected pregnancy, an increased risk of fathering a pre-eclamptic pregnancy can be attributed solely to paternal factors. Brothers who were born after a pregnancy without pre-eclampsia would have a low probability of carrying fetal risk genes, which is confirmed by the near baseline risk of pre-eclampsia among pregnancies they father.

### Mild or severe pre-eclampsia

Recent epidemiological studies<sup>20 21</sup> have supported the hypothesis that pre-eclampsia comprises several pathogenetic entities, rather than a single process, with varying degrees of clinical severity.<sup>22</sup> Placental dysfunction could cause pre-eclampsia in babies with low weight for gestational age<sup>1 22-24</sup> but is less likely for larger babies.<sup>20 21</sup> The familial association is stronger for preterm than for term pre-eclampsia. When we confined analysis to preterm pre-eclampsia in the first generation, the odds ratios were 2.6 (2.0 to 3.4) and 1.7 (1.2 to 2.5) for women and men, respectively. For preterm pre-eclampsia in the second generation the odds ratios were 2.8 (2.3 to 3.3) and 1.7 (1.3 to 2.2). This may suggest that genetic susceptibility to pre-eclampsia, either through maternal or paternal genes, is more likely to cause clinically severe disease.<sup>25</sup> If changes over time in reporting of pre-eclampsia include more mild pre-eclampsia, recurrence of pre-eclampsia between generations will be reduced. The proportion of preterm pre-eclampsia was 10% in the first period (parents) and 22% in the last period (offspring).

### Conclusions

Both maternal and paternal factors contribute to the risk of pre-eclampsia. The risk through affected mothers is higher, presumably because these mothers carry susceptibility genes and also transmit independent genetic risk factors to their fetus. The risk through affected fathers is lower because fathers transmit only fetal risk factors. Also, the differences that we observed between sisters and brothers suggest that genes that determine maternal susceptibility to pre-eclampsia differ from the paternal genes that may trigger pre-eclampsia through the fetus. Finally, familial associations are stronger for the clinically more severe types of pre-eclampsia.

Contributors: RS, LJV, and RTL planned the project, analysed the data, and drafted the manuscript. AJW and LMI advised on study design and analytic strategy and contributed to the writing of the paper. TR was responsible for data management and participated in the analysis of data. RS is guarantor. Funding: Norwegian Medical Research Council.

Competing interests: None declared.

Ethical approval: Medical Birth Registry of Norway.

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## What is already known on this topic

Maternal susceptibility to pre-eclampsia can be passed from mother to daughter

Less is known about fetal propensity to trigger pre-eclampsia and the transmission of such propensity through the father or mother

## What this study adds

Men and women who were born after pre-eclamptic pregnancies contribute to increased risk of pre-eclampsia in the next generation

The risk through affected mothers is higher, presumably because these mothers carry susceptibility genes and also transmit independent genetic risk factors to their fetus

Risk through affected fathers is lower presumably because fathers transmit only fetal risk factors

Other familial patterns are consistent with independent genetic risk in the mother and the fetus and the associations seem to be stronger for the clinically more severe types of pre-eclampsia

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(Accepted 5 July 2005)

doi 10.1136/bmj.38555.462685.8F

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