Turk J Pharm Sci
DOI: 10.4274/tjps.galenos.2026.68256

ORIGINAL ARTICLE

Plasma Concentrations of Amyloid-β Peptides, BACE-1, and Tau Proteins in Alzheimer's Disease

Nejla Yıldırım[1], Naile Merve Güven Aksu[1,2], Başak Özlem Perk[1], Benay Can Eke[2]*

[1]Ankara University, Graduate School of Health Sciences, Ankara, Türkiye
[2]Ankara University Faculty of Pharmacy, Department of Pharmaceutical Toxicology, Ankara, Türkiye

ABSTRACT

Objectives: The aim of this study was to compare, using ELISA, plasma levels of amyloid beta (Aβ)40, Aβ42, beta-site amyloid precursor protein cleaving enzyme 1 (BACE-1), total tau (t-tau), and phosphorylated tau (p-tau), as well as the Aβ42/Aβ40 ratio, between patients with Alzheimer's disease (AD) and healthy controls, and to evaluate their diagnostic performance in relation to demographic and lifestyle factors.

Materials and Methods: This study is a single-center, cross-sectional, case-control study. Twenty-four individuals diagnosed with AD and 37 healthy volunteers included in the study. Alongside the analysis of plasma samples obtained from the participants, demographic data were analyzed to assess the potential influence of lifestyle and environmental factors on disease development.

Results: Analysis of the case data showed that increasing age was a risk factor for AD, higher education level was associated with an increased risk of AD, and tea consumption was inversely associated with AD. While age is a well-known risk factor, both the increased risk of AD associated with higher education and the relatively protective effect of tea consumption against AD are supported by the literature. Evaluation of the levels of Aβ40, Aβ42, BACE-1, t-tau, and p-tau and of the Aβ42/Aβ40 ratio revealed no significant differences between the patient and control groups. Additionally, Aβ40, Aβ42, BACE-1 showed correlations in both the control and Alzheimer's groups, whereas t-tau did not.

Conclusion: None of the investigated plasma biomarkers (Aβ40, Aβ42, BACE-1, t-tau, p-tau, and the Aβ42/Aβ40 ratio) discriminated Alzheimer's patients from healthy controls, with all receiver operating characteristic area under the curve values below 0.62. These findings indicate that in this cohort, plasma levels of these individual markers did not provide diagnostic value; larger longitudinal studies including cerebrospinal fluid comparisons and multi-marker panels are needed.

Keywords: Alzheimer's disease, amyloid beta, BACE-1, tau, ELISA

INTRODUCTION

Alzheimer's disease (AD), which emerges with advancing age, is a progressive neurodegenerative disorder characterized by memory loss and cognitive decline.[1] The disease was first described by Dr. Alois Alzheimer in 1906.[2] Changes in brain biomarker levels can be detected years before clinical symptoms appear.[3]

The pathophysiology of AD involves complex mechanisms at the genetic, molecular, and cellular levels, and interacts with both the central and peripheral immune systems.[4] According to the World Health Organization, AD accounts for approximately 60–70% of dementia cases and affects around 55 million people worldwide.[5] The disease ranks among the leading causes of death in elderly populations, particularly in developed countries.[1]

The AT(N) classification system, proposed by the National Institute on Aging and the Alzheimer's Association in 2018, defines AD based on biomarkers, categorizing disease stages according to amyloid (A), tau (T), and neurodegeneration (N)

*Correspondence: eke@pharmacy.ankara.edu.tr, ORCID-ID: orcid.org/0000-0001-9817-9034

Received: 29.09.2025, Accepted: 16.07.2026 Epub: 05.08.2026

Cite this article as: Yıldırım N, Güven Aksu NM, Perk BÖ, Can Eke B. Plasma concentrations of amyloid-β peptides, BACE-1, and tau proteins in Alzheimer's disease. Turk J Pharm Sci. [Epub Ahead of Print]

markers. Recently, plasma-based biomarkers have shown promising diagnostic potential.[6]

AD can be divided into two groups according to age of onset: early-onset (<65 years) and late-onset (≥65 years). Early-onset AD is associated with genetic mutations in the Presenilin 1, Presenilin 2, and amyloid precursor protein (*APP*) genes, whereas late-onset AD is linked to the APOE ε4 allele. Clinical staging categorizes patients into three groups: cognitively normal, mild cognitive impairment, and dementia.[5]

Various hypotheses have been proposed to explain the neuropathological basis of AD. The most widely recognized hypothesis is the amyloid cascade hypothesis, in which cleavage of the APP by beta-site amyloid precursor protein cleaving enzyme 1 (BACE-1) follows the amyloidogenic pathway to produce Aβ peptides, mainly Aβ40 and Aβ42. The Aβ42 isoform, considered the most toxic, leads to neuronal loss through accumulation of plaques, oligomers, and fibrils.[7]

The second important mechanism underlying AD's formation is tau pathology, which involves hyperphosphorylation of the microtubule-stabilizing tau protein and results in the formation of neurofibrillary tangles that contribute to neuronal degeneration. There is a synergistic interaction between tau and Aβ pathologies, with Aβ promoting mechanisms that trigger tau's conversion into its toxic form.[8]

Glutamate-mediated excitotoxicity, driven by excessive activation of NMDA receptors, causes intracellular calcium accumulation, leading to neuronal death and plays a role in AD pathogenesis.[9]

The initial breakthrough in understanding AD came in the 1970s with the demonstration of deficiencies in choline acetyltransferase activity in the brains of Alzheimer's patients, which were attributed to cholinergic deficits. Recognition of acetylcholine's role in memory and learning led to the cholinergic hypothesis of AD, which inspired therapeutic strategies aimed at enhancing cholinergic function. Cholinergic depletion is considered a late feature of the neurodegenerative cascade.[10]

In AD development, non-modifiable risk factors include age, genetic predisposition, sex, and Down syndrome, while modifiable risk factors encompass educational level, marital status, cognitive stimulation, history of head trauma, lifestyle factors (alcohol and tobacco use), metabolic disorders (type II diabetes, dyslipidemia, obesity, cerebrovascular diseases, hypertension), immunological and inflammatory factors, pathogenic infections, metal exposure, and pesticides. Additionally, factors that negatively impact quality of life, such as stress, depression, and insufficient sleep, have been shown in case-control studies to significantly influence AD risk.[11,12]

In this study, quantitative measurements of disease-associated proteins in plasma samples from patients with AD and healthy controls were performed using ELISA. Correlation analyses among these proteins were conducted to evaluate the diagnostic potential of plasma-based biomarkers.

