Frailty and dementia: what can the body tell us about the brain?

Commentary on "Frailty and neuropathology in relation to dementia status: The Cambridge City over-75s Cohort study " by Wallace et al.

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We have been repeatedly confronted with the failure of tau and amyloid-targeting drugs to meaningfully impact the clinical course of dementia due to Alzheimer's disease. Although tau and amyloid biomarkers have shown promise in the early diagnosis of Alzheimer's disease, they will have limited real-world impact until clinically effective, disease-modifying therapies are attainable. Our attention has increasingly turned to prevention strategies, signaled by the recent Lancet Dementia Commission (Livingston *et al.*, 2020), which reported around 40% of dementias worldwide can be prevented or delayed via a number of potentially modifiable risk factors. Wallace and colleagues (Wallace *et al.*, 2021) retrospectively analyzed post-mortem data and found that frailty, a clinical syndrome of systemic vulnerability, predicted dementia risk in the 'oldest-old' that was not accounted for by age or neuropathological burden, supporting the concept that frailty could be a prevention target for dementia.

Frailty is widely conceptualized as a state of enhanced vulnerability to stressors and adverse health outcomes resulting from age-related physiological decline. So far, there is no gold standard for how to measure this broad concept. One approach has been to define a frailty phenotype when three out of five phenotypic criteria (low grip strength, low energy, slowed walking speed, low physical activity, and unintentional weight loss) are fulfilled (Fried *et al.*, 2001). A second approach defines frailty more broadly as the

accumulation of physical, cognitive and functional deficits with increasing age, expressed as a frailty index (Mitnitski, Mogilner and Rockwood, 2001). The frailty index, employed by Wallace and colleagues' study, is usually calculated as a ratio of deficits present to the total number of deficits considered and has been shown to indicate the level of frailty, despite different deficits being considered across different studies (Searle *et al.*, 2008). Reassuringly, the two distinct definitions of frailty appear to correlate (Rockwood, Andrew and Mitnitski, 2007), and there is converging evidence that frailty could be a proxy measure of aging that can independently predict health outcomes in older patient populations, including cognitive impairment and dementia (Fried *et al.*, 2001; Ma *et al.*, 2020; Petermann-Rocha *et al.*, 2020).

In their study, Wallace and colleagues assumed a causal relationship between frailty and dementia to demonstrate the potential impact of frailty prevention on dementia risk. This deserves close consideration, as the relationship does not appear to be a straightforward one. Since the body and brain are generally exposed to the same internal milieu and external environment during an individual's life course, there are potentially many shared contributing factors between frailty and dementia. Consistent with earlier reports (Gordon and Hubbard, 2020), Wallace and colleagues' study reported a higher frailty index in women versus men, and as women are also more likely to receive a dementia diagnosis, this suggests that hormonal and/or behavioral and social differences between men and women could be important contributors to both conditions. Other shared etiological factors include increased inflammation (Wyss-Coray and Rogers, 2012; Soysal *et al.*, 2016), poor vascular health (Graciani Auxiliadora *et al.*, 2016; Sweeney *et al.*, 2019), and social isolation (Gale, Westbury and Cooper, 2018; Sommerlad *et al.*, 2019), and there is likely to be interaction between multiple factors. Frailty could therefore be a correlative marker of dementia vulnerability, via the integration of several physiological, and/or social and functional factors that are common to both conditions, without necessarily having a direct causal role.

Nonetheless, if there is indeed a causal relationship between frailty and dementia, the direction of causation also needs further investigation, as comorbidities can substantially

overlap with the frailty index (Theou *et al.*, 2012). There appears to be overlap between the dementia syndrome and components of the frailty index; over a third of the items in Wallace et al.'s frailty index were functional measures that assessed the participants' ability to manage activities such as shopping, finances, medicine, transportation or housework. Impairments in activities of daily life such as these are directly impacted by neurodegenerative processes. They are also necessary for a dementia diagnosis, so will likely have impacted the individual's functioning for some time before the diagnosis was made. Clinically, it is not uncommon to see patients' nutritional and subsequent physical health decline alongside worsening cognition, as they gradually lose their independence in preparing food, shopping, and remembering whether they have eaten. The field would benefit from longitudinal studies to clarify the nature, direction and extent of a potential causal relationship between frailty and dementia, while facing the challenge of a higher dropout rate in participants with higher levels of frailty (Wallace *et al.*, 2021). It will also be important for future post-mortem studies of dementia in the oldest-old to include analysis of TDP-43 pathology (Nelson *et al.*, 2019), which was not measured in a high number of cases in Wallace and colleagues' study and led to this variable being excluded.

Wallace and colleagues' study demonstrated the potential impact of frailty prevention, calculating that 14.2% of dementia cases in their sample could have been avoided if severe frailty was eliminated at baseline (on average 5.6 years prior to death). This raises wider issues that need further research: when should frailty ideally be assessed or addressed to achieve overall benefit, and can we avoid severe frailty entirely or is it more achievable (but less ambitious) to mitigate the severity of frailty? There are promising findings that some aspects of frailty can be prevented, such as increasing exercise to reduce muscle weakness and physical inactivity, and further research is needed to ascertain whether this improves overall physiological vulnerability and/or translates to lower dementia risk (Van der Elst *et al.*, 2018). Findings from a recent study (Petermann-Rocha *et al.*, 2020) suggested that frailty could be detected from middle-age and was predictive of later dementia, after accounting for shared social-demographic risk factors and multimorbidity. Frailty might be a modifiable risk variable for dementia largely because the two conditions share modifiable risk factors, such as hypertension, smoking,

obesity, physical inactivity, diabetes and low social contact. Interventions to address some, but not all of these, were shown to be cost-effective in terms of preventing dementia (Mukadam *et al.*, 2020), so if severe frailty can be completely prevented, it would need to make economic sense to inform policy.

How can we reconcile the substantial degree of etiological and conceptual overlap between frailty and dementia with the proposal that frailty is a separate entity situated between comorbidity and disability (Fried *et al.*, 2001)? In other areas of medicine, frailty has been employed as a clinical risk stratification tool to predict adverse outcomes via a final common pathway of major comorbidities (Partridge, Harari and Dhesi, 2012). While it is important to explore the potential of frailty interventions to prevent or delay dementia, it would also have relevance as a predictor of (and prevention target for) adverse outcomes in individuals who already have dementia. It would be useful to know, for example, if individuals with dementia and higher levels of frailty are more likely to be hospitalized (Kelaiditi *et al.*, 2016), institutionalized or develop agitation, and whether mitigation of severe frailty in these individuals can meaningfully reduce these risks. Do these individuals require greater social, nutritional, or end-of-life input and caregiver support, and can overall care costs be reduced with frailty interventions? Frailty clearly measures something that is clinically relevant in older adults, and its potential as an integrative marker of adverse cognitive and functional outcomes in this population needs to be fully investigated. Wallace and colleagues concluded that single-mechanism treatments are unlikely to be widely successful in late-onset dementia. Their study emphasizes the need to further elucidate mechanisms by which frailty contributes to dementia risk and to target the body and brain to cumulatively reduce the burden experienced by individuals with dementia and their caregivers.

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