# Irisin Levels in Cerebrospinal Fluid Correlate with Biomarkers and Clinical Dementia Scores in Alzheimer Disease

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**Objective:** Irisin, released by muscles during exercise, was recently identified as a neuroprotective factor in mouse models of Alzheimer disease (AD). In a cohort of AD patients, we studied cerebrospinal fluid (CSF) and plasma irisin levels, sex interactions, and correlations with disease biomarkers.

**Methods:** Correlations between CSF and plasma irisin levels and AD biomarkers (amyloid β 1-42, hyperphosphorylated tau, and total tau [t-tau]) and Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB) were analyzed in a cohort of patients with Alzheimer dementia (n = 82), mild cognitive impairment (n = 44), and subjective memory complaint (n = 20) biologically characterized according to the recent amyloid/tau/neurodegeneration classification.

**Results:** CSF irisin was reduced in Alzheimer dementia patients ($p < 0.0001$), with lower levels in female patients. Moreover, CSF irisin correlated positively with Aβ42 in both female ($r = 0.379$, $p < 0.001$) and male ($r = 0.262$, $p < 0.05$) patients, and negatively with CDR-SOB ($r = -0.234$, $p < 0.05$) only in female patients. A negative trend was also observed between CSF irisin and t-tau levels in all patients ($r = -0.144$, $p = 0.082$) and in the female subgroup ($r = -0.189$, $p = 0.084$).

**Interpretation:** The results highlight the relationship between irisin and biomarkers of AD pathology, especially in females. Our findings also offer perspectives toward the use of irisin as a marker of the AD continuum.

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Alzheimer disease (AD) is a progressive neurodegenerative disorder that represents the most common cause of dementia in older individuals (approximately 60–70% of all dementia cases).[1] Memory impairment, cognitive and behavioral disorders, including executive dysfunction, and progressive personality and behavioral alterations clinically characterize AD, and the number of patients affected is expected to grow to an estimated 150 million by 2050.[2–4]

In the past decades, many efforts have been made to find new efficient strategies for AD prevention and/or

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treatment through human intervention studies and rodent AD models; however, the management of AD is still challenging.[5] Recently, growing evidence has pointed to the effectiveness of regular physical exercise (PE) as a potential nonpharmacological preventative and interventional strategy to slow down the decline of cognition and/or to improve the cognitive functions in both clinically normal subjects at risk of AD and patients with AD.[6–8] PE notably promotes both structural and neurochemical changes in the brain by enhancing adult neurogenesis and synaptic plasticity in the hippocampus and reducing neuroinflammation.[9] In addition, the salutary effects of PE have been partially related to the prevention of modifiable factors associated with increased risk of developing AD such as hypertension, obesity, and diabetes.[10]

Studies focused on the molecular mechanisms underlying the neuroprotective effects of PE have identified a multitude of factors released into the bloodstream upon exercise and termed "exerkines" by Safdar et al in 2016.[11] Among them is irisin, derived by the cleavage of its membrane precursor fibronectin type III domain containing 5 (FNDC5), whose circulating levels were significantly increased in subjects undergoing aerobic training (~4.3ng/ml) compared to the sedentary individuals (~3.6ng/ml).[12]

Irisin has been initially recognized as crucial in the browning process,[13] able to increase bone and muscle mass,[14,15] and involved in inducing the expression of neuroprotective genes, such as brain-derived neurotrophic factor (*BDNF*) gene, in mouse hippocampus.[16] Considering these neuroprotective effects,[16] recently irisin has been investigated in the context of neurodegenerative diseases, including AD.[17,18] Notably, biological investigations and in silico systems suggested that the FNDC5/irisin system was able to interact with neuropathological features of AD as amyloid precursor protein, regulating the production of insoluble amyloid β (Aβ) and the formation of the senile extracellular plaques.[19]

Interestingly, studies on mouse AD models revealed that the FNDC5/irisin levels were reduced in the hippocampus of mice that developed memory deficits, whereas the increase of the circulating and/or brain irisin levels increased the synaptic plasticity, improving memory and cognitive performance.[20,21] Furthermore, cognitive and memory dysfunctions were observed in global FNDC5 knockout mice.[22] In parallel with these results, human studies showed the presence of decreased levels of FNDC5/irisin in the cerebrospinal fluid (CSF) and in postmortem samples of patients affected by AD.[20] Moreover, several reports evidenced the association of CSF and/or plasma irisin with Aβ deposition, neurotrophins levels (eg, BDNF), and cognition.[23–26] Lastly, recent genetic studies reported the association of single nucleotide polymorphisms in *FNDC5* gene with lower glucose metabolism in memory-linked cerebral regions and increased Aβ deposition, suggesting the possible role of the FNDC5/irisin system in the modulation of metabolism in cerebral regions involved in AD pathophysiology.[27]

Based on the protective effect of irisin in AD shown in animal and cell models, the goal of the present study was to investigate the levels of irisin in the biological fluids of a large cohort of patients biologically characterized according to the amyloid/tau/neurodegeneration (ATN) scheme of the National Institute on Aging–Alzheimer's Association (NIA-AA).[28] We aimed to understand whether there may be variations of irisin levels across the disease stages, identified through the ATN system. We primarily focused our attention on CSF irisin levels, as the AD biomarkers are more often measured in this biological sample and previous studies highlighted the relevance of the cerebral FNDC5/irisin system in AD pathophysiology.[20,21,23] To find a more accessible and less invasive specimen, we extended our analysis on plasma samples obtained from the same subjects. We further studied the correlation between irisin and clinical and fluid AD biomarkers (CSF Aβ 1-42 [Aβ42], hyperphosphorylated tau [p-tau], and total tau [t-tau], and Clinical Dementia Rating Scale Sum of Boxes [CDR-SOB]) to evaluate whether irisin levels positively correlated with Aβ42 and negatively with p-tau, t-tau, and CDR-SOB. As several reports evidenced the importance of sex as a biological variable in AD research,[29,30] we newly investigated the possible sex interaction with irisin in the CSF and plasma of AD patients.

