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Association Between Serum Follicle-Stimulating Hormone Levels and Cognitive Function in Middle-Aged and Older Women

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ABSTRACT

Background: Researchers have proposed that there is a potential link between follicle-stimulating hormone (FSH) and cognitive function, yet the evidence remains inconclusive. The current study aims to identify the association between serum FSH levels and cognitive performance, and to examine whether this association varies by cognitive diagnosis, serum estradiol (E2) levels, or cognitive domain.
Methods: This multicenter cross-sectional study used a clinical database comprising female visitors to memory clinics at three referral hospitals in Korea. Venous blood samples were collected to determine serum FSH and E2 concentrations via immunoradiometric assay. Cognitive performance was evaluated using either the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease or the Seoul Neuropsychological Screening Battery, while cognitive diagnoses were made via clinical diagnostic interviews.
Results: Among the 159 participants (normal cognition [NC], n = 70; mild cognitive impairment [MCI], n = 52; Alzheimer's disease [AD] dementia, n = 37), there were no significant differences in serum FSH levels associated with cognitive diagnosis. In women with NC, serum FSH levels were found to be positively correlated with cognitive performance in global cognition, nonverbal memory, and executive function, even after adjusting for serum E2 level and its interaction with serum FSH level. However, no significant correlations were observed in women with MCI and AD dementia.
Conclusion: The association between circulating FSH and cognition may be independent from circulating E2, but it may depend on disease progression or cognitive domains. This suggests a potential role of gonadotropin in cognitive decline in elderly women.

Keywords: Follicle Stimulating Hormone; Cognition Disorders; Cognitive Dysfunction; Alzheimer Disease

Author Contributions

Conceptualization: Baek KH, Jeong C.
Data curation: Oh DJ, Kang DW, Hong YJ.
Formal analysis: Oh DJ, Kang DW, Hong YJ. Investigation: Oh DJ, Kang DW, Hong YJ. Writing - original draft: Oh DJ, Jeong C.
Writing - review & editing: Oh DJ, Jeong C.

INTRODUCTION

The World Health Organization has identified dementia as a public health issue that requires urgent attention due to its increasing prevalence and significant impact.[1] To reduce the disease burden, it is important to understand the biological underpinnings of cognitive decline and dementia, as this can facilitate early identification of at-risk groups and the delivery of timely interventions.

Existing studies have proposed a possible link between cognitive decline and dementia and the aging-related change in gonadotropins. Follicle-stimulating hormone (FSH), which is a glycoprotein polypeptide hormone that is secreted by the anterior pituitary gland, binds to G protein–coupled FSH receptors on ovarian granulosa cells, thus promoting estrogen production.[2] In contrast to the relatively stable changes in estrogen levels, there is a sharp increase in serum FSH levels during the perimenopausal period.[3] The common transient decline in cognitive performance among perimenopausal women[4-6] warrants further investigation into the estrogen-independent cognitive effects of FSH. FSH has been found to have extragonadal effects wherein it activates the systemic release of pro-inflammatory cytokines.[7] In middle-aged and older women, FSH-induced monocyte activation can rupture atherosclerotic plaques,[8] thereby increasing the risk of cardiovascular diseases[9] as well as contributing to osteoporosis through osteoclast formation.[10] Based on these findings, we could speculate that FSH might also affect cognitive function, as chronic inflammation and cardiovascular diseases significantly increase the risk of cognitive decline.[11,12] However, there has to this point been limited research examining the effects of FSH on the brain and cognitive function.

A recent animal study has shown that FSH directly affects hippocampal and cortical neurons, specifically by accelerating the accumulation of amyloid-β and tau proteins and impairing cognitive function in female mice with Alzheimer's disease (AD).[13] However, previous research on the link between FSH and cognitive function has shown inconsistent findings in humans: In particular, serum FSH levels have been found to have a positive correlation,[14,15] a negative correlation,[16-18] and no correlation[4,19,20] with cognitive performance. These inconsistencies have been attributed to the lack of consideration that has been given to clinical diagnosis for cognitive status. The potential impact of gonadotropins on cognitive function may be diminished in advanced stages of neurodegenerative changes, as the severity of underlying core pathophysiology, such as amyloid deposition and neuronal injury, becomes increasingly prominent.[21] Moreover, most previous studies have not accounted for the potential effect of estradiol (E2) on the relationship between FSH and cognitive function, despite its neuroprotective effect and close interaction with serum FSH levels.[22] Researchers have to this point also used different neuropsychological tests, many of which only assessed some cognitive domains or global cognitive function.