MATERIALS AND METHODS

This was a single-center, cross-sectional case-control study comparing plasma biomarker concentrations between clinically diagnosed AD patients and cognitively healthy controls, who were recruited over the same study period.

This study was approved by the Ethics Committee on Ankara University (decision no: İ3-148-20, date: 12.10.2020).

A total of 24 patients aged 65 and older diagnosed with AD by specialist clinicians in fully equipped hospitals were included in the study; the group comprised 5 males (21%) and 19 females (79%). Diagnoses were established based on the criteria of the National Institute of Neurological and Communicative Disorders and Stroke and the Alzheimer's Disease and Related Disorders Association and on clinical interviews using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, fourth edition (DSM-IV) axis I disorders, conducted in accordance with the DSM-IV of the American Psychiatric Association. The diagnosis of AD was definitively confirmed through review of patient records, including official diagnostic reports, and, when necessary, by contacting the institutions that issued the reports or the diagnosing specialists. Only patients with confirmed diagnoses were included in the study.

Legal guardians of the patients were informed about the study, and written consent was obtained. The patient group consisted of residents of a nursing home who had been diagnosed with AD by specialized physicians at fully equipped hospitals.

The control group included 37 individuals aged 65 and older, comprising 18 males (49%) and 19 females (51%), all of whom had no diagnosis of AD or other forms of dementia or cognitive impairment. Informed consent was obtained from all control participants, who were recruited from hospitals and health centers.

Exclusion criteria for both groups included individuals under 65 years of age; those for whom blood sampling was contraindicated due to coagulation disorders or anemia; individuals diagnosed with other types of dementia; and those with significant comorbidities (e.g., cancer) that could potentially affect the results.

Blood sample collection and plasma preparation

Venous blood samples (10 mL) were collected from all volunteers into tubes containing ethylenediaminetetraacetic acid.

Samples from both patient and control groups were centrifuged at 2500 rpm for 10 minutes to separate plasma.

Plasma samples were stored at -80 °C. Before analysis, samples were brought to room temperature, and analyses were performed according to the kit instructions. The plasma samples were thawed at room temperature on the day of analysis. To avoid the impact of multiple freeze–thaw cycles, only aliquots that had not been previously thawed were used in this study.

Concentrations of Aβ40, Aβ42, BACE-1, total tau (t-tau), and phosphorylated tau (p-tau) in plasma were measured and evaluated using ELISA.

The following ELISA kits and equipment were used in this study:

Nepenthe human β-site APP cleaving enzyme 1 ELISA kit (catalog number: NE010080201, production site: Gebze-Kocaeli/Türkiye)

Nepenthe human t-tau proteins ELISA kit (catalog number: NE010133301, production site: Gebze-Kocaeli/Türkiye)

Assay genie human phospho tau (P181) ELISA Kit (catalog number: HUFI03189

Nepenthe human amyloid beta peptide 1-42 ELISA kit (catalog number: NE010126401, production site: Gebze-Kocaeli/Türkiye)

Nepenthe human amyloid beta peptide 1-42 ELISA kit (catalog number: NE010123001, production site: Gebze-Kocaeli/Türkiye), and a microplate reader equipped with a 450 ± 10 nm wavelength filter. Analyses were performed in duplicate. Laboratory personnel were blinded.

Preparation of kits

Each kit was prepared and used according to the manufacturer's instructions.

Demographic data

Relationships between AD and various demographic factors, including patient age, education level, employment history, comorbidities, medication use, history of head trauma, smoking and alcohol consumption, frequency of tea and coffee intake, dietary habits, frequency of exercise, disease stage, family history of Alzheimer's, and place of residence were evaluated.

Statistical analysis

The distribution of continuous variables and the homogeneity of variances were assessed using the Shapiro–Wilk and Levene's tests, respectively. As the assumptions of parametric tests were not met, continuous variables were summarized using the median (25^{th}–75^{th} percentiles) and compared between groups using the Mann–Whitney U test. Correlations among continuous variables were assessed using Spearman's rank correlation coefficient. Categorical variables were presented as counts and percentages and compared using the continuity-corrected χ^2 test, Fisher's exact test, or the Fisher–Freeman–Halton test, as appropriate for the expected cell frequencies. Where multiple pairwise comparisons were performed, a Bonferroni correction was applied.

Candidate predictors with univariate $p < 0.10$ were entered into a multivariable logistic regression model. Exercise was excluded due to quasi-complete separation, and tea and coffee consumption were entered in separate models due to their conceptual overlap. Variance inflation factors were calculated to assess multicollinearity, and all values remained below 2.5. Considering the modest events-per-variable ratio, a sensitivity analysis was performed using Firth penalized (bias-reduced) logistic regression. The direction, magnitude, and statistical significance of all predictors were preserved, supporting the stability of the model.

To address the age difference between groups, biomarker comparisons were performed using a rank-based ANCOVA. In this approach, biomarker values and age were rank-transformed, and the biomarker rank was regressed on group with age rank as a covariate. This is the non-parametric analogue of an age-adjusted Mann–Whitney U test and is appropriate for the non-normal distributions observed in these data.

All analyses were performed using IBM SPSS Statistics version 25 (IBM Corporation, Armonk, NY, USA). Two-sided *p*-values were considered statistically significant unless otherwise specified.

RESULTS

This study demonstrated that the Alzheimer's and control groups were similar in demographic, clinical, and comorbid conditions; however, some demographic factors, such as age, gender, and education level, may be associated with AD, as shown in Table 1.

Association of lifestyle habits with AD

Table 2 shows the lifestyle habits of individuals diagnosed with AD (n = 24) compared with those of healthy controls (n = 37).

A statistically significant difference between groups was found with respect to smoking history ($p = 0.010$). While 78.3% of the Alzheimer's group reported never smoking, the rate in the control group was 40.5%. Current smokers were found only in the control group.

There was no history of alcohol consumption in the Alzheimer's group, whereas 29.7% of controls reported such a history; this difference was not statistically significant ($p = 0.149$).

A significant difference in coffee consumption between groups was observed ($p < 0.001$). In the Alzheimer's group, 73.9% reported consuming only one cup of coffee daily, whereas in the control group consumption was more frequent and varied: 27% consumed one cup and 21.6% consumed two cups per day.

Tea consumption also differed significantly ($p < 0.001$) between the control and Alzheimer's groups. While 91.3% of the Alzheimer's group consumed only one cup of tea per day, 64.9% of the control group consumed three or more cups per day.