## Patients and Methods

### *Participants*

One hundred forty-six participants with diagnosis of Alzheimer dementia (AD dementia), mild cognitive impairment (MCI), and subjective memory complaint (SMC), referred to the Center for Neurodegenerative Diseases and the Aging Brain of the University of Study of Bari "Aldo Moro" at Pia Fondazione "Card. Panico" Hospital (Tricase), were enrolled in this study.

Each patient underwent a multidisciplinary assessment with a neurological and neuropsychological examination, nutritional assessment, 3T magnetic resonance imaging scan, routine laboratory assessment, and lumbar puncture for CSF biomarkers analysis as part of the diagnostic procedure. Demographic data included age, sex, and years of education were collected. A structured interview exploring familial and medical history and physical and neurological examination were performed, including CDR, a tool designed to grade subjects from normal function through various stages of dementia, assessing 6 cognitive and functional domains, including memory, orientation, judgment, community affairs, home hobbies, and personal care. Cognitive impairment severity was



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assessed with the CDR-SOB, which is the sum score of the 6 domains, ranging from 0 to 18. A comprehensive neuropsychological examination was used to evaluate the global cognition and the main cognitive domains (memory, executive function, attention, visuospatial abilities, and language) by 18 psychometric tests including at least 2 tests for each cognitive domain. As screening tests, the Mini-Mental Status Examination (MMSE), the Frontal Assessment Battery, and the Clock Drawing Test were used. Cognitive domain and neuropsychological test details are summarized in Table S1. To calculate *z* scores, the raw scores of the neuropsychological tests were standardized for education and age based on Italian normative data. For each patient, the single *z* scores of every cognitive domain were summed up and the mean group *z* scores were calculated.

Patients with AD dementia were diagnosed using the standard diagnostic criteria for dementia (Diagnostic and Statistical Manual of Mental Disorders, 5th edition [DSM-V])[31] and the NIA-AA criteria.[32] Patients included in this group had CDR total score = 1 and MMSE score < 24.

Patients with MCI were selected according to the following criteria: (1) cognitive concern reflecting a change in cognition reported by patient or informant or clinician, (2) impairment in one or more of 4 cognitive domains from the neuropsychological test battery, (3) normal functional activities as derived from the CDR and the Functional Activities Questionnaire, and (4) absence of dementia (DSM-V). The presence of biomarkers that directly reflect the pathology of AD by providing evidence of the presence of key proteins deposited in the brain during the course of AD, such as the Aβ and tau, was also considered. These patients are considered to have prodromal AD. All the participants with AD and MCI underwent lumbar puncture and had evidence of Alzheimer pathology.[28]

Patients diagnosed with SMC presented subjective memory concern and were "self-referrals." Criteria for diagnosis were (1) self-experienced persistent decline in memory and cognitive capacity in comparison with a previously normal status and unrelated to an acute event; and (2) normal age-, gender-, and education-adjusted performance on standardized cognitive tests, which are used to classify MCI or prodromal AD.[33] All subjects in this group had CDR = 0 and MMSE score between 24 and 30 (inclusive). Patients in this group were cognitively normal, with no significant impairment in cognitive functions or activities of daily living.

All study participants gave their written informed consent, and the study was approved by the local ethical committee (ASL Lecce verbale No. 6, May 25, 2017), according to the Declaration of Helsinki.[34] The subjects included in this study were only selected on the basis of the clinical diagnosis, without discrimination by age, sex, and race. However, the authors were careful to ensure sex and gender balance in the recruitment of human subjects and to avoid any form of racial discrimination.

### Sample Collection and Storage

All patients underwent lumbar puncture according to standard procedures. The CSF sample was centrifuged at room temperature for 10 minutes at 2,000 × *g* (relative centrifugation force), aliquoted, and stored at −80°C until analysis, according to international biomarker recommendations.[35]

Venous blood was drawn by venipuncture from all patients; blood samples were collected in ethylenediaminetetraacetic acid vacutainers, which were immediately centrifuged for 15 minutes at ~2,000 × *g* at room temperature within 1 hour. After centrifugation, plasma was removed, aliquoted (0.5ml/aliquot) into screw-cap polypropylene tubes, and stored at −80°C until biochemical analyses.

### CSF AD Biomarker Analysis

The CSF Aβ42, t-tau, and p-tau181 levels were measured by chemiluminescent immunoassay (Lumipulse G Amyloid β 1-42, Lumipulse G Total Tau, Lumipulse G pTau181; Fujirebio Europe, Ghent, Belgium) on a fully automatic platform (Lumipulse G600II, Fujirebio Europe). All the assays were performed according to the manufacturer's protocols.

For the interpretation of the CSF biomarker results, the following cutoff values were considered: Aβ42 >599pg/ml, t-tau < 342pg/ml, p-tau181 < 57pg/ml. Consistent with the diagnostic criteria for AD,[36] a CSF biomarker profile was considered to be suggestive for AD if the CSF Aβ42 value was below the cutoff, in combination with t-tau and/or p-tau181 values above the threshold. In some cases, the p-tau/Aβ42 ratio was used for the determination of AD.[37]

### CSF and Plasma Irisin Assay

The irisin levels in CSF and plasma samples were quantified using the competitive enzyme-linked immunosorbent assay kit EK-067-29 (Phoenix Pharmaceuticals, Burlingame, CA), which is the most widely utilized and validated kit for the quantification of irisin concentration in biological samples in the current literature. The assay sensitivity was 1.29ng/ml with a measurement range of 0.1–1,000ng/ml. Inter- and intra-assay variation were <15% and <10%, respectively. All patient samples, standard dilutions, and positive controls were assayed in duplicate. The plate absorbance was read at 450nm in a plate reader (Eon; BioTek, Winooski, VT). Results were reported in nanograms per milliliter.



