Conclusions of women showed no increased risk of ESRD if a child had preeclampsia in first pregnancy (4–8). This has led to a hypothesis that preeclampsia might already identify women with an excess risk of developing ESRD, irrespective of preeclampsia. Other studies have shown that both ESRD (9–11) and preeclampsia (12–15) are aggregated in families. A possible explanation could be that unhealthy lifestyles aggregate in families together with cardiovascular risk factors like hypertension, obesity, dyslipidemia, and insulin resistance (16–18). Alternatively, pleiotropic genes, shared among relatives, may increase risks of both preeclampsia and ESRD. On the other hand, it is also possible that subclinical renal vascular injury induced by preeclampsia could predispose to the development of chronic hypertension. A small clinical study in the 1960s showed that siblings of women with preeclampsia did not have an increased prevalence of hypertension (19), suggesting that it was preeclampsia per se, and not familial factors, that lead to later hypertension. Our previous finding of higher risk in women with recurrent preeclampsia (1) also suggests that the preeclampsia may exacerbate the progression to ESRD.

To assess the role of genetic or environmental contributions to the association between preeclampsia and ESRD, we investigated risk of ESRD in relatives of women with preeclampsia in first pregnancy. This was made possible through linkage of data from the Norwegian Population Registry, the Medical Birth Registry of Norway, and the Norwegian Renal Registry. If genetic factors or family aggregation of risk factors play a role, we hypothesized that the risk of ESRD would be increased, not only in women with preeclampsia, but also in their relatives without preeclamptic pregnancies.

Materials and Methods Since 1967, extensive data on maternal disease and conditions of the newborn have been registered in the Medical Birth Registry of Norway for all births in the

**Familial Factors in the Association between Preeclampsia and Later ESRD**

*Bjørn Egil Vikse,*† Lorentz M. Ingens,‡ S. Ananth Karumanchi,§ Ravi Thadhani,¶ Anna Varberg Reisæter,** and Rolf Skjærven††

**Summary**

**Background and objectives** Women with preeclampsia have increased risk of developing ESRD. This study assessed whether this can be explained by preeclampsia itself or by familial aggregation of common risk factors.

**Design, setting, participants, & measurements** Since 1967, the Medical Birth Registry of Norway has registered data on all births in the country. By linkage with the Norwegian Population Registry, different, but overlapping, cohorts were defined: the first and second cohorts included women and a sibling (first cohort) or child (second cohort) with a registered first birth between 1967 and 2008. Similar cohorts were defined for men. The Norwegian Renal Registry provided data on ESRD from 1980 to June 2009.

**Results** Cohort 1 was used for the main analyses and included 570,675 women, 291 of whom developed ESRD after a median 18.2 years. Compared with women without preeclampsia and no siblings with preeclampsia, women without preeclampsia but a sibling with preeclampsia had a relative risk (RR) of ESRD of 0.96 (95% confidence interval, 0.59–1.6), women with preeclampsia but no siblings with preeclampsia had a RR of 6.0 (4.4–8.1), and women with preeclampsia and a sibling with preeclampsia had a RR of 2.8 (0.88–8.6). Further analyses of women showed no increased risk of ESRD if a child had preeclampsia in first pregnancy.

**Conclusions** Familial aggregation of risk factors does not seem to explain increased ESRD risk after preeclampsia. These findings support the hypothesis that preeclampsia per se may lead to kidney damage.


**Introduction**

We previously showed that preeclampsia is an important risk marker for development of ESRD (1) as well as for kidney disease that needs investigation with a kidney biopsy (2). A recent meta-analysis concluded that a four-time increased risk of microalbuminuria is observed after preeclampsia, possibly due to persistent kidney damage after preeclampsia (3).

Studies have shown excess occurrence of hypertension, obesity, insulin resistance, and endothelial dysfunction both before and after a pre-eclamptic pregnancy (4–8). Alternatively, pleiotropic genes, shared among relatives, may increase risks of both preeclampsia and ESRD. On the other hand, it is also possible that subclinical renal vascular injury induced by preeclampsia could predispose to the development of chronic hypertension. A small clinical study in the 1960s showed that siblings of women with preeclampsia did not have an increased prevalence of hypertension (19), suggesting that it was preeclampsia per se, and not familial factors, that lead to later hypertension. Our previous finding of higher risk in women with recurrent preeclampsia (1) also suggests that the preeclampsia may exacerbate the progression to ESRD.