The present study aims to identify whether there is an association between serum FSH levels and cognitive function, and whether this association differs based on cognitive diagnosis, serum E2 levels, or cognitive domain.

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METHODS

Study design, setting, and participants

This multi-centered cross-sectional study used a clinical database comprised of data from visitors to memory clinics of three referral hospitals in Korea (Seoul St. Mary's Hospital and Yeouido St. Mary's Hospital, Seoul, Korea; Uijeongbu St. Mary's Hospital, Uijeongbu, Korea). We reviewed electronic medical records from January 2014 to March 2022 and included the data of female participants who underwent both neuropsychological tests and laboratory tests measuring their serum FSH level. Participants who had 1) serious medical illnesses including major neurological and psychiatric disorders aside from AD dementia, 2) uncertain cognitive diagnoses, or 3) a time interval between neuropsychological and laboratory tests of more than one year were excluded. In total, this study included 159 participants aged 41 to 86 years old.

Assessment of cognitive performance and cognitive diagnosis

All participants were evaluated according to one of the following standardized neuropsychological assessments: the Korean version of the Consortium to Establish a Registry for Alzheimer's Disease (CERAD-K)[23] or Seoul Neuropsychological Screening Battery (SNSB).[24] Both neuropsychological tests consist of several subtests intended to estimate a wide range of cognitive functions. We used Z-scores obtained based on the norms of each test to estimate the cognitive performance in each cognitive domain. The cognitive domains analyzed here included 1) verbal memory (word list recall test of CERAD-K; delayed recall from Seoul Verbal Learning Test of SNSB), 2) nonverbal memory (constructional recall test of CERAD-K; Rey-Osterrieth Complex Figure Test [RCFT] delayed recall test of SNSB), 3) language (Boston naming test of CERAD-K and SNSB), 4) visuospatial function (constructional praxis test of CERAD-K; RCFT copying test of SNSB), and 5) executive function (color reading from Color Word Stroop Test of CERAD-K and SNSB). Moreover, the global cognition of all participants was evaluated by Mini-Mental State Examination in all participants.

We made cognitive diagnoses of the participants after a review of electronic medical records. In all hospitals participating in this study, geriatric psychiatrists and neurologists conducted diagnostic interviews, physical examinations, and routine laboratory tests to make final cognitive diagnoses. A diagnostic panel consisting of geriatric physicians and neuropsychologists confirmed the diagnoses of AD dementia and mild cognitive impairment (MCI) in each hospital. Diagnoses of AD dementia were made when participants met the criteria for "probable AD," as defined by the diagnostic criteria of the National Institute of Neurological and Communicative Disorders and Stroke as well as the Alzheimer's Disease and Related Disorders Association.[25] The diagnosis of MCI was based on the consensus diagnostic criteria by the International Working Group.[26] After a review of the medical records of 159 included participants, they were categorized into 70 with normal cognition (NC group), 52 with MCI, and 37 with AD dementia.

Assessment of serum FSH and 17β-E2

In all hospitals participating in this study, participants had venous blood samples collected after overnight fasting. Serum FSH (FSH-IRMA; Biosource Europe S.A., Nivelles, Belgium) levels were measured using an immunoradiometric assay. Serum E2 (estradiol MAIA; Biodata Diagnostics, Bologna, Italy) was measured using a radioimmunoassay in all hospitals.

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Statistical analysis

For the comparison of diagnostic groups, we used Pearson's χ^2 tests for categorical variables and one-way analyses of variance for continuous variables. We used analyses of covariance (ANCOVA) to evaluate the differences in serum FSH levels across the different diagnostic groups. Age and serum E2 level were included as covariates for ANCOVA.

