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Understanding frailty to predict and prevent dementia

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Frailty is a crucial intermediate state of the ageing process, characterised by an increased risk of negative health-related events, including hospitalisation and death.[1] More than 40 operational definitions of frailty have been proposed, but three main approaches are commonly used. The first approach is based on the notion of a physical and biological frailty phenotype, for which the operational definition assumes that there is a state of negative energy balance, sarcopenia, diminished muscle strength, and low tolerance for exertion.[1] An alternative, and potentially complementary, definition of frailty is provided by the so-called deficit accumulation model, which incorporates several factors ranging from disease states, symptoms, and signs, to abnormal laboratory values. Deficits are listed and then divided by the total number of deficits identified in a patient to yield a frailty index.[1] The third approach to frailty is based on the biopsychosocial model, which mixes physical and psychosocial domains, and expands the construct of frailty toward the social sciences.[1,2] Due to its multidimensional and multisystem nature, frailty includes physical, cognitive, and psychosocial phenotypes. Different frailty phenotypes are related to neuropathological features of Alzheimer's disease and other dementias.[1] These frailty–cognition links and the potential for reversibility of frailty phenotypes suggest that these phenotypes might be important targets for the prevention of dependency and for secondary dementia prevention in the early or asymptomatic stages of the disease.

The strong links of frailty with Alzheimer's disease and other dementias are now confirmed in *The Lancet Neurology* by Lindsay Wallace and colleagues[3] in a cross-sectional analysis of data from 456 participants from the Rush Memory and Aging Project. Wallace and colleagues suggest that frailty, identified with a deficit accumulation-based frailty index, might be a substantial moderator of the relationship between Alzheimer's disease pathology (derived from counts of neuritic plaques, diffuse plaques, and neurofibrillary tangles) and dementia status, such that frailty makes people more susceptible to dementia. They found a significant interaction between frailty and Alzheimer's disease pathology (odds ratio 0·73, 95% CI 0·57–0·94; p=0·015). The frailty–pathology interaction remained significant after excluding from the frailty index variables on activities of daily living (eg, shopping, handling finances, and meal preparation) and controlling for the effects of risk factors linked to both frailty and Alzheimer's disease pathology (eg, history of stroke, hypertension, diabetes, congestive heart failure, and depression).[3]

Frailty is considered primary or preclinical when the state is not associated directly with a specific disease or when there is no substantial disability.[4] In this context, the physical or biopsychosocial models seem more appropriate to define primary frailty. By contrast, frailty is considered secondary or clinical when it is associated with known comorbidities, such as overt cardiovascular disease, depression, disability, or a combination thereof,[4] which is better defined with the deficit-accumulation-based frailty index used in the study by Wallace and colleagues.[3] This distinction is central in identifying frailty phenotypes with the potential to predict and prevent dementia, using novel models of risk that introduce modifiable factors.

Among frailty phenotypes, cognitive frailty is a clinical construct with operationalised criteria that describe

coexisting physical frailty and mild cognitive impairment.[1] In a recent population-based study,[5] vascular factors and depressive symptoms were hypothesised to change the risk of dementia and all-cause mortality linked to the presence of cognitive frailty. Multidomain interventions might be more effective than monodomain interventions on frailty status, and physical exercise seems to have an essential role in the multidomain intervention, whereby additional interventions might lead to further improvement when physical exercise is part of the intervention. Two recent randomised clinical trials have confirmed this hypothesis that exercise is essential.[6,7] The results of exploratory subgroup analyses from the MAPT trial[6] suggested that the combination of n-3 polyunsaturated fatty acids and a multidomain lifestyle intervention or a multidomain intervention alone might help to slow cognitive decline in old (≥70 years) people with memory complaints at risk of cognitive decline (high dementia risk score and a positive amyloid PET scan at baseline; ie, frail people).[6] Furthermore, recent findings from the LIFE trial[7] showed that a 24-month structured, moderate-intensity physical activity programme reduced the severity of cognitive frailty compared with a health education programme in sedentary old (70–89 years) people and that this benefit was not modified by underlying inflammation. However, in non-demented old (65–84 years) people with increased inflammation (fibrinogen >339 mg/dL), cognitive frailty had a significant additional predictive effect on the risk of disability compared with the individual components of cognitive frailty (ie, physical frailty or mild cognitive impairment).[8]

The vulnerability of old adults at risk of developing dementia is not completely captured by the biological perspective (physical or deficit accumulation approaches), and the biopsychosocial model might add important value in both the assessment and targeting of interventions in patients with frailty; however, at present, this model is not fully operationalised.[2] In light of current knowledge on the cognitive frailty phenotype, secondary preventive strategies for cognitive impairment and physical frailty can be suggested. For instance, individualised multidomain interventions can target physical, nutritional, cognitive, and psychological domains that might delay the progression to overt dementia and secondary occurrence of adverse health-related outcomes, such as disability, hospitalisation, and mortality.

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