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The association of hemopexin, muscle quality, and sarcopenia in Japanese older adults with cognitive impairment: a cross-sectional study

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Abstract

Objective To examine the cross-sectional associations of hemopexin, muscle quality, and sarcopenia status with cognitive function among older Japanese adults with cognitive impairment, and to explore the potential sex-specific differences.

Methods A total of 580 older adults (372 women, 208 men; mean age 83.3 ± 6.2 years) who presented with cognitive impairment at the Kyoto Dementia Comprehensive Center between 2018 and 2022 were enrolled. Cognitive function was assessed using the Mini-Mental State Examination (MMSE). Hemopexin level was measured by enzyme-linked immunosorbent assay. Muscle quality was evaluated via phase angle (PhA) and grip strength, and sarcopenia status was defined using the Asian Working Group for Sarcopenia criteria. Multiple linear regression models, including sex-stratified analyses, were conducted to determine the relationships of these variables with MMSE scores.

Results Higher hemopexin levels (β = 1.19, $p = 0.017$), PhA (β = 0.59, $p = 0.005$), and grip strength (β = 0.14, $p < 0.001$) were independently associated with better MMSE scores, whereas sarcopenia was negatively linked to MMSE scores (β = −2.28, $p < 0.001$). Notably, sex-stratified models indicated that hemopexin positively predicted MMSE scores in men but not in women; meanwhile, sarcopenia showed a stronger negative impact in women. Educational attainment also displayed a significant positive association with cognitive performance in both sexes.

Conclusions In this cross-sectional study of older Japanese adults with cognitive impairment, hemopexin levels and muscle quality emerged as important correlates of cognitive function, particularly in men, while sarcopenia was negatively linked to cognition.

Keywords Dementia, Hemopexin, Muscle quality, Phase angle, Sarcopenia

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Introduction

As skeletal muscle deteriorates in older adults, cognitive impairment poses additional challenges, with dementia being a leading cause of death and disability worldwide [1]. The progressive reduction in muscle mass and function—known as sarcopenia—is increasingly recognized not only as a consequence of aging but also as a contributor to chronic diseases, leading to adverse health outcomes [2]. Sarcopenia is age-related, characterized by reductions in muscle mass, strength, and function [2, 3], often resulting in functional decline and loss of independence in older adults [4–7]. Numerous studies have linked sarcopenia to increased risks of falls, frailty, decreased quality of life, and higher healthcare costs and mortality among this population [8–10].

Modern definitions of sarcopenia tend to view muscle strength and quality as separate entities [11], with muscle quality often represented by muscle strength or power per unit of muscle mass [12]. Including muscle quality in sarcopenia assessments can provide a more comprehensive understanding and potentially position muscle quality as a marker for sarcopenia [3, 13, 14]. While sarcopenia is mainly associated with physical decline, emerging evidence also suggests a link to cognitive impairment [14–17]. However, the strength of this association—particularly around physical frailty, mild cognitive impairment (MCI), and Alzheimer's disease (AD)—may be related to factors [18–20] such as inflammation, oxidative stress, and hormonal changes [21]. These findings have not reached a consensus [15–17, 21], the possibility of cognitive decline among individuals with sarcopenia warrants deeper exploration. Of note, despite physiological differences, the hypothalamus may reflect skeletal muscle's metabolic responses [22], highlighting the need to further investigate mechanisms that bridge muscle health and cognition.

Hemopexin (HPX) is a 60-kDa glycoprotein synthesized locally by central nervous system cells, with the highest known binding affinity for serum heme (Kd < 1 pM) [23]. It has attracted attention for its potential roles in both muscle health [24]and cognitive function [25]. Current research indicates that HPX-derived peptide sequences can be used on nanoparticle platforms for clearing toxic hemin, potentially benefiting hemolytic diseases [26]. Preliminary findings also suggest neuroprotective effects: for instance, HPX administration reduced ischemic damage in rats [24], and HPX-deficient mice have shown reduced myelination in the brain [27]. Conversely, skeletal muscle atrophy has been linked to memory impairment via HPX secretion in an AD mouse model [28], though observations vary across studies [25, 27, 28]. Clinically, higher cerebrospinal fluid HPX levels have been associated with milder AD pathology and better cognitive outcomes [29]. Given that primary HPX synthesis in the brain is relatively limited, peripheral contributions—especially from skeletal muscle—could influence heme levels in the brain [22], supporting the hypothesis that muscle health may be integral to maintaining cognitive function [30].