To identify the association of serum FSH level with cognitive performance by cognitive diagnosis, we conducted multivariate linear regression analyses for each diagnostic group in a stepwise manner. The first models were adjusted for age and *APOE* genotype, while the second models were additionally adjusted for serum E2 level and its interaction with serum FSH level. We conducted separate analyses assessing the performance in each cognitive domain as a dependent variable. To identify the association of serum FSH/E2 ratio with cognitive performance by cognitive diagnosis, we conducted multivariate linear regression analyses while adjusting for age and *APOE* genotype for each diagnostic group. To examine the association between serum FSH levels and the serum FSH/E2 ratio with cognitive function in postmenopausal women only, all linear regression analyses were repeated in participants aged 47 years and older, based on the mean age of menopause in Korean women (46.9 ± 4.9 years).[27]

All analyses were performed using R software (version 4.0.2, R Foundation for Statistical Computing).

Ethics statement

This study was approved by the Institutional Review Board (IRB) of Yeouido St. Mary's Hospital, The Catholic University of Korea (SC22WISB0105). Informed consent was exempted by the IRB since the study was a retrospective analysis.

RESULTS

Table 1 displays the results of the comparison of participants by diagnostic group. The AD dementia group was older than the other groups and had lower cognitive performance compared to the NC and/or MCI groups in all cognitive domains (**Table 1**). **Fig. 1** illustrates the comparison of serum FSH levels across diagnostic groups. The ANCOVA, which is

Table 1. Comparison of participants

Variables	NC[a] (n = 70)	MCI[b] (n = 52)	AD dementia[c] (n = 37)	Statistics*	
				P	*Post hoc*
Age, yr	63.04 ± 8.77	62.90 ± 8.87	68.62 ± 10.16	0.005	a,b<c
Serum FSH, mIU/mL	36.76 ± 22.09	36.46 ± 23.55	39.21 ± 29.06	0.851	-
Serum E2, pg/mL	44.29 ± 56.31	52.97 ± 95.36	49.61 ± 75.27	0.854	-
APOE ε4 carriers	11 (15.7)	10 (20.0)	10 (29.4)	0.263	-
MMSE, Z-score	−0.05 ± 1.69	−0.56 ± 1.43	−2.74 ± 2.77	< 0.001	a,b>c
Verbal memory, Z-score	0.38 ± 1.73	−0.75 ± 1.55	−1.75 ± 1.53	< 0.001	a>b>c
Nonverbal memory, Z-score	−0.11 ± 1.13	−0.71 ± 1.02	−1.18 ± 1.19	< 0.001	a>b,c
Language, Z-score	0.16 ± 1.38	−1.06 ± 2.37	−1.40 ± 2.11	0.008	a>b,c
Visuospatial function, Z-score	0.17 ± 1.33	−0.03 ± 0.98	−1.61 ± 2.53	< 0.001	a,b>c
Executive function, Z-score	0.06 ± 1.50	−0.14 ± 1.15	−1.97 ± 1.81	< 0.001	a,b>c

Continuous variables are presented as mean ± standard deviation and categorical variables as number (percentage).
NC = normal cognition, MCI = mild cognitive impairment, AD = Alzheimer's disease, FSH = follicle-stimulating hormone, E2 = estradiol, *APOE* = apolipoprotein E, MMSE = Mini-Mental State Examination.
*Analysis of variance for continuous variables and χ^2 test for categorical variables.

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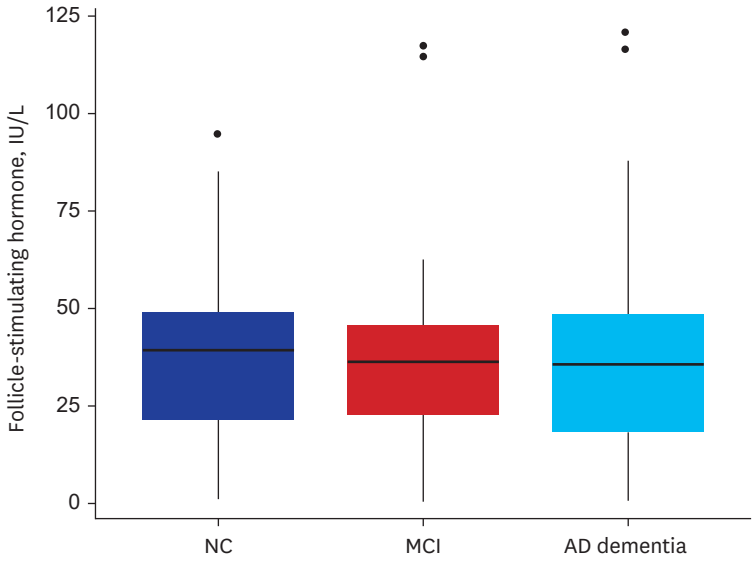

