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Original Article

Lower serum ferritin levels are associated with worse cognitive performance in aging

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ABSTRACT

Objectives: Iron is important for neurogenesis, synaptic development, and neurotransmitter synthesis. Serum ferritin (SF) is a reliable marker for assessing iron stores. Therefore, we evaluated the cognitive function associated with SF levels. We also assessed brain iron content using R2* Magnetic Resonance Imaging (MRI) and its association with SF levels.

Design: Data from three cross-sectional observational studies were used. Aging Imageomics (n = 1030) was conducted on aged subjects. Health Imageomics (n = 971) and IR0NMET (n = 175) were conducted in middle-aged subjects.

Setting and participants: Participants were enrolled at Dr. Josep Trueta University Hospital facilities. The three cohorts included a total of 2176 subjects (mean age, 52 years; 48% men).

Measurements: SF levels were measured by standard laboratory methods. Total Digits Span (TDS), and Phonemic Verbal Fluency (PVF) were used to assess executive function. Language function was assessed by semantic verbal fluency (SVF), attention by the Symbol Digit Modalities Test, and memory by the Memory Binding Tests - Total Free Recall and Total Delayed Free Recall. MRI was used to assess the iron content of the brain by R2*.

Results: In subjects aged 65 years or older, SF levels were associated with increased TDS ($\beta = 0.003$, $p = 0.02$), PVF ($\beta = 0.004$, $p = 0.01$), and SVF ($\beta = 0.004$, $p = 0.002$) scores. After stratification by sex, these findings were

Abbreviations: AUROC, Area under the receiver operating characteristic curve; BMI, Body mass index; EF, Executivefunction; Hb, Hemoglobin; ID, Iron deficiency; IDA, Iron deficiency anemia; MRI, Magnetic Resonance Imaging; MDA, Mediterranean diet adherence; PVF, Phonemic verbal fluency; SVF, Semantic verbal fluency; SF, Serum ferritin; SDMT, Symbol Digit Modalities Test; TDS, Total digit span.

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significant only in men, where SF was associated with increased TDS (β = 0.003, p = 0.01), PVF (β = 0.004, p = 0.03), and SVF (β = 0.004, p = 0.009) scores. In middle-aged subjects, SF was also associated with increased SVF scores (β = 0.005, p = 0.011). Lastly, in men, SF levels were negatively associated with R2*, a surrogate marker of brain iron content, in both the left frontal inferior opercular area (r = −0.41, p = 0.005) and the right frontal inferior opercular area (r = −0.44, p = 0.002).

Conclusions: SF is significantly and positively associated with cognition. In older people with low SF levels, iron supplementation may be a promising therapy to improve cognition.

1. Introduction

Iron is a critical element required for cell survival, proliferation, and metabolism. It plays a vital role in various cellular processes and is a key component of essential molecules and cofactors such as the heme group. Iron is also involved in DNA synthesis and has important implications for the regulation of the immune response. In the brain, iron is essential for maintaining the high metabolic demands of neuronal tissue, facilitating neurogenesis, promoting axon myelination, supporting synaptic development, and facilitating neurotransmitter synthesis [1,2]. Ferritin, an iron-binding protein, serves as the primary form of iron storage and plays a fundamental role in maintaining iron homeostasis [3,4]. In clinical practice, serum ferritin (SF) is routinely measured, among other iron parameters, to assess iron stores [3].

Iron deficiency (ID) is the most prevalent nutritional deficiency worldwide and the leading cause of anemia. More than two billion people worldwide are affected by ID, with iron deficiency anemia (IDA) being the primary form of anemia [5]. From 1990 to 2019, ID has consistently remained one of the leading causes of disability-adjusted life years worldwide [6]. Previous studies primarily investigated cognitive function in young women with ID. The results demonstrated the critical role of iron in cognitive performance, with improvements observed in attention and executive function (EF) following iron-rich diets or supplementation in cases of ID and IDA [7–9].

Cognitive functions encompass a range of processes occurring in various interconnected brain regions. The Diagnostic and Statistical Manual of Mental Disorders categorizes cognitive function into six cognitive domains: memory, attention, executive function, language, visual-spatial skills, and perception [10]. EF, regulated by the frontal lobe, encompass working memory, inhibitory control, cognitive flexibility, planning, reasoning, and problem solving [11]. A recent study in young adults found that higher ferritin levels were associated with better performance on tests measuring working memory [12].

On the other hand, ID or deficient absorption and utilization of iron in the bone marrow leads to impaired erythropoiesis, resulting in IDA and low hemoglobin levels [13]. Although several studies have explored the influence of hemoglobin (Hb) on various cognitive domains in community-dwelling older adults [14–17], most have focused on global cognition [18–21] and included participants with significant comorbidities [22–24]. To date, no studies have examined the association between SF and cognitive domain scores in asymptomatic older individuals residing in the community. Our hypothesis was that iron stores may impact cognition in the general aging population, not limited to individuals diagnosed with moderate or severe ID or IDA. Therefore, this study aimed to evaluate cognitive function associated with SF levels in an aged cohort (Aging Imageomics; n = 1,030) and replicate the findings in a middle-aged population (Health Imageomics; n = 971). We also assessed this association separately in men and women, given the known sex differences in neurobiology and cognitive function [25]. The area under the receiver operating characteristic curve (AUROC) was used to determine a SF threshold associated with worse cognitive performance. Furthermore, as excessive iron deposition in the brain increases the risk of cognitive decline [26], we also assessed brain iron content using R2* Magnetic Resonance Imaging (MRI) and SF in a separate middle-aged cohort (IRONMET, n = 175).

