

Association of Serum High-density Lipoprotein Cholesterol Levels and Triglyceride-glucose Index with Alzheimer's Disease: A Retrospective Case-control Study

Serum Yüksek Yoğunluklu Lipoprotein Kolesterol Düzeyleri ve Trigliserit-glukoz İndeksi ile Alzheimer Hastalığı Arasındaki İlişki: Retrospektif Olgu-kontrol Çalışması

Yeliz Çiftçi, Sevinj Namazova

İzmir Bakırçay University Çiğli Training and Research Hospital, Department of Neurology, İzmir, Türkiye

Cite as: Çiftçi Y, Namazova S. Association of serum high-density lipoprotein cholesterol levels and triglyceride-glucose index with Alzheimer's disease: a retrospective case-control study. Anatol J Gen Med Res. [Epub Ahead of Print]

Abstract

Objective: This study aimed to investigate the relationship between serum high-density lipoprotein cholesterol (HDL-C) levels, the triglyceride-glucose (TyG) index, and Alzheimer's disease (AD).

Methods: A total of 341 patients diagnosed with AD and 101 age- and sex-matched healthy controls were included in this retrospective case-control study. Serum lipid parameters, TyG index (cut-off ≥ 8.5), and clinical features of AD patients [mini-mental state examination (MMSE) scores by severity, medical treatment rates, and statin use] were compared.

Results: Median HDL-C levels were significantly higher in the AD group than in controls [49.9 $\pm$ 0.78 (17.4) vs. 47.80 $\pm$ 1.19 (16.4) mg/dL, $p=0.024$]. The proportion of participants with HDL-C >70 mg/dL was significantly higher in AD patients (11.4% vs. 3.0%, $p=0.026$). TyG ≥ 8.5 was more prevalent in the AD group (74.2% vs. 61.4%, $p=0.017$). In logistic regression, HDL-C >70 mg/dL was associated with 5.3-fold increased odds of AD [$p=0.07$, 95% confidence interval (CI): 1.564-18.103], while TyG ≥ 8.5 was associated with 2.2-fold increased odds ($p=0.001$, 95% CI: 1.366-3.617). Median MMSE scores were 22 $\pm$ 0.12 in mild, 16 $\pm$ 0.24 in moderate, and 7 $\pm$ 0.20 in severe dementia. Use of medical treatment increased with severity (46.8% in mild cases, 73.9% in moderate cases, 83.3% in severe cases), with donepezil being the most common agent (46.7%). Statin use was 9% in the AD group.

Conclusion: In elderly Turkish patients with AD, paradoxically elevated HDL-C levels (particularly >70 mg/dL) and elevated TyG index (≥ 8.5) were associated with higher odds of AD diagnosis. These findings support age-dependent alterations in lipid metabolism and the role of insulin resistance in AD pathogenesis.

Keywords: Alzheimer's disease, HDL cholesterol, TyG index, insulin resistance, dementia



Address for Correspondence/Yazışma Adresi: Asst. Prof., Yeliz Çiftçi, İzmir Bakırçay University
Çiğli Training and Research Hospital, Department of Neurology, İzmir, Türkiye
E-mail: yeliz.ciftci@bakircay.edu.tr
ORCID ID: orcid.org/0009-0007-6304-2944

Received/Geliş tarihi: 08.04.2026

Accepted/Kabul tarihi: 08.06.2026

Epub: 01.07.2026



Copyright© 2026 The Author(s). Published by Galenos Publishing House on behalf of University of Health Sciences Türkiye, İzmir Tepecik Education and Research Hospital. This is an open access article under the Creative Commons AttributionNonCommercial 4.0 International (CC BY-NC 4.0) License.

Öz

Amaç: Bu çalışma, serum yüksek yoğunluklu lipoprotein kolesterol (HDL-K) düzeyleri, trigliserit-glukoz (TyG) indeksi ve Alzheimer hastalığı (AH) arasındaki ilişkiyi araştırmayı amaçlamıştır.

