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TITLE: The epigenome as a biological pathway of the effects of prenatal exposure to tobacco, alcohol, and caffeine on childhood internalising problems in offspring: Two large multi-cohort epigenome-wide association studies.

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KEYWORDS:

epigenetics, intrauterine, smoking, caffeine, alcohol, internalising problems

ABSTRACT:

**Background:** Studies have found potentially causal associations between maternal health behaviours during pregnancy and offspring mental health. We explored whether this could be due to DNA methylation changes in cord blood.

**Method:** We conducted two large multi-cohort epigenome-wide association studies (EWAS) of cord blood DNA methylation in relation to: 1) maternal caffeine consumption during pregnancy (5 cohorts; n = 3742); 2) childhood internalising problems (2 cohorts; n = 1601). We explored whether results from our internalising problems EWAS were enriched for CpGs associated with prenatal maternal caffeine exposure. We also explored enrichment for cord blood CpGs previously identified as associated with prenatal maternal smoking (Joubert 2016, n = 6685) and alcohol drinking (Sharp 2018, n= 3075).

**Results:** At FDR-corrected  $P < 0.05$ , we found 2 CpGs associated with prenatal maternal caffeine, but no CpGs associated with internalising problems. At the top 5000 CpGs with the lowest P-values in each of the maternal behaviour EWASs, 149 caffeine-associated CpGs, 139 smoking-associated CpGs and 137 alcohol-associated CpGs were associated with internalising problems with the same direction of effect and  $P < 0.05$ . Visual inspection of QQ plots showed that P-values in the internalising problems EWAS were inflated at the top 5000 smoking-associated CpGs, but not at the top 5000 CpGs associated with prenatal alcohol or caffeine.

**Conclusion:** In a large, multi-cohort epigenetic analysis, we found some preliminary evidence that maternal smoking could affect childhood internalising symptoms through DNA methylation, but little evidence that this is the case for prenatal alcohol and caffeine consumption.

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