2. Materials and methods

2.1. Study design

Data from three cross-sectional observational studies were used. Aging Imageomics, n = 1030, was conducted in an aged cohort. Health Imageomics, n = 971, and IR0NMET, n = 175, were conducted in middle-aged cohorts. Data analysis was performed independently with Aging Imageomics as the discovery cohort. We then replicated the results in the other two cohorts.

2.1.1. Discovery cohort (Aging Imageomics)

The Aging Imageomics Study was conducted in the province of Girona, Spain. Data were obtained from November 14th, 2017, to June 19th, 2019, at Dr. Josep Trueta University Hospital facilities. The study protocol was approved by the ethics committee of the Dr. Josep Trueta University Hospital and all participants provided written informed consent (Project Code SLT002-16/00250). This cohort comprises participants from two independent study cohorts: the Maturity and Satisfactory Ageing in Girona study (MESGI50 study) and the Improving interMediAte RisK management study (MARK study). The MESGI50 study is a population-based cohort associated with the Survey of Health, Aging, and Retirement in Europe (SHARE) project, which enrolled participants aged ≥50 years. In the MARK study, participants with intermediate cardiovascular risk between 35 and 74 years of age were randomly selected from public primary care centers.

The eligibility criteria for the study were: age ≥50 years, residing in the community (not institutionalized), no record of infection in the last 15 days, no contraindications for MRI, and consent to be informed of potential incidental findings. Participants were visited on two occasions. The appointments included a medical history, physical examination, dietary evaluation, magnetic resonance imaging, and neuropsychological evaluation. Additionally, blood, urine, and stool samples were collected. Recruitment numbers and flows are shown in Figure S1. Extensive information on the study can be found elsewhere [27].

2.1.2. Replication cohort (Health imageomics)

The Health Imageomics study was conducted in the general population of the Girona province. The study was conducted in 2020 at Dr. Josep Trueta University Hospital facilities. This cohort specifically included individuals aged between 16 and 49 years. The study excluded individuals with end-stage diseases, institutionalization, and those with intellectual disabilities. All participants provided written informed consent. The study was validated and approved by the Ethics Committee (Project Code GO03-001848). The recruitment and selection of participants were consistent with the methodology used in the Aging Imageomics study.

2.1.3. Replication cohort (IRONMET)

The IRONMET study was conducted at the Endocrinology Unit of the Josep Trueta University Hospital. Participants were recruited between January 2016 and October 2017. The study enrolled people aged 30–65 years. All participants provided written informed consent. The study was approved by the Ethics Committee of Hospital Dr. Josep Trueta (Project Code PI15/01934). Recruitment numbers and flows are shown in Figure S2.

All IRONMET participants were scanned on a 1.5 T Ingenia system (Philips Healthcare, Best, The Netherlands) with eight-channel head coils. Brain iron content was evaluated by R2* since postmortem studies demonstrated that R2* is more sensitive to brain iron variations [28]. R2* relaxometry was evaluated using a multiecho gradient echo sequence with TR/1stTE/ΔTE = 800/2.2/5 milliseconds, flip angle = 80 °, in-plane resolution = 2 × 2 mm^2, slice thickness = 5 mm without separation and 20 axial slices. To obtain R2*, we used the atlas-based parcellation method and then normalized the R2* maps and co-registered them to the Montreal Neurologic Institute standard space (MNI152). The R2* maps were calculated with the IntelliSpace Portal of Philips. These maps were co-registered and normalized to the MNI standard space with a template of each of these maps by SPM12. R2*-metrics were extracted for each region of the Automated Anatomical Labeling (AAL) atlas and each tract from the International Consortium for Brain Mapping (ICBM DTI-81) atlas using the Brain software library (FSL). The gray matter analysis utilized the 116-region AAL atlas [29], while the white matter analysis employed the 50-region ICBM DTI-81 atlas [30]. After registering the images with the respective atlases, the mean R2* value for each region of interest (ROI) was extracted.

2.2. Laboratory parameters (Aging imageomics, health imageomics, and IRONMET)

The same procedure was used to collect clinical and laboratory data in the three cohorts. Serum ferritin levels were measured in all subjects in the three cohorts using the same laboratory method. In fasting conditions, a blood sample was provided. SF was measured by an in vitro immunoassay for the quantitative determination of SF using the Cobas 8000 c702 analyzer (Roche Diagnostics, Basel, Switzerland) [31]. The technique involves a first incubation in which 6 μL of sample, a biotinylated monoclonal ferritin-specific antibody and a monoclonal ferritin-specific antibody labeled with a ruthenium complex form a sandwich complex. This is followed by a second incubation in which, after addition of streptavidin-coated microparticles, the complex becomes bound to the solid phase via interaction of biotin and streptavidin. The reaction mixture is aspirated into the measuring cell where the microparticles are magnetically captured onto the surface of the electrode. Unbound substances are then removed with ProCell II M. Application of a voltage to the electrode then induces chemiluminescent emission which is measured by a photomultiplier. Results are determined via a calibration curve which is instrument specifically generated by 2-point calibration and a master curve provided via the cobas link [31]. Fasting plasma glucose, lipids profile, serum creatinine, serum urate, and hemoglobin were also measured by standard laboratory methods using an analyzer (Cobas 8000, Roche Diagnostics, Basel, Switzerland). Glycated hemoglobin was determined by performance liquid chromatography (ADAMA1c HA-8180 V, ARKRAY, Kyoto, Japan). Homeostasis Model Assessment of Insulin Resistance (HOMA-IR) values were calculated as follows [(FPG (mmol/L) *FPI (mU/L)]/22,5. Anthropometric and clinical history were obtained using bioimpedance and ad hoc questionnaire respectively.