Fig. 1. Box plots comparing serum follicle-stimulating hormone concentrations by cognitive diagnosis.
NC = normal cognition, MCI = mild cognitive impairment, AD = Alzheimer's disease.

adjusted for age and serum E2 level, revealed a marginal difference in serum FSH level between the NC and AD dementia groups ($df = 2$, $F = 3.245$, $P = 0.075$). There were no significant differences in serum FSH levels between the NC and MCI groups ($df = 2$, $F = 0.293$, $P = 0.590$) or between the MCI and AD dementia groups ($df = 2$, $F = 1.976$, $P = 0.166$).

The distributions of the Z-scores obtained for all cognitive tests by serum FSH levels in the NC groups are shown in **Fig. 2**. Meanwhile, as presented in **Table 2**, the association between serum FSH levels and cognitive performance differed by cognitive diagnosis. In particular, in the NC group, an increase in serum FSH levels was associated with increases in global cognition, nonverbal memory, visuospatial function, and executive function. After adjusting for serum E2 levels and its interaction with serum FSH levels, the association between serum FSH levels and global cognition, nonverbal memory, and executive function remained significant (**Table 2**). There was no statistically significant association between serum FSH * E2 interaction and cognitive performance, aside from an association with nonverbal memory ($P = 0.037$) in the NC group.

Supplementary Figs. 1 and **2** show the distribution of Z-scores for all cognitive tests by serum FSH level in the MCI and AD dementia groups, respectively. In the MCI group, there was no significant association between serum FSH level and cognitive performance in the fully adjusted models. In the AD dementia group, an increase in serum FSH level was only shown to be associated with an increase in nonverbal memory in the fully adjusted models (**Table 2**). The association of serum FSH * E2 interaction with nonverbal memory was found to be statistically significant in the AD dementia group ($P = 0.008$).

Table 3 shows the correlation between serum FSH/E2 ratio and cognitive performance by diagnostic group. In the NC group, an increase in serum FSH/E2 ratio was associated with increases in global cognition, nonverbal memory, and executive function. However, there was no significant association between the serum FSH/E2 ratio and cognitive performance across any of the cognitive domains in the MCI and AD dementia groups (refer to **Table 3** for detailed results).

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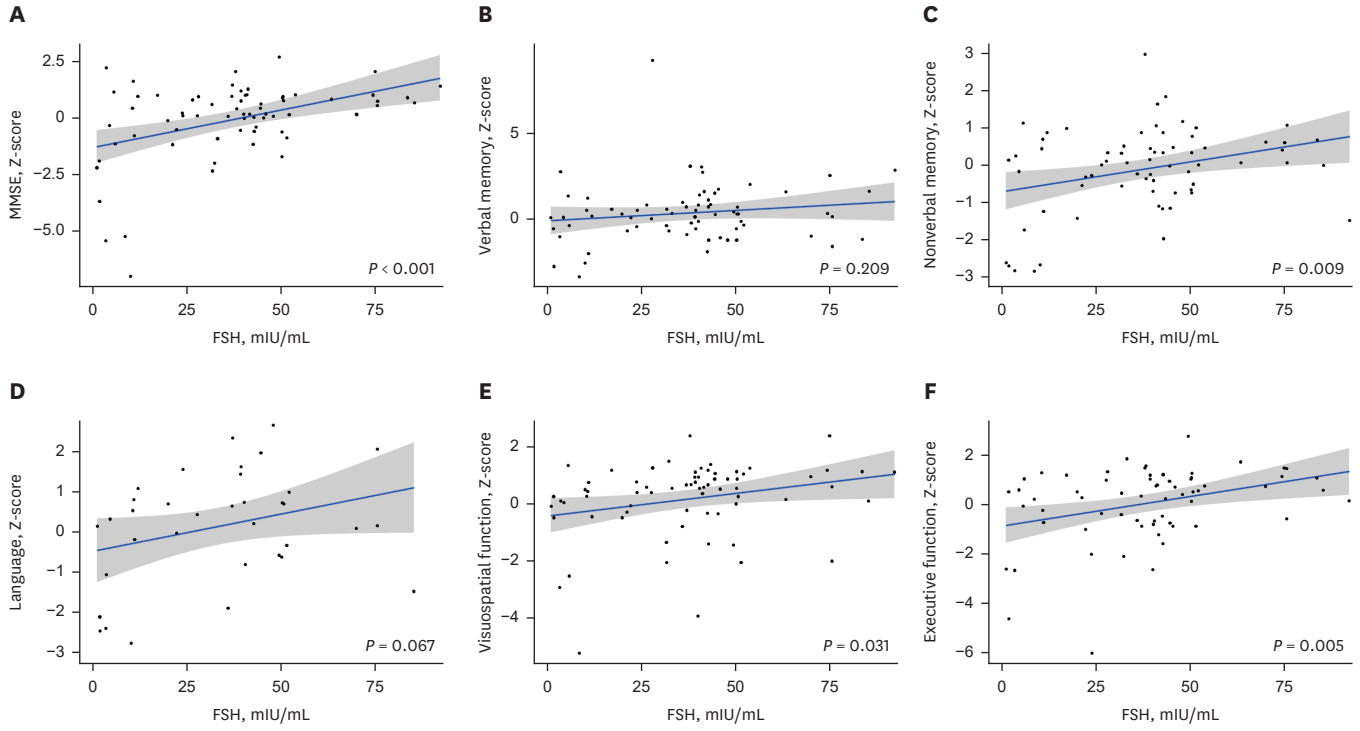