Despite growing interests, many studies examine only individual characteristics of sarcopenia rather than integrating these traits with other biomarkers [31–34]. A 2021 systematic review highlighted the scarcity of research on dementia for individuals with sarcopenia [35], and the study by Nagase et al. was the first to reveal early memory deficits in an AD mouse model with skeletal muscle atrophy through HPX secretion [28].

Building on these insights, our study in older adults with cognitive impairment aims to clarify the relationships between HPX levels, muscle mass, muscle quality, sarcopenia, and cognitive function.

Methods

Data collection and sample selection

The study included 580 participants who visited the Kyoto Dementia Comprehensive Center clinic between 2018 and 2022. Inclusion criteria were consented to participate at the initial visit, presence of subjective or objective cognitive impairment, availability of body composition data assessed using the TANITA multi-frequency body composition analyzer (MC-780 A-N, TANITA Corporation, Tokyo, Japan), annual MMSE assessments for cognitive function, and available blood samples. First, we recruited 1,664 participants who visited and underwent neuropsychological assessments between March 2018 and February 2022. Second, we excluded 19 participants who did not meet the inclusion criteria: 16 lacked MMSE assessment, and 3 had no clinical diagnosis of amnestic mild cognitive impairment (aMCI) or other types of dementia. As a result, 1,645 participants with both MMSE scores and clinical diagnoses. Third, we removed participants with missing bioelectrical impedance analysis (BIA)-measured body composition data ($n = 919$), those who did not have blood and body composition data from the same year ($n = 144$), and those with abnormal blood test results ($n = 2$). Ultimately, 580 participants were included in the final analysis. Details of the sample selection process are shown in Fig. 1.

Data collection

Comprehensive data were collected from participants' medical records, including age (in years), gender, MMSE scores (range: 0–30), grip strength (in kilograms), walking speed (in meters/second), and muscle mass (in kilograms) and limb skeletal muscle mass (in kilograms).

The MMSE comprehensive neuropsychological tests were conducted by neuropsychologists. Clinical examinations, including grip strength analysis and body

