Neuroscience and Biobehavioral Reviews 178 (2025) 106381

Contents lists available at ScienceDirect

Neuroscience and Biobehavioral Reviews

journal homepage: www.elsevier.com/locate/neubiorev

Investigating the mediating effect of myokines on exercise-induced cognitive changes in older adults: A living systematic review and meta-analysis☆

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ARTICLE INFO

Keywords:
Biomarker
Myokine
Cognition
Aged
Exercise
Physical activity
Muscle
Brain

ABSTRACT

Despite strong evidence linking exercise training to cognitive benefits, uncertainty remains regarding the underlying biological mechanisms, with some studies highlighting the need for greater consensus. Muscle-derived exerkines (myokines) are proposed mediators of exercise-induced effects with potential implications for mitigating age-related cognitive decline. This living systematic review and meta-analysis examined randomized controlled trials investigating the effects of exercise on both cognition and any of 1126 potential myokines in individuals aged 50 and older. From 17,177 screened records, 43 studies met inclusion criteria, reporting data on 7 neurotrophic, 11 pro-inflammatory, and 2 anti-inflammatory factors. A three-level meta-analysis revealed significantly improved cognitive performance post-exercise (SMD = 0.579) and elevated neurotrophic factor levels (SMD = 0.427) in exercise groups compared to controls, but no significant changes in pro-inflammatory or anti-inflammatory factor levels. Mediation analysis using meta-analytic structural equation modeling (MASEM) did not detect significant indirect effects of myokines on cognition, with only limited data (9 studies) reporting direct post-test correlations between myokine levels and cognitive outcomes. Exercise improved several cognitive domains and increased certain myokines, particularly BDNF, in older adults. However, current evidence is insufficient to determine whether myokines mediate these benefits, as mediation analyses were limited by small samples, incomplete reporting, and methodological constraints. Future well-powered trials with standardized protocols and comprehensive biomarker reporting are needed to clarify this mechanistic pathway. As a living

☆ Registration
In accordance with the guidelines, our systematic review and meta-analysis was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on the 24th of April, 2023 (registration number CRD42023416996)

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https://doi.org/10.1016/j.neubiorev.2025.106381
Received 18 April 2025; Received in revised form 28 August 2025; Accepted 22 September 2025
Available online 23 September 2025

review, this work will be continuously updated to refine our understanding of whether myokines mediate exercise-induced cognitive benefits in aging populations.

1. Introduction

Neurodegeneration and cognitive decline are well-documented consequences of aging (Hou, 2019), with dementia rates rising faster than the proportion of older adults in society (Davis et al., 2022; Mattiuzzi and Lippi, 2020), posing substantial challenges for aging populations and healthcare systems (World Health Organization, 2021). While the application of physical exercise training programs (herein, physical exercise) is increasingly recognized as a promising non-pharmacological intervention for promoting cognitive health, a critical gap remains in understanding the underlying mechanisms that mediate its neuroprotective effects. In an effort to explore effective strategies for mitigating the impact of aging, the relationship between physical exercise and cognition has been extensively studied in numerous systematic reviews, generally reporting positive effects in healthy older adults (e.g. (Zhang et al., 2023) and older adults with cognitive frailty (e.g., (Tam, 2022; Zhang, 2022). These reviews have highlighted improvements in specific aspects of cognition, such as executive functions (e.g., (Chen, 2020). Clinically relevant changes in global cognition were found to depend on exercise type, duration, and intensity, occurring at exercise volumes of approximately 700 METs-min per week (Gallardo-Gómez, 2022).

In the last decade, advancements in neuroimaging techniques have further expanded our understanding of the brain mechanisms linking exercise to cognition and recently, leading researchers in the field have argued that the growing knowledge of these mechanisms meets Hill's criteria for causality (Dupuy, 2024; Hill, 1965). In contrast, other researchers report inconclusive findings, with some recent reviews reporting no significant effects on cognition (e.g. (Ding et al., 2025; Reparaz-Escudero et al., 2024)), or mixed findings regarding brain structural changes in response to physical exercise (Erickson, 2019). Importantly, an umbrella review published in 2023 has casted significant doubt on the validity of the data regarding the effect of exercise on cognition in healthy adults, emphasizing the remaining lack of consensus on underlying mechanisms (Ciria, 2023; Ciria, 2024). This underscores the continued need for high-quality evidence supporting the effect of physical exercise on cognitive outcomes.

In a structural overview of the mechanisms underlying the effect of exercise on cognition, molecular releases (exerkines including myokines) are presented as the primary mechanisms, which in turn influence structural (e.g., white and grey matter volume and integrity) and functional (e.g., fMRI and PET) brain changes, ultimately leading to improvements in cognitive performance (see Fig. 1 in (Dupuy, 2024). Based on this framework, several potential moderators may influence these primary mechanisms, such as age, health status, and exercise characteristics (type, intensity, frequency, duration). The gap in the literature is therefore twofold: a lack of comprehensive understanding of the role of these primary mechanisms as mediators of the exercise–cognition relationship in older adults, and insufficient assessment of the moderators of these mechanisms, including sex, cognitive health status, and exercise parameters.

The release of exerkines is a promising finding towards understanding the intersection of physical exercise and cognitive health (Tari, 2019; Vints et al., 2022; Dupuy, 2024). Exerkines are exercise-induced

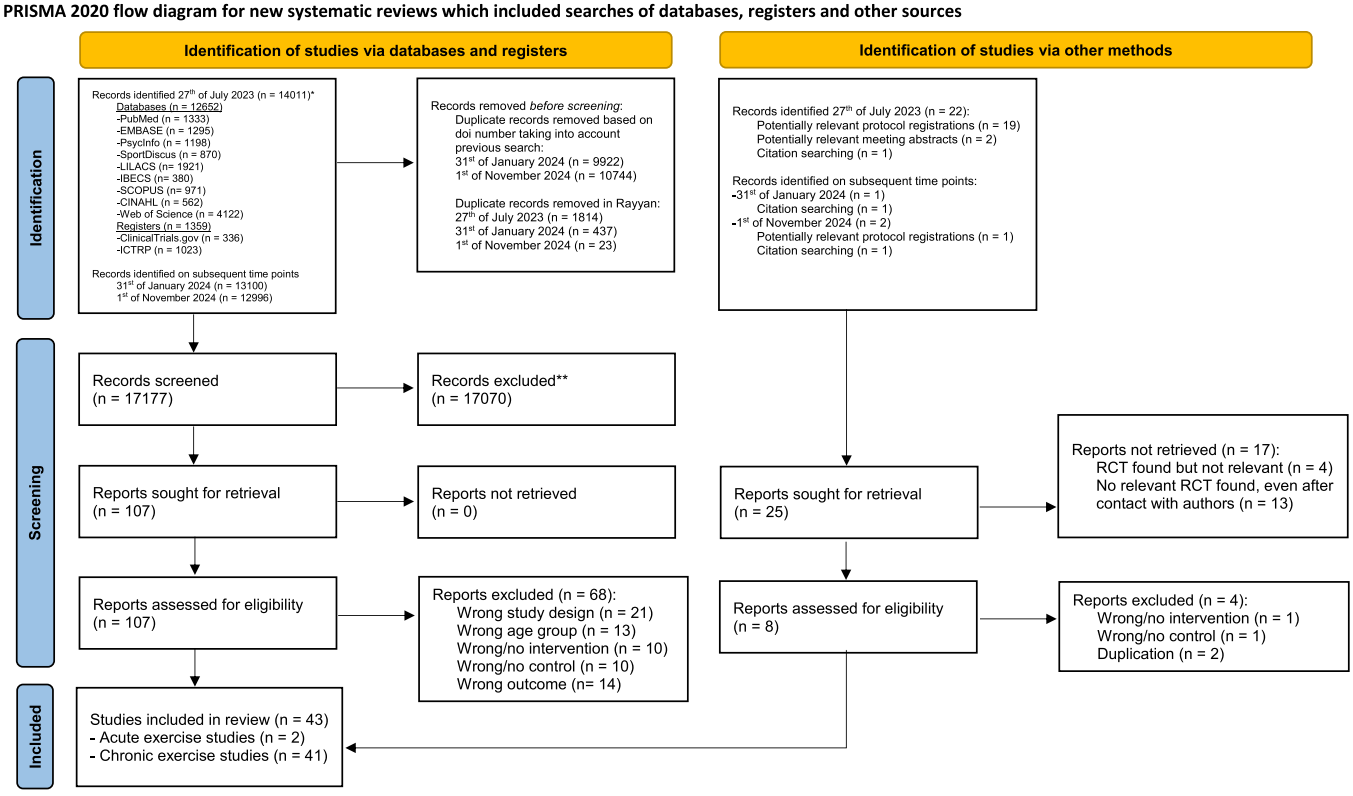

Fig. 1. PRISMA flow chart., *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers).; **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.; *From:* Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/.

factors that are thought to enable a beneficial crosstalk between systems, organs, and tissues, regulating metabolism, inflammation, and cognitive function (Liang, 2022). Muscle-derived exerkines (myokines) are proposed to be key factors in mediating cognitive changes following exercise (Oudbier, 2022; Vints et al., 2022). These molecules target the central nervous system (Onyango et al., 2021; Pedersen, 2019), facilitating neuroplastic processes (Vints et al., 2022). This suggests that myokines may be mediators of a muscle-brain endocrine loop (Chen et al., 2021). More indirect evidence supporting the muscle-cognition connection includes the association between sedentary behavior and cognitive decline (Livingston, 2020; López-Valenciano, 2020); and the cognitive impairments observed in older adults with sarcopenia (Cipolli et al., 2019; Ramoo, 2022). Consequently, a growing number of studies are exploring how exercise interventions may modulate myokine levels and impact cognition.

