Smoking and multiple sclerosis risk: A Mendelian randomization study

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BACKGROUND: Striking changes in the demographic pattern of multiple sclerosis (MS) strongly indicate an influence of modifiable exposures, which lend themselves well to intervention. It is important to pinpoint which of the many environmental, lifestyle, and sociodemographic changes that have occurred over the past decades, such as higher smoking and obesity rates, are responsible. Mendelian randomization (MR) is an elegant tool to overcome limitations inherent to observational studies and leverage human genetics to inform prevention strategies in MS.

METHODS: We use genetic variants from the largest genome-wide association study for smoking phenotypes (initiation: N = 378, heaviness: N = 55, lifetime smoking: N = 126) and body mass index (BMI, N = 656) and apply these as instrumental variables in a 2-sample MR analysis to the most recent meta-analysis for MS. We adjust for the genetic correlation between smoking and BMI in a multivariable MR.

RESULTS: In univariable and multivariable MR, smoking does not have an effect on MS risk nor explains part of the association between BMI and MS risk. In contrast, in both analyses each standard deviation increase in BMI, corresponding to roughly 5 kg/m^2 units, confers a 30% increase in MS risk.

CONCLUSION: Despite observational studies repeatedly reporting an association between smoking and increased risk for MS, MR analyses on smoking phenotypes and MS risk could not confirm a causal relationship. This is in contrast with BMI, where observational studies and MR agree on a causal contribution. The reasons for the discrepancy between observational studies and our MR study concerning smoking and MS require further investigation.

Keywords: multiple sclerosis, susceptibility, environment, genetics, Mendelian randomization