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Body composition as a predictor of cognitive decline in the elderly: what is known so far

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ABSTRACT

Certain aspects of body composition can serve as predictors of cognitive impairment risk, enabling preventive interventions. Adipose tissue plays a complex role in cognitive health and dementia risk. This association appears to be influenced by age, sex and body fat distribution. However, factors like systemic inflammation and metabolic disturbances linked to obesity can negatively impact brain health. Muscle mass and strength are fundamental determinants of cognitive well-being. Interventions designed to increase muscle strength and to prevent muscular loss may hold promises for the maintenance of neurocognitive brain health, based on the role of myokines in pathophysiology and muscle-to-brain axis to healthy aging. Sarcopenia contributes to metabolic dysfunction, inflammation, and neuromuscular deterioration, potentially accelerating cognitive impairment. Sarcopenic obesity presents an elevated risk for adverse health outcomes, including cognitive decline and dementia. Maintaining an optimal balance between muscle and fat mass is crucial. Given these findings, promoting muscle health through resistance training and proper nutrition emerges as a key strategy in preventing cognitive impairment and fostering overall brain health.

Keywords: Dementia; Cognitive decline; Body composition; Adiposity; Sarcopenia

INTRODUCTION

Population ageing brings social, economic and cultural challenges for individuals, families, societies and the global community (United Nations Population Fund &

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HelpAge International, 2012). One of these challenges is related to the occurrence of conditions associated with ageing itself, including neurological alterations, which are the main contributors to Disability Adjusted Life Years (DALYs), i.e. years of healthy life lost due to premature death, illness or disability (Feigin et al., 2019).

Considering neurological changes, normal cognitive ageing can be replaced by mild cognitive impairment. It is estimated that 10 to 20% of the elderly with this last condition develop dementia within 1 year (Morley, 2016; National Institutes of Health - National Institute on Aging, n.d.).

Globally, the prevalence of dementia is expected to increase. In 2019, this condition was the seventh leading cause of death (World Health Organization, 2020), and it is estimated that by 2050 the prevalence will be threefold higher the 57 million people currently affected worldwide (Nichols et al., 2022).

To date, there are no effective treatments for dementias (James & Bennett, 2019), emphasizing the importance of prevention. In this sense, one of the areas that has been studied is the association between cognitive decline and body composition.

Body composition as a predictor of cognitive decline

Adiposity and cognitive decline

Excess of adiposity characterizes obesity and is associated with cognitive impairment and dementia. This association appears to be influenced by age, sex and body fat distribution (Li et al., 2021; Raji et al., 2023).

Excess of adiposity, specially visceral adipose tissue (Anand et al., 2022; Cannavale et al., 2021), epicardial adipose tissue (Mazzoccoli et al., 2014; Verrusio et al., 2019), and non-alcoholic fatty liver disease (Gerber et al., 2021; VanWagner et al., 2017) is considered a risk factor for dementia (Li et al., 2021; Raji et al., 2023). However, in older adults (>80 years), excess adiposity has been associated with a lower risk of cognitive impairment (Li et al., 2021).

Although excess adiposity has the same metabolic consequences, the risk of dementia in people with higher levels of total and regional fat (particularly subcutaneous and gynoid) seems to be lower (Emmerzaal et al., 2015; Mooldijk et al., 2023). This protective effect may be related to the adipokines leptin and estrogen.

Leptin is primarily secreted by adipocytes and exerts its main biological function in the brain (Stephens et al., 1995). In addition to its role in the neuroendocrine regulation of food intake, accumulating studies have suggested that leptin has notable effects on neuroprotection (Fernandez-Martos et al., 2017; Liu et al., 2021), as well as on improving learning and cognitive function in Alzheimer´s disease (Farr et al., 2006; Searcy et al., 2012). In the older elderly and due to the weight loss, there is a decrease in leptin levels, increasing the risk of dementia, which is not so marked in older adults with excess adiposity (Holden et al., 2009; Mooldijk et al., 2022). Nevertheless, higher visceral adipose tissue was associated with amyloid-β (S. Kim et al., 2022; Weinstein et al., 2022), since excessive secretion of leptin by high visceral adipose tissue could inhibit the transport of amyloid-β precursor protein and promote

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the synthesis of amyloid-β (Fewlass et al., 2004).