2.3. Mediterranean diet adherence

The subjects' dietary characteristics and Mediterranean diet adherence were collected in a personal interview using a validated 14-item Questionnaire of Mediterranean diet adherence [32]. The questionnaire consists of 14 questions relating to components of the Mediterranean diet, such as frequency of fruit and vegetable consumption, use of olive oil, consumption of fish, red meat, legumes, etc. [32]. Each question is scored 0 or 1 according to the answers given by the participants. For example, one point is obtained for using olive oil as your primary cooking fat. The final score ranged from 0 to 14 [32]. The cut-off points are ≤5, 6–9, and ≥10 for low, moderate, and high adherence to the Mediterranean diet, respectively.

2.4. Neuropsychological assessment (Aging imageomics, health imageomics, and IRONMET)

The same protocol was used for the neuropsychological assessment in the three cohorts. Four cognitive domains were assessed (attention, executive function, language, and memory). Additionally, depression was assessed to exclude subjects with clinical depression. All tests were presented as raw scores.

2.4.1. Attention

Symbol Digit Modalities Test (SDMT) is a test to measure attention and processing speed. The test involves abstract symbols paired with single digits. The subject is asked to say the number that matches each symbol for 90 seconds. The faster the test is completed correctly, the better the score [32,33].

2.4.2. Executive function

Total Digits Span (TDS) is subtest of the Wechsler Adult Intelligence Scale-III (WAIS-III). TDS evaluates executive function, specifically working memory. TDS includes the Forward and Backward Digit Span tests. In the Forward Digit Span test, the subject repeats a series of numbers in the same order presented, whilst in the Backward Digit Span test, the subject repeats the sequence of numbers in reverse order. The Total Digit Span is the sum of the scores of the two previous tests. The higher the test score, the better the working memory [34].

Phonemic verbal Fluency (PVF) evaluates the executive function and is influenced by processing speed. PVF is a spontaneous verbal production task that requires the production of words with a specific letter (P, M, and R) for one minute each [35,36].

2.4.3. Language function

Semantic verbal fluency (SVF) evaluates language or semantic memory. This is a test that requires producing as many words as possible in one minute for a specified category, typically "animals" [35,36].

2.4.4. Memory

Memory binding test (Total free recall (MBT-TFR) and Total delayed free recall (MBT-TDFR)) evaluates the capacity to encode or obtain information as part of a complex unit. Consists of two lists of words with 16 words each and 16 category cues, such as "helicopter" in the first list and "boat" in the second list. The categories are presented in the same order in both word lists. After controlled learning and cued recall, the next stage is to learn and recall the paired recall condition of both lists. This research has focused on two of the four significant indices produced by the MBT: MBT-TFR (the subject must remember all the words from both lists immediately) and MBT-TDFR (the subject must remember all the words from both lists after 30 min). Detail information can be found elsewhere [37].

2.4.5. Depression

The Patient Health Questionnaire (PHQ-9) is a self-administered questionnaire for the screening of depression. It consists of 9 Likert-type response items with values between 0 and 3 referring to the last two weeks. A total score ranging from 0 to 27 is obtained. The score is divided into the following categories: minimal depression [1–4], mild depression [5–9], moderate depression [10–14], moderate depression severe [15–19], severe depression [20–27,38].

2.5. Statistical analysis

The statistical analysis was conducted using SPSS version 28.0 (Armonk, NY: IBM Corp.) or R Statistics. The normality assumption of

each variable was assessed using the Kolmogorov–Smirnov test. Descriptive results were reported as numbers and frequencies for categorical variables, while continuous variables were presented as the mean and standard deviation for Gaussian variables or median and interquartile range for non-Gaussian variables.

Univariate linear regression models were constructed to predict cognitive performance, considering various factors such as sex, age, years of education, body mass index (BMI), SF, Hb, Mediterranean diet adherence (MDA), and alcohol consumption. These variables were included in the analysis to exclude them as potential confounders. Stepwise regression models were then applied to eliminate non-significant variables from the model. To predict cognitive performance, analyses were conducted on the entire study population and then divided into two age groups based on the median age: ≥65 years and 50–64 years old. Furthermore, separate analyses were performed for males and females.

Anemia was defined using the cut-off points established by the World Health Organization as follows: Hb<13 g/dL for men and Hb<12 g/dL for women [39]. The study included individuals with normal Hb levels and those with mild anemia. Mild anemia was defined as Hb levels between 10.0–11.9 g/dL) in women and 10.0–12.9 g/dL in men [39]. Participants with Hb levels ≤10 g/dL) were excluded from the analysis, as the focus was not on assessing cognition in individuals with moderate or severe anemia. The SF levels of the participants were utilized to evaluate their ability to discriminate cognitive performance, specifically for SVF, PVF, and TDS, using the AUROC.