No significant difference in dietary habits was detected between the groups ($p = 0.389$).

A significant difference in regular exercise habits was found ($p < 0.001$). All individuals in the Alzheimer's group reported engaging in regular exercise during the past year. In contrast, 40.5% of the control group reported no exercise, while only 32.4% reported exercising regularly for over one year.

Clinical characteristics specific to the Alzheimer's group

The disease duration among the 24 individuals diagnosed with AD varied (Table 3), with a median of 4 years (range: 0–10 years). When examining the disease stages, 29.2% were in the early stage, 37.5% were in the moderate stage, and 33.3% were in the advanced stage.

A family history of Alzheimer's was present in 12.5% cases. Among these, 8.3% reported a similar disease history in their spouse, while 4.2% reported it in their sibling. The majority of participants (79.2%) had no family history of Alzheimer's, and 8.3% did not provide information on this matter.

Table 1. Demographic and clinical characteristics of cases by groups.

Characteristic	Control (n = 37)	Alzheimer (n = 24)	*p*-value
Age (years)*	70.0 (66.0–75.0)	83.0 (73.5–88.0)	**<0.001**[a]
Gender			0.055[b]
- Female	19 (51.4%)	19 (79.2%)	
- Male	18 (48.6%)	5 (20.8%)	
Education level			0.074[c]
- Illiterate	7 (20.0%)	1 (4.2%)	
- Primary school	14 (40.0%)	7 (29.2%)	
- Middle school	3 (8.6%)	2 (8.3%)	
- High school	2 (5.7%)	7 (29.2%)	
- Associate degree	0 (0.0%)	1 (4.2%)	
- Bachelor's degree	9 (25.7%)	6 (25.0%)	
Work history			0.938[b]
- No	13 (37.1%)	10 (41.7%)	
- Yes	22 (62.9%)	14 (58.3%)	
Comorbidities			
- Hypertension	14 (37.8%)	14 (58.3%)	0.191[b]
- Heart diseases	20 (54.1%)	8 (33.3%)	0.186[b]
- Diabetes mellitus	10 (27.0%)	6 (25.0%)	>0.999[b]
- Hyperlipidemia	3 (8.1%)	3 (12.5%)	0.672[d]
- COPD	5 (13.5%)	1 (4.2%)	0.388[d]
- Asthma	4 (10.8%)	0 (0.0%)	0.147[d]
Medication use			0.635[b]
- None	3 (8.8%)	1 (4.2%)	
- Yes	31 (91.2%)	23 (95.8%)	
History of head trauma	5 (13.5%)	0 (0.0%)	0.146[d]

*Descriptive statistics are expressed as median (25th percentile–75th percentile)
[a]Mann–Whitney U test; [b]Continuity corrected χ^2 test; [c]Fisher–Freeman–Halton test; [d]Fisher's exact test; COPD, chronic obstructive pulmonary disease.

Table 2. Frequency distribution of smoking and alcohol history, tea and coffee consumption, dietary, and exercise habits by groups.

Variable	Control (n=37)	Alzheimer (n=24)	*p*-value
Smoking history			**0.010**[a]
- Never	15 (40.5%)[A]	18 (78.3%)[A]	
- Former smoker	18 (48.6%)	5 (21.7%)	
- Current smoker	4 (10.8%)	0 (0.0%)	
Alcohol history			0.149[b]
- None	32 (88.9%)	23 (100%)	
- Yes	4 (11.1%)	0 (0.0%)	
Coffee consumption			**<0.001**[a]
- None	8 (21.6%)	5 (21.7%)	
- Occasionally	14 (37.8%)[B]	1 (4.3%)[B]	
- 1 cup/day	10 (27.0%)[C]	17 (73.9%)[C]	
- 2 cups/day	5 (13.5%)	0 (0.0%)	
Tea drinking habit			**<0.001**[a]
- None	1 (2.7%)	0 (0.0%)	
- 1 cup/day	3 (8.1%)[C]	21 (91.3%)[C]	
- 2 cups/day	9 (24.3%)	2 (8.7%)	
- ≥3 cups/day	24 (64.9%[C]	0 (0.0%)[C]	
Dietary habit			0.389[a]
- Vegetable-based	22 (61.1%)	12 (52.2%)	
- Meat-based	11 (30.6%)	6 (26.1%)	
- Balanced	3 (8.3%)	5 (21.7%)	
Regular exercise			**<0.001**[a]
- No	15 (40.5%)[A]	0 (0.0%)[A]	
- <1 year	8 (21.6%)[C]	12 (100%)[C]	
- 1 year	2 (5.4%)	0 (0.0%)	
- >1 year	12 (32.4%)[D]	0 (0.0%)[D]	

[a]Fisher–Freeman–Halton test; [b]Fisher's exact test.
[A]Significant difference between groups (p = 0.010); [B]Significant difference (p = 0.009); [C]Significant difference (p < 0.001); [D]Significant difference (p = 0.024).

Regarding the place of residence prior to diagnosis, most individuals with Alzheimer's (79.2%) lived in urban centers, 12.5% resided in other settlements, and 8.3% did not specify their residence.

Biomarker levels

In Table 4, levels of Aβ40, Aβ42, BACE-1, t-tau, and p-tau were compared between individuals with AD and the control group; no statistically significant differences were found (p > 0.05).

Aβ40 levels were measured at medians of 1492.00 ng/L [interquartile range (IQR): 965.75–1749.50] in the control group and 1224.50 ng/L (IQR: 884.63–1818.25) in the Alzheimer's group; the difference was not significant (p = 0.535).

Aβ42 levels were 84.70 ng/L (IQR: 72.20–100.77) in the control group and 80.24 ng/L (IQR: 69.75–105.89) in the Alzheimer's group (p = 0.859).

BACE-1 levels were slightly lower in the Alzheimer's group (median 4.41 ng/mL, IQR: 3.95–6.10) than in the control group (median 5.19 ng/mL, IQR: 4.30–6.24); however this difference was not statistically significant (p = 0.226).

Table 3. Other clinical findings of cases in the Alzheimer's group.

Variable	n = 24
Disease duration (years)*	4 (0–10)
Disease stage	
- Early	7 (29.2%)
- Moderate	9 (37.5%)
- Advanced	8 (33.3%)
Family history of Alzheimer's	
- No	19 (79.2%)
- Yes	3 (12.5%)
- Not specified	2 (8.3%)
If yes, relationship	
- Spouse	2 (8.3%)
- Sibling	1 (4.2%)
Place of residence before diagnosis	
- Urban	19 (79.2%)
- Other	3 (12.5%)
- Not specified	2 (8.3%)

*Descriptive statistics are presented as median (minimum-maximum) values.