Yöntem: Bu retrospektif olgu-kontrol çalışmasına toplam 341 AH tanısı konmuş hasta ve yaş ve cinsiyet açısından eşleştirilmiş 101 sağlıklı kontrol dahil edilmiştir. Serum lipid parametreleri, TyG indeksi (kesme noktası $\geq 8,5$) ve AH hastalarının klinik özellikleri [şiddete göre mini mental durum değerlendirmesi (MMSE) skortları, tıbbi tedavi oranları ve statin kullanımı] karşılaştırılmıştır.

Bulgular: Ortanca HDL-K düzeyleri, AH grubunda kontrollere göre anlamlı derecede daha yüksekti [$49,9 \pm 0,78$ (17,4) vs. $47,80 \pm 1,19$ (16,4) mg/dL, $p=0,024$]. HDL-K >70 mg/dL olan katılımcıların oranı AH hastalarında anlamlı derecede daha yüksekti (%11,4'e karşı %3,0, $p=0,026$). TyG $\geq 8,5$ AH grubunda daha yaygındı (%74,2'ye karşı %61,4, $p=0,017$). Lojistik regresyonda, HDL-K >70 mg/dL, AH olasılığını 5,3 kat artırırken [$p=0,07$, %95 güven aralığı (GA): 1,564-18,103], TyG $\geq 8,5$ ise 2,2 kat artırdı ($p=0,001$, %95 GA: 1,366-3,617). Hafif demanslı hastalarda MMSE skorlarının medyan değerleri $22 \pm 0,12$, orta şiddette demanslı hastalarda $16 \pm 0,24$ ve şiddetli demanslı hastalarda $7 \pm 0,20$ idi. Tıbbi tedavi kullanımı şiddet arttıkça artmıştır (hafif demanslı hastalarda %46,8, orta şiddette demanslı hastalarda %73,9, şiddetli demanslı hastalarda %83,3), donepezil en sık kullanılan ajan olmuştur (%46,7). Statin kullanımı AH grubunda %9 idi.

Sonuç: Yaşlı Türk AH hastalarında, paradoksal olarak yüksek HDL-K seviyeleri (özellikle >70 mg/dL) ve yüksek TyG indeksi ($\geq 8,5$), AH tanısı olasılığının daha yüksek olmasıyla ilişkilidir. Bu bulgular, lipid metabolizmasında yaşa bağlı değişiklikleri ve insülin direncinin AH patogeneziindeki rolünü desteklemektedir.

Anahtar Kelimeler: Alzheimer hastalığı, HDL kolesterol, TyG indeksi, insülin direnci, demans

Introduction

Alzheimer's disease (AD) is the most common neurodegenerative disorder and the leading cause of dementia in older adults worldwide. Its prevalence is rising rapidly among individuals aged 65 years and older, with the global burden projected to increase dramatically by 2050⁽¹⁾. Its pathogenesis involves β -amyloid accumulation, tau hyperphosphorylation, neuroinflammation, and increasingly recognized metabolic and vascular factors⁽²⁾.

Lipid metabolism plays a critical role in brain health, synaptic function, and amyloid- β clearance. High-density lipoprotein cholesterol (HDL-C) has traditionally been considered protective against cognitive decline due to its anti-inflammatory and antioxidant properties and potential role in amyloid- β clearance⁽³⁾. However, recent large cohort studies have revealed a more complex, often non-linear (U- or J-shaped) relationship between HDL-C levels and dementia risk, particularly in advanced age⁽⁴⁾. Both low and very high HDL-C levels have been linked to increased dementia risk. In initially healthy adults aged ≥ 75 years, very high HDL-C (>80 mg/dL) was associated with a 27% higher risk of incident all-cause dementia, independent of apolipoprotein E (APOE) genotype and other covariates⁽⁵⁾.

Insulin resistance (IR) is recognized as an independent risk factor for AD⁽⁶⁾. The triglyceride-glucose (TyG) index is a simple, cost-effective, and reliable surrogate for IR that is calculated using fasting triglyceride and glucose values. Prospective and population-based studies have shown that an elevated

TyG index is independently associated with increased risk of cognitive impairment, AD, and dementia. It has been reported that TyG index values above the threshold of approximately 8.5-8.9 significantly increase the probability of AD⁽⁶⁻⁸⁾.

Data on the relationships among lipid profiles, the TyG index, and AD in elderly Turkish populations remain limited. This retrospective case-control study aimed to compare serum lipid parameters and TyG index between 341 patients with AD and 101 age- and sex-matched healthy controls.