To assess the role of genetic or environmental contributions to the association between preeclampsia and ESRD, we investigated risk of ESRD in relatives of women with preeclampsia in first pregnancy. This was made possible through linkage of data from the Norwegian Population Registry, the Medical Birth Registry of Norway, and the Norwegian Renal Registry. If genetic factors or family aggregation of risk factors play a role, we hypothesized that the risk of ESRD would be increased, not only in women with preeclampsia, but also in their relatives without preeclamptic pregnancies.

**Materials and Methods** Since 1967, extensive data on maternal disease and conditions of the newborn have been registered in the Medical Birth Registry of Norway for all births in the
country (total population of 5 million inhabitants) with a gestational age of at least 16 weeks (20); for this study, data were available through 2008. The Norwegian Population Registry, with an 11-digit identification number for all Norwegian citizens, allowed the construction of sibling-sibling and parents-children groups; parental information since 1953 was almost complete. Since 1980, data (including date of onset and cause of ESRD) on all patients in Norway developing ESRD (defined as starting chronic dialysis treatment or undergoing renal transplantation) have been registered in the Norwegian Renal Registry; for this study, data were available through June 2009. The national Cause of Death Registry comprises data on all deaths; for this study, data were available through December 2008. Since 1970, the Norwegian Education Database has registered data on completed educations for all Norwegian citizens. The study protocol was approved by the regional ethics committee.

On the basis of the data from the Medical Birth Registry and the Population Registry described above, four different, but overlapping, cohorts were defined. The first cohort included all women (index person) registered with a first birth in the Medical Birth Registry in the period from 1967 to 2008 and who had at least one sibling (male or female) with a registered first birth in the Medical Birth Registry between 1967 and 2008. Siblings were defined as individuals with the same mother and father. The second cohort included all women (index person) with a registered first birth in the Medical Birth Registry in the period from 1967 to 2008 and who had at least one child who themselves had a registered first birth in the Medical Birth Registry between 1967 and 2008. Similarly, the third cohort comprised men with a registered first birth and at least one sibling with a registered first birth, and the fourth cohort comprised men with a registered first birth and at least one child with a registered first birth. In the first and third cohorts, individuals with >6 siblings were excluded (Figure 1). In the second and fourth cohorts, individuals with >4 children were excluded. We used national identification numbers to link data on the included individuals with the Norwegian Renal Registry and the national Cause of Death Registry.

Explanatory Variables
Diagnostic criteria for preeclampsia used by the reporting midwives and obstetricians have been in accordance with the 1972 recommendations by the American College of Obstetricians and Gynecologists (21), and include increased BP after 20 weeks of gestation (BP ≥140/90 mmHg, or an increase in systolic BP of ≥30 mmHg or in diastolic BP of ≥15 mmHg, from measurements before 20 weeks of gestation) and proteinuria (≥0.3 g in a 24-hour urine specimen or ≥1 on urinary dipstick). A diagnosis of preeclampsia in the Medical Birth Registry has not been directly validated, but consistency of rates has been demonstrated across counties and over time (22,23). Preeclampsia in “a man’s pregnancy” implies preeclampsia in a pregnancy for which he was reported as the father.

Registration in the birth record of diabetes mellitus, kidney disease (kidney or urinary tract disease), rheumatic disease (autoimmune connective tissue disease or inflammatory arthritides), and essential hypertension before pregnancy depends on the ascertainment of these conditions by the woman’s general practitioner or obstetrician. Marital status was dichotomized as either single (divorced or not living with partner) or not single (married or living with partner). Educational level was dichotomized as either having finished high school or not.

Outcome Variables
The outcome was ESRD and onset was defined as the date of starting dialysis treatment or undergoing renal transplantation. Women without ESRD were followed until June 30, 2009, or date of death.

Statistical Analyses
Data were analyzed in a cohort design; preeclampsia in index individuals’ first pregnancy, siblings’ first pregnancy, children’s first pregnancy, and partners’ first pregnancy were analyzed as explanatory variables, and ESRD as the outcome variable. As shown in the Results, the risks were mostly similar if a sister or partner of a brother had preeclampsia and the main analyses was therefore performed with preeclampsia in siblings as the exposure variable. The same was observed for offspring and these analyses were therefore performed with preeclampsia in children as the exposure variable. Start of follow-up was set at the date of the index person’s first childbirth; for index males, we used the date of their partner’s first childbirth. Estimates of relative risk (RR) for ESRD according to selected risk factors were obtained by Cox regression analyses. Because no cases with ESRD had been registered between 1967 and 1979, mothers that gave birth during this period were left truncated in the survival analyses before January 1980. Consequently, the counting process formulation of proportional hazards (Cox regression) was applied (24). This method does not include mothers in the analysis until an event could be registered (i.e., a mother with her first birth in 1973 would be included in the analyses 7 years after birth and right censored 32 years after birth if she did not develop ESRD or died). If not otherwise stated, means ± SDs or RR estimates with 95% confidence intervals (95% CIs) are given. The analyses were performed using the STATA MP edition 11.1 statistical package (StataCorp).

