COMMENTARY

Identifying people at risk of dementia

Commentary on "The combination of olfactory dysfunction and depression increases the risk of incident dementia in older adults" by Kalam *et al.*

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The number of people living with dementia worldwide is projected to rise significantly from 57 million in 2019 to 152 million by 2050, with particularly sharp growth anticipated in Africa and the Middle East (Nichols *et al.*, 2022). The associated costs and health burden of dementia are already substantial and are expected to increase exponentially in the coming years (Xu *et al.*, 2017). To halt this trend, effective treatments and preventive strategies will need to be introduced. However, several potential barriers will need to be addressed.

Dementia is a complex clinical syndrome characterized by diverse physiological and neuropathological changes so that interventions targeting a single risk factor may fail to meaningfully alter current trends. Symptomatic treatment with cholinesterase inhibitors and memantine is approved for use in the management of Alzheimer's disease (AD) (Birks, 2006; McShane *et al.*, 2019), but options to manage other types of dementia are not currently available. Recently introduced disease-modifying treatments for AD, such as aducanumab and lecanemab, have reported statistically significant differences compared to placebo in randomized trials, but differences in cognitive function were at best small and were associated with questionable functional gains (Liu *et al.*, 2021; Walsh *et al.*, 2022). Additionally, certain well-established risk factors for dementia, such as age and genetic mutations and polymorphisms, are not amenable to change, although other factors may be.

The 2020 report for Dementia Prevention, Intervention, and Care highlighted various factors that could play a role in the causation of dementia, including education, hearing loss, head injury, hypertension, alcohol use, obesity, smoking, social isolation, physical inactivity, diabetes, air pollution, and depression, with the latter accounting for nearly 4% of dementia cases (Livingston *et al.*, 2020). Data from the Washington Heights/Inwood Columbia Aging Project have identified additional potentially modifiable risk factors in association with incident dementia, such as isolation and restriction of daily activities (Goldberg *et al.*, 2021). It is in such context that a study published in this issue of the journal offers potential insights into other approaches to identify people at high risk of dementia.

Kalam and colleagues examined participants aged 70–90 years recruited for the Sydney Memory and Ageing Study between 2005 and 2007 (Kalam *et al.*, 2023). The study included 780 out of the original 1037 volunteers. The investigators used a time-series design with two yearly assessments, the last taking place during 2018–2020, when 253 participants completed their final evaluation. The main outcome of interest was incident dementia (based on DSM-IV criteria), with olfaction (assessed using the Brief Smell Identification Test, BSIT) and depression (defined by antidepressant use or a score of 5 or greater on the 15-item Geriatric Depression Scale) used as the main explanatory measures. The analyses showed that the presence of a depression marker increased the risk of dementia during follow-up, while better olfaction was associated with decreased risk. These associations were independent of age, sex, educational background, Mini-Mental State Examination (MMSE) score, cardiovascular risk score, and APOE4 status. Consistent with these results, data from the Mayo Clinic Study of Aging revealed that olfaction scores strongly predict incident mild cognitive impairment and incident dementia over a 3.5-year follow-up period (Roberts *et al.*, 2016). However, it is still unclear whether poor olfaction is merely an early marker of dementia or a potentially reversible risk factor. The association between depression and incident dementia reported in the Sydney Memory and Ageing Study is a little more contentious. Defining depression based on antidepressant use may introduce error because as many as

45% of people dispensed antidepressants do not have a depressive disorder (Wong *et al.*, 2016). Even when clinically significant symptoms of depression are present, these may instead represent an early clinical manifestation of an ongoing dementia syndrome (Almeida *et al.*, 2017), and the introduction of antidepressant treatment may fail to reduce the risk of mild cognitive impairment or dementia among older adults at risk (Chan *et al.*, 2019). Nevertheless, the findings reported by Kalam *et al.* (2023) highlight the need for clinicians to be vigilant about the increased risk of dementia when poor olfaction and depression markers are present in later life.