Fig. 2. Scatter plots for the distribution of Z-scores for cognitive performance tests by serum FSH concentration in women with normal cognition. (**A**) MMSE, Z-score; (**B**) Verbal memory, Z-score; (**C**) Nonverbal memory, Z-score; (**D**) Language, Z-score; (**E**) Visuospatial function, Z-score; (**F**) Executive function, Z-score.
FSH = follicle-stimulating hormone, MMSE = Mini-Mental State Examination.

Table 2. Association of serum follicle-stimulating hormone concentration with cognitive performance

Variables	NC (n = 70)		MCI (n = 52)		AD dementia (n = 37)	
	β (95% CI)	*P*	*β* (95% CI)	*P*	*β* (95% CI)	*P*
Model 1						
MMSE, Z-score	**0.03 (0.01, 0.05)**	**< 0.001**	0.01 (−0.01, 0.03)	0.161	−0.01 (−0.05, 0.03)	0.540
Verbal memory, Z-score	0.01 (−0.01, 0.03)	0.203	0.01 (−0.01, 0.03)	0.178	0.00 (−0.02, 0.02)	0.820
Nonverbal memory, Z-score	**0.01 (0.00, 0.03)**	**0.019**	0.01 (0.00, 0.02)	0.139	0.00 (−0.02, 0.01)	0.680
Language, Z-score	0.01 (−0.01, 0.03)	0.378	−0.01 (−0.04, 0.02)	0.472	−0.02 (−0.07, 0.04)	0.521
Visuospatial function, Z-score	**0.02 (0.00, 0.03)**	**0.043**	**−0.01 (−0.02, 0.00)**	**0.041**	0.00 (−0.03, 0.04)	0.861
Executive function, Z-score	**0.02 (0.01, 0.04)**	**0.006**	0.00 (−0.01, 0.02)	0.596	0.01 (−0.02, 0.04)	0.527
Model 2						
MMSE, Z-score	**0.03 (0.00, 0.06)**	**0.038**	0.00 (−0.04, 0.04)	0.900	0.03 (−0.03, 0.10)	0.275
Verbal memory, Z-score	0.01 (−0.03, 0.04)	0.756	0.00 (−0.04, 0.04)	0.943	0.00 (−0.03, 0.03)	0.902
Nonverbal memory, Z-score	**0.03 (0.01, 0.05)**[a]	**0.003**	0.00 (−0.03, 0.03)	0.960	**0.03 (0.01, 0.05)**[a]	**0.011**
Language, Z-score	−0.01 (−0.05, 0.03)	0.476	−0.02 (−0.07, 0.04)	0.511	0.00 (−0.09, 0.08)	0.929
Visuospatial function, Z-score	0.02 (−0.01, 0.05)	0.243	0.00 (−0.03, 0.03)	0.973	0.04 (−0.03, 0.10)	0.237
Executive function, Z-score	**0.04 (0.00, 0.07)**	**0.035**	−0.02 (−0.08, 0.05)	0.639	0.00 (−0.05, 0.05)	0.918

