Health conditions linked to heightened risk of Alzheimer's disease

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Although dementia can affect young adults, the average age of diagnosis is older than 80 years, and therefore most people with dementia are expected to have other illnesses. Understanding the complex dynamics of these pre-existing conditions is a major contemporary dementia research challenge. Some illnesses accelerate neurodegeneration, whereas others co-occur because of shared causes or older age. A third group of illnesses are caused by the preclinical stage before symptomatic dementia and a fourth group by people with dementia being unable to look after their own needs and organise care.

National registries of electronic health records provide an opportunity for well powered analyses on comorbidities preceding dementia onset. In *The Lancet Digital Health*, Thomas Nedelec and colleagues[1] reported a new register study based on the Health Improvement Network from general practitioner record databases. The authors chose a hypothesis-free data-driven approach to examine 123 health conditions coded by the International Classification of Diseases, 10th revision, as predictors of dementia. Although a data-driven approach is standard practice in rapidly progressing omics research, it is rarely used in epidemiological studies of dementia risk factors.[2,3] This innovative feature and large sample sizes are major strengths of the study. Compared with the traditional hypothesis-testing approach, data-driven epidemiological research is less subject to investigator biases, such as selective reporting of expected findings. This approach has a greater potential to report null effects in addition to significant associations, a greater capacity to compare effect sizes to evaluate the relative importance of different diseases in predicting dementia, and, potentially, more policy relevance because a wider range of risk factors is covered.

The retrospective case-control design of the new study included 39 672 patients with Alzheimer's disease from the UK (20 214 patients) and France (19 458 patients) with a median age of 80–81 years at diagnosis (81 years [IQR 76–86] in the UK and 80 years [75–85] in France) and 39 672 age-matched and sex-matched controls with no record of Alzheimer's disease. Nedelec and colleagues[1] set the minimum follow-up for health conditions diagnosed before dementia at 2 years and the maximum at 15 years.

After controlling for multiple testing, none of the 123 general practitioner-diagnosed health conditions were robustly related to Alzheimer's disease 10–15 years before diagnosis, although memory loss and hearing loss were too rare to test associations in the French dataset. On multivariate analysis, only anxiety, constipation, spondylosis, memory loss, and abnormal weight loss were associated with a future diagnosis of Alzheimer's disease over the next 2–10 years. However, for example, depression and anxiety often occur together and were the first conditions associated with Alzheimer's disease at least 9 years before diagnosis. Considering every illness separately in this way might mean a loss of data.

These findings have implications for risk stratification on the basis of general practitioner records. The odds ratios for the identified risks for Alzheimer's disease were modest, varying from 1·16 (95% CI 1·04–1·28) to 1·39 (1·14–1·68) for diagnoses other than weight loss. These low odds ratios combined with the fact that some conditions, such as constipation and mental health problems, are common in dementia-free older populations means the findings are insufficient for general practitioners to identify patients at high risk of Alzheimer's disease. As a next step, future studies could examine whether specific clusters or cascades of diseases (multimorbidities) might be more strongly related to future dementia. This approach seems possible because frailty, which shares components with these Alzheimer's disease-related conditions (eg, abnormal weight loss and fatigue), is characterised by an accumulation of several age-related deficits that might make older adults susceptible to Alzheimer's disease dementia with less neuropathology.[4]

The findings from Nedelec and colleagues[1] also raise important aetiological questions. For example, there is no consensus about the causal relevance of depression and anxiety in dementia aetiology.[5] It is possible that these factors contribute to dementia risk and are a consequence of preclinical dementia or a response to awareness of cognitive decline. Midlife obesity is an established risk factor for old-age dementia.[5]

Nonetheless, mean body-mass index near dementia diagnosis is lower in patients than healthy controls,[6] supporting the notion that preclinical dementia causes abnormal weight loss. This finding is consistent with the observations of Nedelec and colleagues on abnormal wegith loss in both UK and French cohorts.[1] There is a similar pattern in blood pressure, which did not appear as a risk factor, possibly partly because of this preclinical effect of abnormal weight loss.[7] Constipation is a recognised symptom of Lewy body and Parkinson dementias.[8,9] This new link with Alzheimer's disease requires replication to ascertain whether it is a true finding or an artefact arising from undiagnosed dementia subtypes in general practitioner records.

Nedelec and colleagues[1] hypothesise that immune dysfunction could underlie spondylosis and Alzheimer's disease. We hope this hypothesis will inspire basic scientists, immunologists, and experts in musculoskeletal pathophysiology to study the mechanisms linking spondylosis and Alzheimer's disease. These mechanisms could relate for instance to chronic expression of circulating pro-inflammatory markers (inflammaging), compromised adaptive immunity (eg, thymic involution), and altered peripheral-central immune cross—talk (dysfunctional blood brain barrier), as they are increasingly recognised as cardinal features of dementia aetiology.[10]

We declare no competing interests.

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