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The mediating role of lower body muscle strength and IGF-1 level in the relationship between age and cognition. A MIDUS substudy

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ABSTRACT

Objective: Aging is a natural process associated with a decline in cognition. However, the mediating effect of physical function and circulating myokines on this relationship has yet to be fully clarified. This study investigated how muscle strength and circulating insulin-like growth factor-1 (IGF-1) levels mediate the relationship between age and cognitive functions.
Subjects and methods: A total of 1255 participants aged 25–74 years included in the Midlife in the United States II study were retrospectively analyzed. In this cross-sectional analysis, we applied a serial mediation model to explore the mediating effects of muscle strength and circulating IGF-1 levels on the relationship between age and cognitive functions. We included potential confounding factors related to sociodemographics, lifestyle, and health status as covariates in the model.
Results: The results showed that aging had both direct and indirect effects on cognition. As predicted, muscle strength and IGF-1 levels mediated the relationship between age and specific cognitive functions. In addition, mediation analyses indicated that the association between aging and cognitive flexibility, immediate and delayed memory, and inductive reasoning were partially mediated by muscle strength and IGF-1 levels in a serial manner.
Conclusions: Our study demonstrated the serial multiple mediation roles of muscle strength and IGF-1 levels on the relationship between age and specific cognitive functions. Further longitudinal research should be performed to confirm the serial mediation results.

1. Introduction

By 2050, there will be 2.1 billion people worldwide over age 60, and the number of people over age 80 is estimated to reach 426 million (World Health Organization, n.d.). Cognitive aging can challenge older adults to perform everyday tasks such as driving, mobility, and transport. It is crucial to acquire a comprehensive understanding of modifiable mediators of age-related cognitive status to assist older adults in preserving or improving their cognitive functions. A mediator previously proposed to influence age-related cognitive decline is skeletal muscle changes (Sui et al., 2020). Muscle strength, on the one hand, and the levels of muscle-derived factors known as myokines, on the other hand, have both been associated with cognitive performance (Scisciola et al., 2021). Loss of muscle strength begins close to 40 years of age and accelerates with aging (Keller and Engelhardt, 2014). By the age of 50, individuals experience >15 % loss of muscle strength per decade (Lindle et al., 1997), which has consistently been documented to be associated with cognitive decline (Zammit et al., 2021; Peng et al., 2020). Relatedly, lower limb strength has been proposed as a mediator of optimal cognitive functioning (Anstey et al., 1997). Relatedly, the majority of available literature has found that higher quadriceps strength was associated with better cognitive performance (Chen et al., 2015; Bennett

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et al., 2019; Frith and Loprinzi, 2018; Chen et al., 2022).

Skeletal muscle has been posited as an active endocrine organ with the ability to generate and release various bioactive molecules termed myokines (Han et al., 2023). Myokines play a role in signaling pathways originating from skeletal muscles influencing various organs and tissues, including the brain (Hoffmann and Weigert, 2017). Recent research has indicated that myokines, such as insulin-like growth factor-1 (IGF-1), brain-derived neurotrophic factor (BDNF), and Cathepsin B, may potentially contribute to the beneficial effects of exercise on cognitive function (Vints et al., 2023). However, the specific myokines at play, the specific exercise characteristics, and the precise cognitive benefits involved are yet to be fully elucidated.