For the analysis of SF and R2*cerebral data, machine learning methods were employed, specifically a method based on multiple random forests implemented in the Boruta algorithm [40]. The Boruta algorithm selects features based on the learning performance of the model. The Boruta analysis was conducted with 500 iterations, a confidence level of 0.005 for Bonferroni-adjusted p-values, and 5000 trees for growing the forest. The model was controlled for age and BMI.

Pairwise non-parametric Spearman's rank order correlations were used to calculate correlation coefficients (r) and p-values between SF and R2* brain regions identified from the Boruta analysis. Statistical significance was defined as $p < 0.05$ for all analyses. In case of missing values for a variable, the maximum available sample size was utilized.

Table 1
Clinical and neuropsychological data of the Aging Imageomics cohort.

Characteristics	Total population (n = 1.030)
Age (years)	67 ± 7.4
Females n (%)/Males n (%)	473 (46)/557 (54)
Education (years)	8 [8–12]
BMI (kg/m^2)	28 [25–30]
Waist (cm)	99 [91–107]
MBT-TFR (score)	11 [8–14]
MBT-TDFR (score)	11 [8–14]
PVF (score)	12 [9–15]
SVF (score)	16 [13–20]
SDMT (score)	46 [33–59]
TDS (score)	12 [10–14]
PHQ9 (score)	3 [1–6]
MDA (score)	8 [7–10]
FPG (mg/dL)	102 [94–121]
HbA1c (%)	5.7 [5.5–6.2]
Fasting Insulin (mU/L)	8.7 [6.1–12.4]
HOMA-IR	2.3 [1.5–3.6]
Serum creatinine (mg/dL)	0.8 [0.7–1.0]
Serum urate (mg/dL)	5.4 [4.5–6.4]
Total cholesterol (mg/dL)	196 ± 35
HDL-C (mg/dL)	50 [42–61]
LDL-C (mg/dL)	119 ± 31
Fasting triglycerides (mg/dL)	105 [78–146]
Hemoglobin (g/dL)	14 [14–15]
Serum ferritin (ng/mL)	115 [58–210]

Results are expressed as number and frequencies for categorical variables, mean and standard deviation (SD) for normal distributed continuous variables and median and interquartile range [IQ] for non-normal distributed continuous variables. BMI, body mass index; MBT-TFR, memory binding test-total free recall; MBT-TDFR, memory binding test-total delayed free recall; PVF, phonemic Verbal Fluency; SVF, Semantic verbal fluency; SDMT, Symbol Digit Modalities Test; TDS,

3. Results

3.1. Discovery cohort aging imageomics

The clinical and neuropsychological data of the subjects are presented in Table 1. Differences in these parameters were also examined based on the median age (Table S1).

First, we examined the association between sex, age, years of education, BMI, SF, Hb, MDA, and alcohol consumption and cognitive performance. No significant associations were found between MDA score, alcohol consumption, blood Hb levels, and cognitive scores. However, after stratifying by the median age of the population (65 years), MDA was associated with increased scores in TDS ($\beta = 0.56$, $p = 0.03$) and SVF ($\beta = 0.80$, $p = 0.02$) in subjects aged 65 years or older (Table 2). When analyzing the associations by sex, MDA was significantly associated with increased TDS ($\beta = 0.92$, $p = 0.01$), PVF ($\beta = 0.95$, $p = 0.04$), and SVF ($\beta = 1.03$, $p = 0.03$) scores only in men. BMI was also linked to a decreased TDS score only in men. Higher alcohol consumption was associated with decreased PVF scores ($\beta = -1.91$, $p = 0.02$) only in women (Table 3). Hb levels were significantly associated with increased TDS ($\beta = 0.31$, $p = 0.03$) and SDMT ($\beta = 1.38$, $p = 0.01$) scores in subjects aged 65 years or older (Table 2). Interestingly, blood Hb was significantly associated with increased TDS ($\beta = 0.56$, $p = 0.005$), PVF ($\beta = 0.89$, $p = 0.004$), SVF ($\beta = 0.78$, $p = 0.01$), and SDMT ($\beta = 2.481$, $p = 0.015$) scores only in women (Table 3).

SF levels were not associated with performance on cognitive tests in the entire cohort or separately in women or men. When stratifying by age, no significant associations were observed between SF and cognitive scores in subjects aged 50–64 years. However, SF was significantly associated with increased TDS ($\beta = 0.003$, $p = 0.02$), PVF ($\beta = 0.004$, $p = 0.01$), and SVF ($\beta = 0.004$, $p = 0.002$) scores in subjects aged 65 years or older (Table 2). These findings were significant only in men, where SF was associated with increased TDS ($\beta = 0.003$, $p = 0.012$), PVF ($\beta = 0.004$, $p = 0.03$), and SVF ($\beta = 0.004$, $p = 0.009$) scores, while no significant results were found among women (Table 3).

We further examined the discriminatory value of SF levels on cognition. Significantly, we found that only the TDS test yielded significant results, with a cutoff point of 39 being the best value for predicting better cognitive performance. The classification performance of SF values on cognition, based on the AUROC, was 72% (95% CI 0.6 −0.84) for the TDS in the entire cohort. After stratifying the population by the median age, the classification performance of SF values on cognition, based on AUROC, increased to 85% (95% CI 0.74−0.96) for the TDS in subjects aged 65 years or older (Fig. 1). However, we did not obtain significant results with the PVF and SVF tests, nor among subjects aged 50–64 years (Figure S3).

