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Relationship between alcohol consumption and dementia with Mendelian randomization approaches among older adults in the United States

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Abstract

Background: Prior research is mixed concerning the association between alcohol consumption, a modifiable factor, and dementia. Genetic causal inference approaches may help elucidate the relationship between alcohol consumption and dementia.

Method: We performed a two-sample Mendelian randomization study using harmonized, genome-wide significant (p-value<10^{-8}), and independent (r^2<.001) single nucleotide polymorphisms' (SNPs) summary statistics from the largest publicly available meta-analyses of genome-wide association studies of weekly alcohol consumption (Liu et al., 2019, n = 941,280) and late onset Alzheimer's disease (Kunkle et al., 2019, n = 21,982 cases, 41,944 controls). Next, in the 2012 wave of the United States Health and Retirement Study (HRS), we employed individual polygenic scores of alcohol consumption via one-sample Mendelian randomization. Polygenic scores were calculated and standardized within genetic ancestry across 1,399,824 SNPs overlapping Liu et al. without HRS and 23andMe samples (n = 522,159). G-estimation provided odds ratios (ORs) of the relationship between a standard deviation increase in genetic risk of alcohol consumption and dementia and cognitive impairment without dementia compared to normal cognition in models stratified by genetic ancestry.

Result: Of 99 SNPs associated with weekly alcoholic drink consumption and 71 SNPs associated with late onset Alzheimer's disease, 59 overlapping and harmonized SNPs met instrument selection criteria. We did not observe evidence of a relationship between alcohol consumption and late-onset Alzheimer's disease using the inverse variance weighted two-sample Mendelian randomization estimator (OR = 1.15, 95% confidence interval (CI):[0.78, 1.72]), nor with complementary estimators. In HRS, Mendelian randomization revealed no relationship between cumulative genetic alcohol consumption risk and cognitive impairment without dementia (African ancestry sample (n = 2,402, OR = 0.86, 95% CI:[0.47, 1.58]); European ancestry sample (n = 9,576, OR = 0.96, 95% CI:[0.86, 1.07])) and dementia in the African ancestry sample (n = 1,908, OR = 0.50, 95% CI:[0.13, 2.00]). Alcohol consumption genetic risk was inversely associated with dementia in the European ancestry sample (n = 8,518, OR = 0.77, 95% CI:[0.62, 0.95]).

Conclusion: Our results largely suggest there is no causal relationship between alcohol consumption and dementia. The protective association observed between alcohol consumption and dementia among those of European ancestry in an aging American cohort may be due to genetic pleiotropy and/or selection bias in our empirical sample within the Health and Retirement Study.