Results

Does Preeclampsia in Siblings Increase an Individual’s ESRD Risk?
In these analyses, we included 570,675 index women (cohort 1) and 510,598 index men (cohort 3), of whom 291 and 536 developed ESRD during follow-up. The index persons were included at time of first childbirth (mean age 26.0±4.9 years and mean year 1989±10) and followed for a mean duration of 19.6±10.4 years. Mean age at onset of ESRD was 43.9±9.8 years. Individuals with a sibling with preeclampsia had more siblings and more often preeclampsia or other adverse pregnancy outcomes; the latter was more evident for women than for men (Table 1).

Results from Cohort 1. Index women with at least one sibling with preeclampsia in first pregnancy had a RR for developing ESRD during follow-up of 0.90 (95% CI, 0.57–1.42) compared with women without siblings with preeclampsia (Table 2). Separate analyses according to whether the sibling was a sister or a brother showed similar
Figure 1. | Flowcharts of the four cohorts and included individuals, separately for women and men.
results. Compared with women without preeclampsia who had no siblings with preeclampsia, women without preeclampsia who had siblings with preeclampsia had a RR of ESRD of 0.96 (95% CI, 0.59–1.57), women with preeclampsia without siblings with preeclampsia had a RR of 5.95 (95% CI, 4.37–8.11), and women with preeclampsia and siblings with preeclampsia had a RR of 2.76 (95% CI, 0.88–8.63) (Table 3 and Figure 2). Adjustments for age, marital status, number of siblings, and educational status did not affect relative risks, but exclusion of women with pre-existing hypertension, kidney disease, rheumatic disease, or diabetes mellitus before first pregnancy halved the excess risk for women with preeclampsia. When these analyses were repeated according to whether the sibling was a sister or a brother, the results were almost identical (results not shown). The results in Table 2 were similar when analyses were performed separately for index women with one, two, and three or more siblings. Because the registration of siblings was not complete until 1953, we repeated the siblings analyses described in Table 2 for individuals born in 1953 or later. In these analyses, we included 502,502 women, 215 of whom developed ESRD during follow-up. RR for development of ESRD for women with a sibling with preeclampsia was 0.68 (95% CI, 0.38–1.21).

**Results from Cohort 3.** Index men with at least one sibling with preeclampsia in first pregnancy had a RR of 1.31 (95% CI, 0.98–1.76) for developing ESRD during follow-up compared with men with no siblings with preeclampsia; this risk was unchanged after adjustments for age and marital status at own first childbirth (1.33; 95% CI, 1.00–1.78) (Table 2). Further analyses showed that RR was identical if a sister had preeclampsia or if the partner of a brother had preeclampsia.

**Does Preeclampsia in an Individual’s Children Increase ESRD Risk?**

In these analyses, we included 286,589 index women (cohort 2) and 263,646 index men (cohort 4) who themselves (or their partner), as well as at least one of their children, had their first pregnancy registered in the
Medical Birth Registry. Of these, 379 women and 746 men developed ESRD during follow-up. Having children with preeclampsia was associated with higher frequencies of adverse pregnancy outcomes in an individual’s own first pregnancy, both for women and men (Table 1).

**Results from Cohort 2.** Women with at least one child with preeclampsia in first pregnancy had a RR of 1.22 (95% CI, 0.87–1.72) for developing ESRD compared with women without children with preeclampsia (Table 2). The risk was similar if the child was a daughter or a son. As shown in Table 3, Risk of ESRD in index women in Norway according to whether the woman herself or at least one of her siblings had preeclampsia in first pregnancy between 1967 and 2008