3.2. Replication cohort (Health imageomics)

We performed the same analysis in an independent cohort consisting of 971 subjects (442 men). The clinical and neuropsychological data of the subjects can be found in (Table S2). In this cohort, SF was significantly associated with increased SVF scores ($\beta = 0.005$, $p = 0.01$) (Table S3). However, no significant results were found in the remaining neuropsychological tests, even when considering both sexes separately.

3.3. Replication cohort (IRONMET)

We analyzed brain iron content and its relationship with SF in a cohort of 175 subjects (55 men). The clinical and neuropsychological data of the subjects are provided in (Table S4).

Table 2
Univariate regression analysis to predict cognitive performance according to serum ferritin and hemoglobin levels in subjects ≥65 years in the Aging Imageomics cohort.

Model 1 (Method: Stepwise)	TDS[c] (N = 435)		PVF[d] (N = 426)		SVF[e] (N = 434)		MBT- TDFR[f] (N = 395)		MBT-TFR[g] (N = 375)		SDMT[h] (N = 411)		PHQ9[i] (N = 434)	
	β	p	β	p	β	p	β	p	β	p	β	p	β	p
Sex	0.07	0.17	0.02	0.61	0.05	0.34	−2.15	**<0.001****	2.20	**<0.001****	0.02	0.72	1.01	**<0.001****
Education years	2.20	**<0.001****	3.01	**<0.001****	2.06	**<0.001****	1.72	**<0.001****	2.21	**<0.001****	12.91	**<0.001****	−0.04	0.35
BMI[a]	−0.08	0.07	−0.04	0.37	−0.02	0.72	−0.14	**0.02***	−0.07	0.14	−0.005	0.91	0.07	0.11
Hemoglobin	0.31	**0.03***	0.07	0.16	0.06	0.27	−0.04	0.41	−0.03	0.57	1.38	**0.01***	−0.06	0.24
Serum ferritin	0.003	**0.02***	0.004	**0.01***	0.004	**0.002***	0.005	0.92	0.03	0.52	0.05	0.31	−0.09	0.07
MDA[b]	0.56	**0.03***	0.08	0.08	0.80	**0.02***	0.02	0.75	0.02	0.73	0.02	0.68	−0.09	0.07
Alcohol consumption	−0.01	0.07	−0.07	0.12	−0.03	0.57	0.001	0.98	0.02	0.68	0.01	0.75	1.01	**0.01***
Adjusted R2	22%		19%		12%		10%		12%		32%		11%	
P value	**<0.001**		**<0.001**		**<0.001**		**<0.001**		**<0.001**		**<0.001**		**<0.001**	

Significant results with a p-value < 0.05 are shown in bold.

[a] Body mass index.
[b] Mediterranean diet adherence.
[c] Total Digit Span.
[d] Phonemic Verbal Fluency.
[e] Semantic verbal fluency.
[f] Memory binding test-total free recall.
[g] Memory binding test-total delayed free recall.
[h] Symbol Digit Modalities Test.
[i] Patient Health Questionnaire-9.

Interestingly, SF showed a negative association with mean R2* in the Frontal Inferior Opercular Left (r = −0.41, p = 0.005) and Right (r = −0.44, p = 0.002) regions in men, which represent brain iron content. In men, SF was also negatively associated with parahippocampal R2*. However, no significant associations between SF and the R2* variables were observed among women (Fig. 2).

4. Discussion

The primary objective of this study was to examine the association between SF levels and cognition in an aged population without a diagnosis of ID and IDA (moderate or severe). To the best of our knowledge, no previous studies have investigated the impact of SF on various cognitive domains in an aging community-dwelling population.

Among individuals aged 65 years and older, higher SF levels were associated with better EF and language skills. However, after stratifying by sex, these associations remained significant only in men. Using AUROC models, we identified a SF threshold (39 ng/mL) below which cognitive performance on executive function tasks may be reduced, even in the absence of IDA. When we replicated these findings in a younger cohort (mean age 36.8 years), higher SF levels were significantly associated with better language skills. Similarly, a recent study involving 108 university students found that elevated SF levels were associated with improved EF, specifically working memory [12].

Although SF is relatively low in iron content compared to intracellular ferritin, it can still contribute significantly to iron supply in the brain [4,41]. Human studies have demonstrated that oligodendrocytes could acquire a ferritin-heavy chain through the Tim-1 receptor [42]. Oligodendrocytes, the central nervous system's cells with the highest iron concentration, play a primary role in synthesizing and maintaining the myelin sheath [43]. Oligodendrocytes, in addition to absorbing ferritin, can secrete it. Disruption of ferritin release from oligodendrocytes leads to neuronal loss and oxidative damage [44]. Furthermore, defective heme metabolism is associated with aberrations in the electron transport chain (loss of complex IV), dimerization of amyloid precursor protein, and production of free radicals, leading to cell death. These findings represent the major cytopathology of Alzheimer's disease [45]. The binding of heme to amyloid beta prevents the formation of amyloid beta aggregates. In the Alzheimer's brain, amyloid beta sequestration creates a blood-poor environment that leads to dysfunctional mitochondria and altered metabolic activity [45] with brain iron deposition in two frontal regions (frontal Inferior Opercular Left and Right) and the parahippocampal area in men. The prefrontal cortex, precisely the region most implicated in EF, is particularly affected by iron deposition [11]. Consistently, in healthy men, it has been observed that elevated hippocampal iron levels could have a detrimental impact on declarative memory function. Notably, these effects have not been observed in women [46]. Throughout life, men maintain higher brain iron levels compared to women [47]. Excessive accumulation of iron in the brain has been associated with oxidative stress and neuronal cell death [48]. Additionally, in animal models with dysregulated iron metabolism, it has been shown that adult-onset neurodegenerative disease can begin with damage to oligodendrocytes and white matter pathways [49]. Hence, precise regulation of brain iron metabolism is vital. There is currently insufficient evidence linking SF levels in the healthy adult population with brain iron content. According to our findings, we could speculate about a factor that depletes peripheral iron (SF) in association with increased brain iron content. Both processes would be deleterious.