Among all myokines, insulin-like growth factor-1 (IGF-1) is of particular interest as decreased levels of this myokine are associated both with sarcopenia (Bian et al., 2020) and age-related cognitive decline (Frater et al., 2018). IGF-1 is secreted by various cell populations within the skeletal muscle, such as satellite cells, myofibers, fibroblasts, and inflammatory cells (Forcina et al., 2019). Similarly, these cells are responsive to IGF-1 which plays a critical role in muscle growth during regeneration (Schiaffino and Mammucari, 2011). Circulating IGF-1 levels decrease with age and are nearly undetectable in those over 60 years (Junnila et al., 2013). IGF-1 decline has been demonstrated to contribute to the progression of muscular atrophy during aging (Winn et al., 2002) and consequently, to promote frailty in older adults (Giovannini et al., 2008). IGF-1 is not only a growth factor for muscle but also a neurotrophic factor in the brain. Recent research has demonstrated that IGF-1 is important for synaptic plasticity and neurogenesis (Vints et al., 2022). A meta-analysis of 13 studies showed an overall relationship between IGF-I levels and cognitive functioning in healthy older adults (Arwert et al., 2005a). On the other hand, a systematic review of seven experimental studies reported conflicting results for the relationship between exercise-induced peripheral IGF-1 levels and cognitive function in older adults (Stein et al., 2018).

The present study aimed to further elucidate the mechanism by which age affects cognitive function using an integrated approach. Previous studies have explored the independent contributions of muscle strength and IGF-1 factors, but none have explored age, muscle strength, IGF-1 level and cognition in combination. Hence, using a serial mediation model, we investigated the mediating effects of muscle strength and IGF-1 levels on the relationship between age and cognition in adults. As we treated circulating IGF-1 as a muscle-derived myokine, we incorporated muscle strength as the first mediator in our model.

Based on the considerations stated above, we hypothesize that (i) age would demonstrate a negative association with cognitive functions, (ii) variations in muscle strength would mediate the relation between age and cognitive functions, (iii) circulating IGF-1 levels would mediate the relationship between age and cognitive functions, (iv) muscle strength and circulating IGF-1 levels would function in a serial mediation manner in the relationship between age and cognition.

We believe that gaining insight into how muscle strength and IGF-1 level may mediate age-related cognitive differences will contribute to interventional strategies on the human cognitive aging process.

2. Materials and methods

2.1. Data and sample

This cross-sectional analysis is based on The Midlife in the United States (MIDUS) study, a U.S. national-based longitudinal data collection that aims to identify the role of psychological, social, and biological factors determining age-related differences in health and well-being. Participants in MIDUS were surveyed through 30-minute phone interviews and completed self-administered questionnaires. During the phone interview, demographic data was collected, including information on sex, marital status, and educational background. Additionally, participants were asked to provide details regarding their medical history (including their physical and mental/emotional health), and alcohol consumption habits.

In the current study, we used a dataset of MIDUS 2 collected between 2004 and 2009. We used the Project 1, 3, and 4 datasets of MIDUS 2 to assess physical, cognitive, and biomarker outcomes. Samples that completed the Project 1 and 3 baseline surveys in the biomarker project were incorporated into the final analysis (Fig. 1). All participants gave informed consent, and data collection was approved by the Health Sciences Institutional Review Boards at the University of Wisconsin-Madison. Data are available through the MIDUS Portal (Ryff et al., 2022).

2.2. Measures

2.2.1. Cognitive assessment

Cognitive function was assessed using the Brief Test of Adult Cognition by Telephone (BTACT) (Lachman et al., 2014). The BTACT comprises subtests that measure episodic memory (immediate and delayed free recall of 15 words) and executive functions, including working memory (backward digit span), cognitive flexibility (stop and go switch task), verbal fluency (category and phonemic fluency in 60 s), inductive reasoning (number series), and processing speed (backward counting task).

2.2.2. Muscle strength assessment

Lower limb strength was assessed with a standardized five-repetition chair stand task (Jones et al., 1999). Participants were instructed to first assume a seated position with arms crossed over their chest and then stand and sit five times as quickly and safely as possible. Timing began on the instruction to "go" and concluded once the subject became fully erect with a cessation of body movement. Limb strength was measured in seconds to complete the task. Higher scores reflect worse lower extremity strength.