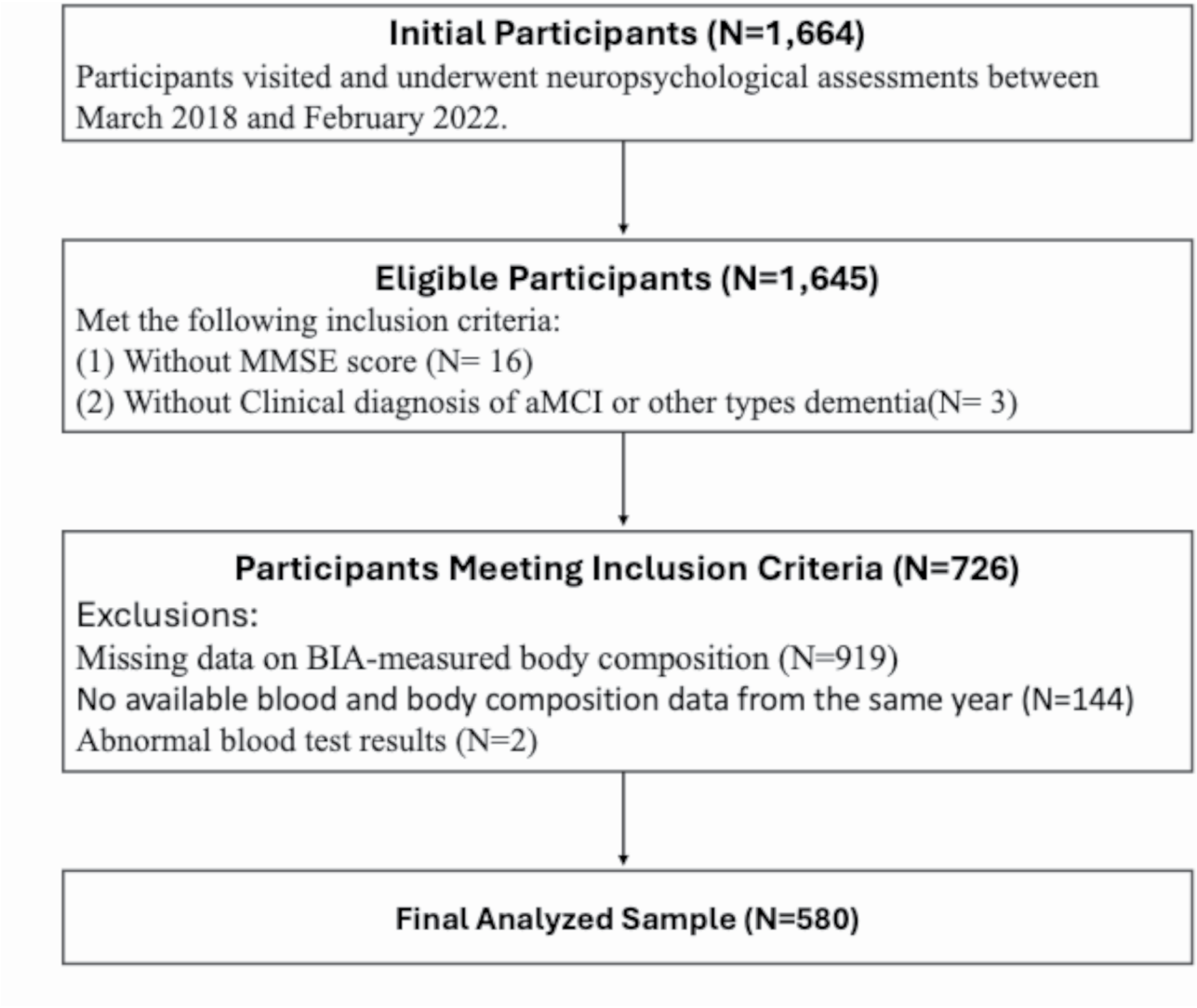

Fig. 1 Sample inclusion flow chart

composition analysis, were performed by clinicians. Walking speed examinations were conducted by nurses.

Blood samples

Blood samples were collected at the initial participants visit by nurses. After collection, the samples were centrifuged at 3000 rpm for 10 min to separate the plasma, which was then stored at -80℃ until analysis by enzyme-linked immunosorbent assay (ELISA).

Human plasma samples were diluted 400-fold, and hemopexin concentration in human plasma was determined using the HPX (Human) ELISA kit (KA0481, ABN, Abnova Corporation). Measurements were performed using a kinetic microplate reader (Molecular Devices, USA) at a wavelength of 450 nm.

The serum hemopexin concentration in adults ranges from 400 to 1500 μg/ml [23, 36, 37]. Heme synthesis occurs in foetuses and neonates, and the serum HPX concentration in neonates is approximately 20% of the adult level, increasing immediately after birth [38]. The lack of an internationally standardized method for HPX preparation complicates the comparison of results across different studies [36].

Cognitive function measurement

Cognitive function was assessed using the MMSE. The MMSE is a widely used tool that evaluates various cognitive domains. The total score ranges from 0 to 30, with higher scores indicating better cognitive function. The staging is defined as follows: the participants with scores ≥ 24 are defined as subjective cognitive decline ~ mild cognitive impairment (SCD~MCI), those with 20–23 as early stage of AD (early AD), and those with ≤ 19 as middle-to-late stages of AD (middle-to-late AD) [39].

Sarcopenia assessment

Sarcopenia assessment followed the 2019 Asian Working Group for Sarcopenia criteria. Grip strength was measured using a hand-held dynamometer, with two tests conducted for each hand and the maximum value averaged. The skeletal muscle mass index (SMI) was measured using the TANITA multi-frequency body composition analyzer. Participants were diagnosed with sarcopenia if they met the criteria for SMI < 7.0 kg/m² for men and < 5.7 kg/m² for women along with either grip strength < 28 kg for men and < 18 kg for women or walking speed < 1 m/second.