Accumulating evidence has linked systemic inflammation to decreasing cognitive health and risk of dementia, especially in the later part of life (Sartori et al., 2012). Depletion of estrogen due to menopausal transition is also associated with a decline in cognitive health in women (Pertesi et al., 2019). This happens since estrogen potentially enhances verbal memory and executive function (Au et al., 2016). Moreover, the depletion of estrogen due to menopause is associated with increasing central obesity, that causes chronic inflammation, which is observed both in the brain and systemically (Christensen & Pike, 2015). Inflammatory processes may mediate the association between low levels of estrogen and cognitive changes (Au et al., 2016). On the other hand, estrogens have been associated with brain health, with adipose tissue being the major source of these molecules in postmenopausal women (Zárate et al., 2017).

However, it cannot be ruled out that the association between high adiposity and a lower risk of dementia in older adults may be the result of reverse causality, given the loss of weight and fat mass that occurs in the pre-clinical phase of dementia (Knopman et al., 2007), resulting in lower weight and fat in people diagnosed with dementia.

Addicionally, different regional fat depots may affect, not only, cognition, but different regions of the brain. The association between excess adiposity and inflammation, metabolic syndrome, insulin resistance, and loss of endothelial integrity may contribute to the impairment of brain health and increase the risk of dementia (Boccara et al., 2023). Beyond cognitive decline, regional fat depots, especially visceral and in the liver, is associated with cortical thinning (Beller et al., 2019; H. Lee et al., 2021) and white matter hyperintensities (Cárdenas et al., 2020), which have been linked to cognitive decline, Alzheimer's disease and dementia (Kaye et al., 1997).

Considering the above, different neurobiological alterations and different cognitive-related outcomes may be the result of different regional fat characteristics.

Muscle and cognitive decline

Another aspect related to body composition is muscle mass and muscle strength/function. Low levels seem to be associated with a higher risk of cognitive impairment in the elderly (Arosio et al., 2023; Beeri et al., 2021; L. Chen, 2023; Chung et al., 2021; Cruz-Jentoft et al., 2019; Lin et al., 2023; Oudbier et al., 2022).

The muscle plays a critical role in many metabolic processes that can improve health or increase the risk of disease. Nevertheless, skeletal muscle is characterized by rapid changes in rates of protein synthesis and degradation in response to physical activity and inactivity, inflammation, and nutritional and hormonal status (Evans et al., 2023).

Sarcopenia is a progressive and generalized skeletal muscle disorder that is associated with increased likelihood of adverse outcomes including falls, fractures, physical disability and mortality. It involves an accelerated loss of muscle mass and function (Cruz-Jentoft et al., 2019). Metabolic alterations, inflammation, mitochondrial dysfunction, declines in cellular stemness, altered intracellular signaling, and age-

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related neuromuscular derangement are some determinants of sarcopenia (Arosio et al., 2023), which prevalence is 10-16% (Yuan & Larsson, 2023). The diagnosis of sarcopenia is made by the presence of low muscle quantity and quality and is severe when physical performance is impaired (Cruz-Jentoft et al., 2019).

The muscle produces and releases myokines, cytokines, and chemokines, which are involved in multiple functions. These proteins can hold both pro- and anti-inflammatory signaling roles (Severinsen & Pedersen, 2020) and they can mediate inter-organ signaling, particularly muscle–brain crosstalk, to support cognitive function, memory, and motor coordination (S. Kim et al., 2019). Thus, sarcopenia may represent a risk factor for cognitive function and dementia.

The exercise induces the myokine release, which mediates a crosstalk between the brain and the muscle (W. Chen et al., 2021; Severinsen & Pedersen, 2020), and improves the cognition and the memory in older adults (S. Kim et al., 2019), besides all the improvement on the functional capacity. Exploring this idea, exercise seems to reduce the permeability of the blood-brain barrier, boost antioxidant capacity, increase the production of neurotrophic factors, reduce oxidative stress and have anti-inflammatory effects (Małkiewicz et al., 2019; Morawin et al., 2023).

On the other hand, physical inactivity leads to cognitive deficit and neurodegenerative events, because of abnormal synthesis and production of myokines. This dysfunctional myokine secretion may cause cognitive impairment and dementia due to systemic inflammation, impaired muscle glucose metabolism, deficient brain protein metabolism, and increased oxidative stress from dysfunctional mitochondria (Oudbier et al., 2022).

So, it seems that muscle contraction improves brain health. In contrast, in sarcopenia, there is an imbalance in myokine secretion (Cruz-Jentoft et al., 2019; S. Kim et al., 2019), which promotes and accelerates the progression of changes in the central nervous system that lead to cognitive decline (Beeri et al., 2021).