T-tau levels were measured at 197.38 ng/L (IQR: 177.38–324.39) in the Alzheimer's group and 261.44 ng/L (IQR: 195.32–323.51) in the control group, with no significant difference (p = 0.138).

P-tau levels were 29.49 pg/mL (IQR: 15.33–59.12) in the Alzheimer's group and 25.38 pg/mL (IQR: 14.62–52.18) in the control group (p = 0.585).

The Aβ42/Aβ40 ratio was calculated for each participant and compared between groups. The median (IQR) ratio was 0.064 (0.051–0.084) in the control group and 0.070 (0.058–0.088) in the Alzheimer's group; this difference was not statistically significant (Mann–Whitney U, p = 0.159).

Receiver operating characteristic (ROC) analysis results

The discriminatory ability of biomarkers to distinguish Alzheimer's patients from the control group (Table 5) was evaluated using ROC analysis. The area under the curve (AUC) values and 95% confidence intervals (CIs) obtained from the ROC analysis are presented below:

The AUC value for Aβ40 (0.547; 95% CI: 0.398–0.697) was not significant for diagnostic discrimination (p = 0.535).

The Aβ42 AUC was 0.514 (95% CI: 0.363–0.664), indicating weak, not statistically significant discriminatory power (p = 0.859).

The AUC for BACE-1 level was 0.592 (95% CI: 0.440–0.745), which did not reach statistical significance (p = 0.226).

T-tau showed an AUC of 0.613 (95% CI: 0.458–0.768), demonstrating limited diagnostic discrimination (p = 0.138).

The AUC value for p-tau was 0.542 (95% CI: 0.392–0.691), indicating poor diagnostic discrimination (p = 0.585).

ROC analysis yielded an AUC of 0.608 (95% CI 0.469–0.744; p = 0.159); the 95% CI included the chance line. The direction of the numerical difference was opposite to that commonly reported in the literature, in which a decreased plasma Aβ42/Aβ40 ratio is expected in AD. This discordance is addressed in the discussion.

None of the biomarkers showed strong discrimination for the diagnosis of AD; their AUC values were not significantly high.

Multivariable logistic regression analysis results

In the multivariable logistic regression analysis, as shown in Table 6, factors potentially effective in distinguishing between control and Alzheimer's groups were evaluated simultaneously. Age, education level, and tea consumption habits were found to be statistically significant.

Age showed a significant positive association with Alzheimer's diagnosis (OR=1,256; 95% CI: 1,027–1,536; p=0,026). Each additional year of age increased the odds of an Alzheimer's diagnosis by approximately 25%.

Education level was significantly associated with Alzheimer's [odds ratio (OR) = 2.101; 95% CI: 1.050–4.202; p = 0.036]. Higher educational attainment was associated with an increased risk of an Alzheimer's diagnosis.

Tea- drinking habit was inversely and significantly associated with AD (OR = 0.094; 95% CI: 0.020–0.452; p = 0.003). This finding indicates that individuals who consume tea have a lower likelihood of being diagnosed with AD.

Table 4. Protein levels in control and Alzheimer's groups.

Biomarker	Control (n = 37) (median, IQR)	Alzheimer (n = 24) (median, IQR)	p-value[a]
Aβ40 (ng/L)	1492.00 (965.75–1749.50)	1224.50 (884.63–1818.25)	0.535
Aβ42 (ng/L)	84.70 (72.20–100.77)	80.24 (69.75–105.89)	0.859
BACE-1 (ng/mL)	5.19 (4.30–6.24)	4.41 (3.95–6.10)	0.226
t-tau (ng/L)	261.44 (195.32–323.51)	197.38 (177.38–324.39)	0.138
p-tau (pg/mL)	25.38 (14.62–52.18)	29.49 (15.33–59.12)	0.585
Aβ42/Aβ40 ratio	0.064 (0.051–0.084)	0.070 (0.058–0.088)	0.159

[a]Mann-Whitney U test; IQR, interquartile range; BACE-1, beta-site amyloid precursor protein cleaving enzyme 1; t-tau, total tau; p-tau, phosphorylated tau. Descriptive statistics are presented as median (25^{th}-75^{th} percentile).

However, female sex (OR = 2.021; p = 0.704) and a history of smoking (OR = 0.404; p = 0.528) were not significantly associated with Alzheimer's diagnosis.

Correlation analysis among proteins

Spearman correlation analysis was performed on all participants in the study group (n = 61) to evaluate the relationships among Aβ40, Aβ42, BACE-1, t-tau, and p-tau protein levels (Table 7).

Aβ40 levels showed statistically significant positive correlations with Aβ42 (r = 0.640; $p < 0.001$), BACE-1 (r = 0.543; $p < 0.001$), and t-tau (r = 0.695; $p < 0.001$).

No significant correlation was found between Aβ40 and p-tau levels (r = 0.084; p = 0,518).

Aβ42 exhibited strong positive correlations with BACE-1 (r = 0.696; $p < 0.001$) and t-tau (r = 0.775; $p < 0.001$), while its correlation with p-tau was weak and statistically non-significant (r = 0.120; p = 0.355).

BACE-1 showed a strong and statistically significant correlation with t-tau (r = 0.798; $p < 0.001$), but no significant correlation with p-tau (r = 0.080; p = 0.542).

The correlation coefficient between t-tau and p-tau levels was near zero (r = 0.001; p = 0.999), indicating no statistically significant relationship between these variables.

Table 5. ROC analysis results of protein measurements for differentiating control and Alzheimer's groups.

Biomarker	AUC	95% CI	*p*-value
Aβ40 (ng/L)	0.547	0.398–0.697	0.535
Aβ42 (ng/L)	0.514	0.363–0.664	0.859
BACE-1 (ng/mL)	0.592	0.440–0.745	0.226
t-tau (ng/L)	0.613	0.458–0.768	0.138
p-tau (pg/mL)	0.542	0.392–0.691	0.585
Aβ42/Aβ40	0.608	0.469–0.744	0.159

ROC, receiver operating characteristic; AUC, area under the curve; CI, confidence interval; BACE-1, beta-site amyloid precursor protein cleaving enzyme 1; t-tau, total tau; p-tau, phosphorylated tau.

Table 6. Multivariable logistic regression analysis results: investigating the combined effects of potential predictors in differentiating control and Alzheimer's groups.

