Pregnancy associated hypertensive disorders and risk of cardiovascular disease: a mendelian randomisation study

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Background: Pregnancy associated hypertensive disorders including pre-eclampsia/eclampsia and gestational hypertension have been related to unfavourable maternal cardiovascular risk factor profiles and a significantly higher risk to develop maternal cardiovascular disease (CVD) events in observational studies. However, whether these associations are causal is not yet fully understood.

Purpose: We conducted a Mendelian Randomisation study to investigate whether genetic liability to pre-eclampsia/eclampsia and gestational hypertension is related to cardiovascular risk factors and the risk of experiencing CVD outcomes.

Methods: We analysed individual-participant data of women and men from the UK Biobank. The rationale for also analysing men was to study the role of genetic liability to pre-eclampsia/eclampsia and gestational hypertension in CVD risk without experiencing the underlying phenotype. We studied a range of CVD outcomes including myocardial infarction, stroke (including subtypes), and combined CVD endpoints. Furthermore, we analysed a set of blood pressure-, lipid-, liver-, and kidney-related cardiovascular risk factors. To study the genetic association with pre-eclampsia/eclampsia and gestational hypertension we used effect sizes and standard errors from a large-scale genome-wide association study. For the genetic associations with cardiovascular risk factors and CVD outcomes, we used individual-participant data from the UK Biobank. We applied Mendelian Randomisation analysis using inverse variance weighted regression in our primary analysis and implemented additional regression methods as sensitivity analyses.

Results: We included 264,160 women and 223,043 men from the UK Biobank with available genetic data. Mean age at baseline was 56.5 (standard deviation 8.1) and 56.7 (8.2) years in women and men, respectively. Of all women and men, 44.3% and 50.9% had a history of hypertension and mean age at hypertension was 50.0 (10.8) and 51.2 (9.1) years, respectively. Genetically proxied pre-eclampsia/eclampsia and gestational hypertension were related to a higher risk of CVD in both sexes, with odds ratios of 1.20 (1.01, 1.43) and 1.22 (1.10, 1.36) in women and 1.29 (1.08, 1.53) and 1.28 (1.16, 1.42) in men, respectively. The relations were more pronounced for ischaemic than for haemorrhagic outcomes. Furthermore, genetically proxied pre-eclampsia/eclampsia and gestational hypertension were associated with higher levels of systolic and diastolic blood pressure and earlier age at hypertension in both women and men.

Conclusion: Genetic liability to pregnancy associated hypertensive disorders including pre-eclampsia/eclampsia and gestational hypertension is associated with higher CVD risk, implying biological mechanisms relating to these disorders are causally related to CVD risk in both women and men.