<table>
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<tr>
<th>Index</th>
<th>Person</th>
<th>Relative Preeclampsia</th>
<th>Total (n)</th>
<th>ESRD (n)</th>
<th>Unadjusted RR (95% CI)</th>
<th>P Value</th>
<th>Adjusted RR (95% CI)a</th>
<th>P Value</th>
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<td>44,278</td>
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<td>21,460</td>
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<td>Daughters</td>
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<td>1.06 (0.82–1.38)</td>
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<td>1.07 (0.82–1.38)</td>
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<td>Men</td>
<td>Partner</td>
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<td>28,541</td>
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<td>Siblingsb</td>
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<td>39,434</td>
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<td>Childrenb</td>
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<td>243,370</td>
<td>682</td>
<td>1.0</td>
<td>1.0</td>
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<tr>
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<td>Yes</td>
<td>20,276</td>
<td>64</td>
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<table>
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<tr>
<th>Index</th>
<th>Women</th>
<th>Sibling with Preeclampsiaa</th>
<th>Total (n)</th>
<th>ESRD (n)</th>
<th>Unadjusted RR (95% CI)</th>
<th>Adjusted Models</th>
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<td>Model 1b</td>
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<td>With</td>
<td>Yes</td>
<td>41,271</td>
<td>17</td>
<td>0.96 (0.59–1.57)</td>
<td>1.0 (0.62–1.66)</td>
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<td>5.83 (4.27–7.96)</td>
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<td>3007</td>
<td>3</td>
<td>2.76 (0.88–8.63)</td>
<td>2.87 (0.92–8.97)</td>
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</table>

| RR, relative risk; 95% CI, 95% confidence interval. |
| aSister or partner of brother with or without preeclampsia in first pregnancy. |
| bFor brothers or sons, preeclampsia denotes whether their partner had preeclampsia in first pregnancy. |

**Results from Cohort 4.** Men with at least one child with preeclampsia in first pregnancy had a RR of 1.06 for developing ESRD (95% CI, 0.82–1.38) compared with men without children with preeclampsia in first pregnancy;
RR was 0.90 (95% CI, 0.63–1.30) if a daughter had preeclampsia and 1.36 (95% CI, 0.95–1.94) if the partner of a son had preeclampsia.

Does Preeclampsia in an Individual’s Female Partner Increase ESRD Risk?
To further investigate genetic and environmental explanations of the association between preeclampsia and risk of ESRD, we investigated if a man had increased risk of ESRD if his partner had preeclampsia in first pregnancy. In these analyses, we included the same men as in the analyses of risk associated with preeclampsia in siblings (cohort 3). Compared with men whose partner had not had preeclampsia in first pregnancy, men who had a partner with preeclampsia had a RR of 1.54 (95% CI, 0.97–2.45) (P=0.07) (Table 2).

Causes of ESRD
In index women with ESRD, cause of ESRD was GN in 39%, interstitial nephritis in 13%, congenital or hereditary disease in 17%, diabetic nephropathy in 16%, and other causes in 15%. Corresponding numbers for index men were 42%, 6%, 15%, 21%, and 16%. Similar patterns were observed in women with and without preeclampsia and in individuals whose siblings, children, or partners had or did not have preeclampsia in first pregnancy. An individual’s own preeclampsia and sibling’s preeclampsia were associated with similar RRs of the different causes of ESRD as with ESRD in total (Supplemental Table 1).

Discussion
This study has shown that only the women who themselves had preeclampsia had an increased risk of ESRD. No excess risks were observed in their siblings and parents, which was unexpected if familial aggregation of renal and cardiovascular risk factors is important in the association between preeclampsia and ESRD.