Other factors may modulate or mediate the risk of dementia in older age. For example, Krishna and colleagues reported that measures associated with early cognitive development, such as birth weight, maternal educational achievement, and adult leg length, were good predictors of cognitive performance in later life (Krishna *et al.*, 2022), a finding that is consistent with the results of studies from other emerging economies (Scazufca *et al.*, 2008). In addition, measures of early or mid-life adversity, such as limited educational attainment and low socioeconomic status (Krishna *et al.*, 2022; Scazufca *et al.*, 2010), have also been associated with declining cognitive function in later life. If these factors are causally related to cognitive impairment, population-based interventions targeting them could contribute to reducing the risk of dementia in the coming decades. Additionally, better management of cardiovascular risk factors in mid-life may explain the recent decline in the prevalence of dementia in some industrialized countries among specific age groups (Dobson *et al.*, 2023; Farina *et al.*, 2022), offering hope that the anticipated surge in dementia cases over the next three decades may not eventuate. However, the timing of such interventions may be critical. For example, randomized controlled trials targeting multiple cardiovascular risk factors concurrently (such as smoking, diet, body mass, physical activity, blood pressure, lipids, and fasting glucose) have not led to improved cognitive outcomes or reduced risk of dementia among community-dwelling adults in their 70s (Hoevenaar-Blom *et al.*, 2021; van Charante *et al.*, 2016). This lack of benefit could be attributed to the older age of participants, or to the fact that the intervention did not target other more relevant risk factors for dementia in this age group.

There are yet other reasons to believe that the future may not be as bleak as some predictions seem to suggest. Our understanding of the clinical and pathophysiological mechanisms associated with AD, dementia with Lewy bodies (DLB), frontotemporal dementia (FTD), and vascular dementia has improved markedly over the past decade. This progress has led to the testing of novel interventions capable of improving the clinical outcomes of people at risk of dementia. For instance, the introduction of thrombolysis (Emberson *et al.*, 2014) and thrombectomy for the management of acute ischemic strokes (Nogueira *et al.*, 2018) has greatly enhanced the clinical outcomes of stroke survivors, and this will most likely contribute to reducing the health burden associated with poststroke cognitive impairment in the coming years. Significant progress has also been made in identifying reliable biomarkers of AD pathology, such as blood tests for the measurement of plasma phosphorylated tau (p-tau181, p-tau217, and p-tau231) (Ashton *et al.*, 2023; Hansson *et al.*, 2022). Similar advancements may also benefit individuals at risk of FTD (Benussi *et al.*, 2021) and DLB (Coughlin *et al.*, 2020). The expectation is that imaging, biological, lifestyle, and clinical markers (such as those described by Kalam *et al.*) will collectively contribute to the development of robust and specific predictive models of dementia that will be capable of identifying high-risk populations for targeted interventions.

Although the exact distance that remains to be traveled is uncertain, at least we seem to be moving along a promising route.

Conflict of interest

The author has no conflict of interest to declare.

References

Almeida, O. P., Hankey, G. J., Yeap, B. B., Golledge, J. and Flicker, L. (2017). Depression as a modifiable factor to decrease the risk of dementia. *Translational Psychiatry*, 7, e1117.

Ashton, N. J. *et al.* (2023). Plasma and CSF biomarkers in a memory clinic: head-to-head comparison of phosphorylated tau immunoassays. *Alzheimers & Dementia*, 19, 1913–1924.

Benussi, A. *et al.* (2021). Prodromal frontotemporal dementia: clinical features and predictors of progression. *Alzheimers Research & Therapy*, 13, 188.

Birks, J. (2006). Cholinesterase inhibitors for Alzheimer's disease. *Cochrane Database of Systematic Reviews*, 2006, CD005593.

Chan, J. Y. C., Yiu, K. K. L., Kwok, T. C. Y., Wong, S. Y. S. and Tsoi, K. K. F. (2019). Depression and antidepressants as potential risk factors in dementia: a systematic review and meta-analysis of 18 longitudinal studies. *Journal of the American Medical Directors Association*, 20, 279–286.

Coughlin, D. G., Hurtig, H. I. and Irwin, D. J. (2020). Pathological influences on clinical heterogeneity in Lewy body diseases. *Movement Disorders*, 35, 5–19.

Dobson, A. J., Flicker, L., Almeida, O. P., Waller, M. and Anstey, K. (2023). Different estimates of the prevalence of dementia in Australia, 2021. *Medical Journal of Australia*, 218, 320–321.