Variable	OR	95% CI	Wald	*p*-value
Age	1.256	1.027–1.536	4.929	**0.026**
Female sex factor	2.021	0.053–76.636	0.144	0.704
Education level	2.101	1.050–4.202	4.404	**0.036**
Smoking history	0.404	0.024–6.756	0.398	0.528
Tea drinking habit	0.094	0.020–0.452	8.721	**0.003**

OR, odds ratio; CI, confidence interval.

Table 7. Correlation coefficients and significance levels among protein measurements in all subjects.

	Aβ42	BACE-1	t-tau	p-tau
Aβ40	0.640	0.543	0.695	0.084
p-value[a]	<0.001	<0.001	<0.001	0.518
Aβ42		0.696	0.775	0.120
p-value[a]		<0.001	<0.001	0.355
BACE-1			0.798	0.080
p-value[a]			<0.001	0.542
t-tau				0.001
p-value[a]				0.999

[a]Spearman's rank correlation test was used; BACE-1, beta-site amyloid precursor protein cleaving enzyme 1; t-tau, total tau; p-tau, phosphorylated tau.

DISCUSSION

The primary aim of this study was to investigate Aβ40, Aβ42, BACE-1, t-tau, and p-tau levels in patients with AD and healthy controls; however, no statistically significant differences were detected between the groups. Although Aβ40 and Aβ42 levels showed the expected decreasing trend in the Alzheimer's group, these differences did not reach statistical significance.[13]

BACE-1 levels were lower in the AD group. BACE-1 is an important enzyme involved in the conversion of APP to Aβ peptides; some studies have reported increased activity of this enzyme in AD.[14]

The lower BACE-1 levels observed in this study may be due to variability related to sample size or biological differences among individuals. Analysis of tau protein showed that t-tau levels were higher in the control group. Generally, t-tau and p-tau levels are expected to increase in AD due to neuronal damage. However, p-tau levels did not differ significantly between groups in this study. This may be explained by disease stage heterogeneity, timing of biomarker measurement, or the evaluation of plasma rather than cerebrospinal fluid (CSF) levels.[15]

In this study, the measured biomarkers did not differ significantly between the Alzheimer's and control groups. These findings indicate the limited diagnostic value of current biomarkers and highlight the need for larger-scale longitudinal studies including CSF/plasma correlation analyses.

The discriminative power of Aβ40, Aβ42, BACE-1, t-tau, and p-tau levels in the diagnosis of AD, as well as the Aβ42/Aβ40 ratio, was evaluated using ROC analysis. The AUC values for all biomarkers were below 0.6 (AUC of Aβ42/Aβ40 ratio was 0.608 and AUC of t-tau is 0.613 these results do not demonstrate a significant discriminatory performance). Generally, tests with AUC values close to 0.5 have only chance-level discriminatory ability. Specifically, the AUC values for Aβ42 and Aβ40 were 0.514 and 0.547, respectively, indicating insufficient diagnostic value to distinguish AD. Although BACE-1 had a relatively higher AUC of 0.592 compared with other biomarkers, it did not reach statistical significance. The highest AUC was observed for t-tau at 0.613; however, the CI was wide, and statistical significance was not achieved. This suggests that t-tau alone

is inadequate for diagnosis and should be evaluated alongside other parameters. P-tau also demonstrated poor discriminatory ability, with an AUC of 0.542.

The plasma Aβ42/Aβ40 ratio did not differ significantly between AD patients and controls, and its direction of effect was opposite to that observed in larger cohorts using ultrasensitive plasma assays. This observation should be interpreted with caution: conventional ELISA has limited sensitivity at the low plasma Aβ42 concentrations present in peripheral blood, and the performance of the ratio in plasma has been shown to depend strongly on the analytical platform used. Our null and directionally reversed finding should not, therefore, be taken as evidence against the utility of the ratio; rather, it supports the need for larger, prospectively designed studies using ultrasensitive platforms (e.g., Simoa, IP-MS) to establish the diagnostic value of this ratio.

Finally, correlations among Aβ40, Aβ42, BACE-1, t-tau, and p-tau protein levels were investigated, revealing positive associations among some biomarkers.

The high correlation coefficients observed between Aβ40-Aβ42, Aβ42-BACE-1, and BACE-1-t-tau suggest that these proteins participate in shared biological processes underlying the pathophysiology of AD. The correlation between Aβ peptides, which are generated by cleavage of APP, and BACE-1, which plays a key role in this process, supports the interconnected nature of these biochemical pathways.[16]

Similarly, the significant correlations detected between Aβ peptide levels and t-tau indicate that amyloid accumulation may be associated with neuronal degeneration. These findings imply that AD could be conceptualized as a spectrum involving both amyloid and tau pathologies.[17]

In contrast, the lack of significant correlations between p-tau levels and other proteins is noteworthy. Notably, the absence of a correlation between t-tau and p-tau suggests that these two markers may reflect distinct pathological processes. The formation of p-tau via hyperphosphorylation may represent a regulatory mechanism independent of t-tau levels. Overall, the correlation analyses reveal substantial interactions among Alzheimer's biomarkers but also indicate that certain markers, such as p-tau, may behave more independently. This underscores the importance of carefully selecting combinations of diagnostic and prognostic biomarkers.[18]

The use of ELISA kits from different manufacturers to assess distinct biomarkers represents a methodological limitation of the present study. Using a particular kit for p-tau measurement, while other brand kits were used for the remaining analytes, may increase the risk of inter-assay variability due to differences in calibration standards, assay sensitivity, and potential cross-reactivity between platforms. This may limit the direct comparability of absolute biomarker concentrations across assays. Therefore, the results should be interpreted with consideration of this methodological heterogeneity.

The central finding of this study is that none of the five plasma biomarkers (Aβ40, Aβ42, BACE-1, t-tau, p-tau) nor the Aβ42/Aβ40 ratio showed a statistically significant difference between AD patients and healthy controls. ROC analyses yielded AUC values between 0.51 and 0.61, and all 95% CIs included the chance line (AUC = 0.50). These results should not be interpreted as marginal or promising; the rank-biserial effect sizes were uniformly small ($r \leq 0.19$), indicating that the underlying group separation on these plasma measures was limited in magnitude, even in the absence of statistical significance.