Acute exercise (i.e., a single exercise session) generally results in an increase of myokines in the blood circulation. In contrast, the effect of chronic exercise (i.e., multiple exercise sessions) on myokines can be expressed in two ways: an increase in *neurotrophic factors* (molecules that support the survival of neurons and facilitate neuroplastic signaling cascades) and *anti-inflammatory markers* (which act as immune modulators, regulating the immune system by suppressing inflammation) on one hand, and a decrease in the concentration of *pro-inflammatory cytokines* (which contribute to damaging of neurons through promoting trafficking and activation of immune cells and impair neuroplastic signaling) on the other hand (Smith et al., 2012; Vints et al., 2022). Currently, 1126 putative myokines have been identified in the literature (see the full list in our protocol paper (Vints, 2023), yet only a few have been explored in relation to exercise programs. Importantly, most of the myokines are believed to exert paracrine rather than endocrine effects (Weigert et al., 2014). Additionally, myokines (and exerkines in general) must either be very small and lipophilic to cross the blood-brain barrier via passive diffusion or rely on specialized transporters or endocytosis to directly signal the brain (Pardridge, 2005). However, some exerkines may influence the brain indirectly via activating signaling cascades in other organs, which can trigger the release of secondary endocrine factors that may, in turn, cross the blood-brain barrier (Chen et al., 2021). This complex network of signaling pathways and the interactions between exerkines remains largely unexplored, making it challenging to fully understand. Appendix A contains an overview of review papers providing evidence for the effect of exercise specifically focused on myokines, and for the relationship between myokines and exercise-induced cognitive improvements. In summarizing the evidence from these reviews, it becomes clear that despite the growing body of literature, findings across studies are often inconsistent. Disparities in exercise protocols, sample characteristics, description of important moderators and outcome measures complicate the establishment of a clear consensus. Furthermore, few reviews have evaluated the relationship between changes in myokine levels and cognitive function, with some suggesting the potential role of myokines as mediators of the exercise-cognition connection (Akalp et al., 2024; de Assis and de Almondes, 2017; Farrukh, 2023; Titus, 2021; Wang, 2020). However, review papers incorporating mediation analysis on this topic are currently nonexistent. Therefore, especially since myokines are only one of the several proposed mechanisms (Dupuy, 2024), it remains unclear to what extent they actually contribute to mediating neuroprotective effects on cognition and which individual and exercise characteristics may act as moderators in this relationship. Finally, the rapid increase in the number of studies and the identification of numerous myokines with unclear effects (Vints, 2023) underscores the potential for future research to uncover new mediators of the exercise-cognition relationship.

Given the primary role attributed to molecular release mechanisms in driving structural and functional brain changes—and ultimately improving cognitive performance (Dupuy, 2024)—this comprehensive living review aimed to synthesize current knowledge on exercise-induced myokines and their role as mediators of cognitive changes in older adults. It encompassed all putative myokines and considered both acute and chronic exercise, as well as cognition in healthy, physically impaired, and cognitively impaired populations. This work addresses ongoing challenges in developing physical activity recommendations for older adults, as outlined by the European Cooperation in Science and Technology (EU COST) Action "PhysAgeNet". For more details, see https://e-services.cost.eu/files/domain_files/CA/Action_CA20104/mou/CA20104-e.pdf. Given the complexity of this topic and the rapid advancement in myokine research, we aim to conduct a living systematic review with meta-analysis (Elliott, 2017). Living reviews are ongoing, regularly updated to include new, relevant evidence even after it is published. The living review approach is valuable in areas like this, where research is progressing quickly and existing evidence is still considered uncertain (Elliott, 2017). A deeper understanding of the mediating role of myokines and the influence of moderators on the effects of exercise on cognition could inform policy and practice decisions regarding the development and implementation of exercise interventions to promote healthy aging. Therefore, research on this topic represents a crucial frontier addressing the global challenge of aging populations.

2. Methods

2.1. Pre-registration

The methods for this living systematic review and meta-analysis were registered in the International Prospective Register of Systematic Reviews (PROSPERO) database on April 24th, 2023 (registration number CRD42023416996) and are described in detail in the cited protocol (Vints, 2023).

2.2. Updating of the living review

This living systematic review and meta-analysis will be updated every six months for a period of at minimum five years, unless determined collectively by the authors that the criteria for conducting a living review are no longer applicable (e.g. if the quality of evidence is judged as high, see 2.7.) (Elliott, 2017). If new evidence is retrieved without altering the main conclusions of the article, details of the new studies and effect estimates will be published on the European Group for Research on Aging and Physical Activity website, https://www.egrapa.org/living_systematic_reviews. If the effect estimates or confidence in evidence change significantly, the need for re-publication will be decided based on a published scheme (Elliott, 2017), and the website will indicate that an update of the review paper is in progress.

2.3. Eligibility criteria

Article eligibility has been described in detail previously (Vints, 2023). Briefly, the following PICOS criteria were used: P) Human participants aged 50 years and older, with a study sample mean age of 60 years or above. I) Acute or chronic voluntary exercise, including cardiorespiratory endurance exercise, high-intensity interval training, resistance exercise, multicomponent exercise, mind-body exercise, balance training and specific sports, but excluding interventions with combined exercise and cognitive or nutritional interventions. C) Waitlist controls, treatment as usual, active non-exercise controls, non-active non-therapeutic activities. O) Both changes in myokine levels, derived from a list of 1126 muscle-secretory products (i.e. putative myokines) (Vints, 2023), and changes in cognitive performance on any of the following cognitive domains: global cognition, executive functioning, long-term memory and retrieval, short-term memory and attention, processing speed, fluid reasoning, or visuospatial processing. Studies reporting only one of both outcomes were excluded. S) Randomized-controlled trials (RCT). Review papers and gray literature

were screened for additional eligible studies. Only English studies were included. Studies were not restricted to participant health or setting.

2.4. Search details

Articles were searched in the following information sources: PubMed, EMBASE (through Elsevier), PsycINFO (through EBSCO), all databases of Web of Science (excluding MEDLINE), SportDiscus (through EBSCO), LILACS (accessed through Portal Regional da BVS), IBECS (accessed through Portal Regional da BVS), CINAHL (through EBSCO), SCOPUS (Elsevier), International Clinical Trials Registry Platform (ICTRP) accessed through CENTRAL, and ClinicalTrials.gov (CT.gov) accessed through CENTRAL. The search string included a combination of free terms restricted to title, abstract and keywords searching and index terms related to: "middle or older age AND physical exercise AND cognition AND myokines", see Appendix B.

2.5. Study selection and data extraction

Searches have been conducted on 27th of July 2023, 31st of January 2024 and 1st of November 2024. Before screening, duplicates were removed in the software system Rayyan. Upon subsequent searches, previously screened studies were removed in Excel based on matching of doi numbers before the studies were entered in Rayyan. The files entered in Rayyan are accessible at https://doi.org/10.5281/zenodo.14967888. All authors contributed to abstract and full text screening in pairs, blinded for each other's decisions using Rayyan for article screening. Conflicts were resolved by a third author, and discussed.

2.6. Data extraction and risk of bias

Pairs of authors worked on separate Excel spreadsheets to extract data and conduct the risk of bias (ROB) assessment, blinded each other's decisions. ROB was assessed using the Cochrane Risk of Bias tool (ROB 2.0) for RCT (Higgins, 2011). ROB was judged as high risk, moderate risk, or low risk. Conflicts were resolved by a third author.

2.7. Quality of evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) working group methodology was used for quality of evidence judgment (Akl et al., 2013). Quality of evidence was evaluated as high, moderate, low or very low; indicating the likeliness that further research will have an important impact on the estimate of effect and our confidence in this estimate.

2.8. Data analysis

Before conducting mediation analysis, a random-effects three-level (not SEM) meta-analysis was performed as a sensitivity analysis for the mediation analysis. The datafile used for analysis, the R code and the statistical output for both analyses can be found on https://doi.org/10.5281/zenodo.14967888.

2.8.1. Three-level meta-analysis

Pooled standardized mean differences (SMD) were calculated in R Core Team, (2023) for the effect of exercise compared to control conditions on neurotrophic, pro-inflammatory and anti-inflammatory factors and cognitive performance separately, so that SMD > 0 signifies an increase and SMD < 0 signifies a decrease in the biomarkers or performance on the cognitive tests in the exercise group compared to control. Studies on acute and chronic exercise interventions were analyzed separately. As many studies reported several outcomes or presented results for more than one treatment group, three-level meta-analyses were conducted, taking into account the dependency of effect sizes presented in the same study (Van den Noortgate et al., 2013). All included studies reported either specific test scores or response times with or without accuracy measures. If a study presented both response time and accuracy on a cognitive test, only the response time results were used in the meta-analysis. Two research groups published different results from the same participants in two separate studies (Baker et al., 2010a; Baker et al., 2010b) and (Solianik et al., 2022; Solianik et al., 2021). Because of the dependency of the effect sizes between these studies, these pairs of studies were considered one study for data analysis. Three-level meta-analysis and moderator analysis and the visual representation of the results were conducted using the metafor package in R (Assink and Wibbelink, 2016; Fernández-Castilla, 2020; Viechtbauer, 2010). Three-level moderator analysis were done with the following moderators: outcome (different neurotrophic, pro-inflammatory, or anti-inflammatory biomarkers, or different cognitive domains), baseline differences in the outcome (in SMD), baseline age (centered for the mean, i.e. 71 years old), baseline cognitive health (healthy, MCI, or dementia), percentage women, body mass index (BMI), exercise type (cardiovascular, resistance, multicomponent, or mind-body exercise, or specific sports), exercise intensity (light, moderate, or vigorous intensity), exercise frequency (sessions per week), session duration (in minutes), program duration (in weeks), risk of bias (low, moderate, or high). In contrast to our published protocol, we did not consider fitness at baseline and educational level, given the large amount of missing data and heterogeneity in reporting of this information. The risk of publication bias was estimated from visual interpretation of funnel plots.

