Title: Two Genomes, Two Pathways: Distinct Maternal and Fetal Contributions to Preeclampsia

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Abstract
Hypertensive disorders of pregnancy are one of the leading causes of maternal and fetal morbidity and mortality. Preeclampsia (PE), a life-threatening condition with a substantial heritable component, is defined by maternal hypertension and proteinuria and affects approximately 2–5% of pregnancies worldwide. Both maternal and fetal factors contribute to the risk of PE, but because mothers and children share ~50% of their genetic variants, disentangling maternal and fetal contributions has been challenging.

To better understand the maternal and fetal factors that predispose to PE and to identify opportunities for prevention and intervention, we conducted a genome-wide association study (GWAS) meta-analysis of maternal and fetal genetic effects on PE. Using 401,597 maternal and 435,076 fetal samples, including unique Finnish mother–child pair data, we identified 25 independent PE-associated genetic variants ($P < 5 \times 10^{-8}$), including 11 novel and 2 fetal-specific loci. We estimate that more than 90% of the genetic risk for PE is attributable to maternal factors. Leveraging genetic data for causal inference analyses, we found evidence that targeted lifestyle interventions in mothers could help prevent PE. Furthermore, we demonstrate that being born from a PE pregnancy directly increases the risk of psychiatric conditions, underscoring the broad health implications of PE.

In summary, we provide novel insights into the genetic mechanisms underlying maternal and fetal contributions to PE, demonstrate that these contributions are largely distinct, and suggest potential targets for interventions aimed at reducing disease burden in both mothers and their children.