Offspring genotype by proxy Mendelian randomization - Investigating potential causal effects of offspring perinatal traits on maternal health. An example using offspring birthweight and maternal cardiometabolic risk in the UK Biobank

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Background: During the perinatal period, the fetus can exert profound effects on processes that alter pre- and post-natal maternal physiology. It is possible to investigate the causal effect of offspring perinatal exposures on their mother's health using Mendelian randomisation (MR). However, as maternal and offspring genotypes are correlated, analyses need to be adjusted for maternal genotype to avoid confounding. Such analyses are difficult to perform at scale due to the of the paucity of genotyped maternal-offspring pairs.

Methods:
We introduce offspring genotype by proxy MR, that can be performed in the absence of offspring genotype by utilising spousal information (i.e. fathers genotype). We use paternal genotype as a proxy for offspring genotype, which in turn will proxy offspring phenotype. As an example, we applied this method to investigate the causal effect of fetal growth (using offspring birthweight) on maternal cardiovascular health in 45,546 spousal pairs in the UK Biobank. Complementary gene-by-environment interaction (GxE) MR analyses stratified by maternal parity were also performed.

Results:
The offspring genotype by proxy MR design found no strong evidence for a causal effect, although confidence intervals were wide. Complementary GxE MR analyses suggest that offspring birth weight is unlikely to causally affect maternal cardiometabolic risk factors.

Conclusions:
Our study serves as a blueprint for future investigations into the putative causal effects of offspring perinatal traits on their mothers using MR in the absence of offspring genotype information.