Potential for Alzheimer's disease prevention

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Around 50 million people worldwide have dementia, with numbers rising due to increasing longevity, making it the major current global health and socioeconomic challenge.[1] However declining incidence rates in several countries [2] have given hope that dementia may be prevented by changing lifestyle. There are many putative risks, including those in the *Lancet Commission on dementia* [3] where we calculated that nine factors may account for over one third of dementias.

In the linked research paper, Larsson and colleagues report the findings of a Mendelian randomisation (MR) analysis aiming to clarify the causal association of lifestyle factors with Alzheimer's disease (AD), the commonest form of dementia. The authors examined 24 socioeconomic, dietary, lifestyle, health and inflammatory factors for which genetic association data was available. They found that genes which predisposed to increased time in education were clearly associated with reduced risk of AD. There was insufficient evidence for a causal link between other factors and AD. The authors did not evaluate the link to four other risk factors in our review;[3] social isolation, depression, physical activity, or the factor with the largest contribution, hearing impairment,.

Mendelian randomisation analyses add to observational evidence, improving the ability to understand if a possible risk factor causes an illness, but are not definitive.[4] The idea is that, for example, those who have genes which predispose to higher intelligence are likely to be more intelligent that the rest of the population. So if those genes are not linked with increased possibility of the outcome, in this case AD, then contradictory findings must be due to confounding or reverse causation. There is no possibility of reverse causation in MR studies, as genes are present at birth, not caused by the illness. MR is predicated on the exclusion restriction, the assumption that the genes only affect the outcome through the causal factor it codes for but this is not always true.[5] So, for example, educational attainment also protects against coronary heart disease and this is another possible pathway.[6]

How to build cognitive reserve

Larsson and colleagues found more education was associated with reduced chances of developing AD. A previous study linked the reduction in dementia prevalence over 12 years in the US to rising levels of education.[7] Education is likely to play a role in dementia risk through building cognitive reserve, the label for having a more resilient brain, able to better withstand neuropathological damage; and increasing healthy behaviours, including that related to heart health.

These findings on the protective effect of education further highlight the importance of provision and prolongation of children's education in lower and middle income countries (LMICs) where equal access is lacking,[8 9] potentially ameliorating the huge projected increase in people with dementia in LMICs.[1]

It's never too early and may never be too late

While improving education should reduce dementia incidence in the whole population, some well-educated individuals will still develop it. Larsson et al found suggestive evidence that university completion and higher intelligence also predicted lower dementia risk. Few young people will prolong their education to avoid dementia decades later, but people in mid-to-late life may want to take steps to reduce their risk. Further evidence is needed about whether cognitive reserve can be increased by late-life cognitive and social activity.

Larsson and colleagues found no evidence that diet, exercise, the metabolic syndrome or its components affected AD risk; and found that smoking may be protective against dementia for a subgroup with a single genetic variant related to nicotinic acetylcholine genes. These findings may

suggest that any causal effect of cardiovascular factors mainly influence vascular and mixed dementias rather than Alzheimer's dementia. However, cohorts used for these analyses may be unrepresentative as there is a healthy volunteer selection bias,[10] so those who have higher cardio-metabolic risk factors are less likely to be included. Additionally, survivor bias may affect these results, meaning that those with highest genetic risk of cardiovascular disease are underrepresented in late-life.

Ultimately, the strongest evidence for the role of modifiable risk factors comes from randomised controlled trials (RCTs). Larsson quotes an RCT of treating hypertension in people aged over 80 years old which was abandoned because of increased level of stroke and mortality in the control group.[11] This incomplete trial showed those with treated hypertension had a lower rate of incident dementia. Similarly, there was a small cognitive benefit of an intensive 2 year programme of cardiovascular risk management in the Finnish FINGER trial.[12] RCT participants, like those in cohorts, are usually healthier than the average population, resulting in less possible effect of such interventions. Future trials of dementia prevention strategies, therefore, need to purposively target high risk people who would benefit most.

Competing interests

We have read and understood the BMJ Group policy on declaration of interests and declare the following interests: None

Copyright statement

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