Each type of cognitive performance was analyzed by a separate model. In each multivariate linear regression model, the serum follicle-stimulating hormone concentration was entered as an independent variable, and the scores for cognitive performances were entered as dependent variables. The *β* estimates and 95% CIs were shown as bold when their *P* values were less than 0.05.
Model 1: adjusted for age and *APOE* genotype; Model 2: adjusted for all covariates of Model 1, serum estradiol concentrations and its interaction with follicle-stimulating hormone concentrations.
CI = confidence interval, NC = normal cognition, MCI = mild cognitive impairment, AD = Alzheimer's disease, MMSE = Mini-Mental State Examination.
[a]Statistically significant association between FSH * E2 interaction and cognitive performance ($P < 0.05$).

In separate multivariate linear regression analyses examining the association between serum FSH levels and the serum FSH/E2 ratio with cognitive function in postmenopausal women, the results remained unchanged (**Supplementary Tables 1** and **2**).

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Table 3. Association of serum follicle-stimulating hormone/estradiol ratio with cognitive performance

Variables	NC (n = 70)		MCI (n = 52)		AD dementia (n = 37)	
	β (95% CI)	*P*	*β* (95% CI)	*P*	*β* (95% CI)	*P*
MMSE, Z-score	**0.55 (0.18, 0.91)**	**0.004**	0.15 (−0.21, 0.50)	0.403	0.11 (−0.57, 0.79)	0.739
Verbal memory, Z-score	0.30 (−0.12, 0.72)	0.155	0.24 (−0.22, 0.69)	0.293	−0.10 (−0.43, 0.23)	0.534
Nonverbal memory, Z-score	**0.32 (0.09, 0.56)**	**0.008**	0.16 (−0.16, 0.48)	0.321	0.08 (−0.18, 0.33)	0.535
Language, Z-score	0.06 (−0.38, 0.49)	0.789	−0.35 (−0.85, 0.15)	0.161	−0.07 (−0.89, 0.75)	0.864
Visuospatial function, Z-score	0.14 (−0.19, 0.47)	0.399	−0.29 (−0.63, 0.06)	0.100	0.08 (−0.70, 0.86)	0.834
Executive function, Z-score	**0.47 (0.11, 0.83)**	**0.012**	0.15 (−0.21, 0.50)	0.403	0.33 (−0.25, 0.90)	0.247

Each type of cognitive performance was analyzed using a separate model. In each multivariate linear regression model adjusted for age and *APOE* genotype, the follicle-stimulating hormone/estradiol ratio was entered as an independent variable, and the scores for cognitive performances were entered as dependent variables. The *β* estimates and 95% CIs were shown as bold when their *P* values were less than 0.05.
CI = confidence interval, NC = normal cognition, MCI = mild cognitive impairment, AD = Alzheimer's disease, MMSE = Mini-Mental State Examination.

DISCUSSION

This cross-sectional study demonstrated that serum FSH level was positively correlated with cognitive function in middle-aged and older women with NC, but this was not the case in those with MCI and AD dementia. The association of serum FSH level with cognitive function in cognitively normal women was independent from serum E2 level, and this association was found to be particularly prominent in nonverbal memory and executive function.

The findings of this study suggest that the link between FSH and cognition should be considered significant only when cognitive decline is absent or mild, remaining under the diagnostic threshold for dementia. The positive correlation between serum FSH level and cognitive function in this study was consistent with the results of some previous works[14,15] but not with those of others.[4,17-20] Since previous studies did not categorize participants based on cognitive diagnosis, such as NC, MCI, and AD dementia, the correlation between FSH and cognition may be biased due to varying proportions of participants with advanced disease progression, which could attenuate the effect of FSH. Based on valid cognitive diagnoses from clinical interviews, this study first demonstrated that the association between serum FSH levels and cognitive function may vary depending on cognitive status or disease progression.

