

Associations Between Pregnancy-Related Predisposing Factors for Offspring Neurodevelopmental Conditions and Parental Genetic Liability to Attention-Deficit/Hyperactivity Disorder, Autism, and Schizophrenia: The Norwegian Mother, Father and Child Cohort Study (MoBa).

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Importance: Several maternal exposures during pregnancy are considered predisposing factors for offspring neurodevelopmental conditions. However, many of these exposures may be noncausal and biased by maternal genetic liability.

Objective: To assess whether pregnancy-related predisposing factors for offspring neurodevelopmental conditions are associated with maternal genetic liability for attention-deficit/hyperactivity disorder (ADHD), autism, and schizophrenia and to compare associations for maternal genetic liability with those for paternal genetic liability, which could indicate that paternal exposures are not suitable negative controls for maternal exposures.

Design, Setting, and Participants: The Norwegian Mother, Father and Child Cohort Study (MoBa) is a population-based pregnancy cohort that recruited parents from June 1999 to December 2008. Polygenic scores (PGS) for ADHD, autism, and schizophrenia were derived in mothers and fathers. The associations between maternal PGS and 37 pregnancy-related measures were estimated, and these results were compared with those from paternal PGS predicting paternal measures during the mother's pregnancy. Analysis took place between March 2021 and March 2022.

Exposures: PGS for ADHD, autism, and schizophrenia, calculated (using discovery effect size estimates and threshold of $P < .05$) from the largest available genome-wide association studies.

Main Outcomes and Measures: Self-reported pregnancy-related measures capturing lifestyle behaviors, metabolism, infectious and autoimmune diseases, other physical health conditions, and medication use.

Results: Data were available for up to 14 539 mothers (mean [SD] age, 30.00 [4.45] years) and 14 897 fathers (mean [SD] age, 32.46 [5.13] years) of European ancestry. Modest but robust associations were observed between specific pregnancy-related measures and maternal PGS, including ADHD PGS with asthma (odds ratio [OR], 1.15 [95% CI, 1.06-1.25]), smoking (OR, 1.26 [95% CI, 1.19-1.33]), prepregnancy body mass index (β , 0.25 [95% CI, 0.18-0.31]), pregnancy weight gain (β , 0.20 [95% CI, 0.10-0.30]), taking folate (OR, 0.92 [95% CI, 0.88-0.96]), and not taking supplements (OR, 1.09 [95% CI, 1.04-1.14]). Schizophrenia PGS was associated with coffee consumption (OR, 1.09 [95% CI, 1.05-1.12]), smoking (OR, 1.12 [95% CI, 1.06-1.19]), prepregnancy body mass index (β , -0.18 [95% CI, -0.25 to -0.11]), and pregnancy

weight gain (β , 0.17 [95% CI, 0.07-0.27]). All 3 PGSs associated with symptoms of depression/anxiety (ADHD: OR, 1.15 [95% CI, 1.09-1.22]; autism: OR, 1.13 [95% CI, 1.06-1.19]; schizophrenia: OR, 1.13 [95% CI, 1.07-1.20]). Associations were largely consistent for maternal and paternal PGS, except ADHD PGS and smoking (fathers: OR, 1.13 [95% CI, 1.09-1.17]).

Conclusions and Relevance: In this study, genetic liability to neurodevelopmental conditions that is passed from mothers to children was associated with several pregnancy-related factors and may therefore confound associations between these pregnancy-related factors and offspring neurodevelopment that have previously been thought to be causal. It is crucial that future study designs account for genetic confounding to obtain valid causal inferences so that accurate advice can be given to pregnant individuals.