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**TABLE 1. Participant Demographic and Clinical Data**

| Patient Characteristic | SMC, n = 20 | MCI, n = 44 | AD, n = 82 | *p* |
|---|---|---|---|---|
| Age, yr | | | | |
| Mean ± SD | 60.35 ± 10.97 | 63.64 ± 10.74 | 67.51 ± 7.81 | =**0.006**, SMC vs AD |
| Median (Q1–Q3) | 59 (50–69.25) | 64 (56.25–71) | 68 (62–73.25) | |
| Sex, n (%) | | | | |
| Women | 9 (45) | 25 (57) | 51 (62) | |
| Men | 11 (55) | 19 (43) | 31 (38) | 0.3669 vs women |
| CSF Aβ42, pg/ml | | | | |
| Mean ± SD | 977.6 ± 228 | 561.9 ± 229.9 | 473.8 ± 135.8 | <**0.0001**, SMC vs MCI and SMC vs AD |
| Median (Q1–Q3) | 895.5 (829.6–1,182) | 511.5 (402.4–653.8) | 485.5 (366.4–569) | |
| CSF t-tau, pg/ml | | | | |
| Mean ± SD | 200.1 ± 81.38 | 459.3 ± 394.7 | 651.5 ± 321.9 | =**0.011**, SMC vs MCI <**0.0001**, SMC vs AD =**0.0005**, MCI vs AD |
| Median (Q1–Q3) | 186.5 (141.7–235.8) | 345.5 (181.5–582.3) | 622 (419.7–845.4) | |
| CSF p-tau, pg/ml | | | | |
| Mean ± SD | 31.45 ± 11.53 | 69.99 ± 67.94 | 91.64 ± 51.13 | =**0.012**, SMC vs MCI <**0.0001**, SMC vs AD =**0.001**, MCI vs AD |
| Median (Q1–Q3) | 28.86 (22.63–37.2) | 47.54 (25.3–81.98) | 82.6 (52.96–112.7) | |
| MMSE | | | | |
| Mean ± SD | 26.85 ± 2.52 | 22.08 ± 4.40 | 15.64 ± 5.18 | =**0.0014**, SMC vs MCI <**0.0001**, SMC vs AD and MCI vs AD |
| Median (Q1–Q3) | 27.11 (26–28.25) | 23 (18.21–25.74) | 16.8 (12.15–19) | |
| CDR-SOB | | | | |
| Mean ± SD | 0.33 ± 0.49 | 2.42 ± 1.49 | 5.92 ± 4.05 | =**0.0073**, SMC vs MCI <**0.0001**, SMC vs AD and MCI vs AD |
| Median (Q1–Q3) | 0 (0–0.5) | 2.5 (1.5–3.5) | 4.5 (3.5–7.5) | |

Bold values highlight statistically significant differences among patient groups (Pearson chi-squared test, $p < 0.05$, for sex; analysis of variance–Tukey test and Kruskal–Wallis–Dunn test, $p < 0.05$, for continuous data).
AD = Alzheimer dementia; Aβ42 = amyloid β 1-42; CDR-SOB = Clinical Dementia Rating Scale Sum of Boxes; CSF = cerebrospinal fluid; MCI = mild cognitive impairment; MMSE = Mini-Mental State Examination; p-tau = hyperphosphorylated tau; Q1 = lower quartile; Q3 = upper quartile; SD = standard deviation; SMC = subjective memory complaints; t-tau = total tau.

### Statistical Analysis

Data are presented as box-and-whisker plots with mean with standard deviation, and median with interquartile range, from maximum to minimum, with all data points shown in figures. The data normal distribution was initially verified via the Shapiro–Wilk test. Differences in CSF and plasma irisin levels and other variables among SMC, MCI, and AD dementia patients were evaluated using nonparametric Kruskal–Wallis test and Dunn multiple comparison test, and analysis of variance followed by

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**TABLE 2. CSF and Plasma Irisin Levels in SMC, MCI, and AD dementia Patients**

| | Groups | | |
|---|---|---|---|
| **Biological fluids of participants** | **All Patients** | **Women** | **Men** |
| CSF irisin, pg/ml | | | |
| SMC, reference | | | |
| Mean ± SD | 1.23 ± 0.42 | 1.37 ± 0.47 | 1.12 ± 0.36 |
| Median (Q1–Q3) | 1.25 (0.94–1.44) | 1.36 (0.96–1.77) | 1.24 (0.86–1.30) |
| *p* | | | n.s. vs women |
| MCI | | | |
| Mean ± SD | 0.95 ± 0.45 | 0.92 ± 0.50 | 0.99 ± 0.38 |
| Median (Q1–Q3) | 0.93 (0.53–1.25) | 0.85 (0.51–1.25) | 0.97 (0.69–1.28) |
| *p* | **0.046** vs SMC | **0.034** vs SMC | n.s. vs SMC<br>n.s. vs women |
| AD | | | |
| Mean ± SD | 0.80 ± 0.47 | 0.70 ± 0.33 | 0.96 ± 0.62 |
| Median (Q1–Q3) | 0.69 (0.53–0.91) | 0.63 (0.52–0.81) | 0.77 (0.53–1.21) |
| *p* | **<0.0001** vs SMC | **0.0003** vs SMC | n.s. vs SMC<br>**0.031** vs women |
| Plasma irisin, pg/ml[a] | | | |
| SMC, reference | | | |
| Mean ± SD | 10.44 ± 3.95 | 10.51 ± 4.05 | 10.36 ± 4.09 |
| Median (Q1–Q3) | 9.79 (7.26–13.16) | 10.27 (7.66–11.17) | 9.31 (6.22–14.35) |
| *p* | | | n.s. vs women |
| MCI | | | |
| Mean ± SD | 9.78 ± 3.21 | 9.69 ± 3.11 | 9.89 ± 3.42 |
| Median (Q1–Q3) | 9.04 (7.14–11.97) | 9.11 (7.21–11.59) | 8.61 (7.11–12.95) |
| *p* | n.s. vs SMC | n.s. vs SMC | n.s. vs SMC<br>n.s. vs women |
| AD | | | |
| Mean ± SD | 9.04 ± 2.60 | 9.34 ± 2.62 | 8.69 ± 2.61 |
| Median (Q1–Q3) | 8.24 (7.04–10.75) | 8.59 (7.58–10.70) | 7.52 (6.70–11.94) |
| *p* | n.s. vs SMC | n.s. vs SMC | n.s. vs SMC<br>n.s. vs women |

Bold values highlight statistically significant differences in respect to the SMC patients (Kruskal–Wallis–Dunn test, $p < 0.05$) and between men and women (2-tailed unpaired Student test or Mann–Whitney test, $p < 0.05$).
AD = Alzheimer dementia; CSF = cerebrospinal fluid; MCI = mild cognitive impairment; n.s. = not significant; Q1 = lower quartile; Q3 = upper quartile; SD = standard deviation; SMC = subjective memory complaints.
[a]Data not available for all participants (n = 18 for SMC, n = 43 for MCI, and n = 41 for AD patients).

