

Aging, Cognition, and Physical Exercise: Interplay Between Muscle Function, Myokines, and Brain Health

GREZIELE DOS SANTOS SILVA

Programa de pós-graduação em Cognição e Linguagem, UENF, Campos dos Goytacazes, RJ, Brazil
Fundação Universitária de Itaperuna, Itaperuna, RJ, Brazil
ORCID: 0009-0005-8348-3750
grezienesantos@gmail.com

CHARLLES VIEIRA FONSECA DE ALMEIDA

Programa de pós-graduação em Cognição e Linguagem, UENF, Campos dos Goytacazes, RJ, Brazil
ORCID: 0009-0005-4869-9150
charlles.vieira@hotmail.com

FABIANA PEREIRA COSTA RAMOS

Programa de pós-graduação em Cognição e Linguagem, UENF, Campos dos Goytacazes, RJ, Brazil
ORCID: 0009-0004-6326-8052
fabianacostapicanco@gmail.com

NELIA DA FONSECA PINTO FERREIRA

Programa de pós-graduação em Cognição e Linguagem, UENF, Campos dos Goytacazes, RJ, Brazil
ORCID: 0009-0002-5215-5939
neliafonseca.psi@gmail.com

FLÁVIO MARTINS DA SILVA

Programa de pós-graduação em Cognição e Linguagem, UENF, Campos dos Goytacazes, RJ, Brazil
ORCID: 0009-0005-1162-5609
martinsflaviosilva@gmail.com

LUÍSA THIEBAUT A ANDRADE DO CARMO

Centro Universitário FAMESC – UniFamesc, Bom Jesus do Itabapoana, RJ, Brazil
ORCID: 0009-0000-4374-0015
luterapiaocupacional@gmail.com

Ana Raquel de Sousa Pourbaix

Programa de pós-graduação em Cognição e Linguagem, UENF, Campos dos Goytacazes, RJ, Brazil
ORCID: 0009-0001-0502-471X
arpourbaix@gmail.com

ROSALEE SANTOS CRESPO ISTOE

Programa de pós-graduação em Cognição e Linguagem, UENF, Campos dos Goytacazes, RJ, Brazil
ORCID: 0000-0001-8959-9280
rosalee@uenf.br

VALTAIR AFONSO MIRANDA

Programa de pós-graduação em Cognição e Linguagem, UENF, Campos dos Goytacazes, RJ, Brazil
ORCID: 0000-0003-4556-2253
vallairmiranda@gmail.com

Abstract

Aging is a complex physiological process associated with structural and functional changes that negatively affect both cognition and muscle function. Strong evidence indicates that physical exercise acts as a protective factor, mitigating cognitive and functional decline through mechanisms such as the release of myokines, increased cerebral vascularization, and neuroplasticity. Experimental studies have demonstrated that exercise stimulates the secretion of key myokines, including brain-derived neurotrophic factor (BDNF), irisin, insulin-like growth factor-1 (IGF-1), interleukin-6 (IL-6), and cathepsin B, all of which regulate neurogenesis, synaptogenesis, and oxidative stress reduction. Recent meta-analyses confirm that aerobic and resistance training can reduce the risk of dementia by up to 28% and significantly improve executive function and memory in older adults. Thus, physical exercise should be understood not only as a tool for maintaining motor capacity but also as a therapeutic strategy for cognitive protection and the prevention of age-related diseases.

Keywords: aging, cognition, physical exercise, myokines, neuroprotection

INTRODUCTION

Global demographic projections indicate that by 2050, approximately 22% of the world's population will be over 60 years old (World Health Organization [WHO], 2021; WHO, 2015). The aging process is associated with sarcopenia, a decline in muscle mass and strength, as well as progressive cognitive impairment and a higher incidence of chronic diseases (Cruz-Jentoft et al., 2019).