Measurement of muscle quality

A multi-frequency body composition analyzer was employed to measure bioelectrical impedance and obtain comprehensive body composition data. Equations specific to this model have been developed for estimating appendicular skeletal muscle mass (ASM), and prior validation studies have shown high correlations between body composition measurements from this device and those obtained via dual-energy X-ray absorptiometry (DXA) [40].

The skeletal muscle mass index (SMI, kg/m²) was subsequently calculated by dividing ASM (kg) by the square of the height (m). The body mass index (BMI, kg/m²) was determined by dividing weight (kg) by the square of the height (m). Additionally, the phase angle (PhA) was calculated using the formula: PhA (°) = -arctan (Xc/R) * (180/π). The phase reactance (Xc) and resistance (R) values measured at a 50 kHz current were utilized for this calculation [41].

Muscle quality was assessed using PhA. Bioimpedance can be divided into resistance (resistance value) of extracellular and intracellular fluids, and reactance (reactance value) caused by cell membranes. PhA is the ratio of resistance to reactance expressed in degrees, typically measured using a 50 kHz current. We used the absolute value of the average PhA of the left and right halves of the body, with a higher absolute PhA value indicating better cell health, higher muscle fiber density, and better muscle quality.

The preprocessing steps included numerical encoding of the 'Sex' variable, log transformation of 'Hemopexin' levels, and categorization of 'Sarcopenia' as a factor. Non-numeric and non-factor columns were excluded from the analysis.

Statistical analysis

Data analysis was conducted using R version 4.2.3. Descriptive statistics were calculated for key variables (Table 1). The distribution of 'Sarcopenia' was presented as counts and percentages stratified by sex. Univariate regression analysis was performed to assess the association between various factors and MMSE scores (Table 2). Multivariable regression analysis was conducted to further explore the factors associated with MMSE scores (Table 3). Table 4 presents the results of multivariable linear regression for MMSE scores stratified by gender. To assess multicollinearity among independent variables, we calculated the Variance Inflation Factor (VIF) using the car package in R. All VIF values were below the commonly accepted threshold of 5, indicating no significant multicollinearity. The results are summarized in Table 5. All statistical tests were two-tailed, and a p-value of less than 0.05 was considered statistically significant.

Results

Among the 580 older adults included in this study, 372 (64.14%) were female and 208 (35.86%) were male. The mean age was 83.3 ± 6.2 years, with slightly higher values observed in female participants (83.8 ± 6.1) compared to males (82.5 ± 6.5). The average Hemopexin level was 2164.0 ± 814.5 μg/mL, and female participants exhibited slightly higher levels (2200.7 ± 805.6) than their male counterparts (2098.3 ± 828.0). The mean MMSE score was 22.4 ± 5.2. In terms of physical performance, the average grip strength was 16.3 ± 7.6 kg, notably higher among males (22.3 ± 7.1) than females (12.9 ± 5.6). The overall mean muscle mass was 36.2 ± 7.3 kg, with male participants showing substantially higher values (43.5 ± 6.0) than females (32.1 ± 4.1). The average BMI was 22.1 ± 3.3 kg/m², and the mean height was 1.5 ± 0.1 m. The phase angle (PhA) averaged 4.8 ± 1.0. On average, 0.3 ± 0.5 of participants were classified as having sarcopenia (binary variable of 1 for sarcopenia, 0 for non-sarcopenia), indicating that approximately 30% of the sample met the criteria. Education level averaged 11.6 ± 2.4 years (n = 516), and the mean walking speed among the 433 participants with gait data was 0.9 ± 0.3 m/s. Detailed information can be found in Table 1.

Univariate regression analysis (Table 2) demonstrated that higher levels of hemopexin were significantly associated with better MMSE scores (β = 1.190, p = 0.017). Age showed a significant negative association with cognitive function (β = −0.140, p < 0.001), while grip strength (β = 0.140, p < 0.001), muscle mass (β = 0.060, p = 0.038), BMI (β = 0.160, p = 0.011), and phase angle (PhA; β = 0.590, p = 0.005) were positively associated with MMSE scores. Sarcopenia was strongly negatively associated with MMSE (β = −2.280, p < 0.001), while height and sex did not show statistically significant effects.