Tukey test. Differences between male and female subgroups were assessed by 2-tailed unpaired Student test and Mann–Whitney test. Categorical variables were compared using Pearson chi-squared test. Correlations were performed using Spearman correlation coefficient test and with partial correlation coefficient test.

Statistical significance was set at $p < 0.05$. Statistical analyses were conducted by SPSS version 22.0

(IBM, Armonk, NY) and Prism statistical software release 7.0 (GraphPad Software, San Diego, CA).

## Results

### Irisin Levels in AD, MCI, and SMC

Irisin levels were measured in CSF and plasma of 82 patients with AD dementia, 44 with MCI, and 20 with SMC. The demographic and clinical data are reported in Table 1.

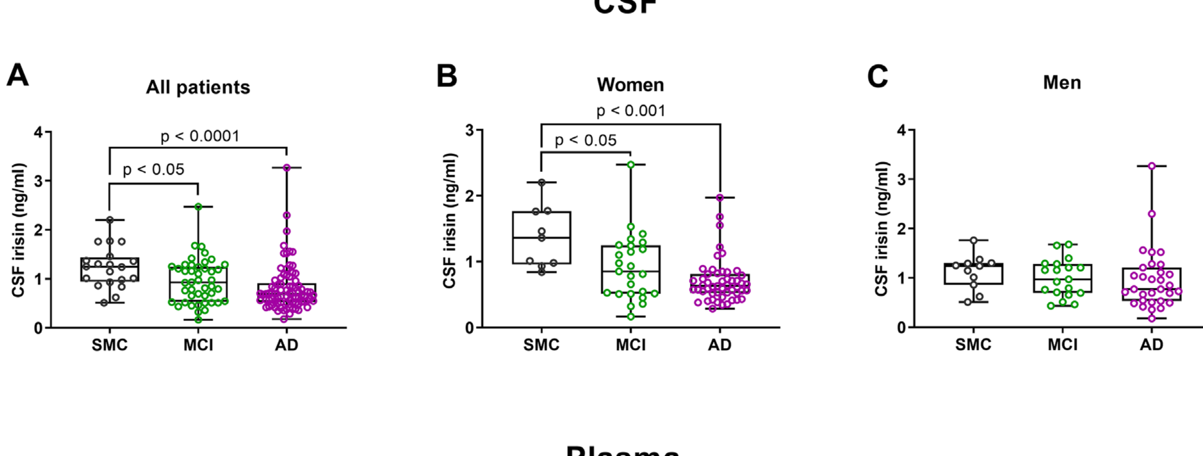
First, we wanted to compare the MCI and AD dementia groups with the SMC group. The analysis results and the relative comparisons among patients are showed in Table 2.

We observed that irisin levels in CSF were significantly reduced in both patients with MCI and AD dementia ($p = 0.046$ and $p < 0.0001$, respectively) compared to SMC (Fig 1). Moreover, lower levels of irisin in CSF of MCI and AD dementia patients were observed when the comparison was restricted to female patients ($p = 0.034$ for SMC vs MCI patients and $p = 0.0003$ for SMC vs AD dementia patients). No difference was noticed among male patients ($p = 0.1963$). Subgroup analysis showed a significant reduction of irisin CSF levels in female AD dementia patients compared with male patients ($p = 0.031$; Figure S1A–C).

Regarding the plasma level of irisin, no difference was observed comparing AD dementia, MCI, and SMC (see Fig 1D). Neither were differences in plasma levels of irisin observed when the comparison was restricted to female or male patients (see Fig 1E, F). In addition, no differences in plasma level of irisin were noted between the subgroups of women and men in patients with SMC, MCI, and AD dementia (Figure S1D–F).

### Irisin Correlation with CSF AD Biomarkers and CDR-SOB

A statistically significant positive correlation was observed between CSF and plasma irisin levels ($r = 0.456$, $p < 0.0001$; Figure S2). Preliminarily, we also analyzed the correlations between CSF or plasma irisin and age. Except for the positive correlation of plasma irisin with age in AD dementia patients ($r = 0.354$, $p = 0.023$), there were no other significant correlations overall ($r = -0.030$, $p = 0.723$ for CSF irisin and $r = 0.007$, $p = 0.942$ for plasma irisin) or among groups.



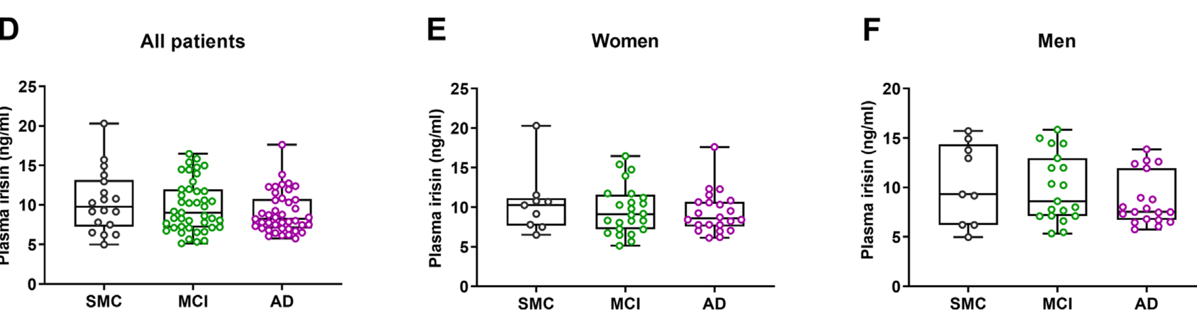




FIGURE 1: Irisin levels in cerebrospinal fluid (CSF; A–C) and plasma (D–F) of subjective memory complaint (SMC), mild cognitive impairment (MCI), and Alzheimer dementia (AD) patients. Data are presented as box-and-whisker plots with median and interquartile range, from maximum to minimum, with all data points shown. Horizontal bars indicate significant differences among groups (Kruskal–Wallis test/Dunn's multiple comparison test). Gray circles represent SMC patients, green circles represent MCI patients, and magenta circles represent AD patients. [Color figure can be viewed at www.annalsofneurology.org]