2.2.3. IGF-1 assessment

Participants were asked to avoid strenuous activity before sampling. Blood samples were drawn in the morning before breakfast, gently inverted 3–5 times, and stored for 15–30 min at room temperature to allow clotting. Subsequently, the tubes were centrifuged at 4 °C for 20 min at 4000*g* and stored until further analysis in a refrigerator compartment set at −60 to −80 °C. Samples were shipped to the MIDUS Biocore Lab monthly. IGF-1 was assessed by an immunochemiluminescent assay, with an inter-assay coefficient of variance (CV) between 4.4 and 6.8 % and the intra-assay CV was between 2 and 5 %.

2.3. Statistical analysis

IBM SPSS v26.0 software (SPSS Inc., Chicago, IL, USA) was used for all analyses. We tested the proposed serial mediation model with SPSS PROCESS macro developed by Hayes (Hayes, 2018), with four factors to examine whether the association between age and cognition was mediated by muscle strength (first mediator) and circulating IGF-1 levels (second mediator). This serial mediation model with two mediators supports three specific indirect effects: 1) through muscle strength (a_1b_1); 2) through circulating IGF-1 levels (a_2b_2); and 3) through muscle strength and circulating IGF-1 levels, in a serial fashion ($a_1a_3b_2$) (Fig. 2). We controlled for the influence of potential confounders by including physical health (excellent; very good; good; fair; poor), mental/emotional health (excellent; very good; good; fair; poor), education level (high school graduation or less; some college; college or more), alcohol problems in the last 12 months (yes; no), and marital status (married; not married) as covariates into the model. All the covariates that entered the model were defined categorically. We used bootstrapping procedures with 5000 samples that provide a point estimate and 95 % confidence intervals to estimate the significant indirect effects when the 95 % CI does not contain zero (Hayes, 2018). The significance level was set at

