Mendelian randomization analysis for attention deficit/hyperactivity disorder: studying a broad range of exposures and outcomes

María Soler Artigas 1 2 3 4, Cristina Sánchez-Mora 1 2 3 4, Paula Rovira 1 2 5 6, Laura Vilar-Ribó 1 2 3, Josep Antoni Ramos Quiroga 1 2 3 7, Marta Ribasés 1 2 3 4

Int J Epidemiol. 2022 Jun 12;dyac128.
doi: 10.1093/ije/dyac128. Online ahead of print.

Abstract
Background: Attention deficit/hyperactivity disorder (ADHD) is a highly prevalent neurodevelopmental disorder caused by a combination of genetic and environmental factors and is often thought as an entry point into a negative life trajectory, including risk for comorbid disorders, poor educational achievement or low income. In the present study, we aimed to clarify the causal relationship between ADHD and a comprehensive range of related traits.
Methods: We used genome-wide association study (GWAS) summary statistics for ADHD (n = 53 293) and 124 traits related to anthropometry, cognitive function and intelligence, early life exposures, education and employment, lifestyle and environment, longevity, neurological, and psychiatric and mental health or personality and psychosocial factors available in the MR-Base database (16 067 ≤n ≤766 345). To investigate their causal relationship with ADHD, we used two-sample Mendelian randomization (MR) with a range of sensitivity analyses, and validated MR findings using causal analysis using summary effect estimates (CAUSE), aiming to avoid potential false-positive results.
Results: Our findings strengthen previous evidence of a causal effect of ADHD liability on smoking and major depression, and are consistent with a causal effect on odds of decreased average total household income [odds ratio (OR) = 0.966, 95% credible interval (CrI) = (0.954, 0.979)] and increased lifetime number of sexual partners [OR = 1.023, 95% CrI = (1.013, 1.033)]. We also found evidence for a causal effect on ADHD for liability of arm predicted mass and weight [OR = 1.452, 95% CrI = (1.307, 1.614) and OR = 1.430, 95% CrI = (1.326, 1.539), respectively] and time spent watching television [OR = 1.862, 95% CrI = (1.545, 2.246)], and evidence for a bidirectional effect for age of first sexual intercourse [beta = -0.058, 95% CrI = (-0.072, -0.044) and OR = 0.413, 95% CrI = (0.372, 0.457), respectively], odds of decreased age completed full time education [OR = 0.972, 95% CrI = (0.962, 0.981) and OR = 0.435, 95% CrI = (0.356, 0.533), respectively] and years of schooling [beta = -0.036, 95% CrI = (-0.048, -0.024) and OR = 0.458, 95% CrI = (0.411, 0.511), respectively].
Conclusions: Our results may contribute to explain part of the widespread

co-occurring traits and comorbid disorders across the lifespan of individuals with ADHD and may open new opportunities for developing preventive strategies for ADHD and for negative ADHD trajectories.
Keywords: ADHD; Mendelian randomization; causal analysis using summary effect estimates.