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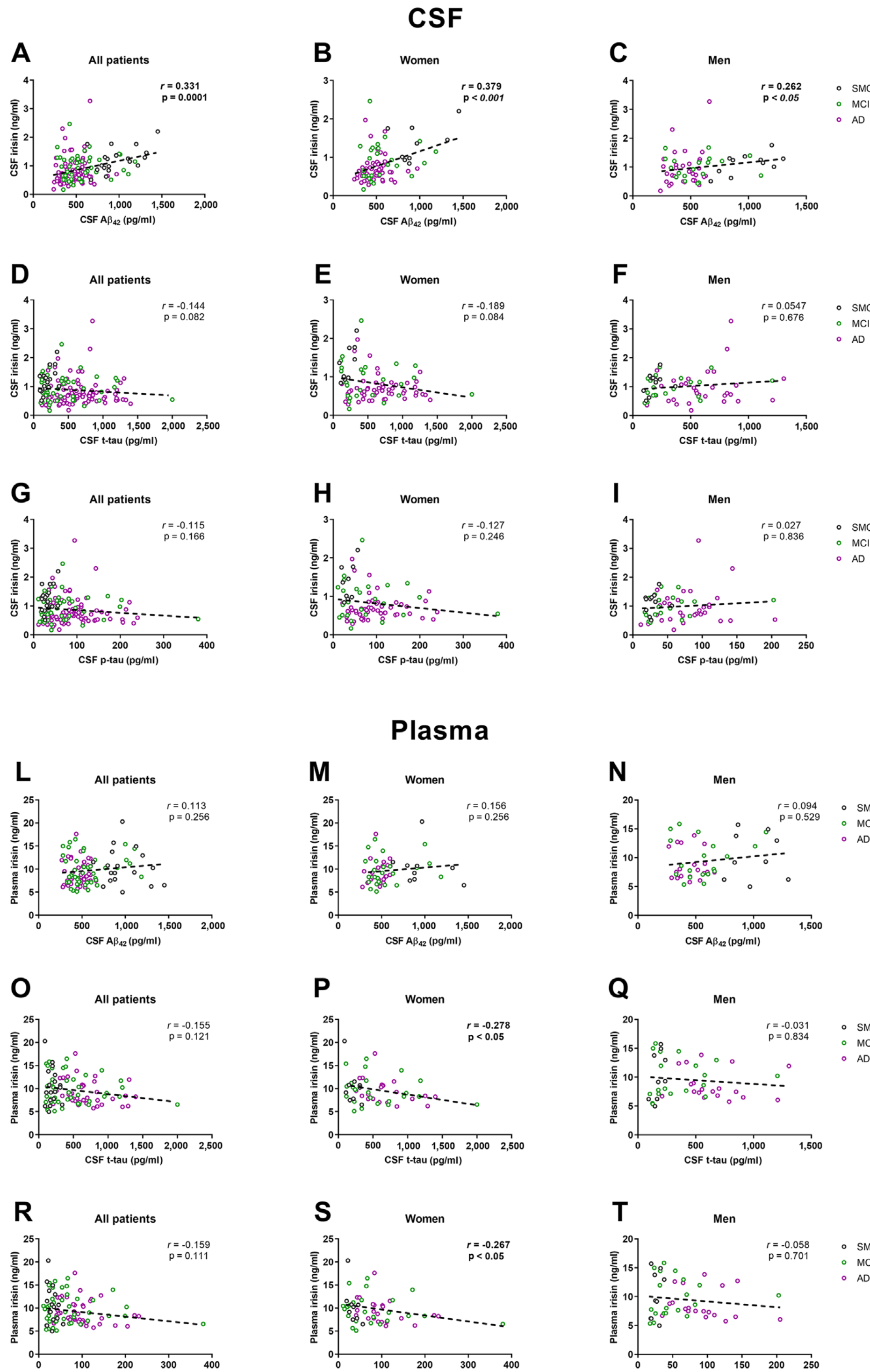


**FIGURE 2:** Correlations between cerebrospinal fluid (CSF) irisin (A–I) or plasma (L–T) irisin levels and Alzheimer dementia (AD) biomarkers. Dotted lines represent Spearman linear regressions (*r* and *p* values as indicated). Bold values highlight statistically significant correlations. AD = Alzheimer dementia; $A\beta_{42}$ = amyloid-β 1-42; MCI = mild cognitive impairment; p-tau = hyperphosphorylated tau; SMC = subjective memory complaints; t-tau = total tau. Gray circles represent SMC patients, green circles represent MCI patients, and magenta circles represent AD patients. [Color figure can be viewed at www.annalsofneurology.org]

Considering the levels of irisin in the CSF and the plasma of the patients enrolled in our study, we evaluated the correlations of irisin levels with AD biomarkers (Aβ42, t-tau, and p-tau) and the clinical dementia score (CDR-SOB).

