

Dementia risk: time matters

Dementia is one of the major global health challenges. With the growing number of older adults in society, dementia poses an increasing threat to global health and has been defined as a public health and social care priority worldwide by WHO.¹ Despite major advances in research on new treatments for dementia, no breakthrough regarding disease-modifying therapy is in sight. However, reports from 2020 indicate that, in theory, up to 40% of dementia cases could be prevented or delayed.² Several modifiable risk factors for dementia have been identified. However, conclusive evidence regarding their effect is scarce and difficult to obtain, as the risk is often established several decades before cognitive impairment or dementia can be diagnosed. Furthermore, the directionality of the association with some risk factors is disputed, and the issue of reverse causality has been raised. This possibility of reverse causality is particularly relevant as the degenerative process in Alzheimer's disease, the most common form of dementia, probably starts decades before cognitive impairment can be determined.³

To clarify associations and directionality, large population-based cohorts with appropriate assessments of risk, and long follow-up with valid assessments of cognition or dementia endpoints are needed. The UK Million Women Study⁴ provides a unique opportunity to address this, with its huge sample size and long follow-up. In *The Lancet Public Health*, Sarah Floud and colleagues report that the association between dementia risk and non-participation in adult education, cultural or art activities, and voluntary work was attenuated with time, indicating that changes in preclinical dementia states could cause increasing inactivity as people age, rather than inactivity being a risk factor for later, clinically-diagnosed dementia. Previous publications have provided similar results regarding a proposed association between dementia risk and low body-mass index, depression, and physical exercise.⁵ The study by Floud and colleagues is an important contribution to the literature but has some limitations, such as potentially imprecise self-reported measures of risk factor exposure, and registry-based outcome data. Further studies are needed to provide more information on the directionality, strength, and

timing of the association between modifiable risk factors and dementia, from a lifecourse perspective.

Cognitive impairment and dementia disorders are characterised by large heterogeneity in terms of risk factors, cognitive and behavioural symptoms, and pathophysiology. It is crucial to address this heterogeneity when developing precise and effective prevention or treatment strategies. In the expansive literature on the epidemiology of cognitive impairment and dementia, sex or gender have been poorly addressed. Studies usually include sex as an adjustment covariate, but rarely stratify according to sex. It is strongly advised that sex differences are addressed in all aspects of dementia research.⁶

Several studies have shown that women have an advantage over men in tests of verbal memory—the cognitive domain most often affected in Alzheimer's disease—and that this advantage persists into the stage of mild cognitive impairment. This difference between the sexes might affect the timing of diagnosis and treatment initiation.⁷ Most studies on prevalence and incidence of dementia indicate that a higher proportion of women have dementia compared with men, but whether this difference can entirely be explained by women having longer life expectancy than men remains controversial.⁸ Two large UK cohort studies with extensive follow-up, the English Longitudinal Study of Ageing (ELSA) and the Whitehall II study, have already generated several key publications on dementia risk, and in this issue of *The Lancet Public Health*, Mikaela Bloomberg and colleagues⁹ report how education affects sex differences in cognitive ageing, across different levels of education and birth cohorts. The researchers confirmed previous findings regarding differences in cognitive function between the sexes, and that memory decline was slower in women than in men. Furthermore, their findings suggest that there are decreasing sex disparities in education due to secular increases in educational attainment among women, which might attenuate sex differences in future dementia risk. These findings are of great importance for the interpretation of secular trends in dementia epidemiology. The ELSA and Whitehall II studies measured immediate recall and semantic fluency, but further studies are needed to investigate whether these findings also apply to other cognitive domains,



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such as delayed recall, which is more closely associated with Alzheimer's disease, or if changing sex disparities in education across birth cohorts more directly impacts dementia risk. If access to education can explain some of the difference in dementia risk between sexes, this finding could have wide-ranging societal consequences. Although women are outperforming men in educational attainment in many high-income countries, there remains a large gap between sexes in terms of access to education in low-income and middle-income countries.¹⁰

Precision medicine garners increasing interest in dementia research, both in terms of prevention and treatment. The studies by Floud and colleagues and Bloomberg and colleagues contribute to increasing the knowledge base needed to develop a precision medicine approach for dementia. A thorough understanding of the timing and directionality of dementia risk factors and how demographic variables, such as sex and education, affect risk profile and disease phenotype is needed to implement precision medicine in dementia.⁶

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