In addition, higher Hb levels were significantly associated with enhanced working memory and processing speed in individuals aged 65 years and older. Higher Hb levels were also significantly associated with improved attention, EF, and language, but this association was observed only in women. Thus, the relationship between Hb and cognition is influenced by sex. These findings are consistent with a study involving women aged 70–80 years with Hb levels ≥10 g/dL, where mild anemia

Table 3
Univariate regression analysis to predict cognitive performance according to serum ferritin and hemoglobin levels in subjects ≥65 years according to sex in the Aging Imageomics cohort.

Women								
	TDS[a] (N = 191)		PVF[b] (N = 184)		SVF[c] (N = 190)		SDMT[d] (N = 178)	
Model 1 (Method: stepwise)	β	p	β	p	β	p	β	p
Education years	2.45	<**0.001****	3.47	<**0.001****	3.09	<**0.001****	17.20	<**0.001****
BMI[e]	−0.04	0.58	−0.07	0.30	−0.07	0.31	0.05	0.39
Hemoglobin	0.56	**0.005***	0.89	**0.004***	0.78	**0.01***	2.48	**0.02***
Serum ferritin	0.08	0.24	0.01	0.85	−0.02	0.77	0.002	0.98
MDA[f]	0.02	0.77	0.04	0.55	0.06	0.38	0.05	0.44
Alcohol consumption	−0.04	0.52	−1.91	**0.02***	−0.002	0.97	−0.02	0.73
Adjusted R2	23%		21%		17%		37%	
P value	<**0.001**		<**0.001**		<**0.001**		<**0.001**	

Men								
	TDS (N = 244)		PVF (N = 242)		SVF (N = 244)		SDMT (N = 233)	
Model 1 (Method: stepwise)	β	p	β	p	β	p	β	p
Education years	1,934	<**0.001****	2.79	<**0.001****	1.51	<**0.001****	11.06	<**0.001****
BMI	−0.14	**0.03***	−0.05	0.43	0.0003	0.99	−0.04	0.52
Hemoglobin	0.03	0.61	−0.01	0.82	−0.05	0.46	0.08	0.16
Serum ferritin	0.003	0,02*	0,004	**0.03***	0.004	**0.009***	0.08	0.14
MDA[f]	0.92	**0.01***	0.95	**0.04***	1.03	**0.03***	0.07	0.25
Alcohol consumption	−0.05	0.37	−0.08	0.19	−0.07	0.24	0.01	0.82
Adjusted R2	19%		19%		9%		27%	
P value	<**0.001**		<**0.001**		<**0.001**		<**0.001**	

Significant results with a p-value < 0.05 are shown in bold.
[a] Total Digit Span.
[b] Phonemic verbal fluency.
[c] Semantic verbal fluency.
[d] Symbol Digit Modalities Test.
[e] Body mass index.
[f] Mediterranean diet adherence.