We found that CSF irisin levels positively correlated with Aβ42 in overall patients ($r = 0.311$, $p = 0.0001$; Fig 2). Moreover, this correlation was maintained in both women and men ($r = 0.379$, $p = 0.0004$ and $r = 0.262$,



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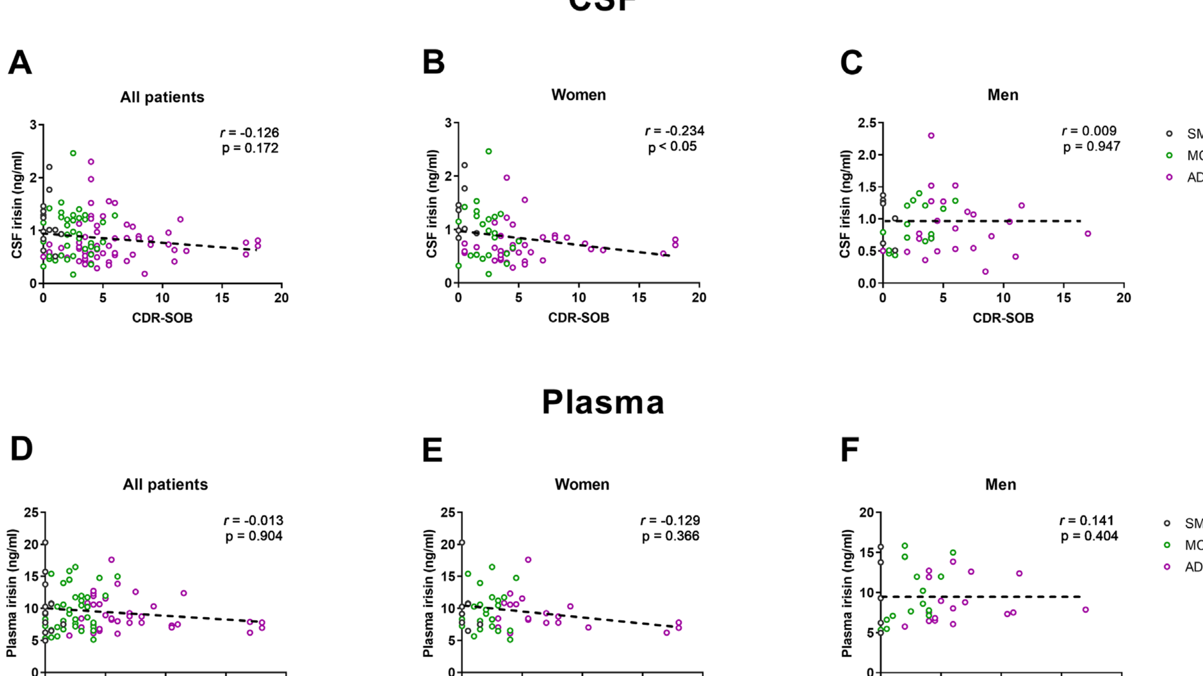


**FIGURE 3: Correlations between cerebrospinal fluid (CSF) irisin (A–C) or plasma irisin (D–F) and Clinical Dementia Rating Scale Sum of Boxes (CDR-SOB). Dotted lines represent Spearman linear regressions (*r* and *p* values as indicated). Bold values highlight statistically significant correlations. AD = Alzheimer dementia; MCI = mild cognitive impairment; SMC = subjective memory complaints. Gray circles represent SMC patients, green circles represent MCI patients, and magenta circle represent AD patients. [Color figure can be viewed at www.annalsofneurology.org]**

$p = 0.042$, respectively). Conversely, a negative correlation was observed between irisin and t-tau levels, although it was not statistically significant, in overall patients ($r = -0.144$, $p = 0.082$) and in female patients ($r = -0.189$, $p = 0.084$).

No correlations were observed between CSF irisin and p-tau in the total patient population ($r = -0.115$, $p = 0.166$), female patients ($r = -0.127$, $p = 0.246$), and male patients ($r = 0.027$, $p = 0.836$; see Fig 2G–I).

Regarding plasma irisin level, no significant correlations with CSF Aβ42 were found ($r = 0.113$, $p = 0.256$; see Fig 2L). Concerning t-tau and p-tau, significant negative correlations were found in female patients for both ($r = -0.278$, $p = 0.040$ and $r = -0.267$, $p = 0.049$, respectively; see Fig 2P, S).

Regarding the correlation with CDR-SOB, the statistical analysis showed a significant negative correlation with CSF irisin in the female subgroup ($r = -\ 0.234$, $p = 0.048$; Fig 3B). No correlations were evidenced in overall patients ($r = -0.126$, $p = 0.172$) and men ($r = 0.009$, $p = 0.947$; see Fig 3A, C).

As far as the plasma irisin is concerned, no correlations were found in overall patients ($r = -0.013$, $p = 0.904$) and female ($r = -0.129$, $p = 0.366$) and male subgroups ($r = 0.141$, $p = 0.404$; see Fig 3D–F).

The results of these correlations are summarized in Table 3.

### *Partial Correlations*

We further analyzed the previous correlations adjusting for some covariates (ie, age, sex, and CDR) separately or in combination with each other. The results of these analyses are included in Table 4.

We noticed that correlation remained significant between CSF irisin and CSF Aβ42 when corrected for sex only ($r = 0.174$, $p = 0.037$), for sex and age ($r = 0.169$, $p = 0.043$), and for sex, age, and CDR ($r = 0.195$, $p = 0.027$). No significant correlations between CSF and plasma irisin and the other biomarkers and CDR-SOB after correction were found.

## Discussion

The present study highlights that CSF irisin levels decrease in the continuum of AD and the reduction is significant in female patients. Irisin levels positively correlate with CSF Aβ42 and display a negative trend with t-tau.

In the past years, the idea is gaining strength that a helpful strategy for the prevention of AD is the performance of regular PE, resulting in the enhancement of memory and cognitive functions.[9,38] In this regard, it has been estimated that daily PE may decrease AD risk by 45% in older adults.[39] PE is also emerging as a possible adjuvant therapy for AD treatment; many systematic reviews and meta-analyses of randomized controlled trials (RCTs) reported that this lifestyle factor can improve



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**TABLE 3. Correlations of CSF and Plasma Irisin Levels with Alzheimer Disease Biomarkers and Clinical Data**

| Fluids and clinical AD biomarkers in participants | CSF Irisin, ng/ml | | Plasma Irisin, ng/ml | |
|---|---|---|---|---|
| | *r* | *p* | *r* | *p* |
| All patients | | | | |
| CSF Aβ42 | 0.311 | **0.0001** | 0.113 | 0.256 |
| CSF t-tau | −0.144 | 0.082 | −0.155 | 0.121 |
| CSF p-tau | −0.115 | 0.166 | −0.159 | 0.111 |
| CDR-SOB | −0.126 | 0.172 | −0.013 | 0.904 |
| Women | | | | |
| CSF Aβ42 | 0.379 | **0.0004** | 0.156 | 0.256 |
| CSF t-tau | −0.189 | 0.084 | −0.278 | **0.040** |
| CSF p-tau | −0.127 | 0.246 | −0.267 | **0.049** |
| CDR-SOB | −0.234 | **0.048** | −0.129 | 0.366 |
| Men | | | | |
| CSF Aβ42 | 0.262 | **0.042** | 0.094 | 0.529 |
| CSF t-tau | 0.0547 | 0.676 | −0.031 | 0.834 |
| CSF p-tau | 0.027 | 0.836 | −0.058 | 0.701 |
| CDR-SOB | 0.009 | 0.947 | 0.141 | 0.404 |

