# Investigating the potential causal relationship between parity and long-term maternal cardiometabolic health outcomes

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**Introduction:** Pregnancy induces substantial physiological changes, and the cumulative stress of multiple pregnancies and childrearing has been proposed to influence long-term maternal cardiometabolic health outcomes.

**Method:** We separately regressed number of children ever born (NEB) on later-life cardiometabolic outcomes in up to 172,122 females and 138,390 males from the UK Biobank (UKBB) and assessed heterogeneity in regression coefficients between sexes to explore potential childbearing and sex-specific childrearing effects. To strengthen causal inference, we performed i) sex-stratified two-sample Mendelian randomization (MR) where males served as negative controls, and ii) a novel spousal MR approach in 53,237 UKBB spousal pairs, which leveraged one partner's genotype to estimate causal effects on the other's health, potentially reducing bias from horizontal pleiotropy.

**Results:** Observational analyses revealed sex-specific associations between NEB and cardiometabolic traits, persisting after adjustment for socioeconomic status and multiple test correction ($P<6.25x10^{-3}$). In females, NEB was inversely associated with blood pressure and cholesterol; in males, it was positively associated with ApoB and LDL. While NEB showed some consistent associations across sexes, effect sizes differed: females showed stronger inverse associations with HDL and ApoA1, while males showed stronger positive associations with BMI, body fat percentage, and basal metabolic rate (BMR). MR analyses supported a causal effect of higher NEB on increased type 2 diabetes risk in females ($P<6.25x10^{-3}$), with weak evidence ($P<0.05$) for lower blood pressure, and elevated BMI and BMR. Spousal MR provided robust evidence for a causal effect of NEB on increased BMI in females ($P<6.25x10^{-3}$), with suggestive effects with higher BMR and lower HDL ($P<0.05$). In males, MR results showed weak evidence of causal effects ($P<0.05$).

**Conclusion:** By triangulating evidence across methods, our findings suggest a possible causal link between NEB and long-term cardiometabolic health in females, with BMI and BMR representing key pathways linking parity to chronic disease risk.