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The causal effect of tobacco smoking on white matter brain aging by Mendelian randomization analysis on UK Biobank participants

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Background and Significance: Tobacco smoking is a known risk factor associated with the accelerated decline of brain structures and functions. However, the causal effect of smoking on neurophysiology remains unclear. To close this knowledge gap, we perform Mendelian randomization analysis to estimate the causal effect of smoking on brain white matter microstructure integrity based on diffusion weighted imaging data. The brain age gap (BAG), which quantifies the brain-aging by measuring the difference between chronological age and predicted brain age estimated from neuroimaging data, is used to characterize the relative brain aging status.

Hypothesis and Methods: In this study, we estimated BAG by machine learning models based on 10,717 participants from the UK Biobank (UKB). We then test the hypothesis that smoking adversely affects brain aging based on a separate UKB cohort of 12,907 participants (independent of the BAG estimation cohort) by performing Mendelian randomization (MR) analysis. Smoking status (SS) and the number of cigarettes taken per day (CPD) are used as the smoking phenotypes.

Results and Discussion: Our results revealed the significant causal effects of smoking phenotypes (SS: $\hat{\theta}_M = 0.5898,\ p-\text{value} = 0.0007;$ CPD: $\hat{\theta}_M = 0.1452,\ p-\text{value} = 0.0103$) on BAG in MR analyses. In general, the severer smoking behavior (i.e., smokers or higher CPD) increased the risk of accelerating brain-aging. This study investigates the causal effect rather than the traditional association evaluation of the impact coming from smoking and thus assist in understanding the potential health benefits of smoking intervention.