Life expectancy in dementia subtypes: exploring a leading cause of mortality

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Dementia affects around 40 million people worldwide, and due to the rapid ageing of the population, especially in low-income and middle-income countries, this number is expected to double over the next two decades.[1] Dementia is known to be associated with shortened life expectancy, making it the fifth leading cause of death in high-income countries.[2] Dementia, also called major neurocognitive disorder, is clinically defined as a cognitive disorder severe enough to affect activities of daily living, leading to loss of autonomy, which gradually worsens over time. Many neurodegenerative or non-neurodegenerative diseases can lead to a dementia state. Alzheimer's disease (AD) is the most common one, accounting for 60–80% of all dementia cases. Vascular dementia is another frequent cause of dementia, accounting for around 20% of dementia cases in North America and Europe.[3] Frontotemporal lobar degeneration is a frequent cause of dementia before the age of 60 years, and should be suspected in the case of early onset dementia, particularly when associated with a history of several familial cases. Over the past decade, Lewy body dementia has increasingly been recognised as a frequent cause of dementia and is now considered to be the second leading cause of dementia after AD.[4] Lewy body dementia is likely to be widely underdiagnosed, due to the variability of its initial clinical presentations as well as the lack of awareness of this pathology. Many studies have explored the effect of dementia, regardless of its cause, on mortality, or have focused only on AD dementia, but whether life expectancy differs by subtype of dementia remained largely unknown.

In *The Lancet Healthy Longevity*, Chih-Sung Liang and colleagues[5] did an impressive systematic review and meta-analysis of mortality risk in people with AD and other dementia subtypes. They analysed 78 studies encompassing 63 125 cases of dementia and 152 353 controls without dementia and found that people with dementia have a much higher mortality risk compared with people without dementia (hazard ratio [HR] 5·9, 95% CI 3·5–9·9). When analysing the data by subtype of dementia, the highest HRs of mortality were found for Lewy body dementia (17·9, 5·9–54·5) and frontotemporal degeneration (15·3, 4·3–53·7) compared with the control group, although these estimates were based on few studies with small samples, resulting in large confidence intervals. Given the higher number of studies that compared survival time between dementia subtypes and not with a control group, the meta-analysis of these studies provides robust findings. The median survival time after AD diagnosis was estimated to be 5·8 years, whereas it was on average 1·1 (0·7–1·5) years lower among patients with non-AD dementia, with no differences by subtype of non-AD dementias.

During the past decade, research on dementia biomarkers has been crucial to improving diagnostic criteria and has allowed a more accurate diagnosis of dementia subtypes. Nevertheless, the natural history of these diseases remains poorly known, particularly the prognostic factors of the disease. The work of Liang and colleagues provides useful insights to show that mortality associated with non-AD dementias is higher than that seen in AD dementia. These findings should be interpreted with caution. One of the most important considerations to keep in mind is probably that previous studies have mainly used diagnostic criteria for dementia subtypes on the basis of clinical evaluation only, which has been shown to have poor specificity. Neuropathological studies have shown that the specificity of the clinical criteria used for AD dementia diagnosis is around 70%, leading to many false positives, with patients wrongly diagnosed to have AD although having another dementia subtype. Another source of complexity is the neuropathological demonstration of the entanglement of various co-pathologies between the several proteinopathies known to be associated with neurodegenerative diseases. Evidence has shown that co-pathologies nearly always exist in cases of AD,[6] particularly associations with Lewy body dementia and cerebral amyloid angiopathy brain lesions. Patients diagnosed with Lewy body dementia who have evidence of AD biomarkers in cerebrospinal fluid have been shown to have an increased mortality risk.[7] Furthermore, the limbic-predominant age-related TDP-43 encephalopathy syndrome has been shown to

be a frequent cause of dementia in people aged 80 years or older,[8] and is challenging to diagnose on the basis of clinical symptoms due to its high similarities in clinical expression with AD.

In conclusion, there is an urgent need to better understand the natural history of dementia subtypes and to identify corresponding prognostic factors. Non-AD dementias appear to have an even poorer prognosis than AD dementias, particularly in the case of Lewy body dementia. In the near future, biomarker-based epidemiology[9] will hopefully help to better understand the complex interplay involved in the various proteinopathies associated with dementia.[10]

We declare no competing interests.

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