NAME OF PRESENTING AUTHOR: Jenny van Dongen

EMAIL ADDRESS OF PRESENTING AUTHOR: j.van.dongen@vu.nl

Examining causality of the association between smoking and DNA methylation

Jenny van Dongen[1], Camelia C. Minică[2,3], Joshua N. Pritikin[4,5], Gonneke Willemsen[1], BIOS Consortium[6], Jouke-Jan Hottenga[1], René Pool[1], Benjamin M. Neale[2,3,7], Conor V. Dolan[1], Eco J.C. de Geus[1], Dorret I. Boomsma[1], Michael C. Neale[4,5,8]

[1]Department of Biological Psychology, Vrije Universiteit, Amsterdam, The Netherlands

[2]Stanley Center for Psychiatric Disease, Broad Institute of MIT and Harvard, Cambridge, MA, 02142, USA

[3]Analytic and Translational Genetics Unit, Center for Genomic Medicine, Massachusetts General Hospital, Boston, MA, USA

[4]The Department of Psychiatry, Virginia Commonwealth University, Richmond, USA

[5]The Virginia Institute for Psychiatric and Behavioral Genetics, Virginia Commonwealth University, Richmond, USA

[6] The Biobank-based Integrative Omics Studies Consortium

[7] Program in Medical and Population Genetics, Broad Institute of MIT and Harvard, Cambridge, MA, USA.

[8] The Department of Human and Molecular Genetics, Virginia Commonwealth University, Richmond, USA

View author publication

KEYWORDS: Causality, smoking, DNA methylation, MR-DoC model, epigenetics.

ABSTRACT:

Previous epigenome-wide association studies (EWAS) have identified widespread robust differences in DNA methylation between smokers and non-smokers. Smoking-associated methylation levels might reflect: causal effects of smoking on methylation; causal effects of DNA methylation on smoking behavior; a genetic predisposition to smoking, epiphenomena of other exposures that correlate with smoking (e.g., alcohol use); or some combination of these processes. The contributions of different mechanisms to the association between smoking and methylation level may also vary across different CpGs. Here we analyze reversibility and bi-directional causal relationships between smoking and DNA methylation, and address the role of genetic pleiotropy. We analyze whole blood genome-wide DNA methylation data (Illumina 450k arrays) from the Biobank-based Integrative Omics Study (BIOS) consortium, and from twin pairs in the Netherlands Twin Register (NTR). We performed EWAS analyses to compare DNA methylation between current, former, and never smokers (N= 5318 from the BIOS consortium), and to assess the relationship between DNA methylation and additional smoking phenotypes, including pack years, cigarettes per day, time since quitting smoking, cotinine levels, and nicotine dependence (N=577-2786 from the NTR; the exact N varies with different smoking phenotypes). We also report results of causal analyses, including the Mendelian Randomization-Direction of Causation (MR-DoC) model (Minică et al. 2018).

Minică, Camelia C., Conor V. Dolan, Dorret I. Boomsma, Eco de Geus, and Michael C. Neale. 2018. "Extending Causality Tests with Genetic Instruments: An Integration of Mendelian Randomization with the Classical Twin Design." *Behavior Genetics*. doi:10.1007/s10519-018-9904-4.

GRANT SUPPORT: We acknowledge funding from the National Institute on Drug Abuse grant DA049867, the Netherlands Organization for Scientific Research (NWO): Biobanking and Biomolecular Research Infrastructure (BBMRI–NL, NWO 184.033.111) and the BBRMI-NL-financed BIOS Consortium (NWO 184.021.007), NWO Large Scale infrastructures, X-Omics (184.034.019), and the Royal Netherlands Academy of Science Professor Award (PAH/6635).