Physical exercise has emerged as one of the most effective non-pharmacological strategies to counter these changes (Liu et al, 2024; Fontes et al, 2022; Liu & Latham, 2009). Beyond improvements in metabolic and cardiovascular health, exercise acts as a neuroendocrine modulator through the release of myokines—muscle-secreted peptides with systemic effects, including neuroprotective roles (Pedersen, 2019; Pedersen & Saltin, 2015).

This narrative review critically explores the interplay between aging, cognition, and exercise, with an emphasis on the biological role of myokines and the evidence from experimental and meta-analytical studies.

METHODS

This paper is a narrative review based on a qualitative synthesis of the literature. Searches were conducted in PubMed, Scopus, and Web of Science for studies addressing aging, cognition, myokines, and physical exercise. Priority was given to randomized controlled trials, experimental studies, and meta-analyses published in the last two decades, complemented by cross-sectional and comparative studies when relevant.

Age-related muscular and cognitive decline

Cognition can be broadly defined as the set of mental processes that allow individuals to acquire, store, process, and use information. It includes domains such as memory, attention, language, executive functions, and problem-solving, which are essential for learning, decision-making, and adapting to environmental demands (Anderson, 2010; Machado & Waldie, 2020). In the context of aging, cognitive performance may decline due to structural and functional brain changes, although the degree and rate of decline vary considerably among individuals and can be positively influenced by lifestyle factors, including physical activity.

Aging is accompanied by sarcopenia and dynapenia, which reduce functional capacity and autonomy (Schettino et al, 2013). Longitudinal studies show that muscle mass decreases by approximately 8% per decade after the age of 40, accelerating after 70 years (Hughes et al., 2001). Cognitive functions such as working memory, attention, and processing speed also decline progressively, increasing the risk of dementia (Mattson & Arumugam, 2018).

Myokines and brain health

Skeletal muscle is recognized as an endocrine organ capable of secreting more than 700 myokines (Pedersen, 2019). Among the most relevant to cognitive health are:

- **BDNF (Brain-Derived Neurotrophic Factor):** supports synaptic plasticity and neurogenesis; aerobic exercise consistently elevates circulating BDNF (Szuhany et al., 2015).
- **Irisin:** derived from FNDC5 cleavage, stimulated by PGC-1 α during exercise; promotes neuronal differentiation and neuroprotection (Wrann et al., 2013).
- **IGF-1 (Insulin-like Growth Factor-1):** crosses the blood-brain barrier and facilitates neuronal growth and synaptogenesis (Deak & Clarke, 2019).
- **IL-6 (Interleukin-6):** secreted in large amounts during exercise, plays an anti-inflammatory role and counteracts pro-inflammatory cytokines linked to cognitive decline (Pedersen & Fischer, 2007).
- **Cathepsin B:** increases after aerobic exercise and is associated with hippocampal neurogenesis and memory enhancement (Moorthy et al., 2020).

Evidence from experimental studies

Randomized controlled trials (RCTs) provide compelling evidence for the neuroprotective potential of exercise in aging populations. Erickson et al. (2011), in a landmark RCT involving 120 older adults aged 55 to 80, demonstrated that six months of moderate-intensity aerobic training (walking 40 minutes, three times per week) led to a 2% increase in hippocampal volume compared to a control group, which exhibited a 1.4% decline over the same period. This structural brain change was accompanied by elevated serum levels of BDNF and correlated with improvements in spatial memory, highlighting the link between exercise-induced neuroplasticity and cognition.

Similarly, Cassilhas et al. (2007) investigated the effects of 24 weeks of progressive resistance training in elderly men. The results revealed significant improvements in memory and executive functions, with cognitive gains positively associated with increased circulating IGF-1 levels, suggesting that resistance training exerts benefits not only through muscle strengthening but also via endocrine modulation. These findings are particularly relevant for frail older adults, in whom muscle and cognitive decline often coexist.

Other RCTs reinforce the relationship between exercise and cognitive preservation. Colcombe et al. (2006) found that a 6-month aerobic exercise intervention improved attentional control and executive function in sedentary older adults, with associated increases in brain activity in the prefrontal and parietal cortices as measured by fMRI. Voss et al. (2013) further showed that exercise enhances functional connectivity within the default mode network (DMN), a key network disrupted in early stages of dementia.