Multivariable regression analysis (Table 3) further confirmed the significant association of hemopexin with MMSE after adjusting for physical parameters and sarcopenia. In Model 1 (without sarcopenia), hemopexin (β = 1.166, p = 0.016), PhA (β = 0.517, p = 0.021), and grip

Table 1 Descriptive characteristics of study participants, including demographic, clinical, and physical performance variables

Variable	Group	*N*	Mean	SD	Median	Min	Max	Range
Hemopexin (μg/mL)	Total	580	2164.0	814.5	2219.2	192.0	7007.0	6814.9
	Female	372	2200.7	805.6	2247.4	192.0	7007.0	6814.9
	Male	208	2098.3	828.0	2143.6	406.0	6121.0	5715.7
Age(years)	Total	580	83.3	6.2	84.0	63.0	98.0	35.0
	Female	372	83.8	6.1	84.0	63.0	98.0	35.0
	Male	208	82.5	6.5	83.0	63.0	97.0	34.0
MMSE (score)	Total	580	22.4	5.2	23.0	1.0	30.0	29.0
	Female	372	22.5	5.1	23.0	1.0	30.0	29.0
	Male	208	22.2	5.3	23.0	6.0	30.0	24.0
Grip strength (kg)	Total	580	16.3	7.6	15.0	1.3	59.3	58.0
	Female	372	12.9	5.6	12.3	1.3	59.3	58.0
	Male	208	22.3	7.1	22.0	5.4	42.0	36.6
Muscle Mass (kg)	Total	580	36.2	7.3	34.1	19.8	58.3	38.5
	Female	372	32.1	4.1	32.0	19.8	55.2	35.4
	Male	208	43.5	6.0	43.5	26.4	58.3	31.9
BMI(kg/m^2)	Total	580	22.1	3.3	21.9	9.8	33.6	23.8
	Female	372	22.0	3.6	21.6	13.6	33.6	20.0
	Male	208	22.3	2.9	22.3	9.8	28.4	18.6
Height (m)	Total	580	1.5	0.1	1.5	1.2	1.8	0.7
	Female	372	1.5	0.1	1.5	1.2	1.8	0.6
	Male	208	1.6	0.1	1.6	1.5	1.8	0.4
PhA (degrees)	Total	580	4.8	1.0	4.7	3.2	11.0	7.8
	Female	372	4.7	1.0	4.5	3.2	11.0	7.8
	Male	208	5.0	1.0	5.0	3.2	10.1	6.9
Sarcopenia	Total	580	0.3	0.5	0.0	0.0	1.0	1.0
	Female	372	0.2	0.4	0.0	0.0	1.0	1.0
	Male	208	0.4	0.5	0.0	0.0	1.0	1.0
Education(years)	Total	516	11.6	2.4	12.0	6.0	18.0	12.0
	Female	336	11.3	2.1	12.0	6.0	16.0	10.0
	Male	180	12.3	2.7	12.0	6.0	18.0	12.0
Walk speed(m/s)	Total	433	0.9	0.3	0.9	0.0	1.8	1.8
	Female	280	0.9	0.3	0.9	0.0	1.8	1.8
	Male	153	0.9	0.2	0.9	0.3	1.8	1.5

Walk speed data were available for 433 participants; education data were available for 516 participants. Values are presented as mean ± standard deviation unless otherwise indicated. Sarcopenia is a binary variable (0 = non-sarcopenia, 1 = sarcopenia)

Table 2 Univariate regression analysis of factors associated with MMSE scores

Variable	Estimate	Standard Error	t-value	*p*-value	
Hemopexin	1.190	0.490	2.400	0.017	*
Age	-0.140	0.030	-4.100	0.000	***
Sex	-0.340	0.450	-0.770	0.441	
Grip strength	0.140	0.030	5.170	0.000	***
Muscle Mass	0.060	0.030	2.080	0.038	*
BMI	0.160	0.060	2.550	0.011	*
Height	3.750	2.100	1.790	0.075	
PhA	0.590	0.210	2.850	0.005	**
Sarcopenia	-2.280	0.470	-4.880	0.000	***