Our findings suggest that systemic FSH may have a potential neuroprotective effect in cognitively normal women. FSH can activate monocytes through the release of pro-inflammatory cytokines such as interleukin-6,[28] interferon-γ,[29] and tumor necrosis factor-α.[30] Neuroinflammation induced by the activation and infiltration of peripheral monocytes, followed by microglial activation, is known to promote the clearance of cerebral amyloid-β proteins.[31,32] This process may contribute to the neuroprotective effect observed in women with NC, as suggested by this study. Our findings are consistent with previous research indicating that the positive correlation between microglial activation and cognitive performance is prominent only in prodromal or preclinical AD, but not in AD dementia.[33] Further longitudinal studies are needed to elucidate the dynamic interplay between serum FSH levels and the trajectories of cognitive decline and AD-related pathophysiology including neuroinflammation.

Our interpretation is at odds with the findings of a previous animal study in which FSH was found to induce cognitive impairment, thus facilitating the accumulation of amyloid-β and tau proteins in the hippocampus and cortical neurons of mice.[13] However, this earlier study involved three months of daily intravenous FSH administration to ovariectomized mice. This resulted in a rapid increase in systemic FSH levels, which mimicked the peri-menopausal period more closely than the postmenopausal period, during which FSH levels typically

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remain stable. This aligns with findings from the prospective cohort studies indicating that cognitive decline related to menopausal transition primarily occurs during the peri-menopausal period and then tends to improve afterward.[5,18] It can therefore be postulated that the detrimental impact of FSH on cognition is contingent upon the episodic surge of systemic FSH, rather than being contingent on the maintenance of consistently elevated levels of systemic FSH.

This study found a notable correlation between serum FSH levels and cognitive performance among cognitively normal women, specifically in two key domains: nonverbal memory and executive function. These domains have previously been respectively associated with the right hemisphere, particularly the right hippocampus, and the frontal-limbic circuit.[34-36] Thus, we cautiously speculate that FSH might primarily influence these regions. While several studies have explored FSH and its receptor expression in the hippocampus and cerebellar cortex of rat brains,[37,38] none have investigated FSH expression in the human brain Consequently, it is imperative to conduct further neuroimaging studies to elucidate the neuroanatomical actions and cognitive effects of FSH in the aging human brain.

This study has several limitations that must be noted. First, the database we used did not contain information about the menopausal stages of the participants. To address this, we conducted a sensitivity analysis in postmenopausal women only, based on the mean age of menopause in Korean women,[27] and found that the results remained unchanged. However, due to the limited number of participants of premenopausal age, this study could not identify the FSH-cognition link in premenopausal women. Second, the current or past history of hormone replacement therapy was not explored. Despite adjusting for serum E2 levels in analyses, this study was unable to fully overcome the effect of hormone replacement. Third, the cross-sectional design of this study precludes the identification of a causal relationship between FSH and cognitive performance. Fourth, this study did not examine information about luteinizing hormone and its interplay with FSH, E2, and cognition. Finally, the generalizability of the findings is limited by the relatively small number of clinic-based samples used.

Despite these limitations, this study is the first to indicate that an association between circulating FSH levels and cognitive performance could be influenced by disease progression, with this association being independent from circulating E2 as well as particularly pronounced in nonverbal memory and executive function. Future investigations are therefore warranted to elucidate the role that gonadotropins play in cognitive decline and their interaction with AD-related pathophysiology.

SUPPLEMENTARY MATERIALS

Supplementary Table 1

Association of serum FSH concentration with cognitive performance in postmenopausal women

Supplementary Table 2

Association of serum FSH/E2 ratio with cognitive performance in postmenopausal women

Supplementary Fig. 1

Scatter plots for the distribution of Z-scores for cognitive performance tests by serum FSH concentration in women with mild cognitive impairment. (**A**) MMSE, Z-score; (**B**) Verbal

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memory, Z-score; (**C**) Nonverbal memory, Z-score; (**D**) Language, Z-score; (**E**) Visuospatial function, Z-score; (**F**) Executive function, Z-score.

Supplementary Fig. 2

Scatter plots for the distribution of Z-scores for cognitive performance tests by serum FSH concentration in women with Alzheimer's disease. (**A**) MMSE, Z-score; (**B**) Verbal memory, Z-score; (**C**) Nonverbal memory, Z-score; (**D**) Language, Z-score; (**E**) Visuospatial function, Z-score; (**F**) Executive function, Z-score.

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