

Sex-Specific Effects of Birth Weight on Longitudinal Behavioural Outcomes: A Mendelian Randomisation Approach Using Polygenic Scores

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INTRODUCTION: It is unclear whether sex differences in behaviour associated with birth weight (BW) are genuine, given the cross-sectional design and potential confounding in previous studies. We aimed to test whether sex differences associated with the BW phenotype were reproducible using a Mendelian randomisation approach, i.e., the association between the polygenic score (PGS) for BW and behavioural outcomes across childhood and adolescence.

MATERIALS AND METHODS: Using data from the Raine Study, we had 1484 genotyped participants with a total of 6446 Child Behaviour Checklist assessments from ages 5 to 17 years. We used BW-PGSs in linear mixed-effect models to predict parentally assessed attention, aggression, and social problems scales; we also derived estimates and significance for a sex-by-genotype interaction. We used a Bonferroni-corrected significance threshold and tested the robustness of the results with teacher assessments of behaviour and a second PGS.

RESULTS: We found a sex-by-genotype interaction with lower BW-PGSs associated with increased aggression in males compared with females. These findings were consistent across various analyses, including teacher assessments. Surprisingly, a lower BW-PGS showed protective effects in females. In contrast, a lower BW phenotype had detrimental effects in males, with evidence of a genotype-phenotype mismatch increasing aggression problems in males only.

CONCLUSIONS: This study highlights the genuine nature of behavioural sex differences linked to low BW and the sex-dependent effects of environmental and genetic factors. While previous research suggested a connection between low birth weight and poor behavioural outcomes, it remains unclear if these effects vary by sex. Our findings show genes affecting birth weight influence aggressive behaviour differently in males and females across childhood and adolescence. Additionally, birth weight environment and genetic factors impact behaviour differently; in males, a mismatch between genetically determined and measured birth weight led to increased aggression.