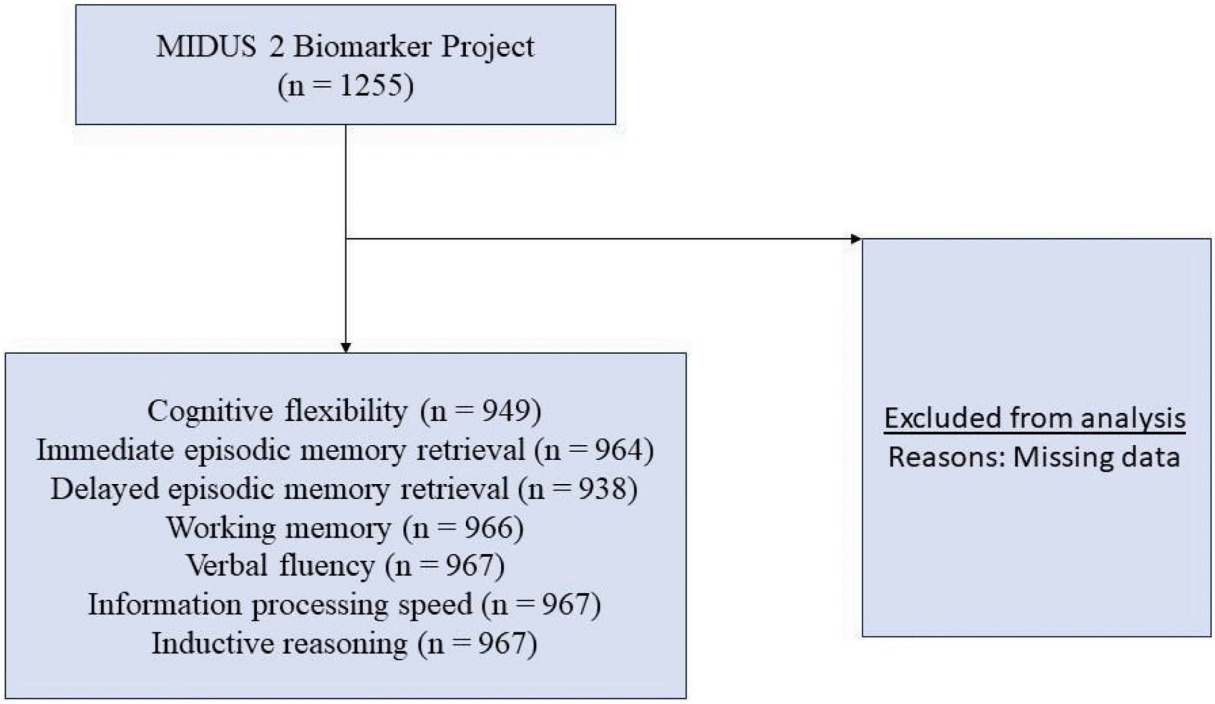

Fig. 1. Available data chart.

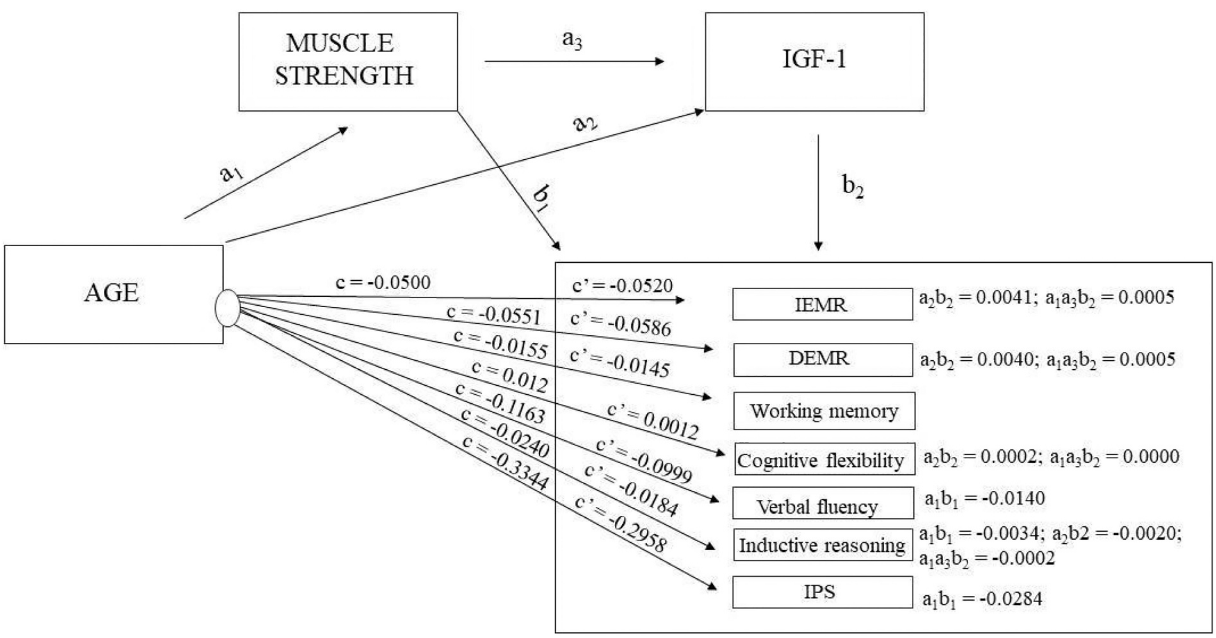

Fig. 2. IEMR, immediate episodic memory retrieval; DEMR, delayed episodic memory retrieval; IPS, Information processing speed. (c) A direct effect of the impact of Age on Cognition. (a_1b_1) An indirect effect of Age on Cognition, including Muscle Strength. (a_2b_2) An indirect effect of Age on Cognition, including circulating IGF-1 level. ($a_1a_3b_2$) An indirect effect of Age on Cognition, including Muscle Strength and circulating IGF-1 level. (c') A direct effect of Age on Cognition, taking account of the impact of both mediators.

<0.05.