The action of myokines is not limited to the brain. They contribute to the autocrine regulation of muscle metabolism and to the paracrine/endocrine regulation of other adjacent/distant organs (W. Chen et al., 2021), representing a key element in the intervention of sarcopenia. Although exercise is the main intervention for increasing and maintaining muscle mass, strength and function, it is supported by diet (Calvani et al., 2023), and the prescription of exercise and nutritional intervention is recommended as soon as low muscle strength is detected (Cruz-Jentoft et al., 2019). Interventions designed to increase muscle strength, particularly among middle-aged adults, may hold promises for the maintenance of neurocognitive brain health (Esteban-Cornejo et al., 2022).

Sarcopenic obesity

Sarcopenic obesity is characterized by the concomitant occurrence of obesity and sarcopenia, which could enhance their independent effects on insulin resistance, inflammation, and vascular dysfunction (Jensen, 2008). Consequently, sarcopenic obesity tends to elevate the risk of cardio-cerebrovascular diseases and diabetes (Zhang et al., 2024). Addicionally, these

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conditions are considered as risk factors for dementia (Khadra et al., 2019; Sabia et al., 2019), as they may be associated with vascular injury and the build-up of misfolded amyloid-β peptides and tau proteins (Scheltens et al., 2021). So, sarcopenic obesity may lead to dementia and may enhance the risk of chronic diseases, which are related to dementia (Zhang et al., 2024).

Hence, sarcopenic obesity plays a major role in increasing dementia risk and significantly hastening its onset in both men and women. Thus, for dementia prevention and intervention, it is essential to preserve and improve muscle mass and strength through a balanced diet and proper resistance training.

Ratio of fat mass to muscle mass

Using predictive equations (G. Lee et al., 2021), research estimated lean body mass index, appendicular skeletal muscle index, and body fat mass index to explore the relationship between changes in predicted body composition and the subsequent risk of dementia. A decline in lean body mass index and appendicular skeletal muscle index or a rise in body fat mass index was associated with an increased risk of dementia, whereas higher lean body mass index and appendicular skeletal muscle index or lower body fat mass index had a protective effect. This trend remains consistent across individuals regardless of body mass index or whether their weight is stable, decreasing, or increasing. Therefore, proactively building muscle mass and reducing fat mass may contribute to lowering dementia risk across all age groups (S. M. Kim et al., 2024).

However, it seems that higher muscle mass in the thighs (lean appendicular skeletal muscle index) was associated with a lesser risk of amyloid-β positivity in females. In turn, higher fat mass (gluteofemoral fat percentage) was associated with a lesser risk of amyloid-β positivity in males. Thus, there may be gender differences in the effects of body composition on amyloid-β deposition (Kang et al., 2022).

In this regard, the relation between dementia and different proportions of fat and muscle was investigated, resulting in the suggestion that different fat to muscle mass ratios may influence the risk of dementia, with variations depending on the body region analyzed. Fat-muscle ratio may be a relevant indicator for predicting dementia risk, suggesting that body composition plays an important role in neurological health (Wang et al., 2022).

CONCLUSION

The population ageing brings challenges at various levels, and cognitive impairment and dementia are often at the centre of them. To date, there are no effective treatments for dementia, emphasizing the importance of prevention. Aspects related to body composition can be predictors of the risk of cognitive impairment, allowing for preventive intervention.

Adipose tissue plays a complex role in cognitive health and the risk of dementia. While excess adiposity, especially visceral fat, has been linked to cognitive decline and dementia, certain fat depots, such as subcutaneous and gynoid fat, may have protective effects. However, factors such as systemic inflammation and metabolic

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disturbances related to obesity may contribute to brain health deterioration.

Muscle mass and strength play a crucial role in cognitive health, with lower levels being linked to an increased risk of cognitive decline in older adults. Sarcopenia contributes to metabolic dysfunction, inflammation, and neuromuscular deterioration, potentially accelerating cognitive impairment.

Sarcopenic obesity presents a compounded risk for adverse health outcomes, including cognitive decline and dementia. Maintaining a balanced ratio of muscle and fat mass is crucial, as higher muscle mass appears protective against amyloid-β accumulation.

Given these findings, promoting muscle health through resistance training and proper nutrition emerges as a key strategy for preventing cognitive impairment and supporting overall brain health.

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