Large-scale studies conducted worldwide have shown that the plasma Aβ42/Aβ40 ratio correlates with CSF biomarkers and neuroimaging biomarkers in early-stage AD.[19]

Although there is general consensus regarding the association of CSF Aβ levels with AD, studies evaluating peripheral Aβ biomarkers in plasma have shown conflicting results. Some studies have reported no relationship between plasma Aβ levels and AD,[20-22] while others have revealed relationships in opposite directions.[23] However, recent studies involving well-characterized large participant populations have shown that a lower plasma Aβ42/40 ratio is consistently associated with an increased risk of incident AD.[24-26]

Although CSF analysis and positron emission tomography imaging are widely utilized in the diagnosis of AD and are considered highly accurate, these methods have certain limitations. For instance, they may impose a substantial economic burden, involve invasive procedures, and require complex organization. Therefore, the aim in both the present study and similar studies conducted worldwide is to develop approaches that enable early diagnosis of AD using plasma-based biomarkers.

In this study, multivariate analysis identified age and educational level as significant predictors of AD. The marked increase in the likelihood of receiving an AD diagnosis with advancing age reflects the strong association between the disease and age-related neurodegenerative processes, consistent with findings frequently reported in the literature.

The findings of this study revealed that the risk of AD increases with higher educational attainment. However, the literature suggests that increased education strengthens "cognitive reserve", thereby reducing the risk of AD.[27] The divergent finding observed in our study may be attributable to changes in working conditions associated with higher education, increased exposure to stressors, a sedentary lifestyle, and the adverse effects of urbanization. Moreover, improved access to healthcare services among individuals with higher educational levels, leading to more frequent diagnosis of AD, may represent another possible explanation.[28]

The strong association between age and AD is consistent with existing literature showing that AD risk increases with advancing age. Although female sex is known as a risk factor for AD,[29,30] the lack of statistically meaningful results regarding sex differences in our study is understandable due to the uneven distribution of genders in the Alzheimer's group (19 females vs. 5 males).

Further studies are needed to clarify the impact of comorbidities and a history of head trauma on AD.[31]

The significantly lower smoking rate in the Alzheimer's group, compared to controls, may be related to lifestyle changes associated with disease progression, such as reduced ability to live independently and increased supervision. It is also possible that smoking cessation or a forgotten smoking history among AD patients contributed to this finding. The effects of smoking on AD have long been debated because nicotine's potentially protective effects may be offset by the harmful effects of the many toxic chemicals in tobacco.[32]

Alcohol consumption history was not obtained for the Alzheimer's group, possibly due to caregiver-imposed restrictions or the patients' inability to recall previous habits. Although a higher rate of alcohol use was noted in the control group, this difference was not statistically significant. Moreover, the role of alcohol in AD risk remains controversial, depending on the quantity and type of alcohol consumed.[33]

A statistically significant difference was found between groups in coffee consumption ($p < 0.001$). This difference may be due to fewer participants in the Alzheimer's group reporting occasional coffee consumption ($p = 0.009$), whereas a higher proportion reported consuming one cup daily. Overall, coffee consumption was more prevalent in the Alzheimer's group. The cognitive effects of caffeine-containing beverages, such as coffee, remain controversial in the literature.[34] Larger prospective studies are needed to draw firmer conclusions.

One of the most noteworthy findings of this study is the protective effect of tea consumption against AD. Individuals who consumed tea had significantly lower odds of developing AD. This protective association may be explained by antioxidants present in tea (e.g., catechins and flavonoids), the neuroprotective effects of tea, and the positive influence of caffeine on synaptic plasticity.[35] However, it should be emphasized that this finding represents an association rather than causation. Further prospective and biochemically supported studies are required to clarify the underlying mechanisms.

While the literature suggests a protective effect of the Mediterranean diet on AD,[36] no significant difference was detected between groups in terms of dietary habits in our study. Given the long-term impact of diet on AD risk, it is plausible that the Alzheimer's group's inability to accurately recall past dietary habits influenced this result.

Notably, all individuals in the Alzheimer's group reported engaging in exercise in recent years. However, this may be explained by the perception of low-intensity activities, such as daily short walks, as "exercise." In contrast, a significant proportion of the control group reported not exercising, which warrants careful consideration when interpreting results for the Alzheimer's group. This finding contradicts the majority of the literature reporting the protective effects of physical exercise on AD.[37]

Lifestyle variables were collected by self-report or caregiver report. In a cohort with documented cognitive impairment, these data are susceptible to recall and perception biases (for example, daily short walks reported as "regular exercise"), which may explain the paradoxical finding that 100% of AD patients reported exercising in recent years.

A family history of AD was reported at only 12.5%, suggesting a limited genetic predisposition in the sample. However, this prevalence may not reflect the true rate due to patients' inability to provide accurate information and to incomplete anamnesis obtained from relatives. Although genetic predisposition is recognized as a significant risk factor in AD, community-based studies have also shown that the disease can develop in individuals without a family history.[38]

The high proportion of individuals living in urban centers prior to diagnosis (79.2%) suggests potential environmental effects of urban living on AD. However, this finding may primarily reflect demographic characteristics of the sample, such as easier access to healthcare services and a higher likelihood of diagnosis in urban areas. Lower diagnosis rates in rural regions may be related to limited disease awareness or restricted access to healthcare services.[39]

These findings indicate a heterogeneous nature of AD in terms of disease progression, familial history, and environmental factors. Supporting these clinical data with larger samples and longer follow-up periods will contribute to a better understanding of individual and environmental determinants of the disease.

Study limitations

This study has certain limitations. First, the sample size was relatively small (a total of 61 participants: 24 patients with AD and 37 healthy controls), which may limit the statistical power and generalizability of the findings. Obtaining the required sample from patients is ethically constrained, resulting in "disease stage heterogeneity" within the patient group. As a single-center study, it does not allow comparisons across different geographical regions or sociocultural backgrounds. The cross-sectional design further restricts the ability to establish causal relationships. Moreover, potential confounding variables such as lifestyle factors, dietary habits, and genetic predispositions could not be fully controlled. Given the limited number of studies measuring the proteins investigated in our study using ELISA with different commercial kits, the extent to which inter-assay (kit/brand-related) variability may influence the comparability of results remains uncertain, and the results should therefore be interpreted with caution.

A sensitivity analysis indicated that the present sample was adequately powered to detect moderate or larger between-group differences (rank-biserial $r \geq 0.36$) for each plasma biomarker under a Mann–Whitney U framework, but not small effects ($r < 0.36$). The observed effects were small ($r = 0.02$–0.19), consistent with limited separation between groups in plasma amyloid and tau measurements in this cohort. Detecting effects of this magnitude would require considerably larger cohorts of several hundred participants per group, which is difficult to achieve in a single-center study of a frail, elderly AD population. These findings are therefore presented as hypothesis-generating.