3. Results

3.1. Descriptive statistics

A total of 1255 adults were enrolled in the study. Descriptive statistics are presented in Table 1.

3.2. Mediation analysis

The results of the serial mediating role of muscle strength and IGF-1 levels on the relationship between age and cognition are shown in Fig. 2 and Table 2.

3.2.1. Immediate episodic memory retrieval

A total of 964 participants successfully completed the assigned task.

Table 1
Descriptives of the sample.

Full sample (n = 1255)	
Age (years) (M, SD)	54.52 (11.71)
33 to 49	37.8 %
50 to 65	43.7 %
66 to 85	18.5 %
Sex (%) (f)	56.8
Marital status (%) (married)	72.4
Education	
High school or less	28.0 %
Some college	30.0 %
College or more	42.0 %
Subjective health (M,SD) (1 = excellent, 5 = poor)	2.41 (0.99)
Physical health (M,SD) (1 = excellent, 5 = poor)	2.30 (0.92)
Mental/emotional health (M,SD) (1 = excellent, 5 = poor)	2.09 (0.91)
Alcohol problem (%)	4.3
Serum IGF-1 level (ng/ml) (M, SD)	126.85 (50.17)

Note. M, mean; SD, standard deviation.

The total effect of age on immediate episodic memory retrieval was significant and older age was associated with lower scores (c = −0.0500, SE = 0.0055, $p < 0.0001$). The direct effect of age on immediate episodic memory retrieval was also significant indicating partial mediating effects (c' = −0.0520, SE = 0.0059, $p < 0.0001$). The indirect effect of age on immediate episodic memory retrieval through muscle was not significant whereas the indirect effect of age through IGF-1 level and the indirect effect of age through muscle and IGF-1 level were significant.

3.2.2. *Delayed episodic memory retrieval*

A total of 938 participants successfully completed the assigned task. The total effect of age on delayed episodic memory retrieval was significant and older age was associated with lower scores (c = −0.0551, SE = 0.0064, $p < 0.0001$). The direct effect of age on delayed episodic memory retrieval was also significant indicating partial mediating effects (c' = −0.0586 SE = 0.0068, $p < 0.0001$). The indirect effect of age on delayed episodic memory retrieval through muscle was not significant whereas the indirect effect of age through IGF-1 level and the indirect effect of age through muscle and IGF-1 level were significant.

3.2.3. *Working memory*

A total of 966 participants successfully completed the assigned task. The total effect of age on working memory was significant and older age was associated with lower scores (c = −0.0155, SE = 0.0038, $p <$ 0.0001). The direct effect of age on working memory was also significant (c' = −0.0145, SE = 0.0041, $p = 0.0004$) whereas none of the indirect effects on working memory were significant.

3.2.4. *Cognitive flexibility*

A total of 949 participants successfully completed the assigned task. The total effect of age on cognitive flexibility was significant and older age was associated with lower scores (c = 0.012 SE = 0.0004, p = 0.0037). The direct effect of age on cognitive flexibility was also significant when two mediators, muscle strength and circulating IGF-1 level were added to the model (c' = 0.0012, SE = 0.0005, p = 0.0312), indicating partial mediating effects. The indirect effect of age on cognitive flexibility through muscle was not significant whereas the indirect effect of age through IGF-1 level and the indirect effect of age through muscle and IGF-1 level were significant.

3.2.5. *Verbal fluency*

A total of 967 participants successfully completed the assigned task. The total effect of age on verbal fluency was significant and older age was associated with lower scores (c = −0.1163, SE = 0.0149, $p <$ 0.0001,). The direct effect of age on verbal fluency was also significant indicating partial mediating effects (c' = −0.0999, SE = 0.0159, $p <$ 0.0001). The indirect effect of age on verbal fluency through muscle was significant whereas the indirect effect of age through IGF-1 level and the indirect effect of age through muscle and IGF-1 level were not significant.

