Associations between Modifiable Risk Factors and Alzheimer's Disease

Editors' Summary

Why Was This Study Done?

Researchers are interested in identifying risk factors for AD, particularly **modifiable** risk factors, because if such risk factors exist, it might be possible to limit the predicted increase in future AD cases. Epidemiological studies (investigations that examine patterns of disease in populations) have identified several potential risk factors for AD, including hypertension (high blood pressure), obesity, smoking, and dyslipidemia (changes in how the body handles fats). However, epidemiological studies cannot prove that a specific risk factor causes AD. For example, people with hypertension might share another characteristic that causes both hypertension and AD (confounding) or AD might cause hypertension (reverse causation). **Information on causality** is needed to decide which risk factors to target to help prevent AD. Here, the researchers use **"Mendelian randomization"** to examine whether differences in several epidemiologically identified risk factors for AD have a causal impact on AD risk. In Mendelian randomization, causal associations are inferred from the effects of genetic variants (which predict levels of modifiable risk factors) on the outcome of interest. Because gene variants are inherited randomly, they are not prone to confounding and are free from reverse causation. So, if hypertension actually causes AD, genetic variants that affect hypertension should be associated with an altered risk of AD.

What Did the Researchers Do and Find?

The researchers identified causal associations between potentially modifiable risk factors and AD risk by analyzing the occurrence of single nucleotide polymorphisms (SNPs, a type of gene variant) known to predict levels of each risk factor, in genetic data from 17,008 individuals with AD and 37,154 cognitively normal elderly controls collected by the International Genomics of Alzheimer's Project. They report that genetically predicted higher systolic blood pressure (SBP; the pressure exerted on the inside of large blood vessels when the heart is pumping out blood) was associated with lower AD risk (and with a higher probability of taking antihypertensive medication). Predicted smoking quantity was also associated with lower AD risk, but there was no evidence of causal associations between any of the other risk factors investigated and AD risk.

What Do These Findings Mean?

In contrast to some epidemiological studies, these findings suggest that hypertension is associated with **lower** AD risk.

However, because genetically predicted higher systolic blood pressure (SBP) was also associated with a higher probability of taking antihypertensive medication**, it could be that exposure to blood pressure lowering drugs, rather than having hypertension, reduces AD risk.**

Like all Mendelian randomization studies, the reliability of these findings depends on the validity of several assumptions made by the researchers and on the ability of the SNPs used in the analyses to explain variations in exposure to the various risk factors. Moreover, because all the participants in the International Genomics of Alzheimer's Project are of European ancestry, these findings may not be valid for other ethnic groups. Given that hypertension is a risk factor for cardiovascular disease, the researchers do not advocate raising blood pressure as a measure to prevent AD (neither do they advocate that people smoke more cigarettes to lower AD risk). **Rather, given the strong association between higher SBP gene scores and the probability of exposure to antihypertensive treatment, they suggest that the possibility that antihypertensive drugs might reduce AD risk independently of their effects on blood pressure should be investigated as a priority.**