2.8.2. Mediation analysis with MASEM

Mediation analysis was performed through meta-analytic structural equation modeling (MASEM) using TSSEM in the metaSEM package in R (Cheung, 2015; Cheung and Chan, 2005) to assess whether myokines mediate the effect of physical exercise on cognitive performance. This method uses a random-effects multivariate meta-analysis on correlation coefficients, estimated from transformation of the SMDs on myokines and cognitive performance to point-biserial correlations with a target base-rate of 0.50 (McGrath and Meyer, 2006). The risk of publication bias for the mediation analysis was based on visual interpretation of funnel plots after entering the myokine-cognition correlation coefficients in a meta-analytic model. As MASEM is restricted to the use of one correlation per study for each of the cognitive outcomes, the mean of the correlations within a study were used for analysis and the funnel plots. A minimum of two studies providing correlations was required in order to create the funnel plots.

3. Results

3.1. Study selection

A total of 17,177 study records were screened and 115 full texts were assessed for eligibility, see Fig. 1 and Appendix C for the PRISMA flowchart and extended flowchart for living reviews, based on Kahaleet et al. (2021). We included 43 studies from 41 patient cohorts, 39 patient cohorts undergoing chronic exercise with a total of 46 treatment arms (Adriani et al., 2020; Alghadir et al., 2016; Arrieta et al., 2020; Baker et al., 2010a,b; Barha et al., 2017; Cassilhas et al., 2007; Čekanauskaitė et al., 2020; Cho and Roh, 2019; Chupel et al., 2018; Damirchi et al., 2018; Enette et al., 2020; Fragala et al., 2014; Griffen, 2024; Guazzarini et al., 2024; Hardman et al., 2020; Heissel et al., 2015; Hyang-Beum and Tae-Sang, 2021; Ismail and Ahmad Yusof, 2024; Jung and Kim, 2024; Kang et al., 2020; Kim et al., 2021; Leckie et al., 2014; Li et al., 2021; Mashhadi et al., 2024; Muscari et al., 2010; Ploydang et al., 2023; Ruiz et al., 2015; Ruscheweyh et al., 2011; Smith et al., 2020; Solianik et al., 2021, 2022; Stroehlein et al., 2021; Sungkarat et al., 2018; Tsai et al., 2015, 2019; Vaughan et al., 2014; Vedovelli et al., 2017; Vints et al., 2024; Zhang et al., 2023), and two patient cohorts undergoing acute exercise with a total of three treatment arms (Devenney, 2019; Tsai et al., 2018). The excluded articles and reasons for exclusion are

presented in Appendix D, Supplementary Table 1. Studies were searched at three time points. Subsequent searches yielded fewer studies, which may seem contradictory. However, this can be explained by limitations in the number of search terms allowed when accessing databases via EBSCO during the initial search. As a result, we had to conduct multiple searches, each covering a subset of the myokines, leading to a higher number of duplicates in the first search. Additionally, at the third time point, no new studies could be retrieved from the IBECS database due to an update that affected its accessibility.

3.2. Study characteristics

Of the 43 included studies, six were conducted in the United States, four in Korea, and four in Lithuania. Three studies were from Brazil, Germany, and Taiwan each. Two studies per country were included from Australia, China, Iran, Spain, and Thailand. Additionally, one study was conducted in each of the following countries: France, Canada, Indonesia, Ireland, Italy, Malaysia, Portugal, Saudi Arabia, Sweden, and the United Kingdom. All studies were published in 2007 or later. Twenty-three interventions did not target any specific diagnosis. The remaining studies focused on various health conditions, including mild cognitive impairment (MCI), type 2 diabetes mellitus (T2DM), amnestic mild cognitive impairment (aMCI), Alzheimer's disease (AD), major depressive disorder (MDD), and other chronic or cognitive health conditions. The sample sizes ranged from $n = 12$ to $n = 120$ total participants. BDNF and IGF-1 were the most commonly measured myokines, being reported in 40/49 and 14/49 treatment arms, respectively. Appendix D Supplementary Table 2 contains an overview of the main study characteristics.

The ROB assessment is presented in Fig. 2. Four (9.30 %) out of 43 studies had a high risk of bias. There were some concerns about bias in 25 (58.14 %) trials.

3.3. Data analysis

Data analysis was limited to studies involving chronic exercise interventions, as only two of the included studies examined the effects of acute exercise on myokine levels and cognitive function. All data and R codes used for these analyses are accessible at https://doi.org/10.5281/zenodo.14967888.

3.3.1. Acute exercise studies

The two studies assessing acute exercise effects included participants with MCI undergoing moderate or vigorous intensity cardiorespiratory or moderate intensity resistance exercise. There was an increase in levels of serum BDNF after acute vigorous (Devenney, 2019) and moderate intensity cardiorespiratory exercise and an increase in IGF-1 after acute moderate intensity cardiorespiratory or resistance exercise (Tsai et al., 2018). Acute moderate intensity cardiorespiratory or resistance exercise induced improvement in executive functioning (Tsai et al., 2018), but no improvements in cognitive performance on a sustained attention task, visuospatial learning, executive functions or memory were found after acute vigorous intensity cardiorespiratory exercise (Devenney, 2019).

3.3.2. Chronic exercise studies

Concerning the neurotrophic factors, a total of 57 effect sizes from 28 chronic exercise studies were extracted. The pooled effect showed that individuals in the exercise groups had significantly higher levels of the neurotrophic factors post-intervention than individuals in the control groups (SMD = 0.427 [0.127; 0.728], p = 0.007), see Fig. 3. The total variance not attributable to sampling error was $I^2 = 77.931$ % (between study variance $\sigma = 0.508$, $I^2 = 77.931$ %, $p < 0.0001$; within study variance $\sigma = 0.000$, $I^2 = 0.000$ %, $p = 1.000$). Cognitive status and session duration were significant moderators, with healthy participants showing significantly larger increases in neurotrophic factors compared to participants with dementia, and longer session duration being associated with a larger neurotrophic factor level increases (results from

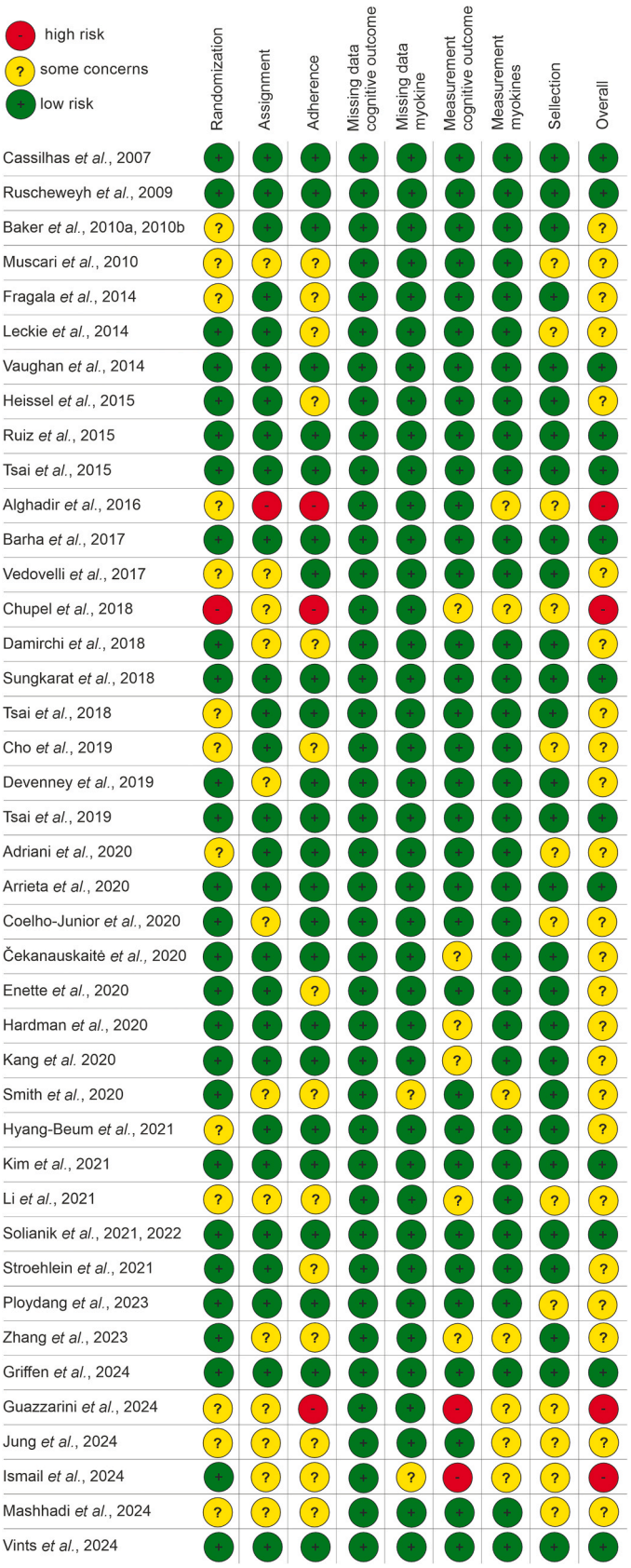

Fig. 2. Risk of bias assessment according to the ROB-2 tool.

