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Maternal Smoking During Pregnancy Interacts with Genetic Factors to Increase Risk for Low Birth Weight but not Harmful Offspring Smoking Behaviors in Europeans

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Pregnant individuals who smoke face increased health risks because smoking harms both the mother and their developing offspring. Using 307 417 Europeans from the UK Biobank, we examined whether exposure to maternal smoking during pregnancy (MSP) interacts with genetic risk to predict offspring birth weight (BW) and smoking behaviors. We investigated interactions between MSP and genetic risk at multiple levels: single variant, gene-level, and polygenic score. We examined self-reported BW, smoking initiation status (SI), age of smoking initiation, cigarettes per day, and smoking cessation status. One SNP rs72689499 on chromosome 14 reached significance for an interaction with MSP on the multiplicative (log10) scale for BW ($p = 5.13x10-9$). In gene-level testing, three genes on chromosome 1 and one gene on chromosome 14 (tagged by SNP rs72689499) reached significance for an interaction with MSP on both the additive and multiplicative scale for BW. These genes include: PTCH2, EIF2B3, PLK3, and TSHR. SNP and gene-level results were insignificant for all offspring smoking behaviors. We also detected an interaction between polygenic risk for smoking and MSP on SI on both the additive ($p = 4.4x10-5$) and multiplicative ($p = 1.0x10-5$) scale. We found evidence of gene-environment correlation in the polygenic risk analysis using a post-hoc t-test which showed that MSP-exposed offspring had a higher SI PGS than those unexposed to MSP ($p = 5.9x10-623$). Our results support the main effect of MSP on BW and show a genetic interaction between MSP and genetic factors influencing BW and SI.