The existing literature contains a limited number of studies investigating the relationship between Alzheimer's dementia, the serum lipid profile, and the TyG index in the elderly Turkish population. The aim of this study is to (1) examine whether serum HDL-C levels in patients with AD differ from those in healthy controls and (2) investigate whether a high TyG index poses a risk for Alzheimer's dementia.

Materials and Methods

Study Design

This was a single-center, retrospective case-control study conducted at a tertiary medical center in İzmir, Türkiye. The study was approved by the İzmir Bakırçay University Local Institutional Ethics Committee (approval no: 2654, date: 17.12.2025). All procedures were performed in accordance with the ethical standards of the Declaration of Helsinki (1964) and its subsequent amendments. Due to the retrospective nature of the study, informed consent was waived.

Participants

A total of 442 individuals were included: 341 patients with AD group and 101 age- (± 5 years) and sex-matched healthy controls. Participants were recruited from the records of the cognitive disorders outpatient clinic between January 2021 and December 2025.

The diagnosis of AD was established in all patients according to the revised 2024 National Institute on Aging-Alzheimer's Association (NIA-AA) criteria based on clinical history, neuropsychological assessment [mini-mental state examination (MMSE)], and neuroimaging findings (magnetic resonance imaging or computed tomography) that were consistent with AD⁽²⁾. Medical records, neuropsychological assessments, and available neuroimaging data for patients initially evaluated between 2021 and 2023 were re-evaluated retrospectively according to the 2024 NIA-AA biological framework to ensure diagnostic consistency across the study period.

Exclusion criteria for the AD group were: presence of other types of dementia (vascular, Lewy body, frontotemporal, etc.); significant psychiatric disorders (major depression, schizophrenia); acute or chronic systemic diseases that could affect lipid metabolism (uncontrolled diabetes, severe liver or kidney disease, active malignancy, thyroid dysfunction); or use of medications known to markedly alter lipid profiles (except stable statin therapy, which was recorded).

Healthy controls were individuals who presented for routine health check-ups or for minor non-cognitive complaints (e.g., headache, vertigo, or musculoskeletal pain) and who had no subjective cognitive complaints. All controls underwent cognitive screening with the MMSE before enrollment. A score of ≥ 27 was required to be considered normal (adjusted for age and education when necessary). Individuals using statins or who met any of the exclusion criteria applied to the AD group were not included in the control group. Only those with complete laboratory data were selected.

The case-to-control ratio was approximately 3.4:1. This unequal ratio resulted from the retrospective design: all eligible AD patients with complete data during the study period were included, whereas controls were selected from a more restricted pool of strictly defined healthy individuals without statin use.

Laboratory Measurements

Fasting venous blood samples were collected after 8-12 hours of overnight fasting. Serum glucose, total cholesterol, low-density lipoprotein cholesterol (LDL-C), HDL-C, and triglycerides (TG) were measured using enzymatic colorimetric methods on an automated biochemistry analyzer.

The TyG index was calculated using the formula:

$$\text{TyG} = \ln [\text{fasting TG (mg/dL)} \times \text{fasting glucose (mg/dL)} / 2]$$

The cut-off value of $\text{TyG} \geq 8.5$ was selected based on previous validation studies showing high sensitivity and specificity for identifying IR, and its use in prior research investigating metabolic risk and cognitive impairment.

All laboratory analyses were performed in the central laboratory of the same institution using standardized protocols.

Statistical Analysis

All statistical analyses were performed using SPSS v.23.0 (Statistical Package for Social Sciences, SPSS Inc., Chicago, Ill., USA). The normality of continuous variables was tested using the Shapiro-Wilk test since the study population was small. Age, total cholesterol, and HDL-C were normally distributed in the control group, whereas LDL-C, TG, and very-low-density lipoprotein cholesterol (VLDL-C) were not normally distributed.