3.2.6. *Inductive reasoning*

A total of 967 participants successfully completed the assigned task. The total effect of age on inductive reasoning speed was significant and older age was associated with higher scores (c = −0.0240, SE = 0.0038, $p < 0.0001$). The direct effect of age on information processing speed was also significant indicating partial mediating effects (c' = −0.0184, SE = 0.0041, $p < 0.0001$). All indirect effects were significant.

3.2.7. *Information processing speed*

A total of 967 participants successfully completed the assigned task. The total effect of age on information processing speed was significant and older age was associated with higher scores (c = −0.3344, SE = 0.0277, $p < 0.0001$). The direct effect of age on information processing speed was also significant indicating partial mediating effects (c' = −0.2958, SE = 0.0295, $p < 0.0001$). The indirect effect of age on information processing speed through muscle was significant whereas the indirect effect of age through IGF-1 level and the indirect effect of age through muscle and IGF-1 level were not significant.

4. Discussion

The present study examined whether muscle strength and circulating

Table 2
Bootstrapping indirect effects for the final mediation model.

Cognitive performance	Model pathways								
	(Indirect 1) Age → Muscle → Cognition			(Indirect 2) Age → IGF-1 → Cognition			(Indirect 3) Age → Muscle → IGF-1→ Cognition		
	Effect	95 % CI		Effect	95 % CI		Effect	95 % CI	
		LLCI	ULCI		LLCI	ULCI		LLCI	ULCI
IEMR	−0.0025	−0.0061	0.0011	0.0041	**0.0016**	**0.0068**	0.0005	**0.0001**	**0.0009**
DEMR	−0.0010	−0.0055	0.0034	0.0040	**0.0012**	**0.0073**	0.0005	**0.0001**	**0.0010**
Backward digit span	−0.0017	−0.0038	0.0006	0.0006	−0.0011	0.0024	0.0001	−0001	0.0003
SGST	0.0000	−0.0002	0.0003	0.0002	**0.0000**	**0.0004**	0.0000	**0.0000**	**0.0001**
Verbal fluency	−0.0140	**−0.0239**	**−0.0051**	−0.0022	−0.0091	0.0045	−0.0003	−0.0012	0.0005
Number series	−0.0034	**−0.0057**	**−0.0012**	−0.0020	**−0.0038**	**−0.0003**	−0.0002	**−0.0005**	**0.0000**
Backward counting	−0.0284	**−0.0461**	**−0.0118**	−0.0092	−0.0238	0.0038	−0.0011	−0.0030	0.0004

Note. IEMR, immediate episodic memory retrieval; DEMR, delayed episodic memory retrieval; SGST, The Stop And Go Switch Task; LLCI, lower limit confidence interval; ULCI, upper limit confidence interval; Effect: unstandardized regression coefficient. Significant results are presented in bold.

IGF-1 levels mediate the relationship between age and cognition in a large sample of adults. We established that age was associated with cognition, at least in reported specific domains, indirectly through the mediation effects of lower extremity muscle strength and circulating IGF-1 levels and their serial multiple mediating roles. To our knowledge, this is the first study to demonstrate the above-mentioned mediating pathways, providing new research and intervention perspectives to minimize age-related cognitive decline.

4.1. The mediating role of muscle strength on cognitive function

The model presented in this study revealed that the relationships between age and verbal fluency, inductive reasoning and information processing speed were mediated through the muscle strength pathway whereas immediate and delayed episodic memory retrieval, working memory, and cognitive flexibility have not been predicted by this path. Specifically, aging is associated with lower muscle strength, which, in turn, indirectly related to lower cognitive abilities.