In addition to aerobic and resistance training, mind–body interventions have also been studied. A trial by Lam et al. (2012) demonstrated that tai chi practice over 40 weeks improved global cognition and delayed progression to dementia in individuals with mild cognitive impairment, suggesting that multimodal exercise incorporating motor, cognitive, and social components may provide synergistic benefits.

Taken together, these experimental studies demonstrate that structured exercise interventions can induce measurable structural, functional, and biochemical changes in the aging brain, mediated in part by myokines such as BDNF and IGF-1. The evidence suggests that different modalities of exercise—whether aerobic, resistance, or

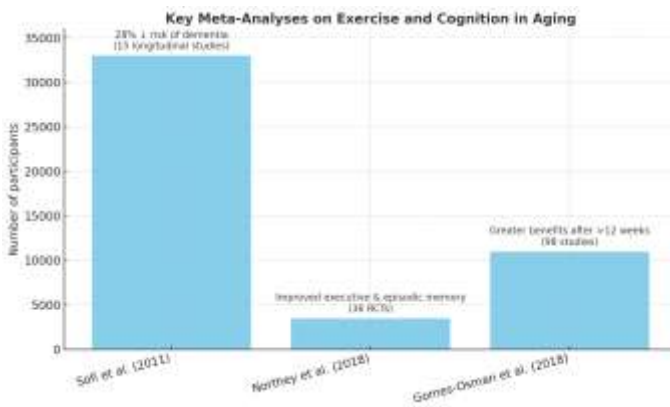
mind–body—can each contribute uniquely to neuroprotection, and that multimodal programs may offer the most comprehensive benefits.

Evidence from meta-analyses

Meta-analytical evidence further reinforces the neuroprotective role of physical exercise during aging. Sofi et al. (2011), in a prospective meta-analysis of 15 longitudinal studies with over 33,000 participants, demonstrated that physically active older adults had a **28% lower risk of cognitive decline and dementia** compared to sedentary individuals. The analysis highlighted that even moderate-intensity activity conferred significant protection, with a clear dose–response relationship suggesting that higher volumes of physical activity are associated with greater benefits.

Northey et al. (2018) reviewed 36 randomized controlled trials (RCTs) with more than 3,500 participants aged 50 years and older. Their findings revealed that both **aerobic and resistance training interventions** led to significant improvements in global cognition, executive functions, and episodic memory. Importantly, the study emphasized that **combined training programs**—integrating aerobic, resistance, and mind–body exercises such as tai chi—were particularly effective in enhancing executive function. The authors also noted that exercise frequency (at least twice per week) was a key determinant of cognitive outcomes.

Gomes-Osman et al. (2018), in a systematic review and meta-analysis including 98 studies and approximately 11,000 participants, provided further granularity by evaluating the effect of intervention duration and intensity. They concluded that **programs lasting longer than 12 weeks** produced the most consistent cognitive improvements, especially in attention, processing speed, and memory. Furthermore, their analysis suggested that **neuroplastic adaptations may require sustained engagement in exercise**, reinforcing the idea that short-term interventions may not be sufficient to induce robust changes in brain structure and function.



Collectively, these meta-analyses demonstrate that exercise not only mitigates the risk of dementia but also contributes to measurable improvements in specific cognitive domains. The converging evidence underscores the importance of structured and

sustained physical activity as a preventive and therapeutic strategy for age-related cognitive decline.

CONCLUSION

Aging is accompanied by declines in both muscle function and cognition, but regular physical exercise represents a powerful strategy to attenuate these changes. The secretion of myokines such as BDNF, irisin, IGF-1, IL-6, and cathepsin B provides a biological explanation for the neuroprotective effects of exercise. Evidence from randomized trials and meta-analyses confirms that exercise reduces the risk of dementia, enhances cognitive performance, and helps manage comorbidities. Public health policies should prioritize exercise-based interventions to promote healthy aging, autonomy, and quality of life.

