GENETIC LIABILITY FOR ADHD AND PHYSICAL HEALTH OUTCOMES – A TWO-SAMPLE MENDELIAN RANDOMIZATION STUDY

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Background Attention-deficit/hyperactivity disorder (ADHD) is associated with a broad range of physical health problems, including cardiometabolic, neurological and immunological conditions. Determining whether ADHD plays a causal role in these associations is of great importance not only for early treatment and prevention but also because comorbid health problems further increase the serious social and economic impacts of ADHD on individuals and the society.

Methods We used a two-sample Mendelian randomization (MR) approach to examine the causal relationships between genetic liability for ADHD and previously implicated physical health conditions. Genetic variants associated with ADHD were obtained from the latest summary statistics for European ancestry from the combined PGC + iPSCYCH meta-analysis of ADHD. Consistent effects obtained from IVW, weighted median and MR Egger methods were taken forward for sensitivity analysis. The direction of effect was investigated in a bidirectional MR analysis. Multivariable MR was applied to assess effects of genetic liability for ADHD when adjusted for genetic liability for childhood obesity and lifetime smoking heaviness.

Results We found evidence of a causal effect of genetic liability for ADHD on childhood obesity (OR: 1.29 (95% CI: 1.02, 1.63)) and coronary artery disease (CAD) (OR: 1.11 (95% CI: 1.03, 1.19)) with consistent results across different MR approaches. There was further evidence for a bidirectional relationship between genetic liability for ADHD and childhood obesity. The effect of genetic liability for ADHD on CAD was independent of smoking heaviness in a multivariable MR setting (OR: 1.14 (95% CI: 1.08, 1.20)) but was attenuated when simultaneously entering genetic liability for childhood obesity (OR: 1.06 (95% CI: 0.95, 1.17)). There was little evidence for a causal effect on other cardiometabolic, immunological, neurological disorders and lung cancer.

Conclusion Our findings strengthen the argument for early treatment and support for children with ADHD and their families and especially promoting physical activity and providing them with dietary advice to reduce the future risk for developing CAD.
The risk of stillbirth increased monotonically with increasing FPG, suggesting no biological justification for one GDM diagnostic threshold over another. **Conclusion** Women with raised FPG experience higher risk of late stillbirth. If diagnosed with GDM and managed accordingly, this appears to be largely mitigated. Inconsistent diagnostic practices however leave many women with borderline hyperglycaemia exposed to higher risks of stillbirth.

**Background** Lower socioeconomic position (SEP) has consistently been associated with poorer health. Chronic inflammation has been proposed as having a prominent role in the construction of social inequalities in health. Disentangling the effects of social disadvantage along the life course on inflammation is key in elucidating biological mechanisms underlying socioeconomic disparities. In this study we investigate how life course socioeconomic conditions influence omics measures of inflammation at different molecular level traits from a subset of 173 Italian participants of the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort. **Methods** We used genome-wide methylation and transcriptional profiles obtained from blood samples from 178 Italian participants of the EPIC cohort. Starting from 824 genes involved in human inflammatory responses and corresponding to 11,502 CpG sites, we first identified 61 potential acting genes by sequentially controlling for time-ordered SEP. The RR comprised a GS search for health plus each of the four political themes plus backward citation chasing. Internationally comparative studies assessing the relationship between any of four political themes (democracy, globalisation, political tradition, and welfare state) and any population health outcome, excluding healthcare expenditure, were eligible for inclusion. A RR version of this review was conducted with the same search dates. The RR comprised a GS search for health plus each of ‘politics’, ‘political’ and the four political themes plus backward and forward citation chasing. The RR and SR were compared on completeness (% of total included studies identified), efficiency (% of reviewed records that were included) and results profile (% of included studies with positive vs non-positive results). Analysis was descriptive in terms of n(%) and used chi-square and McNemar test as appropriate in SPSS v.25. **Results** Our results consistently show that participants with a less advantaged SEP in young adulthood or in adulthood exhibit, later in life, a lower inflammatory methylome score (β=-0.0075, P-value=0.0067, β=-0.0076, P-value=0.0073 for educational level and highest household occupational position respectively), hence suggesting an overall increased level of inflammation for the corresponding inflammatory-related genes. Adjusting for either behavioural factors (smoking status, alcohol consumption and physical activity) and bmi, or all of them together only marginally affected our results: effect size estimates showed consistent signs, and associations reach statistical significance (P<0.05) for both participant’s education and highest household occupational position. Adopting a life course approach weakened these associations suggesting a common pathways between young and later in life SEP. Sensitivity analyses indicated that our findings were not affected by the way the inflammatory methylome score was calculated. **Conclusion** Our results support the hypothesis that social inequalities impacts, independently from behavioural factors, adult physiology through inflammation and can be observed at the DNA methylation level. Understanding biological mechanisms by which social environment influences the inflammatory system has important implications in treatment and especially in prevention, by potentially identifying modifiable factors in the environment that affect physiological health.