Emberson, J. et al. (2014). Effect of treatment delay, age, and stroke severity on the effects of intravenous thrombolysis with alteplase for acute ischaemic stroke: a meta-analysis of individual patient data from randomised trials. *The Lancet*, 384, 1929–1935.

Farina, M. P., Zhang, Y. S., Kim, J. K., Hayward, M. D. and Crimmins, E. M. (2022). Trends in dementia prevalence, incidence, and mortality in the United States (2000–2016). *Journal of Aging and Health*, 34, 100–108.

Goldberg, T. E., Choi, J., Lee, S., Gurland, B. and Devanand, D. P. (2021). Effects of restriction of activities and social isolation on risk of dementia in the community. *International Psychogeriatrics*, 33, 1207–1215.

Hansson, O. et al. (2022). The Alzheimer's Association appropriate use recommendations for blood biomarkers in Alzheimer's disease. *Alzheimers & Dementia*, 18, 2669–2686.

Hoevenaar-Blom, M. P. et al. (2021). Targeting vascular risk factors to reduce dementia incidence in old age: extended follow-up of the prevention of dementia by intensive vascular care (preDIVA) randomized clinical trial. *JAMA Neurology*, 78, 1527–1528.

Kalam, S., Numbers, K., Lipnicki, D. M., Lam, B. P., Brodaty, H. and Reppermund, S. (2023). The combination of olfactory dysfunction and depression increases the risk of incident dementia in older adults. *International Psychogeriatrics*.

Krishna, M. et al. (2022). Size at birth, lifecourse factors, and cognitive function in late life: findings from the MYsore study of Natal effects on Ageing and Health (MYNAH) cohort in South India. *International Psychogeriatrics*, 34, 353–366.

Liu, K. Y., Schneider, L. S. and Howard, R. (2021). The need to show minimum clinically important differences in Alzheimer's disease trials. *The Lancet Psychiatry*, 8, 1013–1016.

Livingston, G. et al. (2020). Dementia prevention, intervention, and care: 2020 report of the Lancet Commission. *The Lancet*, 396, 413–446.

McShane, R. et al. (2019). Memantine for dementia. *Cochrane Database of Systematic Reviews*, 3, CD003154.

Nichols, E. et al. (2022). Estimation of the global prevalence of dementia in 2019 and forecasted prevalence in 2050: an analysis for the Global Burden of Disease 2019. *The Lancet Public Health*, 7, E105–E125.

Nogueira, R. G. et al. (2018). Thrombectomy 6 to 24 hours after stroke with a mismatch between deficit and infarct. *New England Journal of Medicine*, 378, 11–21.

Roberts, R. O. et al. (2016). Association between olfactory dysfunction and amnestic mild cognitive impairment and Alzheimer disease dementia. *JAMA Neurology*, 73, 93–101.

Scazufca, M., Almeida, O. P. and Menezes, P. R. (2010). The role of literacy, occupation and income in dementia prevention: the Sao Paulo Ageing & Health Study (SPAH). *International Psychogeriatrics*, 22, 1209–1215.

Scazufca, M. et al. (2008). Risk factors across the life course and dementia in a Brazilian population: results from the Sao Paulo Ageing & Health Study (SPAH). *International Journal of Epidemiology*, 37, 879–890.

van Charante, E. P. M. et al. (2016). Effectiveness of a 6-year multidomain vascular care intervention to prevent dementia (preDIVA): a cluster-randomised controlled trial. *The Lancet*, 388, 797–805.

Walsh, S., Merrick, R., Richard, E., Nurock, S. and Brayne, C. (2022). Lecanemab for Alzheimer's disease. *British Medical Journal*, 379, o3010.

Wong, J., Motulsky, A., Eguale, T., Buckeridge, D. L., Abrahamowicz, M. and Tamblyn, R. (2016). Treatment indications for antidepressants prescribed in primary care in Quebec, Canada, 2006-2015. *Journal of the American Medical Association*, 315, 2230–2232.

Xu, J. F., Zhang, Y. Q., Qiu, C. X. and Cheng, F. (2017). Global and regional economic costs of dementia: a systematic review. *The Lancet*, 390, S47.