Consistent with our result, other studies have also suggested that muscle strength has a domain-specific association with cognition, including inductive reasoning, information processing speed, and verbal fluency. A systematic review of 29 studies reported a consistent bidirectional association between processing speed and lower limb muscle strength (Heaw et al., 2022). A meta-analysis of nine cohort studies reported a positive association between linear rates of change in hand grip strength and changes in reasoning ability (Zammit et al., 2021). Similarly, Anstey et al. demonstrated that lower limb strength predicted reasoning ability in older adults (Anstey et al., 1997). A longitudinal study including 8236 individuals demonstrated that hand grip strength predicted cognitive decline in different domains, and the strongest association with muscle strength was in verbal fluency in women (Haagsma et al., 2023). Moreover, Sui (2020) demonstrated that muscle strength is a better indicator of cognitive function than muscle mass, especially in the domain of information processing, further supporting the use of strength tests in medical evaluations in older age (Sui et al., 2020).

Consequently, the impact of age on cognition in adults may be mediated through the intermediary influence of muscle strength; in other words, diminished muscle strength could ultimately result in a decline in specific cognitive abilities during the aging process.

4.2. The mediating role of circulating IGF-1 levels on cognitive function

We demonstrated that age was associated with immediate and delayed memory retrieval, cognitive flexibility, and inductive reasoning through circulating IGF-1 levels.

Our results are partially supported by prior studies that reported an association between age-related decline in IGF-1 levels and cognitive functions. A meta-analysis of 13 studies showed a positive relationship between IGF-I levels and cognitive functioning in healthy older adults (Arwert et al., 2005b). Dik demonstrated the association of a low IGF-1 level with reduced cognitive function, including immediate and delayed episodic memory retrieval (Dik et al., 2003). Relatedly, individual increases in IGF-I were associated with improved memory in healthy middle-aged and older adults (Arwert et al., 2003). Also, Aleman et al. (1999) demonstrated that IGF-I level was significantly associated with cognitive flexibility task performance.

Robust evidence suggests that normal aging is associated with decreased activity of the Growth Hormone (GH)/IGF-1 axis, which leads to declined IGF-1 concentration (Frater et al., 2018; Wrigley et al., 2017). In rodents, central IGF-1 replacement has improved age-related memory deficit, suggesting a possibility of its strong neuroprotective feature (Markowska et al., 1998). More interestingly, systemic IGF-1 administration has prevented cognitive impairment in diabetic rats (Lupien et al., 2003). Considering IGF-1 crosses the blood-brain barrier (Carro et al., 2000), it is likely that circulating levels of IGF-1 affect cognitive functioning. Furthermore, either systemic injection of IGF-1 or exercise-induced elevations of IGF-1 have increased the transcription of hippocampal BDNF (Carro et al., 2000; Ding et al., 2006), widely known as a mediator of exercise-induced cognitive enhancement (Vaynman et al., 2004). Thus, the interaction between IGF-1 and BDNF might be a possible indirect mechanism which explains the effects of IGF-1 levels on cognitive functions.

According to our results and the above-mentioned literature, it is fair to say that age influenced cognition partly through the mediation effect of circulating IGF-1 levels. However, results from human studies support conflicting results on the relationship between IGF-1 levels and cognition, including positive (Arwert et al., 2005b; Dik et al., 2003; Arwert et al., 2003; Aleman et al., 1999), inverse (Tumati et al., 2016), and no associations (Licht et al., 2014). Therefore, future research focusing on the underlying mechanism would provide more knowledge on the effects of circulating IGF-I levels on cognitive functioning during the aging process.

4.3. The serial multiple mediation model

The present results showed that aging has influenced immediate and delayed episodic memory retrieval, cognitive flexibility, and inductive reasoning indirectly through muscle strength and IGF-1 level. Specifically, our results reinforce the idea that age-related IGF-1 level declines may be related to age-related muscle strength declines. Identifying mediational factors such as those found here implies that addressing low muscle strength and its negative consequences, such as low IGF-1 levels, may ultimately impact cognitive functions in the context of aging. In this context, higher muscle strength and circulating higher IGF-1 levels may help adults maintain better cognition. To our knowledge, this study is the first to demonstrate this mediating pathway.