Note: ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$

Univariate regression analysis identifying individual associations between clinical and physical parameters and MMSE scores in older adults with cognitive impairment. Variables include demographic characteristics, muscle-related indicators, and sarcopenia status

strength ($\beta = 0.224$, $p < 0.001$) were significantly associated with MMSE. Interestingly, muscle mass was negatively associated with MMSE ($\beta = -0.141$, $p = 0.002$). In Model 2 (with sarcopenia), the effect of PhA was attenuated and became non-significant, while sarcopenia remained an independent predictor of lower MMSE scores ($\beta = -1.871$, $p < 0.001$).

Multivariable regression analysis stratified by sex (Table 4) confirmed sex-specific associations. In males, hemopexin ($\beta = 1.992$, $p = 0.019$), grip strength ($\beta = 0.250$, $p < 0.001$), and education ($\beta = 0.472$, $p < 0.001$) were positively associated with MMSE scores, while other variables showed no significant effects. In contrast, among females, sarcopenia ($\beta = -2.273$, $p = 0.001$), grip strength ($\beta = 0.111$, $p = 0.047$), and education ($\beta = 0.483$, $p < 0.001$) were significant predictors. Notably, hemopexin did not show a significant effect in females ($p = 0.412$).

Table 3 Multivariable regression analysis of factors associated with MMSE scores, including the effect of sarcopenia

Variable	Model 1					Model 2				
	Estimate	Std.Error	t-value	p-value		Estimate	Std.Error	t-value	p-value	
Hemopexin	1.166	0.480	2.427	0.016	*	1.221	0.475	2.568	0.010	*
PhA	0.517	0.224	2.310	0.021	*	0.235	0.234	1.008	0.314	
Muscle Mass	-0.141	0.045	-3.136	0.002	**	-0.146	0.044	-3.278	0.001	**
Grip Strength	0.224	0.041	5.480	0.000	***	0.212	0.041	5.229	0.000	***
Sarcopenia						-1.871	0.499	-3.750	0.000	***

Note: ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$

Multivariable regression models examining the associations between MMSE scores and various physical indicators. Model 1 excludes sarcopenia, while Model 2 includes sarcopenia as an independent variable. Both models adjust for hemopexin, phase angle (PhA), muscle mass, and grip strength

Discussion

This study demonstrates positive correlations between hemopexin levels and MMSE scores, suggesting that higher hemopexin levels may be associated with better cognitive function. Our findings also indicate a negative correlation between sarcopenia, PhA, and cognitive function. This research significantly deepens our understanding of the relationships between hemopexin, muscle quality, muscle mass, sarcopenia, and cognitive function, particularly in older adult's populations with cognitive impairment. The results underscore the potential role of hemopexin as a biomarker for muscle and cognitive health in such populations.

Firstly, both univariate and multivariate regression analyses revealed positive correlations between hemopexin levels and MMSE scores, indicating that higher hemopexin levels may be linked to better cognitive function. This finding is consistent with previous studies [25, 29]. For example, hemopexin-deficient mice exhibit inadequate brain myelination, and intracerebroventricular injection of hemopexin in ischemic rats reduces infarct volume and improves neurological measures [25]. Additionally, higher hemopexin levels are associated with increased cerebrospinal fluid amyloid beta (indicating reduced amyloid deposition in the brain), improved hippocampal metabolism, and enhanced cognitive abilities [29]. In sex-stratified analyses, the positive correlation between hemopexin levels and MMSE scores was observed only in men and not women. This sex difference may be attributed to several factors: firstly, physiological differences in iron metabolism and oxidative stress responses between men and women. Iron imbalance is related to the pathogenesis of Alzheimer's disease [29].