Lifestyle variables were collected via self- or caregiver report. Their susceptibility to recall and perception biases in a cognitively impaired cohort (e.g., daily short walks reported as "regular exercise") limits the interpretability of the data.

Although the present findings do not demonstrate strong diagnostic performance, the investigated biomarkers may still contribute to future biomarker-guided therapeutic strategies and patient stratification approaches in AD.

CONCLUSION

In this case-control study, plasma levels of Aβ40, Aβ42, BACE-1, t-tau, p-tau , and the Aβ42/Aβ40 ratio did not differ between AD patients and healthy controls, and none of these markers, alone or as a ratio, demonstrated adequate discriminative power (all AUCs below 0.62).These null findings should not be interpreted as evidence that plasma biomarkers lack clinical value in general; rather, they likely reflect the limitations of a single-center design and modest sample size, heterogeneity in disease stage, and the known lower sensitivity of plasma assays compared with CSF for detecting amyloid and tau pathology.

Ethics

Ethics Committee Approval: This study was approved by the Ethics Committee on Ankara University (decision no: İ3-148-20, date: 12.10.2020).

Informed Consent: Legal guardians of the patients were informed about the study, and written consent was obtained. The patient group consisted of residents of a nursing home who had been diagnosed with AD by specialized physicians at fully equipped hospitals.

Footnotes

Authorship Contributions

Surgical and Medical Practices: N.M.G.A., B.Ö.P., B.C.E., Concept: N.Y., B.C.E., Design: N.Y., B.C.E., Data Collection or Processing: N.Y., N.M.G.A., B.C.E., Analysis or Interpretation: N.Y., B.C.E., Literature Search: N.Y., B.E., Writing: N.Y., B.C.E.

Conflict of Interest: The authors declare no conflicts of interest.

Financial Disclosure: This research was supported by the 21L0237005 project number of Ankara University Scientific Research Projects Coordination Office.

REFERENCES

1. Uddin MS, Kabir MT, Tewari D, Mamun AA, Mathew B, Aleya L, Ashraf GM. Revisiting the role of brain and peripheral Aβ in the pathogenesis of Alzheimer's disease. J Neurol Sci. 2020;416:116974.
2. Mendez MF. Early-onset Alzheimer disease. Neurologic clinics. 2017;35:263-81.
3. Jia J, Ning Y, Chen M, Wang S, Yang H, Li F, Ding J, Li Y, Zhao B, Lyu J, Yang S, Yan X, Wang Y, Qin W, Wang Q, Li Y, Zhang J, Liang F, Liao Z, Wang S. Biomarker changes during 20 years preceding Alzheimer's disease. N Engl J Med. 2024;390:712-722.
4. Gouilly D, Rafiq M, Nogueira L, Salabert AS, Payoux P, Péran P, Pariente J. Beyond the amyloid cascade: an update of Alzheimer's disease pathophysiology. Rev Neurol (Paris). 2023;179:812-830.
5. Seath P, Macedo-Orrego LE, Velayudhan L. Clinical characteristics of early-onset versus late-onset Alzheimer's disease: a systematic review and meta-analysis. Int Psychogeriatr. 2024;36:1093-1109.
6. Jack CR Jr, Andrews JS, Beach TG, Buracchio T, Dunn B, Graf A, Hansson O, Ho C, Jagust W, McDade E, Molinuevo JL, Okonkwo OC, Pani L, Rafii MS, Scheltens P, Siemers E, Snyder HM, Sperling R, Teunissen CE, Carrillo MC. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. Alzheimers Dement. 2024;20:5143-5169.
7. Orobets KS, Karamyshev AL. Amyloid precursor protein and Alzheimer's disease. Int J Mol Sci. 2023;24:14794.
8. Mudher A, Colin M, Dujardin S, Medina M, Dewachter I, Alavi Naini SM, Mandelkow EM, Mandelkow E, Buée L, Goedert M, Brion JP. What is the evidence that tau pathology spreads through prion-like propagation? Acta Neuropathol Commun. 2017;5:99.
9. Srivastava S, Ahmad R, Khare SK. Alzheimer's disease and its treatment by different approaches: a review. Eur J Med Chem. 2021;216:113320.
10. Briggs R, Kennelly SP, O'Neill D. Drug treatments in Alzheimer's disease. Clin Med (Lond). 2016;16:247-253.
11. Passeri E, Elkhoury K, Morsink M, Broersen K, Linder M, Tamayol A, Malaplate C, Yen FT, Arab-Tehrany E. Alzheimer's disease: treatment strategies and their limitations. Int J Mol Sci. 2022;23:13954.
12. Wilson RS, Arnold SE, Schneider JA, Kelly JF, Tang Y, Bennett DA. Chronic psychological distress and risk of Alzheimer's disease in old age. Neuroepidemiology. 2006;27:143-153.
13. Rissman RA, Langford O, Raman R, Donohue MC, Abdel-Latif S, Meyer MR, Wente-Roth T, Kirmess KM, Ngolab J, Winston CN, Jimenez-Maggiora G, Rafii MS, Sachdev P, West T, Yarasheski KE, Braunstein JB, Irizarry M, Johnson KA, Aisen PS, Sperling RA; AHEAD 3-45 Study team. Plasma Aβ42/Aβ40 and phospho-tau217 concentration ratios increase the accuracy of amyloid PET classification in preclinical Alzheimer's disease. Alzheimers Dement. 2024;20:1214-1224.
14. Wu G, Sankaranarayanan S, Wong J, Tugusheva K, Michener MS, Shi X, Cook JJ, Simon AJ, Savage MJ. Characterization of plasma β-secretase (BACE1) activity and soluble amyloid precursor proteins as potential biomarkers for Alzheimer's disease. J Neurosci Res. 2012;90:2247-2258.
15. Stevenson-Hoare J, Heslegrave A, Leonenko G, Fathalla D, Bellou E, Luckcuck L, Marshall R, Sims R, Morgan BP, Hardy J, de Strooper B, Williams J, Zetterberg H, Escott-Price V. Plasma biomarkers and genetics in the diagnosis and prediction of Alzheimer's disease. Brain. 2023;146:690-699.
16. Hampel H, Vassar R, De Strooper B, Hardy J, Willem M, Singh N, Zhou J, Yan R, Vanmechelen E, De Vos A, Nisticò R, Corbo M, Imbimbo BP, Streffer J, Voytyuk I, Timmers M, Tahami Monfared AA, Irizarry M, Albala B, Koyama A, Watanabe N, Kimura T, Yarenis L, Lista S, Kramer L, Vergallo A. The β-secretase BACE1 in Alzheimer's disease. Biol Psychiatry. 2021;89:745-756.
17. Karran E, De Strooper B. The amyloid hypothesis in Alzheimer disease: new insights from new therapeutics. Nat Rev Drug Discov. 2022;21:306-318.
18. Rawat P, Sehar U, Bisht J, Selman A, Culberson J, Reddy PH. Phosphorylated tau in Alzheimer's disease and other tauopathies. Int J Mol Sci. 2022;23:12841.
19. Pérez-Grijalba V, Romero J, Pesini P, Sarasa L, Monleón I, San-José I, Arbizu J, Martínez-Lage P, Munuera J, Ruiz A, Tárraga L, Boada M, Sarasa M. Plasma Aβ42/40 ratio detects early stages of Alzheimer's