We previously showed that women who have preeclampsia in first pregnancy have a four- to five-time increased risk of developing ESRD during the next 40 years (1). By excluding women with known diabetes,
hypertension, or rheumatic or kidney disease, the RR was reduced by 30% (1). In a later study of women with diabetes mellitus, the effect was only present in women who only had one pregnancy (25). In women considered healthy before pregnancy, preeclampsia seems to be associated with a three-time increased risk of later ESRD that could be explained by a chronic kidney damage induced by preeclampsia. Other explanations are also possible and the one that has been most discussed is the aggregation of cardiovascular risk factors observed in women with preeclampsia both before and after the pre-eclamptic pregnancy (4–8), which would predispose to development of ESRD irrespective of whether the women had preeclampsia. If this was true, one would expect an increased risk of ESRD in relatives of women with preeclampsia because the cardiovascular risk factors associated with preeclampsia tend to aggregate in families (16–18). Previous studies have also shown familial aggregation of renal insufficiency (9–11). In this study, we did not find any increased risk in women who have siblings or children with preeclampsia. Overall, the results seem robust and were similar after stratification for all combinations of relatives with preeclampsia, although the number of endpoints in subgroups often was low with wide CIs. Although this study shows that preeclampsia only seems to be important to the affected women, it cannot rule out the possibility of aggregated cardiovascular risk factors in the affected women as a possible explanation for the association. These do not seem to have a genetic origin and this study suggests that there may be a more direct association between preeclampsia and kidney disease (e.g., by a kidney-damaging effect of preeclampsia). Alternatively, preeclampsia may uncover or aggravate pre-existing subclinical hypertensive or kidney disease. Preeclampsia involves extensive endothelial dysfunction as well as hypertension and, although often of short duration, it is possible that these conditions can aggravate an underlying subclinical kidney disease that can present with increasing proteinuria and hypertension during the end of pregnancy. Our finding of a somewhat lower risk of ESRD in women with preeclampsia who had a sibling with preeclampsia compared with women with preeclampsia who did not have siblings with preeclampsia was based on very small numbers of women and is an uncertain finding.

For men, we found a nonsignificant indication of a 30%–50% increased risk if the partner or a sibling had preeclampsia in first pregnancy. After adjustments for age and marital status, the association of an increased risk if a sibling had preeclampsia had a P value of 0.05. It has previously been shown that men born in a preeclamptic pregnancy have a 50% increased risk of fathering a pre-eclamptic pregnancy; this was interpreted as a likely genetic effect mediated through the father’s genes in the unborn offspring (12). If this was true, the same genetic contribution could be seen for the men’s siblings. It is thus possible that the trend toward an increased risk of ESRD in men whose siblings or partner experience preeclampsia can be explained by genetic factors. Another explanation could be that environmental cardiovascular risk factors tend to aggregate in partners (16,17), increasing both the risk of his partner having preeclampsia and his own risk for ESRD. Previous studies have shown stronger genetic contributions to risk of preeclampsia in women. In addition, the fact that we could not find any increased risk in female siblings or mothers of individuals with preeclampsia suggests that the genetic contributions to the association between preeclampsia and ESRD are less than might have been expected.

The major strengths of this study are that we were able to include data on the pregnancies of the siblings, children, and partners of the included individuals as well as the large national cohort with complete long-term follow-up with regard to ESRD. A weakness is that data on siblings were only complete for individuals who lived with their parents in 1970 and therefore nearly complete only for individuals born 1953 or later, for individuals born 1949 the registration was about 67% complete. Results were similar when we only included individuals born after 1953, and we therefore do not believe that this influenced our results to a significant extent. A limitation of this study is that we had to rely on preeclampsia diagnoses set by the treating physicians at the time of birth. Distinguishing preeclampsia from underlying renal disease can often be difficult and diagnostic guidelines
have changed over the last decades, although the 1972 guidelines (21) are most in line with the practice during the time period of interest. Individuals were included from 1967 to 2004, whereas outcomes were not registered until 1980. We addressed this limitation by using a statistical method that does not include women in the analyses until an outcome can be registered. Assuming that the association between preeclampsia and ESRD did not change from 1967 to 1980, the statistical method is adequate. This study only included Norwegians and the findings should not be extrapolated to non-European populations.

We conclude that it is the women with preeclampsia who have an increased risk of ESRD and that we cannot find evidence for familial contributions to the increased risk of ESRD after preeclampsia. It would be critical to establish experimental animal models of preeclampsia to determine the mechanisms by which preeclampsia could cause persistent renal damage in the mother, increasing her risk of future disease, including ESRD. This study has underlined the direct effect of preeclampsia as a risk marker for kidney disease and more studies are needed to investigate this further.

Acknowledgments
The authors are grateful to the Norwegian nephrologists who report data to the Norwegian Renal Registry.

The results of this study were presented as a poster at the 2011 Annual Meeting of the American Society of Nephrology, November 8–13, 2011, Philadelphia, Pennsylvania, and was published as an abstract for that meeting.

Disclosures
S.A.K. is an investigator of the Howard Hughes Medical Institute; is a co-inventor of multiple patents related to angiogenic proteins for the diagnosis and therapy of preeclampsia, and these patents have been licensed to multiple companies; and served as a consultant to Roche and Beckman Coulter and has financial interest in Aggamin LLC. R.T. is a co-inventor on patents related to the prediction of preeclampsia that have been out licensed to diagnostic companies and has financial interest in Aggamin LLC.

References

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