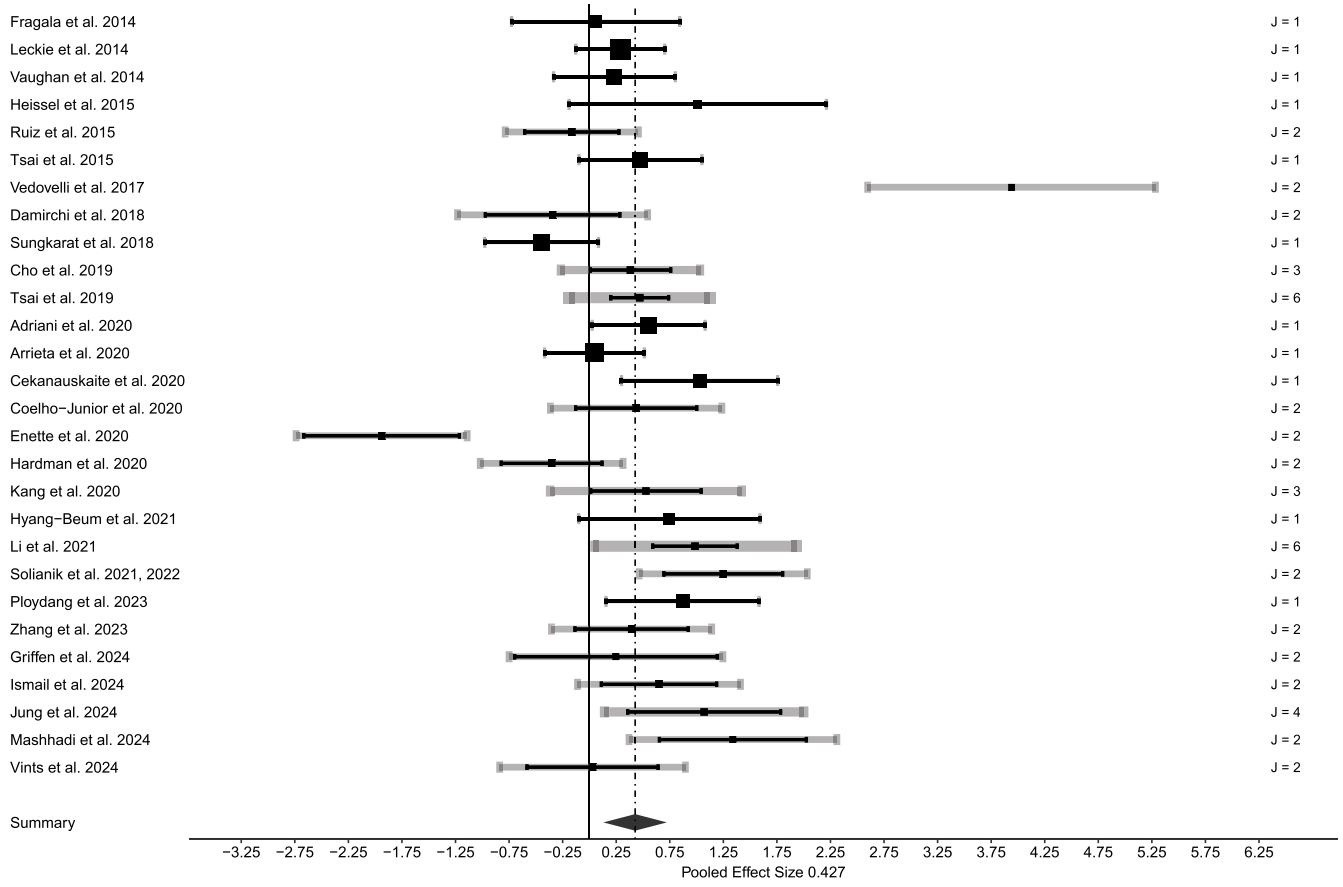

Fig. 3. Forest plot neurotrophic factors, Effect sizes are presented as SMD. Studies are ordered chronologically per year. The black CI represents the total precision of the respective study and depends on the number of outcomes within a study, the variability among effect sizes and the sample size. The size of the box is proportional to the weight of the study. The grey CI represents the median precision of the effect sizes within a study and depends on the sample size. The thickness of the grey CI is proportional to the number of effect sizes within the study. The number of comparisons is presented as $J = n$.

moderator analysis are presented in Table 1). Subgroup analyses showed significant effects for increases in BDNF and Neurotrophin-3 in the experimental group, for healthy individuals, for multicomponent exercise interventions, for moderate and vigorous intensity interventions and for studies with moderate risk of bias. Funnel plot (see Appendix D, supplementary figures) showed two studies outside the 95 % CI, one with small and one with large standard error. Calculating Cook's distances on effect sizes indicated that both of these studies were not significantly influential (Cook's distance < 0.50).

Concerning the pro-inflammatory factors, a total of 37 effect sizes from 11 chronic exercise studies were extracted. The pooled effect showed that individuals in the exercise groups did not have significantly different levels of pro-inflammatory factors post-intervention compared to individuals in the control groups (SMD $= -0.013$ [-0.316; 0.290], $p = 0.926$), see Fig. 4. The total variance not attributable to sampling error was $I^2 = 62.841$ % (between study variance $\sigma = 0.132$, $I^2 = 43.075$ %, $p = 0.018$; within study variance $\sigma = 0.061$, $I^2 = 19.766$ %, $p = 0.169$). Baseline differences between exercise and control group significantly moderated the result, see Table 1. Subgroup analyses showed significant effects for increases in IL-1β in the experimental group. However, this effect is the result of one study showing higher levels of IL-1β in the exercise group (mean = 0.53, SD = 0.02) compared to the control group (mean = 0.50, SD = 0.02, SMD = 1.465) (Ploydang et al., 2023), while two other studies with three exercise groups all reported higher levels in the control group (SMD $= -0.412$; -0.082; -0.167) (Chupel et al., 2018; Tsai et al., 2019). Funnel plot did not suggest significant publication bias.

Concerning anti-inflammatory factors, a total of 4 effect sizes from 4 chronic exercise studies were extracted. The pooled effect showed that individuals in the exercise group did not significantly differ in post-intervention levels of anti-inflammatory factors compared to the control group (SMD $= 0.009$ [-0.551; 0.569], $p = 0.351$), see Fig. 5. The variance was completely attributable to sampling error variance. There were no significant moderators. Funnel plot did not suggest significant publication bias.

Concerning cognitive function, a total of 143 effect sizes from 33 chronic exercise studies were extracted. The pooled effect showed that individuals in the exercise groups had significantly better cognitive test performance post-intervention than individuals in the control groups (SMD $= 0.579$ [0.327; 0.831], $p < 0.001$), see Fig. 6. The total variance not attributable to sampling error was $I^2 = 79.582$ % (between study variance $\sigma = 0.427$, $I^2 = 69.763$ %, $p < 0.001$; within study variance $\sigma = 0.060$, $I^2 = 9.819$ %, $p = 0.048$). Baseline differences was a significant moderator. Results from moderator analysis are presented in Table 1. Subgroup analyses showed significant effects for better performance on global cognition, executive functioning, long-term memory and retrieval, short-term memory and attention, and processing speed for individuals in the exercise groups than individuals in the control groups, for healthy individuals and individuals with MCI, for cardiorespiratory exercise, resistance exercise, multicomponent exercise and mind-body exercise, for light and moderate intensity exercise, and in studies with moderate and high risk of bias. Funnel plot showed some asymmetry in studies with larger standard errors.

3.3.3. Mediation analysis

We were able to perform mediation analysis for the overall

Table 1
Moderator analysis.