Bold values highlight statistically significant correlations (Spearman correlation coefficient test; *r*, Spearman correlation coefficient).
Aβ42 = amyloid-β 1-42; CDR-SOB = Clinical Dementia Rating Scale Sum of Boxes; CSF = cerebrospinal fluid; p-tau = hyperphosphorylated tau; t-tau = total tau.

**TABLE 4. Partial Correlations of CSF and Plasma Irisin Levels with Alzheimer Disease Biomarkers and CDR-SOB**

| Correlation | Group, Age | | Group, Sex | | Group, Age, Sex | | Group, Age, Sex, CDR | |
|---|---|---|---|---|---|---|---|---|
| | *r* | *p* | *r* | *p* | *r* | *p* | *r* | *p* |
| CSF irisin | | | | | | | | |
| CSF Aβ42 | 0.160 | 0.055 | 0.174 | **0.037** | 0.169 | **0.043** | 0.195 | **0.027** |
| CSF t-tau | 0.004 | 0.959 | 0.038 | 0.651 | 0.028 | 0.737 | 0.019 | 0.829 |
| CSF p-tau | −0.024 | 0.772 | 0.013 | 0.875 | 0.002 | 0.984 | −0.016 | 0.857 |
| CDR-SOB | 0.032 | 0.732 | 0.022 | 0.814 | 0.029 | 0.755 | 0.057 | 0.549 |
| Plasma irisin | | | | | | | | |
| CSF Aβ42 | 0.041 | 0.688 | 0.041 | 0.683 | 0.041 | 0.685 | 0.037 | 0.718 |
| CSF t-tau | −0.143 | 0.157 | −0.148 | 0.143 | −0.151 | 0.137 | −0.150 | 0.145 |
| CSF p-tau | −0.140 | 0.164 | −0.146 | 0.147 | −0.149 | 0.142 | −0.146 | 0.156 |
| CDR-SOB | −0.052 | 0.635 | −0.055 | 0.616 | −0.052 | 0.635 | 0.082 | 0.459 |

Bold values highlight statistically significant correlations.
Aβ42 = amyloid-β 1-42; CDR = Clinical Dementia Rating Scale; CDR-SOB = CDR Sum of Boxes; CSF = cerebrospinal fluid; p-tau = phosphorylated tau; t-tau = total tau.

cognitive functions and decrease neuropsychiatric symptoms in AD patients.[6,8,9] RCTs included older subjects diagnosed with AD who participated in different PE programs ranging from moderate to high-intensity aerobic exercise, resistance exercise, et cetera. Exercise interventions were conducted for 12 to 24 weeks with sessions of at least 1 hour per week.[8] The cognitive functions were primarily evaluated by the MMSE that was administered before and after the intervention period.[6,8] The majority of the RCTs evidenced significant improvement in cognition in the exercising AD patients in respect to the control group, with the few exceptions often attributable to the type and/or duration of training.[6,8,9]

These effects seem to be mediated by a wide range of soluble factors released by skeletal muscle (myokines) that act on several organs, including brain.[11] Recently, among them emerged the exercise-mimetic myokine irisin, as a positive brain mediator of exercise that might prevent and/or decelerate the progress of neurodegenerative diseases (AD, Parkinson disease, etc) as well as psychiatric disorders such as major depression.[17,26,40–42]

Of note, irisin is currently recognized as one of the pivotal factors responsible for the exercise-induced cognitive improvements in both AD mouse models and patients.[17,20,23]

In this context, we investigated the associations of CSF and plasma irisin levels with AD biomarkers in a large group of participants that included patients with SMC, MCI, and AD dementia. The classification among these 3 groups was performed according to the 2018 NIA-AA research framework (2018-NIA-AA-RF), which is based on the biological definition of AD by neuropathologic change or biomarkers (Aβ, p-tau, and t-tau). Of note, this classification system considers the cognitive impairment a disease symptom/sign instead of a condition that defines the disease.[28] It is very important to highlight that, within the studies concerning irisin and AD patients, the use of patients stratified on the basis of the recent NIA-AA-RF criteria is herein applied for the first time.

Furthermore, this approach gave us the opportunity to study the relationship between irisin and AD biomarkers in the so-called "prodromal AD" represented by the MCI group.

The evaluation of possible variations in the irisin levels across the disease stages led us to compare irisin concentration in the CSF and plasma of the 3 groups of patients, finding significantly lower CSF levels in both AD dementia and MCI patients compared to SMC. Notably, the reduction of CSF irisin was less marked in MCI compared to AD dementia patients, indicating that irisin levels decreased as the disease progressed, and suggesting that the myokine could be a potential prognostic index of disease development and progression. These results not only are in agreement with those obtained by Lourenco et al[20] in a population of AD patients differently characterized and selected, but are also supported by studies on postmortem hippocampi of late stage AD patients showing reduction of FNDC5/irisin protein levels.[20] The absence of differences in the levels of circulating irisin in our cohort of patients further supports that the FNDC5/irisin system in the CSF might be a possible disease biomarker in AD and, at the same time, confirmed that the variations in irisin levels are limited to the central nervous system in both neurodegenerative and psychiatric disorders.[20,26] It is noteworthy that AD affects disproportionately women rather than men, and several reports suggest the need to consider the impact of sex in AD research.[29,30] As a novelty, our sex-stratified analysis showed the significant impact of the female subgroup compared to the male one in the progression of the disease. Remarkably, only in AD dementia females did we find reduced irisin concentration in the CSF. Therefore, our findings are in line with previous evidence showing reduced CSF irisin in healthy women compared to men,[43] so that we could speculate that women might be more prone to AD development. On the other hand, like irisin, other biofluid-based biomarkers vary between females and males for sex differences in brain structure and function.[44] In addition, as irisin secretion seems to be involved in a reciprocal interplay with the ovarian and testicular hormones,[45] we cannot exclude that the reduced irisin levels in the CSF of female AD dementia patients could be linked to sex hormone fluctuations after menopause. Links between AD and estrogen levels have been clearly shown in imaging studies.[46]