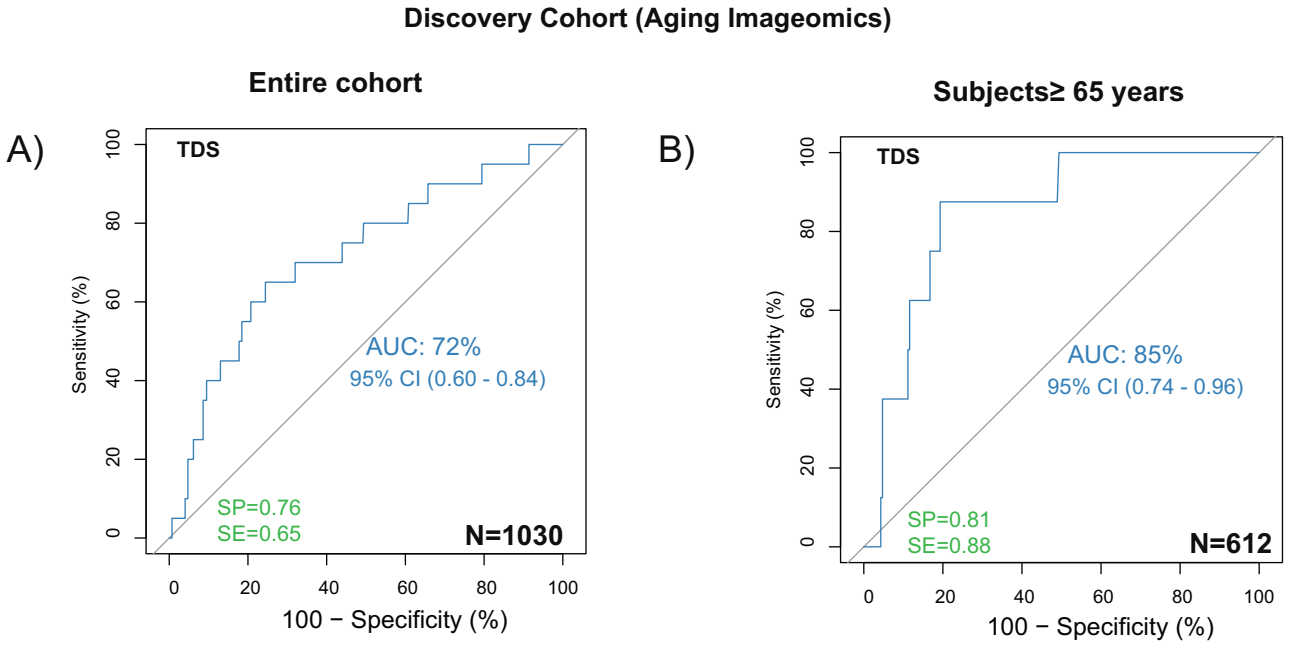

Fig. 1. The area under the receiver operating characteristic curve to discriminate subjects' cognitive performance based on serum ferritin levels (Aging Imageomics cohort).
The area under the receiver operating characteristic curve (AUCROC) to discriminate subjects' cognitive performance based on serum ferritin levels (serum ferritin <39, >39 (ng/mL) for Total Digit Score (TDS). A) Entire cohort, B) Subjects ≥65 years.