	F-statistics	n (con)/ n (exp)	Estimate (95 % CI)	p-value
Neurotrophic factors				
Biomarker	F(6,50) = 1.321	546/563	BDNF: 0.474 (0.164; 0.784)**	0.265
		136/139	IGF−1: 0.287 (−0.159; 0.733)	
		54/56	Irisin: 0.344 (−0.250; 0.938)	
		64/66	VEGF: 0.012 (−0.513; 0.538)	
		20/20	ACE: 0.649 (−0.253; 1.551)	
		18/20	Neurotrophin−3: 1.221 (0.213; 2.228)*	
		18/20	Neurotrophin−4: 0.320 (−0.627; 1.268)	
Baseline differences (SMD)	F(1,54) = 3.389		β = 0.092 (−0.008; 0.192)	0.071
Age	F(1,26) = 0.996		β = −0.022 (−0.069; 0.024)	0.328
Cognitive Health	F(2,52) = 3.603	585/612	Healthy: 0.583 (0.277; 0.888)***	0.034
		189/202	MCI: 0.132 (−0.460; 0.724)	
		54/42	Dementia: −0.721 (−1.785; 0.342)	
Percentage women	F(1,25) = 2.187		β = 0.008 (−0.003; 0.018)	0.152
BMI	F(1,23) = 0.276		β = 0.048 (−0.141; 0.238)	0.604
Exercise Type	F(4,23) = 0.488	300/290	Cardiorespiratory: 0.215 (−0.295; 0.725)	0.744
		136/142	Resistance: 0.363 (−0.277; 1.002)	
		280/304	Multicomponent: 0.739 (0.145; 1.334)*	
		280/304	Multicomponent: 0.739 (0.145; 1.334)*	
		86/91	Mind-body: 0.412 (−0.302; 1.126)	
		54/57	Specific sports: 0.383 (−1.208; 1.974)	
Exercise Intensity	F(2,54) = 1.536	161/156	Light intensity: 0.458 (−0.092; 1.008)	0.225
		555/571	Moderate intensity: 0.335 (0.001; 0.669)*	
		40/157	Vigorous intensity: 0.715 (0.241; 1.190)**	
Exercise Frequency	F(1,25) = 0.375		β = 0.098 (−0.231; 0.427)	0.546
Session Duration	F(1,25) = 5.408		β = 0.026 (0.003; 0.048)	0.028
Program Duration	F(1,55) = 0.244		β = −0.006 (−0.031; 0.019)	0.624
Risk of Bias (ROB)	F(2,25) = 0.414	323/333	Low ROB: 0.237 (−0.301; 0.774)	0.665
		479/491	Moderate ROB: 0.514 (0.112; 0.915)*	
		54/60	High ROB: 0.601 (−0.540; 1.742)	
Pro-inflammatory factors				
Biomarker	F(11,25) = 1.893	173/159	CRP: −0.083 (−0.536; 0.370)	0.090
		122/124	TNF-α: −0.061 (−0.511; 0.389)	
		12/13	IL−1ra: 0.806 (−0.193; 1.806)	
		65/67	IL−1β: 0.643 (0.099; 1.187)*	
		134/141	IL−6: 0.148 (−0.284; 0.579)	
		36/37	IL−8: 0.501 (−0.167; 1.169)	
		36/37	IL−15: −0.068 (−0.749; 0.613)	
		12/13	IL−17: −0.693 (−1.720; 0.334)	
		131/46	Kynurenine: −0.220 (−0.915; 0.476)	
		19/23	Kynurenic acid: −0.007 (−0.873; 0.860)	
		19/23	Quinolinic acid: −0.009 (−0.876; 0.858)	
		12/13	S100β: −0.134 (−1.128; 0.861)	
Baseline differences (SMD)	F(1,34) = 13.041		β = 0.555 (0.243; 0.868)***	0.001
Age	F(1,9) = 0.239		β = 0.007 (−0.065; 0.079)	0.636
Cognitive Health	F(1,35) = 0.106	454/470	Healthy: −0.028 (−0.356; 0.300)	0.747
		217/226	MCI: 0.075 (−0.511; 0.661)	
Percentage women	F(1,9) = 0.160		β = 0.002 (−0.011; 0.015)	0.699
BMI	F(1,8) = 0.064		β = −0.014 (−0.142; 0.114)	0.807
Exercise Type	F(4,6) = 1.657	260/242	Cardiorespiratory: 0.242 (−0.215; 0.699)	0.276
		56/70	Resistance: −0.204 (−0.939; 0.532)	
		252/263	Multicomponent: −0.372 (−0.939; 0.217)	
		27/29	Mind-body: 0.546 (−0.610; 1.703)	
		76/92	Specific sports: −0.323 (−1.201; 0.556)	
Exercise Intensity	F(2,8) = 1.724	116/103	Light intensity: 0.261 (−0.370; 0.892)	0.239
		531/569	Moderate intensity: −0.027 (−0.388; 0.333)	
		24/24	Vigorous intensity: −0.756 (−1.855; 0.342)	
Exercise Frequency	F(1,9) = 0.867		β = 0.237 (−0.339; 0.812)	0.376
Session Duration	F(1,9) = 0.639		β = −0.012 (−0.048; 0.023)	0.445
Program Duration	F(1,9) = 0.287		β = 0.007 (−0.021; 0.035)	0.605
Risk of Bias (ROB)	F(2,8) = 0.515	329/344	Low ROB: −0.133 (−0.629; 0.364)	0.616
		220/224	Moderate ROB: 0.013 (−0.553; 0.578)	
		122/128	High ROB: 0.271 (−0.505; 1.048)	
Anti-inflammatory factors				
Biomarker	F(1,2) = 1.295	47/50	IL−10: 0.128 (−0.752; 1.007)	0.373
		17/17	Adiponectin: −0.329 (−1.815; 1.157)	
Baseline differences (SMD)	F(1,2) = 1.714		β = −0.848 (−3.633; 1.938)	0.321
Age	F(1,2) = 2.525		β = 0.048 (−0.083; 0.179)	0.686
Cognitive Health	F(1,2) = 0.004	37/38	Healthy: 0.034 (−1.294; 1.361)	0.955
		27/29	MCI: 0.000 (−1.862; 1.862)	
Percentage women	F(1,2) = 1.016		β = 0.006 (−0.019; 0.031)	0.420
BMI	F(1,2) = 2.046		β = 0.138 (−0.277; 0.552)	0.289
Exercise Type	F(3,1) = 1.093	17/17	Cardiorespiratory: −0.329 (−4.716; 4.059)	0.591
		27/29	Resistance: −0.157 (−6.519; 6.206)	
		12/13	Multicomponent: 0.618 (−4.588; 5.825)	

(*continued on next page*)

Table 1 (*continued*)

	F-statistics	n (con)/ n (exp)	Estimate (95 % CI)	p-value
		8/8	Mind-body: 0.000 (−3.398; 3.398)	
Exercise Intensity	F(1,2) = 0.050	27/29	Light intensity: 0.000 (−7.796; 7.796)	0.953
		29/30	Moderate intensity: 0.119 (−5.889; 6.127)	
		8/8	Vigorous intensity: −0.157 (−9.629; 9.316)	
Exercise Frequency	F(1,2) = 0.118		β = 0.204 (−2.341; 2.748)	0.764
Session Duration	F (1,2) = 1.844		β = 0.032 (−0.069; 0.132)	0.307
Program Duration	F(1,2) = 0.010		β = 0.004 (−0.166; 0.174)	0.929
Risk of Bias (ROB)	F(2,1) = 1.601	35/37	Low ROB: −0.035 (−3.032; 2.963)	0.488
		17/17	Moderate ROB: −0.329 (−4.716; 4.059)	
		12/13	High ROB: 0.618 (−4.588; 5.825)	
Cognition				
Cognitive domain	F(6136) = 1.981	499/ 494	Global cognition: 0.808 (0.521; 1.094)***	0.073
		848/ 950	Executive functioning: 0.465 (0.211; 0.719)***	
		187/ 203	Long-term memory and retrieval: 0.579 (0.196; 0.962)**	
		203/ 226	Short-term memory and attention: 0.710 (0.364; 1.056)***	
		609/ 661	Processing speed: 0.347 (0.073; 0.621)*	
		6/6	Fluid reasoning: 0.431 (−0.927; 1.789)	
		42/44	Visuospatial processing: 0.399 (−0.268; 1.066)	
Baseline differences (SMD)	F(1140) = 6.767		β = 0.225 (0.054; 0.396)**	0.010
Age	F(1,31) = 0.017		β = 0.003 (−0.044; 0.050)	0.898
Cognitive Health	F(2134) = 0.348	1754/ 1969	Healthy: 0.490 (0.231; 0.750)***	0.707
		376/ 396	MCI: 0.672 (0.202; 1.141)**	
		180/ 135	Dementia: 0.708 (−0.333; 1.750)	
Percentage women	F(1,30) = 0.725		β = 0.004 (−0.005; 0.013)	0.410
BMI	F(1,27) = 0.559		β = 0.046 (−0.081; 0.174)	0.461
Exercise Type	F(4,28) = 0.883	785/ 702	Cardiorespiratory: 0.570 (0.164; 0.976)**	0.884
		335/ 342	Resistance: 0.605 (0.002; 1.208)*	
		837/ 1059	Multicomponent: 0.626 (0.081; 1.170)*	
		270/ 290	Mind-body: 0.765 (0.180; 1.350)*	
		167/ 191	Specific sports: 0.163 (−0.907; 1.232)	
Exercise Intensity	F(2140) = 1.401	639/ 616	Light intensity: 0.542 (0.131; 0.953)*	0.250
		1415/ 1500	Moderate intensity: 0.659 (0.377; 0.941)***	
		340/ 468	Vigorous intensity: 0.349 (−0.065; 0.762)	
Exercise Frequency	F(1,30) = 1.004		β = 0.145 (−0.151; 0.442)	0.324
Session Duration	F(1,30) = 0.009		β = −0.001 (−0.023; 0.021)	0.927
Program Duration	F(1141) = 0.081		β = −0.003 (−0.022; 0.016)	0.777
Risk of Bias (ROB)	F(2,30) = 2.913	928/ 1015	Low ROB: 0.400 (−0.012; 0.811)	0.070
		1294/ 1390	Moderate ROB: 0.517 (0.215; 0.819)**	
		172/ 179	High ROB: 1.331 (0.635; 2.028)***	

Moderator analysis for continuous and categorical moderators. For continuous moderators, the meta-regression β-value is provided. For categorical moderators, the subgroup SMD-value (95 % CI) is provided. Significance of SMD-values for subgroup analyses are presented as * $p < 0.05$, ** $p < 0.01$, *** $p < 0.001$. The total number (n) of participants per subgroup is presented.

mediating effect of all neurotrophic factors combined, all pro-inflammatory factors combined, and for the specific myokines BDNF and IGF-1, see Table 2. None of the indirect effects were statistically significant. Importantly, total group post-intervention correlations between myokines and cognitive performance were only available for nine studies (34 correlations for neurotrophic factors [2 global cognition, 13 executive functioning, 14 processing speed, 3 long-term memory and retrieval, 2 short-term memory and attention], 22 correlations for pro-inflammatory factors [6 global cognition, 8 executive functioning, 5 processing speed, 1 long-term memory and retrieval, 2 short-term memory and attention], 1 correlation for anti-inflammatory factors [1 global cognition]). MASEM is restricted to using one correlation per study for each of the cognitive outcomes. Thus, in case multiple correlations were provided by one study, the mean of the correlations was used for analysis. Hence, the regression coefficient between myokine and cognition (β32) was based on little information (derived from correlations provided by range 1–5 studies) in each of the mediation analyses, and in some cases (indicated by a $^{\pm}$-sign in Table 2) only fixed-effect analysis was possible to calculate the pooled correlations (pooled correlations are provided on https://doi.org/10.5281/zenodo.14967888). This also restricted interpretation of potential publication bias for these correlations (for funnel plots, see Appendix D, supplementary figures). The mediation model confirmed the findings from the three-level meta-analyses presented above that physical exercise significantly increased neurotrophic factor levels, IGF-1 levels and BDNF levels and in general improved cognitive performance. In contrast, the relationship between myokines and cognition (β32) was not significant in any of the analyses.