Heme/iron toxicity is mitigated by the scavenger protein hemopexin (HPX), which strongly binds to heme and regulates its biology to maintain iron homeostasis [42, 43]. The sex-specific differences in iron metabolism might lead to a higher susceptibility to iron overload in men, enhancing the protective role of hemopexin. Higher iron loads in men may require more hemopexin to maintain iron homeostasis, possibly explaining the more significant positive correlation between hemopexin levels and cognitive function in men. Secondly, differences in sex hormones might influence hemopexin's function. Estrogen appears to prevent cognitive impairment induced by cholinergic deficits in middle-aged women and female animals [44], which may partially compensate for hemopexin's protective role in women, reducing dependence on hemopexin. Thus, the association between hemopexin levels and cognitive function might be less significant in women. Finally, there may be differences in the pathological progression and development of Alzheimer's disease between men and women. For example, studies indicate that the lack of estrogen's neuroprotective effects in postmenopausal women results in more severe amyloid pathology at the same age as men, further increasing their risk of Alzheimer's disease compared to age-matched men [45]. Therefore, the different associations of hemopexin by sex may reflect pathophysiological differences in Alzheimer's disease between genders. Despite a recent animal study suggesting that heme secreted by atrophic skeletal muscle affects memory impairment in mice, the mechanisms involving intracerebroventricular infusion or clamp fixation-induced hippocampal LCN2 mRNA remain unclear. These findings highlight the importance of considering sex differences in studying neurodegenerative diseases. Understanding how sex influences the relationships between iron metabolism, hemopexin function, and cognitive function is crucial for developing personalized therapeutic strategies.

Our study shows that sarcopenia is negatively correlated with both PhA and MMSE scores. Sarcopenia is characterized by decreased muscle mass, strength, and function [2, 3], while PhA reflects cell membrane structure, cell mass, cell integrity, and cell function [46, 47], and has been shown to be a useful indicator for easily measuring muscle quality [48].Therefore, higher muscle quality may be associated with a lower risk of sarcopenia. This supports the critical role of muscle quality in reducing sarcopenia risk and aligns with previous studies [49–51]. The negative correlation between sarcopenia and MMSE scores is consistent with several prior studies. Since physical exercise can reduce the occurrence of sarcopenia [52] and delay cognitive decline [53], another

Table 4 Multivariable linear regression analysis of factors associated with MMSE scores by gender

Variable	Model 1				Model 2				Model 3			
	Estimate	Std.Error	t-value	p-value	Estimate	Std.Error	t-value	p-value	Estimate	Std.Error	t-value	p-value
Age	-0.045	0.036	-1.250	0.212	0.019	0.060	0.311	0.756	-0.071	0.046	-1.540	0.125
Muscle Mass	-0.179	0.045	-4.005	0.000 ***	-0.069	0.090	-0.770	0.442	-0.117	0.084	-1.383	0.168
Pha	0.224	0.228	0.979	0.328	0.371	0.402	0.924	0.357	0.036	0.279	0.130	0.897
BMI	0.083	0.062	1.326	0.186	-0.053	0.134	-0.395	0.693	0.122	0.070	1.732	0.084
Hemopexin	0.380	0.467	0.814	0.416	1.992	0.838	2.377	0.019 *	-0.457	0.556	-0.822	0.412
Sarcopenia	-1.557	0.500	-3.112	0.002 **	0.790	0.978	0.808	0.420	-2.273	0.696	-3.267	0.001 **
Grip Strength	0.163	0.041	4.011	0.000 ***	0.250	0.061	4.084	0.000 ***	0.111	0.056	1.993	0.047 *
Education	0.480	0.088	5.456	0.000 ***	0.472	0.133	3.557	0.000 ***	0.483	0.118	4.083	0.000 ***

Note: ***$p < 0.001$, **$p < 0.01$, *$p < 0.05$

Multivariable linear regression analysis examining the associations between MMSE scores and clinical factors, stratified by gender. Model 1 includes all participants; Model 2 includes males only; and Model 3 includes females only. Independent variables include age, muscle mass, phase angle (PhA), BMI, hemopexin, sarcopenia status, grip strength, and years of education

Table 5 Variance inflation factor (VIF) for independent variables in the multivariable regression model

Variable	VIF
Hemopexin	1.00
PhA	1.36
Muscle Mass	2.52
Grip Strength	2.28
Sarcopenia	1.21