REFERENCES

1. Cassilhas, R. C., Viana, V. A., Grassmann, V., Santos, R. T., Santos, R. F., Tufik, S., & Mello, M. T. (2007). Resistance exercise improves hippocampus-dependent memory. *Brazilian Journal of Medical and Biological Research*, 40(9), 1215–1222. <https://doi.org/10.1590/S0100-879X2006005000158>
2. Cruz-Jentoft, A. J., Bahat, G., Bauer, J., Boirie, Y., Bruyère, O., Cederholm, T., ... & Cooper, C. (2019). Sarcopenia: revised European consensus on definition and diagnosis. *Age and Ageing*, 48(1), 16–31. <https://doi.org/10.1093/ageing/afy169>
3. Deak, F., & Clarke, R. J. (2019). The role of IGF-1 in cognition: A critical review. *Frontiers in Aging Neuroscience*, 11, 267. <https://doi.org/10.3389/fnagi.2019.00267>
4. Erickson, K. I., Voss, M. W., Prakash, R. S., Basak, C., Szabo, A., Chaddock, L., ... & Kramer, A. F. (2011). Exercise training increases size of hippocampus and improves memory. *Proceedings of the National Academy of Sciences*, 108(7), 3017–3022. <https://doi.org/10.1073/pnas.1015950108>
5. Pontes, R. F., Leite, M. O., & Machado, M. (2022). Comparison of the effects of physical activity in elderly women and medicine use: Short communication. *Gerontology & Geriatric Studies*, 8(1), 753–755. <https://doi.org/10.31031/GGS.2022.08.000678>
6. Gomes-Osman, J., Cabral, D. F., Morris, T. P., McInerney, K., Cahalin, L. P., Rundek, T., ... & Pascual-Leone, A. (2018). Exercise for cognitive brain health in aging: A systematic review for an evaluation of dose. *Neurology: Clinical Practice*, 8(3), 257–265. <https://doi.org/10.1212/CPJ.0000000000000460>
7. Hughes, V. A., Frontera, W. R., Wood, M., Evans, W. J., Dallal, G. E., Roubenoff, R., & Singh, M. A. F. (2001). Longitudinal muscle strength changes in older adults: Influence of muscle mass, physical activity, and health. *The Journals of Gerontology: Series A*, 56(5), B209–B217. <https://doi.org/10.1093/gerona/56.5.B209>
8. Liu, C. J., & Latham, N. K. (2009). Progressive resistance strength training for improving physical function in older adults. *The Cochrane Database of Systematic Reviews*, (3), CD002759. <https://doi.org/10.1002/14651858.CD002759.pub2>
9. Liu, C., Shiroy, D. M., Jones, L. Y., & Clark, D. O. (2024). Systematic review of progressive resistance strength training in older adults. *The Journals of Gerontology: Series A*, glae028. <https://doi.org/10.1093/gerona/glae028>
10. Machado M. Creatine alone is not enough: the need for rigorous evidence in older populations. *J Sports Med Phys Fitness*. Published online January 29, 2026. doi:10.23736/S0022-4707.25.17624-X