The analysis of the correlations between CSF irisin and AD biomarkers (CSF Aβ42, t-tau, and p-tau) in the continuum of AD pathology showed that CSF irisin correlated positively with cerebral Aβ42 and maintained its significance when corrected for sex and for sex and age. Of note, we found a similar positive correlation with CSF Aβ42 if the analysis was restricted to female or male subgroups. In accordance with these findings is a previous work on a population of nondemented controls and AD patients.[23] Many studies highlighted that PE may modulate Aβ levels by inhibiting Aβ production and/or increasing its clearance in the brain.[47] Although there is no direct evidence for the action of irisin in reducing Aβ deposits in exercising AD animal models and/or patients, it has been demonstrated that the FNDC5/irisin pathway is upregulated in the hippocampus of an AD rat model submitted to moderate treadmill exercise.[48] Moreover, a recent study demonstrating the role of irisin in amyloid deposition reduction by inducing the release of the



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astrocyte Aβ-degrading enzyme neprilysin further supports previous findings regarding the involvement of the FNDC5/irisin system in the neuroprotective functions of exercise in AD patients.[49]

The correlation between irisin and tau protein was also evaluated. Like Aβ42, t-tau is a core CSF biomarker in the continuum of AD correlating with neurodegeneration.[28,50] It has been suggested that tau and Aβ pathology may develop independently, with Aβ accelerating pre-existing tau pathology[51]; moreover, tau accumulation is more associated with the degree of neuronal loss and consequently with the clinical presentation of the disease, including cognitive impairment.[52]

In our study, a negative association between CSF irisin and t-tau was revealed, in overall patients and female subgroups. It is important to point out that, whereas prior analysis showed no correlations between t-tau and CSF irisin in a restricted population of healthy (nondemented) controls and AD patients,[23] the present study evidenced, for the first time, a negative trend toward significance between these factors. The relation between higher CSF irisin levels, less amyloid-β pathology, and better cognitive function was already observed in patients with AD and non-AD.[23] Our finding may suggest a similar relationship between irisin, neurodegeneration (ie, t-tau), and cognitive performance. However, further investigations are required to elucidate this interesting finding.

To complete our analysis, we evaluated the association between plasma irisin and AD biomarkers, and we found a significant correlation with t-tau and p-tau only in the female patients, which possibly reflects the process of neurodegeneration and tau pathology, respectively.

In summary, our results suggest that, unlike other works that evaluated similar correlations in a limited cohort of patients differently stratified,[23] irisin seemed to correlate with neurodegeneration.

We also considered the correlations with CDR-SOB, the clinical scale for the staging of dementia. Interestingly, our results showed a negative correlation with CSF irisin in women. This supports the link between irisin and AD pathology, and further suggests that irisin may be associated differently in female and male patients with AD.

A significant positive correlation was observed between CSF and plasma irisin levels; however, CSF irisin better reflects the Aβ deposition and the neurodegeneration process. These findings, probably imputable to AD biomarkers being measured in CSF, might explain why these correlations were lost when irisin levels were assessed in plasma samples. Nonetheless, we cannot exclude that such correlations might emerge when evaluated with respect to circulating AD biomarkers and may be a challenge for future research.

Our study has some limitations that need to be discussed. First, this is a cross-sectional study; therefore, the biomarkers were only detected once, without longitudinal measurements, which limits interpretation on causality. Further large-scale longitudinal studies need to be conducted to demonstrate the dynamic of irisin alteration along the spectrum of AD and its correlation with clinical and biological markers. We acknowledge the potential for spurious findings due to multiple comparisons as a significant factor in interpreting our results. Although our primary analyses were rigorously corrected for multiple comparisons, our exploratory analyses of correlations were not subjected to such corrections. These findings, therefore, represent initial observations that necessitate further investigation and should be regarded with caution.

Although other studies investigated the correlations of CSF or plasma irisin with markers related to Alzheimer pathology and/or cognitive parameters,[23–26] this study, for the first time, focuses on the correlations with AD biomarkers and clinical dementia scores by adopting the 2018-NIA-AA-RF criteria for patient characterization and selection and by investigating possible sex differences.

The true ability of irisin to represent a biomarker of disease progression and severity remains to be further investigated. Independent cohorts may be required to confirm a correlation between irisin levels and disease severity and to test the hypothesis of irisin as a marker of disease progression.

However, our findings might offer interesting perspectives toward the potential role of irisin in the modulation of AD pathology and can guide the exploration of medication targeting the irisin system.

Finally, the Lancet Commission on dementia prevention, intervention, and care life course[38] identified 12 risk factors that could prevent or delay up to 40% of dementias, including physical inactivity. Irisin, an exercise-inducible myokine, might be considered a biomarker of efficacy of interventions aimed at preventing or modifying the course of AD. At present, the increase of circulating irisin levels induced by PE has been demonstrated in healthy subjects participating in aerobic training by tandem mass spectrometry,[12] but studies on AD patients are still lacking. In this respect, future investigations might be helpful to further elucidate the role of irisin as a brain mediator of the benefits of exercise in AD.

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## Author Contributions

S.C., G.L., and M.G. contributed to the conception and design of the study. M.D., P.P., C.Z., M.T.D., D.U., V.G., A.G., F.B., R.Z., A.O., and G.C. contributed to the acquisition and analysis of data. M.D., P.P., C.Z., M.T.D., D.U., S.C., G.L., and M.G. contributed to drafting the text or preparing the figures. All authors contributed to editing and approving the text.

## Potential Conflicts of Interest

Nothing to report.

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