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TITLE: Do maternal intrauterine environmental influences that lower offspring birthweight causally increase offspring cardiometabolic risk factors in later life? A Mendelian randomization study of 45,849 genotyped parent offspring pairs in the HUNT study using the OpenMx software

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ABSTRACT:

There is a robust and well-documented observational relationship between lower birthweight and higher risk of cardiometabolic disease in later life. We investigated whether there was evidence for causal effects of the intrauterine environment, as proxied by maternal SNPs that influence offspring birthweight independent of offspring genotype, on offspring cardiometabolic risk factors. We investigated whether a genetic risk score of maternal SNPs associated with offspring birthweight was also associated with offspring cardiometabolic risk factors, after controlling for offspring genotypes at the same loci, in up to 45,849 parent-offspring pairs from the Nord-Trøndelag Health (HUNT) Study. We implemented a computationally efficient genetic linear mixed model using the OpenMx software package, which allowed us to take into account the considerable cryptic relatedness in the HUNT study, making maximum use of the data. We found little evidence for a maternal genetic effect of birthweight associated variants on offspring cardiometabolic risk factors after adjusting for offspring genotypes at the same loci. Likewise, we found little evidence for paternal genetic effects on offspring cardiometabolic risk factors performing similar analyses in father-offspring pairs. In

contrast, offspring genetic risk scores of birthweight-associated variants were strongly related to many cardiometabolic risk factors, even after conditioning on maternal genotypes at the same loci. Our results suggest that the maternal intrauterine environment, as proxied by maternal SNPs that influence offspring birthweight, is unlikely to be a major determinant of adverse cardiometabolic outcomes. In contrast, genetic pleiotropy in the offspring genome explains some of the observational relationship between birthweight and cardiometabolic risk.

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