3.4. Quality of evidence

The quality of existing evidence for a mediation effect was graded 'very low'; indicating that further research is very likely to have an important impact on our confidence in the estimate of effect and is very likely to change the estimate. Main reasons for grading down the quality level were inconsistency (given the considerable heterogeneity in effect sizes), imprecision and indirectness of evidence (the lack of studies providing information on the correlation between myokines and cognitive performance made it necessary to make estimations of the real correlation between myokines and cognitive performance, sometimes using fixed-effects instead of random-effects analysis to pool the correlations).

4. Discussion

The present review targeted two major knowledge gaps in the exercise–cognition literature: (1) the limited understanding of primary molecular mechanisms—specifically myokines—as mediators of the exercise–cognition relationship, and (2) the insufficient exploration of moderators that may influence these mechanisms. Myokines have long been hypothesized to play a key role in mediating cognitive changes

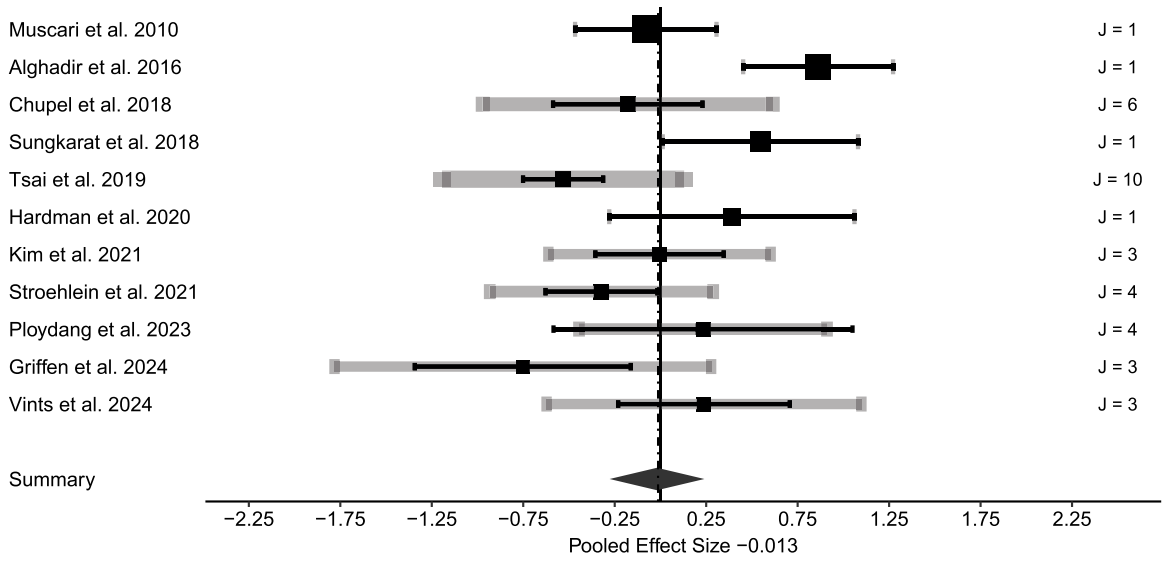

Fig. 4. Forest plot pro-inflammatory factors, Effect sizes are presented as SMD. Studies are ordered chronologically per year. The black CI represents the total precision of the respective study and depends on the number of outcomes within a study, the variability among effect sizes and the sample size. The size of the box is proportional to the weight of the study. The grey CI represents the median precision of the effect sizes within a study and depends on the sample size. The thickness of the grey CI is proportional to the number of effect sizes within the study. The number of comparisons is presented as $J = \text{n}$.

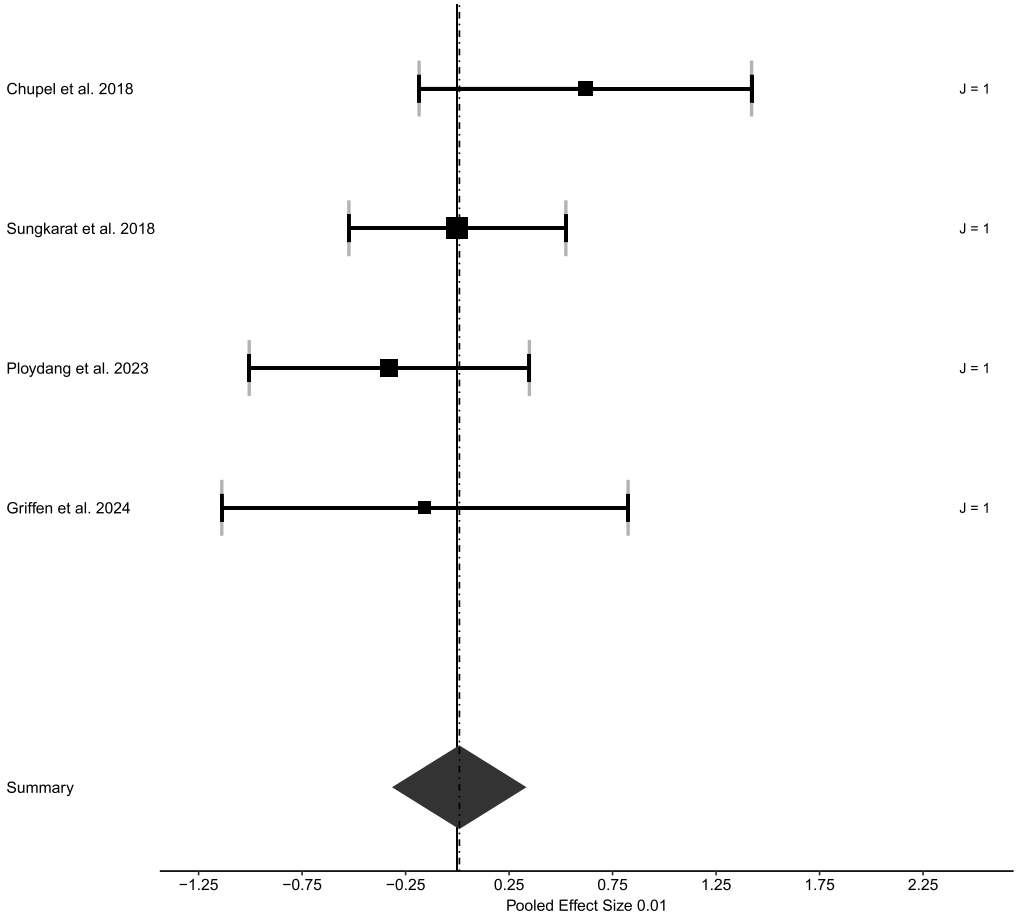

Fig. 5. Forest plot anti-inflammatory factors, Effect sizes are presented as SMD. Studies are ordered chronologically per year. The black CI represents the total precision of the respective study and depends on the number of outcomes within a study, the variability among effect sizes and the sample size. The size of the box is proportional to the weight of the study. The grey CI represents the median precision of the effect sizes within a study and depends on the sample size. The thickness of the grey CI is proportional to the number of effect sizes within the study. The number of comparisons is presented as $J = \text{n}$.

