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## **Exposomics of Cocaine Use Disorder: A new paradigm to study the impact of environmental exposures in Substance Use Disorders**

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Introduction: Exposomics is the study of cumulative environmental exposures that predispose to and predict diseases across the life span by triggering biological responses. Unfortunately, no major advances have been made in building tools and strategies to address it in Substance Use Disorders (SUD). Aim: Combining whole genome methylation data with an exposome-wide approach, our study aimed to build an Exposome Load Index (ELI) associated with epigenetic aging in SUD. Method: We used blood DNAm data of 1217 participants (554 with Cocaine Use Disorder, CUD and 663 controls) to investigate 2nd and 3rd generation epigenetic clocks. Using ASI-6 supplemented by Childhood Trauma Questionnaire, we developed Elastic Net Regression Models to identify the best predictors of addiction severity. A principal component analysis was implemented over the shrinkage exposures and the ELI was computed. To test if our model would have biological impact, we investigated its impact in the epigenetic clocks. Results: CUD was related with epigenetic aging. Twenty environmental variables were selected as main contributors to CUD severity. They were reduced to two different principal components: a substance use dimension and a social determinants dimension. We found that higher ELI was related with epigenetic aging acceleration. Conclusion: This is the first study attempting to generate Exposomics data using recognized and widely used clinical instruments. We highlight the relevance of Exposome when considering epigenetic studies and suggest that instead considering only drug use-related variables as predictors, a combination of drug and social exposures should be considered in future models of addiction research.