Accordingly, normally distributed variables [age (sig. 0.130), total cholesterol (sig. 0.510), and HDL-C (sig. 0.191)] were compared using the independent samples t-test and presented as mean $\pm$ standard error of the mean. Non-normally distributed variables (LDL-C, TG, and VLDL) were compared using the Mann-Whitney U test and presented as median (interquartile range) values. Categorical variables are expressed as counts and percentages. Comparisons between groups for categorical variables were performed using Pearson's chi-square test or Fisher's exact test. Multivariate logistic regression analysis was performed to evaluate the independent associations of HDL-C categories and TyG index with AD diagnosis. The model was adjusted for age, sex, and statin use; results are reported as odds ratios (ORs) with 95% confidence intervals (CIs). A p-value < 0.05 was considered statistically significant. No imputation was performed for missing data; only complete cases were included in the final analysis.

Results

A total of 442 participants were included in this retrospective case-control study: 341 patients with AD group and 101 age- and sex-matched healthy controls. The mean age was 79.0 ± 0.36 years in the AD group and 77.37 ± 0.87 years in the control group ($p=0.084$). No significant difference in sex distribution was observed between the groups (females: 58.4% in AD vs. 63.4% in controls, $p=0.420$).

Serum lipid profiles are summarized in Table 1. Serum HDL-C levels were significantly higher in the AD group compared to controls (52.21 ± 0.78 mg/dL vs. 48.65 ± 1.19 mg/dL, $p=0.024$).

No significant differences were observed between the groups for total cholesterol, LDL-C, TG, or VLDL levels (all $p>0.05$).

Statin use was 9% ($n=31$) in the AD group. No participants in the control group were taking statins, as statin users were excluded during enrollment.

Categorical analysis showed that a significantly higher proportion of AD patients had HDL-C >70 mg/dL (11.4% vs. 3.0%, $p=0.026$). TyG index ≥ 8.5 was more prevalent in the AD group (74.2% vs. 61.4%, $p=0.017$). Distributions of other lipid parameters did not differ significantly (Tables 1 and 2).

Table 1. Comparison of demographic and laboratory parameters between Alzheimer's disease patients and healthy controls [median (IQR) or mean $\pm$ SEM]

Parameter	Alzheimer's disease (n=341)	Controls (n=101)	p-value*
Age (years)	79.0 ± 0.36	77.37 ± 0.87	0.084
Total cholesterol (mg/dL)	202.23 ± 2.37	196.44 ± 3.84	0.201
LDL-C (mg/dL)	120.4 [47.1]	125.26 [47.4]	0.792†
Triglycerides (mg/dL)	118.0 [68.4]	112.90 [61.2]	0.190†
HDL-C (mg/dL)	52.21 ± 0.78	48.65 ± 1.19	0.024
VLDL-C (mg/dL)	23.6 [13.7]	22.58 [12.2]	0.190†

Data are presented as median $\pm$ SEM (IQR)

∗: Independent t-test, †: Mann Whitney U-test, IQR: Interquartile range, SEM: Standard error of the mean, LDL-C: Low-density lipoprotein cholesterol, HDL-C: High-density lipoprotein cholesterol, VLDL-C: Very-low-density lipoprotein cholesterol

Table 2. Categorical distribution of lipid parameters and TyG index between groups [n (%)]

Parameter	Category	Alzheimer (n=341)	Control (n=101)	p-value*
Sex (female)	-	199 (58.4)	64 (63.4)	0.420†
Total cholesterol	<180	109 (32.0)	36 (35.6)	0.768
	180-200	61 (17.9)	18 (17.8)	
	>200	171 (50.1)	47 (46.5)	
LDL	<100	93 (27.3)	27 (26.7)	0.569
	100-130	110 (32.3)	34 (33.7)	
	130-160	87 (25.5)	30 (29.7)	
	>160	51 (15.0)	10 (9.9)	
Triglycerides	<200	292 (85.6)	90 (89.1)	0.495
	200-400	46 (13.5)	11 (10.9)	
	>400	3 (0.9)	0 (0)	
HDL	<40	67 (19.6)	26 (25.7)	0.026
	40-70	235 (68.9)	72 (71.3)	
	>70	39 (11.4)	3 (3.0)	
VLDL	<30	242 (71.0)	78 (77.2)	0.254†
	≥ 30	99 (29.0)	23 (22.8)	
TyG index	<8.5	88 (25.8)	39 (38.6)	0.017
	≥ 8.5	253 (74.2)	62 (61.4)	