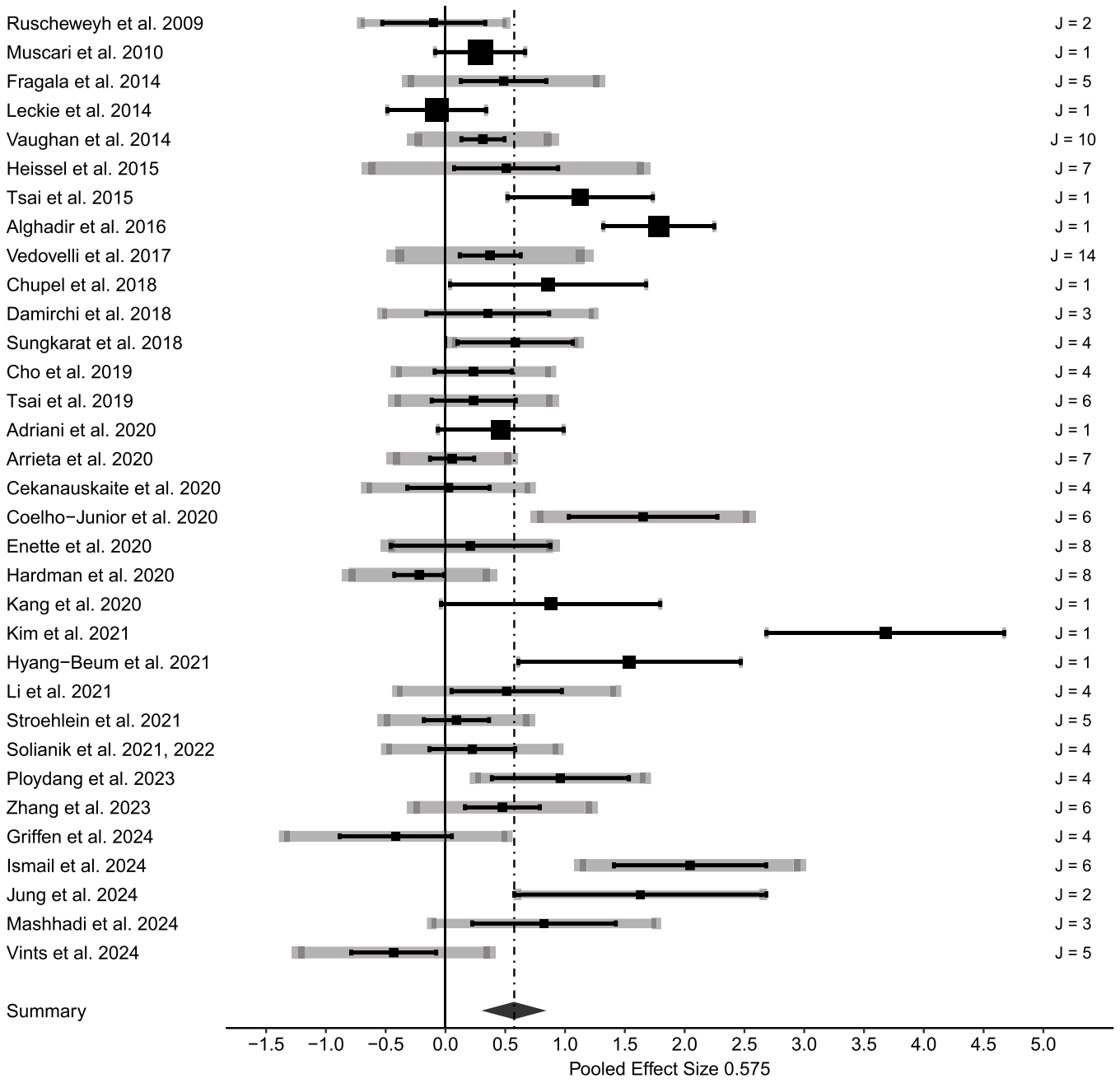

Fig. 6. Forest plot cognitive function, Effect sizes are presented as SMD. Studies are ordered chronologically per year. The black CI represents the total precision of the respective study and depends on the number of outcomes within a study, the variability among effect sizes and the sample size. The size of the box is proportional to the weight of the study. The grey CI represents the median precision of the effect sizes within a study and depends on the sample size. The thickness of the grey CI is proportional to the number of effect sizes within the study. The number of comparisons is presented as $J = n$.

following exercise (Oudbier, 2022; Vints et al., 2022) but this hypothesis has not been convincingly demonstrated. Given the cognitive deterioration in advanced age (Davis et al., 2022; Hou, 2019; Mattiuzzi and Lippi, 2020), our main aim in this comprehensive review was to test this hypothesis on older adults by systematically identifying all randomized controlled exercise studies that assessed both myokine levels and cognitive performance within the same study, and then performing meta-analytic structural equation modeling (MASEM) to test the potential mediation effects of myokines on cognition following exercise. Analyses were conducted separately for each group of myokines: neurotrophic factors, pro-inflammatory factors and anti-inflammatory factors.

Overall, the present review did not provide sufficient evidence to confirm or reject the hypothesized mediating role of myokines. Several methodological limitations restricted our ability to address the hypothesis robustly. First, mediation analysis could only be conducted for chronic exercise studies, as only two acute exercise studies, testing only MCI patients, met the inclusion criteria. This is a limitation as quite a few studies have at this moment reported effects of acute exercise on myokines (e.g., (Bekkos, 2025)), and on cognition (e.g. (De Block et al., 2025)), and it has been shown that acute and chronic exercise distinctly modulate the level of myokines (Máderová, 2019). Furthermore, the lack of information regarding the timing of blood collection and consideration of the known duration of acute effects of the tested myokines in the study methods makes it difficult to determine whether chronic exercise studies truly assessed chronic myokine level changes

Table 2
Mediation model.

	Neurotrophic factors	Pro-inflammatory factors
Global cognition	$\beta_{32} = 0.167$ (−0.247; 0.578) $\beta_{31} = 0.347$ (0.176; 0.516) * $\beta_{21} = 0.191$ (0.079; 0.304) * indirect = 0.031 (−0.055; 0.127)	$\beta_{32} = -0.048$ (−0.126; 0.221)$^{\pm}$ $\beta_{31} = 0.457$ (0.216; 0.696) * $\beta_{21} = 0.047$ (−0.088; 0.182) indirect = 0.002 (−0.012; 0.021)$^{\pm}$
Executive functioning	$\beta_{32} = 0.088$ (−0.046; 0.221) $\beta_{31} = 0.152$ (0.049; 0.254) * $\beta_{21} = 0.191$ (0.078; 0.304) * indirect = 0.017 (−0.010; 0.050)	$\beta_{32} = -0.114$ (−0.352; 0.123)$^{\pm}$ $\beta_{31} = 0.094$ (−0.075; 0.264) $\beta_{21} = 0.044$ (−0.093; 0.182) indirect = −0.005 (−0.041; 0.017)$^{\pm}$
Long-term memory and retrieval	$\beta_{32} = 0.241$ (−0.116; 0.598) $\beta_{31} = 0.083$ (−0.134; 0.294) $\beta_{21} = 0.191$ (0.077; 0.305) * indirect = 0.046 (−0.024; 0.140)	$\beta_{32} = -0.229$ (−0.510; 0.052)$^{\pm}$ $\beta_{31} = -0.275$ (−0.177; 0.725) $\beta_{21} = 0.045$ (−0.091; 0.182) indirect = 0.010 (−0.066; 0.026)$^{\pm}$
Short-term memory and attention	$\beta_{32} = 0.046$ (−0.267; 0.358)$^{\pm}$ $\beta_{31} = 0.242$ (0.010; 0.474) * $\beta_{21} = 0.191$ (0.078; 0.306) * indirect = 0.009 (−0.060; 0.078)$^{\pm}$	$\beta_{32} = -0.056$ (−0.353; 0.239)$^{\pm}$ $\beta_{31} = -0.049$ (−0.244; 0.146) $\beta_{21} = 0.046$ (−0.090; 0.182) indirect = 0.005 (−0.054; 0.021)$^{\pm}$
Processing speed	$\beta_{32} = 0.002$ (−0.139; 0.143) $\beta_{31} = 0.084$ (−0.029; 0.197) $\beta_{21} = 0.192$ (0.077; 0.306) * indirect = 0.000 (−0.032; 0.031)	$\beta_{32} = -0.103$ (−0.492; 0.285)$^{\pm}$ $\beta_{31} = -0.118$ (−0.294; 0.057) $\beta_{21} = 0.046$ (−0.089; 0.181) indirect = 0.005 (−0.054; 0.021)$^{\pm}$
	BDNF	
Global cognition	$\beta_{32} = -0.092$ (−0.350; 0.159)$^{\pm}$ $\beta_{31} = 0.400$ (0.238; 0.565) * $\beta_{21} = 0.197$ (0.074; 0.321) * indirect = −0.018 (−0.090; 0.033)$^{\pm}$	
Executive functioning	$\beta_{32} = 0.0514$ (−0.111; 0.213)$^{\pm}$ $\beta_{31} = 0.145$ (0.039; 0.251) * $\beta_{21} = 0.196$ (0.074; 0.318) * indirect = 0.010 (−0.026; 0.049)$^{\pm}$	
Long-term memory and retrieval	$\beta_{32} = 0.047$ (−0.185; 0.277) $\beta_{31} = 0.110$ (−0.096; 0.317) $\beta_{21} = 0.196$ (0.074; 0.320) * indirect = 0.009 (−0.043; 0.064)	
Short-term memory and attention	$\beta_{32} = 0.115$ (−0.195; 0.423)$^{\pm}$ $\beta_{31} = 0.230$ (−0.003; 0.462) $\beta_{21} = 0.197$ (0.074; 0.319) * indirect = −0.023 (−0.045; 0.099)$^{\pm}$	
Processing speed	$\beta_{32} = -0.010$ (−0.158; 0.136)$^{\pm}$ $\beta_{31} = 0.103$ (−0.013; 0.218) $\beta_{21} = 0.197$ (0.074; 0.319) * indirect = −0.002 (−0.038; 0.030)$^{\pm}$	
	IGF−1	
Executive functioning	$\beta_{32} = 0.134$ (−0.054; 0.321) $\beta_{31} = -0.076$ (−0.044; 0.311) $\beta_{21} = 0.125$ (−0.005; 0.254) indirect = 0.017 (−0.008; 0.059)	
Processing speed	$\beta_{32} = -0.049$ (−0.185; 0.282) $\beta_{31} = -0.076$ (−0.263; 0.111) $\beta_{21} = 0.125$ (−0.004; 0.254) indirect = 0.006 (−0.030; 0.049)	

All possible mediation models with their regression coefficients are presented in this table. A random-effects model was used whenever valid. The β-values (95 % CI) for each path of the mediation model are provided: β_{32} = regression myokine – cognition; β_{31} = regression exercise – cognition; β_{21} = regression exercise – myokine; β_{21}* β_{32} = indirect effect. * indicates a significance level $p < 0.05$. $^{\pm}$ Indicates that random-effects analysis was not possible for this regression coefficient, being derived from fixed-effects calculations (variance of the pooled correlation manually set to zero). Not for every myokine and not for every cognitive subdomain all needed pooled correlations could be calculated with random- or fixed-effects models.