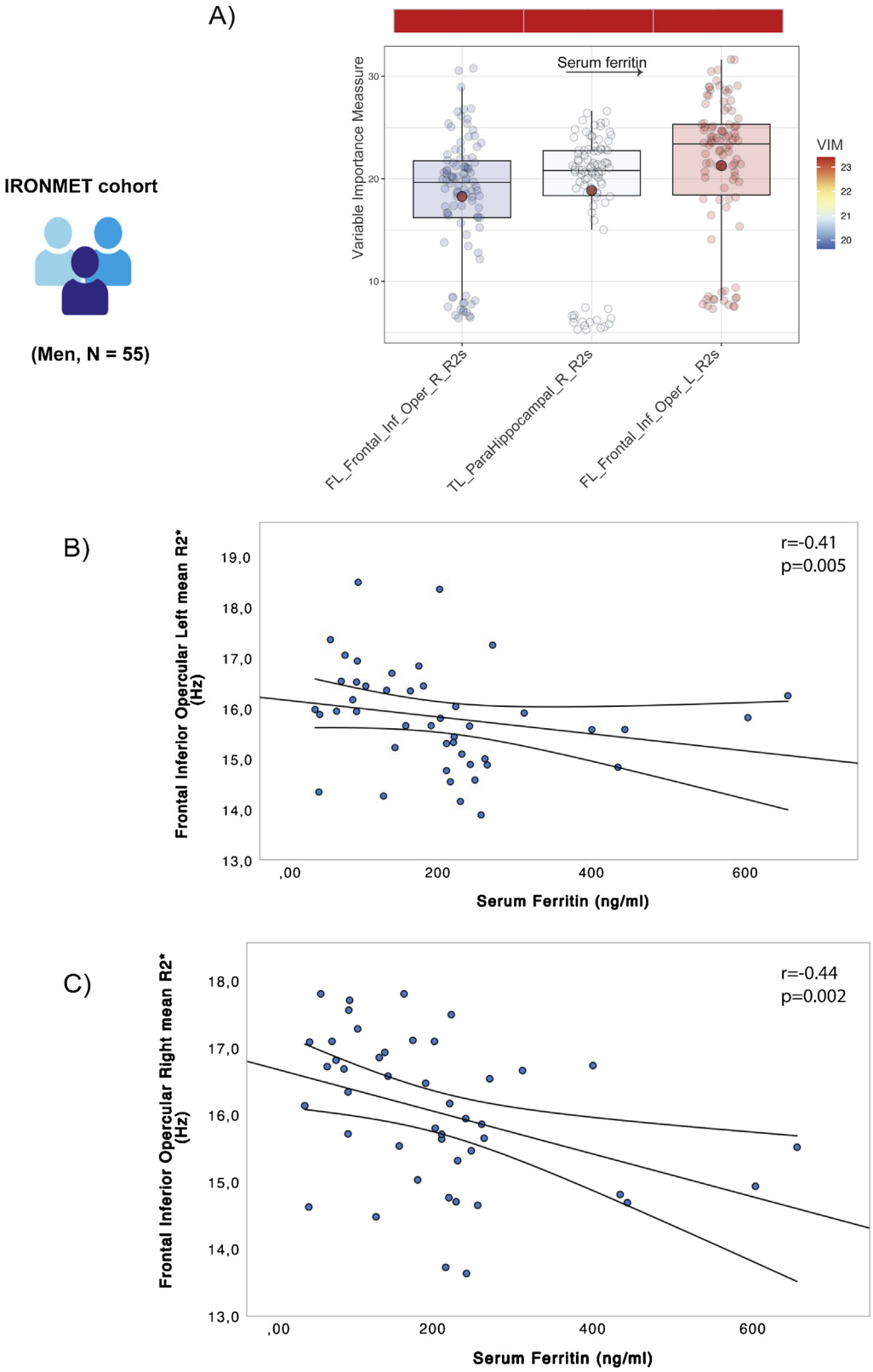

Fig. 2. R2* regions of the brain associated with serum ferritin in men (IRONMET cohort).
(A) Boxplot of the normalized variable importance measure (VIM) for the R2* brain regions associated with serum ferritin in men (IRONMET cohort). Significant metabolites (confirmed) were identified using a machine learning variable selection strategy based on the application of multiple random forests as implemented in the Boruta algorithm. The Boruta algorithm was run with 500 iterations, a confidence level of 0.005 for Bonferroni adjusted p-values, and 5000 trees to grow the forest. The model was controlled for age and BMI. Bivariate correlation between serum ferritin and Magnetic Resonance Imaging R2* variables in men (n = 45), Frontal Inferior Opercular Left R2* (B), and Frontal Inferior Opercular Right R2* (C).
FL_Frontal_Inf_Oper_R_R2s, Frontal Inferior Opercular Right R2* (Frontal Lobe); FL_Frontal_Inf_Oper_L_R2s, Frontal Inferior Opercular Left R2*(Frontal Lobe); TL_ParaHippocampal_R_R2s, Parahippocampus Right R2* (Temporal Lobe)

was associated with poorer EF [14]. In a study of 793 participants with a mean age of 81 years, Hb levels were not associated with cognition in men, whereas low Hb levels in women were associated with worse language and attention (perceptual speed), but not with episodic memory, working memory, or visuospatial ability [15]. Another study that followed 436 women between the ages of 70 and 80 for three years found that women with Hb levels <12 g/dL performed worse on tests assessing EF [16]. More recently, a study involving 13 133 subjects with a mean age of 57 years showed that Hb levels <13 g/dL in men and <12 g/dL in women were associated with worse EF and information processing speed [17]. Prolonged low Hb levels have been proposed to worsen cerebral ischemia by inducing a chronic state of cerebral hypoxia and contributing to microvascular damage [50]. This hypoxic state leads to increased levels of amyloid beta [51]. Amyloid angiopathy is also exacerbated by hypoxia-induced damage to the smooth muscle cells of the cerebral microvasculature [52]. Reduced Hb levels are also associated with cerebral microbleeds, particularly in the lobar region [53]. There is also evidence that the nucleus accumbens is more susceptible to amyloid and tau deposition. The precuneus, cingulate gyrus, and medial temporal lobe, which are involved in language function, are directly connected to the accumbens [53]. Thus, lower Hb levels are per se a potential risk factor for poor cognitive status.

Most studies investigating the association between anemia and cognition have focused on patients with heart failure [22], chronic kidney disease [23], and cancer [54]. In the general population, studies of cognition have often taken a unified approach, assessing cognition as a whole rather than examining independent cognitive domains [18–21].

Lastly, the other variable associated with better cognitive performance was the MDA. In individuals aged 65 years and older, MDA was associated with better EF and language skills, with these associations being observed only in men after stratifying by sex. These findings are in line with several meta-analyses that have demonstrated the positive effects of MDA on global cognition, episodic memory, and a reduced risk of cognitive decline and neurodegenerative diseases [55]. Furthermore, an intervention study revealed that individuals consuming extra virgin olive oil, a key component of the Mediterranean diet, exhibited improved executive and global cognitive function, as assessed by the Mini-Mental State Examination [56]. The protective effects of the Mediterranean diet on cognition may be attributed to the abundance of antioxidants and anti-inflammatory agents present in the diet [56].

It is important to interpret these results with caution as the underlying pathophysiological mechanisms linking cognition, Hb, and SF are not fully understood. Our results indicate a significant and positive association between SF and cognition; however, the β value are low. Therefore, further research is necessary to determine the clinical significance of these findings in aged populations, along with longer follow-ups. Extended investigations are essential to replicate and extend our findings while excluding potential confounding factors that may influence these results. Additionally, the MRI and SF data were obtained from a middle-aged adult population. While SF is known to play a crucial role in iron transport to certain neuronal cells, it has not been definitively established whether SF is directly related to brain iron. Although our hypothesis is that low SF levels may be associated with poorer cognition due to inadequate iron transport to the central nervous system, additional studies in animal models and humans are necessary. Other hypotheses involving the composition and functionality of the gut microbiota are being explored in a companion article.

5. Conclusions

SF is significantly and positively associated with EF ($\beta = 0.003$, $p = 0.02$), and language skills ($\beta = 0.004$, $p = 0.02$). Hence, SF could serve as a biomarker for impaired cognition, especially in the aged population. Considering the simplicity of its measurement, future studies should focus on SF and explore therapeutic approaches to increase iron stores to evaluate their potential impact on cognition.

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CRediT authorship contribution statement

M.R-D. Conceptualization, Data curation, Formal analysis, Methodology, Visualization, Writing-original draft. E.S-G. and L.G-N Formal analysis. A.M-A. and C.C-M Resources. J.P., J.G-O., R.R., and L.R-T. Resources and Supervision. J.M.-P and J.M.F.-R. Conceptualization, Methodology, Visualization, Supervision, Writing-review & editing.

Ethics approval and consent to participate

The studies were approved by The Ethics Committee of the Dr. Josep Trueta University Hospital. All the participants provided informed consent.

Consent for publication

Not applicable.

Conflict of interest

The authors declare no conflict of interest.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.jnha.2024.100190.

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