∗: Pearson's chi-square test, †: Fisher's exact test, LDL: Low-density lipoprotein, HDL: High-density lipoprotein, VLDL: Very-low-density lipoprotein, TyG: Triglyceride-glucose

Clinical features of AD patients by severity: mean MMSE scores were 21.84 ± 0.12 in mild dementia, 15.37 ± 0.24 in moderate dementia, and 7.39 ± 0.20 in severe dementia. Medical treatment rates increased with severity: 46.8% for mild cases, 73.9% for moderate cases, and 83.3% for severe cases. Donepezil was the most frequently used medication (46.7%), followed by the combination of donepezil and memantine. Other agents included rivastigmine, memantine, rivastigmine plus memantine, and Ginkgo biloba extracts. Statin use was observed in 9% of AD patients.

In the multivariate logistic regression model adjusted for age, sex, and statin use, patients with HDL-C >70 mg/dL had 5.3-fold higher OR of AD ($p=0.007$, 95% CI: 1.564-18.103). TyG ≥ 8.5 was associated with 2.2-fold increased OR of AD ($p=0.001$, 95% CI: 1.366-3.617).

Discussion

This retrospective case-control study found that elderly patients with AD had significantly higher serum HDL-C levels than age- and sex-matched controls, with a notably higher proportion in the >70 mg/dL category. Additionally, TyG ≥ 8.5 was more prevalent in AD patients and independently associated with increased OR of AD diagnosis. These findings add to the growing evidence of complex, age-dependent relationships between lipid metabolism, IR, and AD.

Previously, HDL-C has been viewed as protective against cognitive decline due to its roles in reverse cholesterol transport, anti-inflammation, and potential amyloid- β clearance. However, recent large-scale studies challenge this notion, particularly in older adults. In a cohort of initially healthy individuals aged ≥ 75 years, very high HDL-C (>80 mg/dL) was associated with a 27% increased risk of incident all-cause dementia, independent of traditional risk factors and APOE genotype. Similarly, a U-shaped relationship between HDL-C and AD and related dementias has been reported, with both low and high HDL-C levels associated with an elevated risk. Our observation of elevated HDL-C levels (especially >70 mg/dL) among AD patients aligns with paradoxical associations reported in advanced age⁽⁵⁾. These findings are also consistent with a retrospective analysis of 111 AD patients, which found that higher serum HDL-C levels were significantly associated with lower MMSE scores ($t=-2.38$, $p=0.019$), indicating greater disease severity⁽⁹⁾.

The underlying mechanisms may involve impaired HDL functionality rather than quantity^(10,11). In older adults, HDL particles can become dysfunctional due to oxidative stress, chronic inflammation, or their altered composition, thereby reducing their neuroprotective and vasoprotective effects⁽¹²⁾.

The dysfunctional HDL hypothesis is supported by several recent publications showing that elevated HDL-C in older adults is associated with an increased risk of dementia. In our cohort, low statin use (9%) suggests minimal medication effects.

Regarding the TyG index, our finding of increased prevalence of TyG ≥ 8.5 and its independent association with AD (OR=2.2) is consistent with multiple studies linking IR to AD pathology. Population-based research has shown that higher TyG levels are associated with an increased likelihood of dementia and AD, even after adjustment for cardiovascular risk factors⁽⁷⁾. The cut-off of ≥ 8.5 was chosen based on previous studies that demonstrated optimal predictive performance for IR and metabolic risk in various populations, including those investigating cognitive outcomes. Prospective data from the Framingham Heart Study Offspring cohort indicated that moderately elevated TyG was linked to a higher incidence of AD (adjusted hazard ratio 1.69 for one category)⁽⁶⁾. Meta-analyses further support a positive association between elevated TyG and risk of cognitive impairment/dementia⁽⁸⁾.

Mechanistically, peripheral and central IR may promote AD through impaired brain insulin signaling, reduced amyloid- β degradation, increased tau hyperphosphorylation, neuroinflammation, and blood-brain barrier dysfunction. These pathways appear particularly relevant in AD⁽⁷⁾.

The lack of significant differences in other lipid parameters (total cholesterol, LDL-C, TG, and VLDL) is consistent with the literature showing that associations between lipids and dementia often weaken or reverse in late life, possibly due to reverse causation, frailty, or nutritional changes.

