Several recent studies reveal the link between preeclampsia and future development of ESRD, CKD, and microalbuminuria (1–3). Preeclampsia is also associated with the subsequent development of cardiovascular disease (CVD) (4–6). Whether the pathogenesis of preeclampsia represents an unmasking of subclinical or unrecognized kidney disease, an independent insult to the kidneys leading to progressive CKD, or a sign of underlying systemic endothelial dysfunction destined to progress to end-organ vascular disease with heightened risk for subsequent CVD and CKD remains unknown.

In an attempt to answer this important clinical question, Vikse et al. evaluated associations between the long-term risk for ESRD by linking comprehensive registries that contained birth and subsequent health records in large numbers of Norwegians (7). Index cases were selected on the basis of their personal history of preeclampsia, along with the presence or absence of preeclampsia in their siblings and children and the families of their spouses. The subsequent rates of ESRD were computed in those with sporadic preeclampsia, as well as those with differing family histories of preeclampsia (7). Traditional risk factors for preeclampsia are known to include a paternal or maternal history of this pregnancy-associated disorder (8–11). In addition, ESRD clusters in the families of index cases of European and European American ethnicity (12–14). Therefore, it was reasonable for the authors to postulate that if the rate of subsequent ESRD was higher among preeclamptic women who had siblings or offspring also affected by preeclampsia, then a heritable or genetically mediated systemic disorder (perhaps susceptibility to generalized vascular endothelial dysfunction) might be present in families. This process could ultimately lead to both renal and CVD complications. However, their exhaustive evaluation using large and unique databases suggests this is not the case.

The authors performed a retrospective analysis involving four Norwegian cohorts. They examined the siblings and children of 510,598 men and 570,675 women who had a registered birth during a 41-year study period. The long-term risk for development of ESRD was compared in women without preeclampsia and without a sibling who had preeclampsia, relative to the following: (1) women without preeclampsia but with a sibling who had preeclampsia, (2) women with preeclampsia who lacked siblings with preeclampsia, and (3) women with preeclampsia who had a sibling with preeclampsia. The authors collected and analyzed maternal, paternal, sibling, and partner relationships. Results were ultimately truncated for those who were entered in the registry in later years, when no further cases of ESRD were ascertained. Compared with women without preeclampsia and without an affected sibling, women experiencing preeclampsia without a similarly affected sibling had a profound and statistically significant six-fold increase in their long-term risk for ESRD. When the sibling of a preeclamptic woman also had preeclampsia, the risk for ESRD in the index case was somewhat attenuated (relative risk, 2.8). However, when only a sibling had preeclampsia (not the woman in question), no increase in risk for ESRD was observed (relative risk, 0.96). As expected, adjustment for pre-existing hypertension, CKD, rheumatic disease, and diabetes mellitus halved the excess risk for subsequent nephropathy. The sex of the sibling did not appear to alter the observed risk.

This study clearly demonstrates that familial aggregation of preeclampsia in Europeans is insufficient to explain the increased risk for subsequent ESRD among preeclamptic patients. Although preeclampsia and ESRD are known to aggregate in families, women with preeclampsia who develop ESRD later in life do so independently from their familial history of preeclampsia. This study is therefore instrumental in demonstrating that preeclampsia alone is an important risk factor for ESRD.

Paternal family history of preeclampsia and change in paternity (although the latter may be explained by the length of time between births) can confer increased risk for preeclampsia (9,10,15,16). Cohorts centered on the father as the index subject were also examined in this report. Men with siblings who had preeclampsia in their first pregnancies had slightly increased risk for ESRD after adjustment for age and marital status. This might suggest that different phenomena occur in males and females, with a slightly increased risk for ESRD among males in the presence of a family member with preeclampsia; this effect could potentially be inherited (biologically mediated) or due to familial aggregation of environmental risk factors. The sex effect was observed along with a higher ESRD event rate in the male-indexed cohort.
It is important to note that the registries interrogated in this report were limited to Norwegians, a cohort in whom 0.05% of women and 0.1% of men developed ESRD after 18.2 years of follow-up. This compares to lifetime risks for ESRD of >2% in European Americans and 7% in African Americans (17). Mean age ± SD at ESRD onset in the Norwegian cohort was 43.9 ± 9.8 years, compared with a mean age at incident dialysis of 63 years in the United States (18). The cited causes of ESRD later in life among women from this registry included GN in 39% and diabetic nephropathy in 16%; 42% of men had GN and 21% had diabetic nephropathy. These frequencies differ markedly from those reported in the United States, where >44% of patients have ESRD attributed to diabetes mellitus (18). As such, generalizability of study results to other population groups is unknown.

Preeclampsia is more common, and familial aggregation of ESRD far stronger, in African Americans than European Americans (19). Polymorphisms in the apolipoprotein L1 gene (APOL1) clearly contribute to the clustering of disparate causes of ESRD in African American families (20,21). However, APOL1 nephropathy risk variants are virtually absent in European-derived populations (22,23). The effect of APOL1 alleles on the risk for preeclampsia is unknown; however, presence of subclinical nephropathy in women with two APOL1 risk variants might promote preeclampsia. A limitation of this report, one present in all epidemiologic studies that use registry data, is the inability to confirm the presence or absence of preeclampsia among patients. Preeclampsia may be difficult to differentiate from other hypertensive disorders of pregnancy, and the authors note that the diagnostic criteria for preeclampsia have evolved during the time frame in this study. We can only add that if cases with preeclampsia were frequently misdiagnosed when undetected CKD was present, observed familial risk for ESRD would probably have been higher among female index cases. This supports the likelihood that diagnoses of preeclampsia were accurate in these registries.

A strength of this study was the large sample size. Adjustment for conventional CKD risk factors (e.g., preexisting hypertension, nephropathy, rheumatic disease, and diabetes mellitus) was performed and mitigated the increased risk for ESRD in index cases with preeclampsia. Other factors may further mitigate this risk. For example, the effect of thrombophilia on preeclampsia has frequently been cited (24). Although many established risk factors for preeclampsia and ESRD overlap, the degree of shared risk remains incompletely defined. The results of this report suggest that preeclampsia is an independent risk factor for subsequent CKD.

Preeclampsia is a heterogenous disease. Whether the results in this report would change if the index cases were divided into those with mild, severe, or superimposed preeclampsia is unknown. Understanding whether these subtypes would have differing effects on the relative risk for ESRD in each cohort might help better define whether the same pathophysiological processes occurred on the basis of severity of the underlying preeclampsia. Interpretation of study results evokes different theories about causality in the complex relationship between preeclampsia, CVD, and kidney disease. The authors make an elegant argument that preeclampsia itself, not the grouping of familial factors (be they genetically or environmentally mediated), increases the risk for ESRD after preeclampsia.

This large analysis failed to show any trend toward an increased risk for subsequent ESRD in women with siblings or children who were affected by preeclampsia. Whether preeclampsia is a primary insult to the kidney that subsequently leads to progressive CKD in those affected or is a manifestation of underlying renal or vascular disease will continue to be debated. Regardless of cause, preeclampsia can now be listed as an independent risk factor for ESRD in individuals of European ancestry. Finally, it should be appreciated that the overall risk for ESRD in patients with prior preeclampsia was relatively low. Nonetheless, nephrologists and primary care physicians should be aware that a medical history of preeclampsia is important to record in all patients with and at risk for kidney disease.

Disclosures
None.

References


Published online ahead of print. Publication date available at www.cjasn.org.