

The use of “Mendelian randomization” to understand the etiology of age-related cognitive decline
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The B vitamins, specifically folate, have been implicated in neurological disorders, including poor cognitive performance. However, evidence from folate intervention studies on cognitive function in the general population is inconclusive. Many trials have employed small study populations, lacked a control group or placebo treatment or allocated multiple interventions. In contrast, a wealth of observational studies has reported on the association between low folate concentrations and poor performance on cognitive function tests. However, this association may be confounded: low concentrations of folate may be a consequence rather than a precedent of age-related cognitive decline. Studies that measure common genetic polymorphisms important for folate metabolism are able to exploit the random assignment of genes (“Mendelian randomization”) to help unravel the temporal relationship between risk factors and disease. In the case of folate and age-related cognitive decline, measurement of polymorphisms in folate-dependent enzymes improves the interpretation from conventional cross-sectional studies, gives insight into the etiology of cognitive decline and may legitimize the optimism for the possible therapeutic effect of folate on cognitive decline. Using baseline data from a randomized controlled trial that investigates the effect of daily folic acid supplementation on performance on cognitive tests, we illustrate how “Mendelian randomization” contributes to our understanding on the relationship between folate and cognitive function.

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