Study Limitations

Strengths include a relatively large AD sample, age- and sex-matching, evaluation of both continuous and categorical lipid variables, and inclusion of clinical details (MMSE, medication, statin use). Limitations include the retrospective single-center design (limiting causal inference and generalizability), lack of assessment of HDL particle functionality and inflammatory markers, absence of APOE genotyping, and incomplete data on fasting glucose details or on longitudinal follow-up. Prospective studies with biomarker confirmation (cerebrospinal fluid A β /tau or imaging) and HDL quality assessment are warranted. Although HDL-C >70 mg/dL was associated with significantly increased OR of AD in the multivariate model ($p=0.007$), this finding should be interpreted with caution due to the very small number of controls in this category ($n=3$), which resulted in a wide CI and limited statistical power.

Conclusion

In this elderly Turkish cohort, AD patients exhibited paradoxically higher serum HDL-C levels (particularly >70 mg/dL) and a higher prevalence of elevated TyG index (≥ 8.5), both associated with increased OR of AD. These results highlight age-dependent changes in lipid metabolism and the importance of IR in AD pathogenesis. Routine evaluation of TyG index in older adults may help identify individuals at higher metabolic risk for AD. Future research should focus on HDL functionality, longitudinal metabolic trajectories, and potential interventions targeting IR to reduce AD risk or slow progression.

Ethics

Ethics Committee Approval: The study was approved by the İzmir Bakırçay University Local Institutional Ethics Committee (approval no: 2654, date: 17.12.2025).

Informed Consent: Due to the retrospective nature of the study, informed consent was waived.

Footnotes

Authorship Contributions

Concept: Y.Ç., S.N., Design: Y.Ç., S.N., Data Collection or Processing: Y.Ç., S.N., Analysis or Interpretation: Y.Ç., Literature Search: Y.Ç., S.N., Writing: Y.Ç.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

1. Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP. The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement*. 2013;9:63-75.e62.
2. Jack CR Jr, Andrews JS, Beach TG, et al. Revised criteria for diagnosis and staging of Alzheimer's disease: Alzheimer's Association Workgroup. *Alzheimers Dement*. 2024;20:5143-69.
3. Button EB, Robert J, Caffrey TM, Fan J, Zhao W, Wellington CL. HDL from an Alzheimer's disease perspective. *Curr Opin Lipidol*. 2019;30:224-34.
4. Ferguson EL, Zimmerman SC, Jiang C, et al. Independent associations of high-density lipoprotein cholesterol and triglyceride levels with Alzheimer's disease and related dementias. *Alzheimers Dement*. 2025;21:e14575.
5. Hussain SM, Robb C, Tonkin AM, et al. Association of plasma high-density lipoprotein cholesterol level with risk of incident dementia: a cohort study of healthy older adults. *Lancet Reg Health West Pac*. 2023;43:100963.
6. Sun J, Xie Z, Wu Y, et al. Association of the triglyceride-glucose index with risk of Alzheimer's disease: a prospective cohort study. *Am J Prev Med*. 2023;65:1042-9.
7. Tian N, Fa W, Dong Y, et al. Triglyceride-glucose index, Alzheimer's disease plasma biomarkers, and dementia in older adults: the MIND-China study. *Alzheimers Dement (Amst)*. 2023;15:e12426.
8. Wang H, Ling Q, Wu Y, Zhang M. Association between the triglyceride glucose index and cognitive impairment and dementia: a meta-analysis. *Front Aging Neurosci*. 2023;15:1278730.
9. Tiftikcioğlu B, Tuncay N, Korucuk M, Zorlu Y. Evaluation of vascular risk factors in Alzheimer's dementia: clinical experience. *Anatol J Gen Med Res*. 2012;22:53-8.
10. Koch M, Jensen MK. HDL-cholesterol and apolipoproteins in relation to dementia. *Curr Opin Lipidol*. 2016;27:76-87.
11. Rohatgi A, Khera A, Berry JD, et al. HDL cholesterol efflux capacity and incident cardiovascular events. *N Engl J Med*. 2014;371:2383-93.
12. Qi M, Billheimer J, Chang CH, et al. High-density lipoprotein over midlife and future cognition in women: the SWAN HDL ancillary study. *J Clin Endocrinol Metab*. 2025;110:1980-8.