Evaluating risk of dementia in older people: A pathway to personalised prevention?

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Over 40 million people worldwide have dementia (1) with an estimated global cost of US$1 trillion annually (2). The number of people with dementia is expected to double every 20 years due to rapid global demographic changes, making dementia one of the largest socioeconomic and health challenges worldwide. Age-standardised rates of dementia are reported to have decreased in several high-income countries over the past 20 years, (3) likely related to successive generations' higher levels of education, and earlier detection and treatment of illness risk factors, (4) and this suggests that dementia can be prevented by modifications to dementia risk factors with recent evidence showing that feasible interventions targeting some of these risk factors could result in savings of £1.9 billion per year in England (5). That 'prevention is better than care' is even clearer in the light of repeated failures of novel drug approaches to treating established dementia. (6) However, while we have strong evidence for a causal relationship for many risk factors for dementia, (7) there is still very limited evidence that we can actually prevent it, so future approaches are likely to require personalised prevention, meaning that it will need to be targeted towards the right risk factors in the right people.

In the linked research paper (8) Rasmussen and colleagues, aim to develop risk score tools to identify people at high risk of developing dementia according to established genetic and lifestyle factors. Two large Danish cohorts were combined to generate a sample of over 60,000 people who were followed for up to 25 years and a combination of traditional statistical approaches and machine learning were used to identify the strongest predictors of dementia risk from a shortlist of candidates: age, sex, education, diabetes, hypertension, smoking status and genetic risk according to both apolipoprotein E (APOE) genotype and a polygenic score (*Figure 1*). These were then incorporated in predictive statistical models which accounted for the competing possibility of dying before dementia development (9) to give the probability of developing dementia during 10 years according to risk factor status. The authors then created a series of colour-coded charts indicating that, for example, a non-smoking man aged 50-59 years with high educational attainment, no diabetes and favourable genetic profile has less than 1% chance of developing dementia during the subsequent 10 years, whereas a female smoker aged over 80, with limited education, diabetes, two APOE ε4 alleles and a high number of risk genes has a 66% chance of developing dementia over the next decade.

Several previous risk scores have been developed for dementia either to guide prevention (10) or support identification of people for more detailed assessment (11) but this study's approach has

methodological strengths and includes a more comprehensive range of risk factors. The generation for the first time of dementia risk charts, akin to those used for cardiovascular risk from the Framingham study (12) is a potentially important step forward as it facilitates the identification of high risk individuals based on a range of risk factors, which could help to target prevention towards those who need it most. This is particularly important as some recent multicomponent trials aimed at preventing dementia, found the most benefit was in those who had the highest baseline risk (13) so more targeted prevention could yield greater impact. Focusing on potentially modifiable risk factors for dementia could also promote a positive public health message related to the potential modification of dementia risk by changing risk factors. The pessimism felt by those who assume that dementia is an inevitable consequence of aging, or that a positive family history of dementia indicates that they will follow the same disease course, is misplaced according to this paper and previous research (14) which have shown the likely modifiability of dementia risk with positive lifestyle approaches, even in the face of unmodifiable age, genotype and sex. Perhaps stopping smoking and effective diabetes management in the woman described above may reduce her risk from 66% to 55%?

The evidence for dementia being truly preventable is, however, scarce. Only one randomised controlled trial (RCT) has successfully reduced risk from dementia, with effective management of hypertension, (15) and several other studies have not resulted in dementia reduction. It may be that the insidious onset of dementia from neuropathological damage accumulated over many decades means that RCTs of dementia prevention conducted in late-life are too late to find efficacy and that preventative approaches are likely to be most effective during midlife. Additionally, those at higher risk from dementia may benefit more from preventive trials even if treating their risk factors does not, in itself, prevent dementia.

Models such as that developed by Rasmussen and colleagues must be able to evolve over time for several reasons; understanding of risk factors continues to develop, genetic and biomarker availability is changing, and validation in diverse populations is important particularly as genetic markers are likely to differ in those with different ancestry. Dementia's long prodromal period means that associations reported with insufficient interval between ascertainment of risk factor and dementia status may be due to reverse causation bias. The example of the association of body mass index with dementia is illustrative, as low BMI appears to be associated with dementia when follow-up to dementia diagnosis is less than 5 years, but high BMI is associated with dementia when follow-

up is more than 10 years; (16) low weight therefore is a consequence rather than cause of dementia and in fact obesity is a risk factor which should be addressed in midlife. The associations included in this risk score are uncontroversial, but inclusion of other emerging modifiable risk factors may improve predictive accuracy.