11. Machado M. Creatine supplementation and cognitive aging: The challenge of crossing the blood-brain barrier. *Nutr Health*. Published online December 8, 2025. doi:10.1177/02601060251404327
12. Machado, L., & Waldie, K. (2020). Understanding cognition and how it changes with aging, brain disease, and lifestyle choices. *Journal of the Royal Society of New Zealand*, 51(1), 128-142. <https://doi.org/10.1080/03036758.2020.1796102>
13. Machado, M. & Pereira, R. The Potential and Challenges of Creatine Supplementation for Cognition/Memory in Older Adults. *Eur J Geriatr Gerontol* 2023;5(1):1-5 <https://doi.org/10.4274/ejgg.galenos.2022.2022-9-9>
14. Machado, M. (2024). Is it now appropriate to assert that creatine supplementation holds cognitive benefits for the elderly?. *Journal of Geriatric Medicine*, 6(1), 1–3. <https://doi.org/10.30564/jgm.v6i1.6205>
15. Machado, M. Insufficient evidence to recommend creatine supplementation as a therapeutic option for osteoporosis. *Osteoporos Int* 36, 2579–2580 (2025). <https://doi.org/10.1007/s00198-025-07713-9>
16. Mattson, M. P., & Arumugam, T. V. (2018). Hallmarks of brain aging: Adaptive and pathological modification by metabolic states. *Cell Metabolism*, 27(6), 1176–1199. <https://doi.org/10.1016/j.cmet.2018.05.011>
17. Moorthy, L., Arumugam, T. V., & Mattson, M. P. (2020). Cathepsin B and exercise: Emerging roles in memory function. *Frontiers in Physiology*, 11, 528. <https://doi.org/10.3389/fphys.2020.00528>
18. Northey, J. M., Cherbuin, N., Pumpa, K. L., Smee, D. J., & Rattray, B. (2018). Exercise interventions for cognitive function in older adults: A meta-analysis. *British Journal of Sports Medicine*, 52(3), 154–160. <https://doi.org/10.1136/bjsports-2016-096587>
19. Oliveira, E. & Machado, M. (2024). Avaliando a Influência da Creatina Dietética na Memória Visuoespacial em Homens Idosos: Insights de um Estudo Piloto. *Cadernos de pesquisa campus V*, 11, 69-82. <https://doi.org/10.5281/zenodo.18888775>
20. Pedersen, B. K. (2019). Muscle as an endocrine organ: Regulation by exercise. *Frontiers in Physiology*, 10, 511. <https://doi.org/10.3389/fphys.2019.00511>
21. Pedersen, B. K., & Fischer, C. P. (2007). Beneficial health effects of exercise – the role of IL-6 as a myokine. *Trends in Pharmacological Sciences*, 28(4), 152–156. <https://doi.org/10.1016/j.tips.2007.02.002>
22. Pedersen, B. K., & Saltin, B. (2015). Exercise as medicine – evidence for prescribing exercise as therapy in 26 different chronic diseases. *Scandinavian Journal of Medicine & Science in Sports*, 25(S3), 1–72. <https://doi.org/10.1111/sms.12581>
23. Schettino, L., Luz, C. P. N., Oliveira, L. E. G., Assunção, P. L., Coqueiro, R. S., Fernandes, M. H., ... & Machado, M. (2013). Comparison of explosive force between young and elderly women: Evidence of an earlier decline from explosive force. *AGE*, 35(5), 1785–1796. <https://doi.org/10.1007/s11357-013-9612-1>
24. Sofi, F., Valecchi, D., Bacci, D., Abbate, R., Gensini, G. F., Casini, A., & Macchi, C. (2011). Physical activity and risk of cognitive decline: A meta-analysis of prospective studies. *Journal of Internal Medicine*, 269(1), 107–117. <https://doi.org/10.1111/j.1365-2796.2010.02281.x>
25. Szuhany, K. L., Bugatti, M., & Otto, M. W. (2015). A meta-analytic review of the effects of exercise on brain-derived neurotrophic factor. *Journal of Psychiatric Research*, 60, 56–64. <https://doi.org/10.1016/j.jpsychires.2014.10.003>
26. World Health Organization. **Global report on ageism**. Geneva: World Health Organization; 2021. Available from: <https://www.who.int/publications/i/item/9789240016866>
27. World Health Organization. **World report on ageing and health**. Geneva: World Health Organization; 2015. Available from: <https://www.who.int/publications/i/item/9789241565042>
28. Wrann, C. D., White, J. P., Salogiannis, J., Laznik-Bogoslavski, D., Wu, J., Ma, D., ... & Spiegelman, B. M. (2013). Exercise induces hippocampal BDNF through a PGC-1 α /FNDC5 pathway. *Cell Metabolism*, 18(5), 649–659. <https://doi.org/10.1016/j.cmet.2013.09.008>