A multidimensional frailty approach in predicting and preventing dementia

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Frailty, a critical intermediate status of the ageing process, can be defined as a unidimensional entity, mainly based on the physical or biological dimension, or as a non-specific multidimensional status based on a deficit accumulation model and different and interconnected domains.[1] Due to its multidimensional and multisystem nature, frailty could include physical, sensorial, social, cognitive, psychological, and nutritional domains or phenotypes that need to be taken into account in its definition, management, and prevention.[2] In particular, the physical frailty unidimensional model, which uses five practically measurable components (ie, exhaustion, involuntary weight loss, low grip strength, slow gait speed, and low energy expenditure), could be associated with late-life cognitive impairment and decline, incident Alzheimer's disease, mild cognitive impairment, vascular dementia, non-Alzheimer's dementias, and Alzheimer's disease pathology.[2] Frailty indexes based on the deficit accumulation model have been associated with late-life cognitive impairment and decline, incident dementia and Alzheimer's disease in hospital-based and population-based studies.[2] Attention should be paid to the possible mechanisms behind reported associations of different frailty operational definitions with cognitive impairment or decline, predementia, and dementia syndromes. Beyond the possible role of vascular or metabolic risk factors, there are several other potential pathways by which frailty could contribute to cognitive decline, including inflammation.[2] Although not completely understood, frailty and its cognitive phenotype share several mechanisms with motoric cognitive risk syndrome, a predementia construct characterised by slow gait and cognitive complaints that also predict dementia.[3]

Despite an increasing body of evidence on the association between frailty and dementia, no study has yet shown an association of the physical frailty phenotype, along with its individual components, with all-cause dementia incidence. In *The Lancet Healthy Longevity*, Fanny Petermann-Rocha and colleagues[4] report findings from a prospective study of 143 215 participants from UK Biobank during a mean follow-up period of 5·4 years. The most notable finding was that physical frailty was associated with a higher risk of dementia incidence and that among the five components used to define frailty, slow gait speed and low grip strength made the largest contributions to dementia incidence. Compared with the other individual components, low grip strength accounted for the greatest proportion of incident dementia cases (8·84%; 95% CI 3·99–13·40). Individuals with slow gait speed were likely to experience dementia 2·3 years (95% CI 1·20–3·25) before those with normal gait speed.

In this regard, motor and cognitive performances appear to share a common, preferential trajectory in terms of their underlying central and peripheral neural control mechanisms. Their association is probably related to neuroanatomical changes. Alterations in specific areas of the brain, such as the primary and supplementary motor cortices, the substantia nigra, and the striatum, are associated with modifications in different components of frailty, in particular, the physical frailty phenotype.[5] Alterations in these brain areas are associated with modifications of the components of physical frailty such as weight loss and gait speed,[5] suggesting that changes in neural systems that control motor function, metabolism, and fatigue could be present in frailty. Other potential mechanisms include decreased energy production or metabolic issues and stress. Sarcopenia, a progressive and generalised skeletal muscle disorder involving the accelerated loss of muscle mass and function, could also be ascribed in a novel frailty phenotype (ie, nutritional frailty contributing to the aforementioned motoric cognitive risk syndrome).[6] Among frailty phenotypes, nutritional frailty was first defined as a state commonly seen in older adults, characterised by sudden, significant sarcopenia or an essential loss of physiological reserves, making the individual susceptible to disability.

In recent years, frailty has been acknowledged as not only a biological or physiological state, but also a multidimensional concept that demands a multidisciplinary approach.[7] The effects of psychosocial and lifestyle factors, in accordance with the biopsychosocial model of frailty, also associated with dementia incidence,[7] combine psychosocial adversity with biological deficits at a crucial stage of the ageing process,[8] culminating in

a cascade of vascular and neurodegenerative changes. The influence of modifiable risk factors has already been incorporated into strategies for dementia prevention, which aim to encourage healthy lifestyles and behaviours, decrease brain damage due to vascular, neurotoxic, inflammatory, or oxidative insults, and to promote mental and social enrichment.[9]

These strategies are supported by the findings of Petermann-Rocha and colleagues.[4] Compared with non-frail people, those with frailty were likely to be older, more deprived, obese, and a current smoker. They were less likely to have a formal education, social activities, or visits from friends or family outside the household. However, in contrast to similar studies, pre-frail and frail individuals with lower levels of deprivation had a higher risk of dementia incidence compared with their counterparts with greater levels of deprivation. Of note, the evaluation of social dysfunction in older age is challenging, because proper validation and distinction across different dimensions, including subjectivity, structural, and functional aspects, are lacking. Several categories of social dysfunction differ only in the degree of health deprivation, not in material deprivation.[9]

Petermann-Rocha and colleagues' findings also suggest that frailty could be associated with dementia risk much earlier than the onset of cognitive impairment.[4] A significant interaction between frailty and age was observed. Although in the study, only older individuals with pre-frailty had a higher risk of dementia compared with non-frail individuals, individuals with frailty who were younger than 60 years had a 5·78-times higher risk of incident dementia compared with a 1·76-times higher risk among those aged 60 years and older, suggesting that the onset of frailty could start much earlier than 60 years. Therefore, the study provided novel evidence regarding the association between frailty and dementia incidence not only in older adults, but also in middle-aged adults, highlighting the importance of the early management of frailty in dementia prevention.

In conclusion, frailty can include different phenotypes, and pathological mechanisms (eg, inflammatory, cardiovascular, or metabolic factors), lifestyle factors (eg, obesity and smoking status), and psychosocial factors involved in the comprehensive construct of cognitive reserve could affect both cognitive and physical trajectories of ageing for an individual.[10]

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