

LETTER

To understand the diabetes–dementia association, frailty may prove more fruitful than neuropathology

The study of Sadrolashrafi and colleagues recently published in the journal¹ on the association between type 2 diabetes mellitus (T2DM) and Alzheimer's disease pathology (ADP) raises important questions about the study of associations in dementia. Their finding that "T2DM is not associated with increased AD pathology in clinically and pathologically confirmed cases of AD" (p. 4¹) may at first seem paradoxical: people with T2DM generally have worse cognitive health,² and people with a greater burden of ADP are thought to have a greater probability of worsened dementia.³ Would it not be reasonable to expect them to be correlated? But this study and others like it suggest that it is not useful to understand T2DM as a stochastic factor contributing to cognitive decline for a given level of ADP. Instead, they suggest it might be most useful to move away from the centrality of ADP when considering dementia outcomes.

The concept of frailty—the accumulation of health deficits leading to worsened homeostasis and overall health outcomes—may be more useful than ADP for modelling cognitive decline. It is notable that like T2DM, "frailty contributes to the risk for dementia beyond its relationship with the burden of traditional dementia neuropathologies"⁴ and longitudinal changes in frailty are "not significantly associated with neuropathology after controlling for possible confounders."⁵ Furthermore, diabetes is highly prevalent in frail older patients⁶ and may be best understood as a contributing factor to mixed dementia, which becomes increasingly relevant with advanced age, as opposed to more focal forms of earlier-onset dementia.⁷

In conclusion, the study of Sadrolashrafi and colleagues and others like it suggest that ADP may not be the most useful prism through which to understand and study the role of different contributions to dementia such as T2DM. Instead, frailty may offer a more fruitful framework (add r), particularly when studying the very old.

CONFLICTS OF INTEREST

The author has no financial declarations or conflicts of interest to report.

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