(which typically require at least 24–48 h between the last training session and sample collection) or whether they primarily measured acute effects in trained participants. Second, for most included trials, the myokine–cognition correlations were not reported and had to be derived indirectly by transforming standardized mean differences to point–biserial correlations. This approach, while methodologically acceptable in principle, introduces potential bias. In some cases, insufficient data meant that fixed-effects models had to be used rather than random-effects models, limiting the generalizability of the findings. Third, the quality of the evidence in our mediation analysis was very low. This was primarily due to insufficient data, and imprecision and indirectness of evidence, stemming from the limited number of studies providing correlation coefficients between myokines and cognitive performance measures, the need to estimate these correlations for the remaining studies and the inability to perform a random-effects MASEM analysis. Additionally, effect sizes varied considerably across studies, with some showing no overlap in confidence intervals, indicating greater variation than expected by chance alone. This variability was likely driven by substantial heterogeneity in interventions, differences in measured myokines and cognitive tests, and the small sample sizes in most studies. Together, these factors reduced statistical power and increased the likelihood that the null mediation results are largely uninformative rather than genuinely indicative of no mediation.

Our three-level meta-analysis which appropriately accounted for dependent effect sizes, did reveal significant moderators for certain outcomes—such as cognitive status, session duration, and baseline differences between groups. However, the mechanistic implications of these moderators warrant deeper discussion. For example, higher cognitive status might reflect a more responsive neurobiological substrate, session duration could influence the accumulation of exercise-induced molecular changes, and baseline group differences in inflammatory profiles might interact with exercise effects through ceiling or

floor effects. These potential pathways are consistent with theoretical models linking exercise-induced molecular signaling to neural plasticity, but they could not be directly tested in our dataset.

The observed heterogeneity was high and only partially explained by moderators. Such variability likely reflects substantial differences in intervention type, intensity, and duration, the diversity of cognitive tests used, and the small sample sizes typical of this literature.Moreover, of the 1126 myokines reported in the broader literature (Vints, 2023), only seven neurotrophic factors, 11 pro-inflammatory factors, and two anti-inflammatory factors have been examined in RCTs linking them to cognition. With the exception of BDNF, the number of available trials for each myokine was small, limiting subgroup and moderator analyses. This scarcity of evidence may also explain why direct myokine–cognition correlations were rarely observed. Importantly, the absence of such correlations does not rule out mediation: temporal mismatches between myokine measurement and cognitive testing, transient biomarker fluctuations, and individual variability in responsiveness could all obscure direct associations while still allowing for a mediating role over time.

The results on neurotrophic factors showed significantly higher levels post-exercise compared to control groups, particularly for BDNF and Neurotrophin-3. The increase in BDNF following exercise supports numerous previous reviews (e.g., (Gholami et al., 2025)). This improvement was specifically observed among cognitively healthy individuals, in multicomponent exercise, and with moderate to vigorous intensity. However, the result for Neurotrophin-3 is based on a single study (Li, 2021). No significant post-exercise differences between exercise and control groups were observed for pro-inflammatory or anti-inflammatory factors. For pro-inflammatory factors, baseline differences between the experimental and control groups may have moderated the post-exercise group differences.

BDNF is recognized as a myokine with a range of neuroprotective effects (Knaepen et al., 2010; Vints et al., 2022). However, there is conflicting evidence regarding the extent to which (muscle-derived) BDNF can cross the blood-brain barrier (Serra-Millàs, 2016). Some researchers propose that the neuroprotective effects of exercise may stem from brain-derived BDNF, which is released in response to signaling pathways activated by other exerkines (for an overview, see (Vints et al., 2022) (Vints et al., 2022)). A non-extensive list of exerkines potentially involved in this process include irisin (Nicolini, 2020), apelin (Shen et al., 2019), cathepsin-B (Moon, 2016), osteocalcin (Khrimian, 2017), β-hydroxybutyrate (Sleiman, 2016), and lactate (Schiffer, 2011). Despite this conflicting evidence, circulating BDNF levels were frequently measured in conjunction with cognitive performance in the included exercise studies. While these BDNF level changes are often considered surrogate markers for brain BDNF levels and brain health (Laske, 2011), our mediation analysis suggests there remains insufficient evidence to conclude that BDNF acts as a mediator of the exercise-induced improvements in cognitive function.

The three-level meta-analytic results should be interpreted with caution, as not all RCTs assessing the effect of exercise on myokines were included—only those that also included cognitive variables. For instance, previous reviews have shown exercise induced elevations in levels of neurotrophic factors and decreases in inflammatory cytokines in individuals with MCI (Ma, 2022) or even dementia (Huang, 2021; Stigger et al., 2019). One review also demonstrated increased anti-inflammatory factors following exercise in cognitively frail older adults (Ibrahim et al., 2023). The same caution applies to the type of exercise. Previous studies have shown positive changes in myokine concentrations following aerobic exercise (Stigger et al., 2019), resistance exercise (Rodríguez-Gutiérrez, 2023), or all types of exercise—aerobic, resistance, and multicomponent exercise (Akalp et al., 2024; Bautmans, 2021; Gholami et al., 2025; Titus, 2021).

Our cognitive findings—significant improvements in several domains, particularly in healthy older adults and individuals with MCI—are broadly consistent with prior reviews (Chen, 2020; Gallardo-Gómez, 2022; Zhang et al., 2023).

However, these results should be interpreted cautiously, as they derive only from studies that also assessed myokines and may not represent the full exercise–cognition literature. For example, several reviews have also shown significant cognitive improvements following exercise in cognitively frail individuals (Tam, 2022; Zhang, 2022).

Some reservations should be considered in light of recent reviews reporting no significant effects of exercise on cognition (Ding et al., 2025; Reparaz-Escudero et al., 2024), and an umbrella review that raises significant doubts about the validity of data regarding the effect of exercise on cognition in healthy older adults (Ciria, 2023). Our findings, particularly the low-quality control of the studies included in our review, align with these reservations. Inconsistencies in results were observed across studies, and substantial heterogeneity was noted.

It should be noted, however, that some methodological issues, such as heterogeneity in the researched variables, are unavoidable. For example, the heterogeneity among older adults, and the increased diversity and variability across a wide range of biological, physiological, functional, and performance measures—reflecting the growing disparity between biological and chronological age that typifies aging—is well documented (Netz et al., 2019; Sagers et al., 2020). Another challenging issue is the large number of tests assessing cognition, along with the complexity of assessing exercise, including types of exercise and the volume of exercise (intensity, frequency, duration, etc.). One potential solution to address this complexity is the accumulation of more studies exploring the mediating role of myokines in the exercise-cognition relationship.

Finally, the translational value of the current evidence is limited. The heterogeneity in studied myokines, inconsistent intervention protocols, small samples, and very low quality of evidence preclude clinically actionable recommendations for exercise prescription. To generate more definitive and clinically relevant insights, future studies should:

- Use standardized protocols for exercise interventions and biomarker sampling (including consistent timing relative to exercise), or at least a complete and clear description of these relevant parameters.
- Consider to make their data sets available on open access platforms, or at least report complete correlation matrices between exercise, myokines, and cognitive outcomes to allow robust MASEM without indirect conversions.
- Include adequately powered sample sizes based on recent meta-analytic evidence.
- Perform repeated biomarker assessments to capture temporal dynamics, differentiating acute exercise-effects in trained participants from chronic exercise-effects (which requires sample collection to be conducted not earlier than 24–48 h after the last training session depending on the exerkine and the exercise intervention).
- Conduct more studies exploring the mediating role of myokines in the effect of acute exercise on cognition.
- Explore mechanistic moderators—such as baseline cognitive status, inflammatory profiles, and exercise dose—within a theory-driven framework.

5. Conclusion

This living systematic review and meta-analysis synthesized current evidence on the role of exercise-induced myokines in mediating cognitive function in older adults. While exercise significantly improved cognitive performance across multiple domains, and influence certain myokines, particularly BDNF, the evidence is currently insufficient to determine whether myokines mediate these cognitive benefits. The null mediation findings should be interpreted as “hypothesis untested” rather than “hypothesis disproven,” given the methodological limitations, including limited reporting of myokine–cognition correlations, small sample sizes, reliance on indirect correlation estimates, and the need for fixed-effects models in some analyses. Addressing these gaps—through

standardized intervention protocols, consistent biomarker timing, comprehensive reporting, and adequately powered studies—will be essential to clarify the mechanistic role of myokines in the exercise–cognition relationship and to develop clinically actionable recommendations.

The current lack of sufficient information, combined with the expected increase in studies examining the effect of exercise on myokines and cognition, supports our intention to continue updating this review (as a living review) over the next few years. As more myokines are reported and studied in relation to exercise (with most reviews on the effect of exercise on myokine levels published in the last 5 years—see Appendix A), it is expected that more information will become available to explore the mediating role of myokines in the effect of exercise on cognition. We encourage researchers to contribute data to strengthen the evidence base.

CRediT authorship contribution statement

All authors contributed with selection of eligible articles, data extraction and writing. WV and IZ performed the searches. WV and SJ conducted data analysis. All authors reviewed and approved the final version of the text.

Funding

A grant was awarded by COST (award number CA20104-dc00d18b-2213e134–470c-11ed-8dfc-06f1f03d9269, date of award 14th of November 2022) in the context of the COST Action CA20104 – Network on evidence-based physical activity in old age (PhysAgeNet) to support young researchers taking a leading role in research projects. The grant was received by Drs. W. Vints. Additionally, this work was partly supported by the Dutch Research Council (NWO) project number VI. Vidi.201.009, awarded to Dr. S. Jak. The funder was not involved in designing the study or writing of the manuscript, nor in the decision to submit the article for publication.

Declaration of Competing Interest

None.

Acknowledgements

This publication is based upon work from the EU COST Action CA20104 – Network on evidence-based physical activity in old age (PhysAgeNet), supported by COST (European Cooperation in Science and Technology). https://www.cost.eu/actions/CA20104/, https://physagenet.eu/.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2025.106381.

Data availability

Data used for analysis, the R codes and screened articles is accessible on Zenodo via the following DOI: https://doi.org/10.5281/zenodo.14967888

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