VIF values for hemopexin, phase angle (PhA), muscle mass, grip strength, and sarcopenia were all below the commonly accepted threshold of 5, indicating no significant multicollinearity among the predictors

possible explanation is that cytokines and peptides secreted by skeletal muscle can enhance brain function, including cognitive abilities, indicating muscle-brain crosstalk [54]. Although hemopexin is primarily synthesized in the liver, Nagase et al.'s study suggests that skeletal muscle in mouse AD models can also secrete hemopexin [28]. Our study also reveals a positive correlation between PhA and MMSE scores, which is consistent with previous findings [55]. This indicates that muscle quality is closely related to cognitive health. Based on the aforementioned protective effects of hemopexin in iron metabolism and oxidative stress response on cognitive function, hemopexin secreted from skeletal muscle may act as a mediator between muscle and cognitive function.

In the multivariate model incorporating grip strength and years of education, the significance of these two factors on cognitive function became evident. Grip strength, a widely used indicator of overall muscle strength and physical function, showed a significant positive correlation with MMSE scores. The positive effect of grip strength was more pronounced in men ($\beta = 0.250$, $p < 0.001$) than in women ($\beta = 0.111$, $p = 0.047$), though women followed a similar trend. These findings align with the large-scale study based on the UK Biobank, which reported that a 5 kg reduction in grip strength significantly decreased fluid intelligence and prospective memory scores, while increasing the risk of vascular dementia and Alzheimer's disease—also relating grip strength declines to heightened white matter hyperintensity [56]. Similarly, years of education were positively correlated with MMSE scores, underscoring education as a key predictor of cognitive function in both men and women, consistent with previous literature. A Mendelian randomization study found that the protective effect of education on Alzheimer's disease was primarily mediated by enhanced intelligence, rather than an independent mechanism [57]. This suggests that education can strengthen cognitive reserve, thereby slowing cognitive decline, especially among populations with lower levels of education. Extending formal schooling or adopting cognitive training interventions thus remains a promising strategy for mitigating the risk of cognitive impairment.

Conclusion

Our study indicates a strong association between hemopexin levels and cognitive function, particularly among men, offering new insights for individualized therapeutic strategies in neurodegenerative diseases. Grip strength and years of education also significantly affect cognitive outcomes, highlighting the potential role of muscle-strengthening exercises and educational enhancements in delaying cognitive decline.

Study limitations and future directions

Our cross-sectional design constrains the ability to infer causality between hemopexin, muscle indices, and cognition. Future longitudinal work is needed to clarify temporal and bidirectional effects. Moreover, measures like muscle mass, grip strength, and phase angle may be affected by participants' cognitive status, potentially introducing variability. Unmeasured confounders (e.g., comorbidities, inflammatory markers, lifestyle) could also influence outcomes and reduce the precision of our findings. Mechanistic interpretations regarding hemopexin are partly derived from animal research, underscoring the need for human longitudinal or interventional validation. Finally, while our sex-stratified analyses highlighted notable sex differences, the sample sizes for subgroup analyses were relatively small, warranting larger, more diverse cohorts to confirm these observations.

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Author contributions

D.Z., K.M., A.K. Investigation: D.Z., K.M., M.A., T.K., I.A., A.K. Methodology: D.Z., K.M., X.Q., M.A., B.W., T.K., I.A., A.K. Software: D.Z., K.M., M.A., T.K., I.A., A.K. Validation: D.Z., K.M., M.A., T.K., I.A., A.K. Writing—original draft: D.Z. Writing—review & editing: D.Z., K.M., X.Q., M.A., B.W., T.K., I.A., A.K. All authors read and approved the final manuscript.

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Data availability

The datasets generated and/or analyzed during the current study are not publicly available due to the ethical restrictions stipulated by the Ethics Committee of Kyoto University Hospital but are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

The study was conducted according to the Declaration of Helsinki and the International Conference on Harmonisation Tripartite Guideline on Good Clinical Practice. All patients provided written informed consent before participation and agreed to participate in this study.
This study was conducted in accordance with the ethical standards of the Kyoto University Medical Ethics Committee (approval number: R3258).

Consent for publication

Not applicable.

Competing interests

The authors declare no competing interests.

Clinical trial number

Not applicable.

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