Risk models may also need to develop according to changes in the availability of data. The risk score developed by Rasmussen and colleagues assumes that genetic data will be available for individuals. While the excess risk due to APOE status and GWAS scores are clearly important, use of genetic testing is variable in clinical diagnostic practice for dementia and rare for non-clinical groups; genetic data availability is likely to increase in future, but remains controversial. In addition, several cerebrospinal fluid and imaging biomarkers for dementia risk currently show reasonable predictive value, and work continues to develop accurate markers which are more feasible to collect on a large scale such as in plasma, so incorporating these markers in risk score models may be instructive. Furthermore, the accuracy of cardiovascular risk score models have been criticised for lacking validity in different populations (17) so validating these models in diverse ethnic and social settings is likely to be required, especially in view of global variations in risk factor profiles for dementia. (18) Risk scores need to balance simplicity of use with accuracy, however, and evolution of previous scores has been criticised for creating confusion. (19)

Improving public understanding of dementia is a key component of prevention. In a US study, just over half of adults aged 50-64 reported it 'unlikely' that they would develop dementia and only 5% had discussed dementia prevention strategies with a doctor while many were using non-evidence based approaches such as nutritional supplementation. (20) An international survey of 70,000 people from 155 countries found that one-quarter thought there is nothing that can be done to prevent dementia. (21) The message from the Lancet Commission on Dementia that steps towards dementia prevention can be taken at any point during the life-course (7) suggests that action is required from individuals and organisations. In the UK, the National Health Service offers a 'Health check' to all adults aged between 40 and 74 to look for early signs of illness and dementia prevention advice is built into this. Quantifying dementia risk using a score such as that developed by Rasmussen and colleagues may be a valuable addition if it allowed the clinician to accurately model the effect of lifestyle modifications and to triage high-risk individuals towards more intensive preventative measures. The economic, social, and individual costs of dementia mean that its prevention should be a priority for all those at risk as well as policymakers and clinicians.

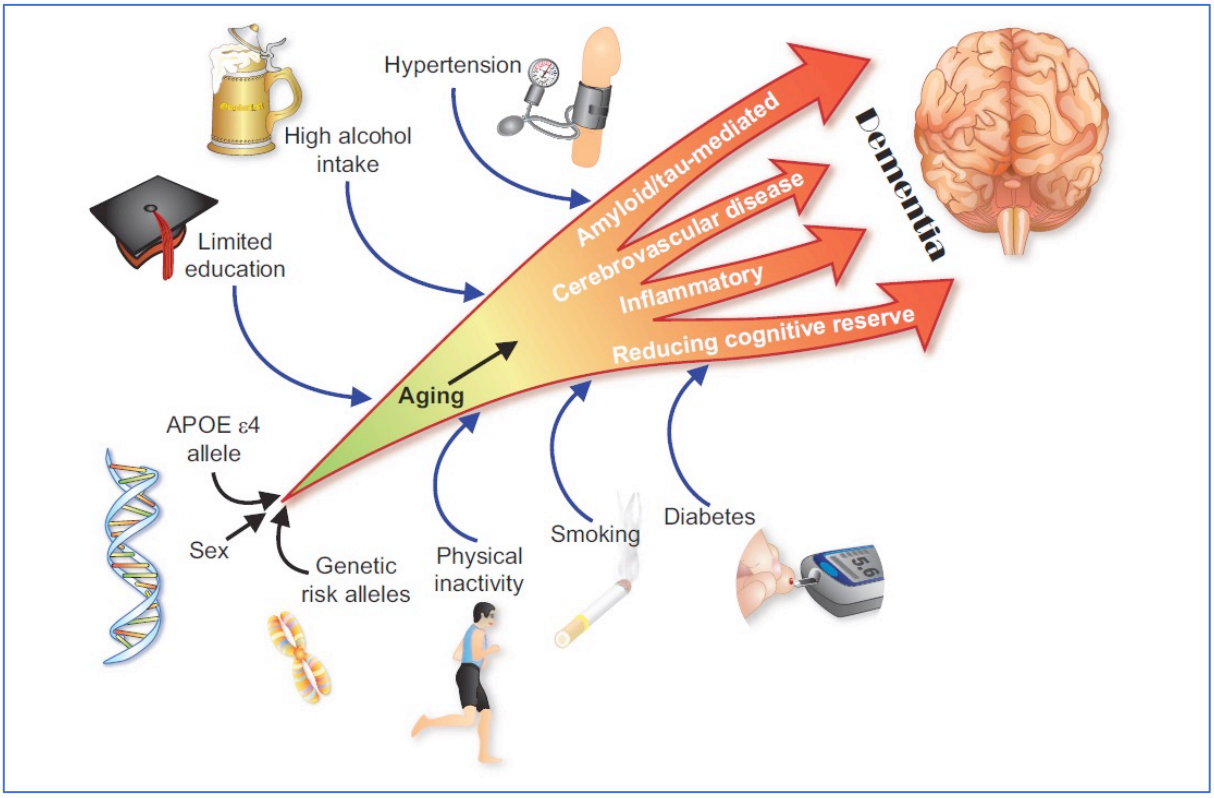

Figure 1. Risk factors for dementia. Several established risk factors contribute to dementia risk: these can be divided in to those which are unmodifiable, which are age, sex, and genetic risk, and potentially modifiable risk factors, which include low level of education, physical inactivity, high alcohol intake, smoking, hypertension and diabetes. These interact throughout the life-course to increase dementia risk by amyloid and tau-mediated neuropathology, cerebrovascular and inflammatory mechanisms and reduced cognitive reserve. The linked article by Rasmussen et al (8) has generated a colour coded risk calculator where green indicates low risk and red shows high risk of developing dementia during the subsequent 10 years.

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Conflict of interest

None declared.

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