In line with our results, a meta-analysis of 11 studies supported the idea that resistance training was associated with elevated muscle strength, which in turn, elevated serum IGF-1 levels (Amiri et al., 2021). Similarly, a longitudinal study of 1292 older adults demonstrated that lower muscle strength was associated with lower IGF-1 levels (van Nieuwpoort et al., 2018). On the contrary, elevated plasma levels of IGF-1 have been shown to be negatively associated with lower extremity maximal muscle strength in older patients admitted to an acute care unit (Ramírez-Vélez et al., 2020). However, this result should be interpreted with caution, taking into account homeostasis dysregulation due to the health status of acute care patients.

Our results indicated that muscle strength and IGF-1 did not serially mediate the relationship between age and verbal fluency, and processing speed, but muscle strength did. This finding seems remarkable and suggests that myokines may have function-specific roles. There is probably no single, ideal myokine to anticipate overall cognitive functions, but a panel of complementary myokines may be used to gain a better understanding of an individual's cognitive status through muscle-related factors (Vints et al., 2023).

One intriguing finding of this study is that the impact of age on working memory appears to be independent of muscle strength, IGF-1 levels, or their serial mediation, suggesting that age-related working memory deterioration may stem from distinct factors. Further studies investigating the underlying mechanisms of age-related working memory decline could enhance our understanding of these factors and potentially lead to the development of more effective strategies for addressing it.

In summary, our findings on the intricate interplay between aging, muscle strength, IGF-1 levels, and cognitive performance shed light on the multifaceted nature of cognitive aging. Future research employing a more integrated approach that emphasizes the dynamic interplay between muscle-related factors and cognitive processes may propose novel therapeutic solutions for enhancing the cognitive well-being of the aging population.

5. Limitations and future directions

The benefit of serial mediation models is that they can be used to test for a specific theoretical sequence between variables. Indeed, our study validated an important chain relationship between age and specific cognitive functions through muscle strength and IGF-1. Moreover, given the domain-specific effect of age on cognition through muscle strength, muscle strengthening exercises may be particularly important in intervention strategies planned to improve specific cognitive functions in older adults. However, there are some limitations of the present research that should be addressed. The study's cross-sectional design limits the interpretation of causality between age and cognition, and only associations can be drawn. Our serial mediation model should be examined in further longitudinal research before developing intervention strategies based on the present results. Furthermore, our study only evaluated a single myokine, namely IGF-1. Future work may benefit from a broader analysis of different myokines to specify the function-specific effects of myokines on the aging brain.

6. Conclusions

The present study demonstrated that the association between age and cognition is serially mediated by muscle strength and circulating IGF-1 levels. Taken together, the results of the current study identify potentially modifiable mechanisms that mediate the association between aging and cognition in adulthood, suggesting that intervening to improve muscle strength and trigger higher IGF-1 levels has the potential to mitigate age-related cognitive decline.

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CRediT authorship contribution statement

Evrim Gökçe: Writing – review & editing, Writing – original draft, Visualization, Methodology, Formal analysis, Data curation, Conceptualization. **Navin Kaushal:** Writing – review & editing, Resources. **Theo Fontanille:** Writing – review & editing, Visualization, Software, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Tudor Vrinceanu:** Writing – review & editing, Resources, Project administration. **Kathia Saillant:** Writing – review & editing, Visualization, Validation. **Wouter A J Vints:** Writing – review & editing, Visualization, Software. **Thomas Freret:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Investigation, Conceptualization. **Antoine Gauthier:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Conceptualization. **Louis Bherer:** Writing – review & editing, Validation, Project administration, Conceptualization. **Antoine Langeard:** Writing – review & editing, Validation, Supervision, Resources, Project administration, Methodology, Investigation, Funding acquisition, Data curation, Conceptualization.

Declaration of competing interest

None.

Data availability

I have shared the data file at the Attach File step.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.exger.2024.112399.

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