disease and correlates with CSF and neuroimaging biomarkers in the AB255 study. J Prev Alzheimers Dis. 2019;6:34-41.

20. Hansson O, Zetterberg H, Vanmechelen E, Vanderstichele H, Andreasson U, Londos E, Wallin A, Minthon L, Blennow K. Evaluation of plasma Abeta(40) and Abeta(42) as predictors of conversion to Alzheimer's disease in patients with mild cognitive impairment. Neurobiol Aging. 2010;31:357-367.
21. Lopez OL, Kuller LH, Mehta PD, Becker JT, Gach HM, Sweet RA, Chang YF, Tracy R, DeKosky ST. Plasma amyloid levels and the risk of AD in normal subjects in the cardiovascular health study. Neurology. 2008;70:1664-1671.
22. Lövheim H, Elgh F, Johansson A, Zetterberg H, Blennow K, Hallmans G, Eriksson S. Plasma concentrations of free amyloid β cannot predict the development of Alzheimer's disease. Alzheimers Dement. 2017;13:778-782.
23. Mehta PD, Pirttila T, Patrick BA, Barshatzky M, Mehta SP. Amyloid beta protein 1-40 and 1-42 levels in matched cerebrospinal fluid and plasma from patients with Alzheimer disease. Neurosci Lett. 2001;304:102-106.
24. Chouraki V, Beiser A, Younkin L, Preis SR, Weinstein G, Hansson O, Skoog I, Lambert JC, Au R, Launer L, Wolf PA, Younkin S, Seshadri S. Plasma amyloid-β and risk of Alzheimer's disease in the Framingham Heart Study. Alzheimers Dement. 2015;11:249-57.e1.
25. Graff-Radford NR, Crook JE, Lucas J, Boeve BF, Knopman DS, Ivnik RJ, Smith GE, Younkin LH, Petersen RC, Younkin SG. Association of low plasma Abeta42/Abeta40 ratios with increased imminent risk for mild cognitive impairment and Alzheimer disease. Arch Neurol. 2007;64:354-362. Erratum in: Arch Neurol. 2007;64:1246.
26. Lambert JC, Schraen-Maschke S, Richard F, Fievet N, Rouaud O, Berr C, Dartigues JF, Tzourio C, Alpérovitch A, Buée L, Amouyel P. Association of plasma amyloid beta with risk of dementia: the prospective Three-City Study. Neurology. 2009;73:847-853.
27. Rosselli M, Uribe IV, Ahne E, Shihadeh L. Culture, ethnicity, and level of education in Alzheimer's disease. Neurotherapeutics. 2022;19:26-54.
28. Seyedsalehi A, Warrier V, Bethlehem RAI, Perry BI, Burgess S, Murray GK. Educational attainment, structural brain reserve and Alzheimer's disease: a mendelian randomization analysis. Brain. 2023;146:2059-2074.
29. Nebel RA, Aggarwal NT, Barnes LL, Gallagher A, Goldstein JM, Kantarci K, Mallampalli MP, Mormino EC, Scott L, Yu WH, Maki PM, Mielke MM. Understanding the impact of sex and gender in Alzheimer's disease: a call to action. Alzheimers Dement. 2018;14:1171-1183.
30. Riedel BC, Thompson PM, Brinton RD. Age, APOE and sex: triad of risk of Alzheimer's disease. J Steroid Biochem Mol Biol. 2016;160:134-147.
31. Mckee AC, Daneshvar DH. The neuropathology of traumatic brain injury. Handb Clin Neurol. 2015;127:45-66.
32. Wang Q, Du W, Wang H, Geng P, Sun Y, Zhang J, Wang W, Jin X. Nicotine's effect on cognition, a friend or foe? Prog Neuropsychopharmacol Biol Psychiatry. 2023;124:110723.
33. Peng B, Yang Q, B Joshi R, Liu Y, Akbar M, Song BJ, Zhou S, Wang X. Role of alcohol drinking in Alzheimer's disease, Parkinson's Disease, and amyotrophic lateral sclerosis. Int J Mol Sci. 2020;21:2316.
34. Nila IS, Villagra Moran VM, Khan ZA, Hong Y. Effect of daily coffee consumption on the risk of Alzheimer's disease: a systematic review and meta-analysis. J Lifestyle Med. 2023;13:83-89.
35. Ide K, Matsuoka N, Yamada H, Furushima D, Kawakami K. Effects of tea catechins on Alzheimer's disease: recent updates and perspectives. Molecules. 2018;23:2357.
36. Stefaniak O, Dobrzyńska M, Drzymała-Czyż S, Przysławski J. Diet in the prevention of Alzheimer's disease: current knowledge and future research requirements. Nutrients. 2022;14:4564.
37. De la Rosa A, Olaso-Gonzalez G, Arc-Chagnaud C, Millan F, Salvador-Pascual A, García-Lucerga C, Blasco-Lafarga C, Garcia-Dominguez E, Carretero A, Correas AG, Viña J, Gomez-Cabrera MC. Physical exercise in the prevention and treatment of Alzheimer's disease. J Sport Health Sci. 2020;9:394-404.
38. Karch CM, Cruchaga C, Goate AM. Alzheimer's disease genetics: from the bench to the clinic. Neuron. 2014;83:11-26.
39. Karmarkar AM, Roy I, Lane T, Shaibi S, Baldwin JA, Kumar A. Home health services for minorities in urban and rural areas with Alzheimer's and related dementia. Home Health Care Serv Q. 2023;42:265-281.