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# Serum atherogenic index in migraine subtypes and disease duration

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## Abstract

*Background:* Migraine has been associated with an increased risk of vascular disease, and the atherogenic index of plasma (AIP) has been proposed as a potential marker of cardiovascular risk. However, the relationship between AIP and migraine subtypes as well as disease duration remains unclear. *Methods:* This retrospective cross-sectional study included 99 patients with migraine with aura (MwA), 104 patients with migraine without aura (MwoA), and 100 healthy controls. Clinical and laboratory data were obtained from medical records. AIP was calculated as the logarithmic ratio of triglycerides to high-density lipoprotein cholesterol. Correlation and partial correlation analyses were performed to assess the association between AIP and disease duration, with adjustment for age, sex, and migraine severity. Multinomial logistic regression analysis adjusted for age and sex was used to evaluate the independent association of AIP with migraine subtypes. *Results:* AIP levels were significantly higher in patients with MwA compared to controls. AIP showed a significant positive correlation with disease duration in both MwoA ($r=0.860$, $p<0.001$) and MwA ($r=0.751$, $p<0.001$), and this association remained significant after adjustment for age, sex, and migraine severity. Receiver operating characteristic analysis demonstrated modest discrimination of MwA from controls (AUC=0.630, $p=0.002$). In multinomial logistic regression analysis adjusted for age and sex, AIP was not independently associated with migraine subtypes (MwA or MwoA).
*Conclusion:* AIP may be associated with migraine subtype and disease duration; however, this association was not independent after adjustment for confounding variables, and its independent predictive value appears limited.

*Keywords:* Migraine with aura; migraine without aura; atherogenic index; lipid profile

## INTRODUCTION

Migraine is a common primary headache disorder characterized by recurrent attacks and complex neurovascular mechanisms. It has been demonstrated that migraine with aura carries a higher risk of ischemic stroke and other cerebrovascular events compared with migraine without aura.[1,2] Although the exact pathophysiological mechanisms underlying this increased risk have not been fully elucidated, endothelial dysfunction, inflammation, oxidative stress, and atherosclerotic processes have emerged as key contributing factors.[3,4]

In recent years, the relationship between migraine and disturbances in lipid metabolism has attracted increasing attention. Individuals with migraine, particularly those with migraine with aura, have been reported to exhibit higher levels of total cholesterol, low-density lipoprotein cholesterol, and triglycerides, along with lower levels of high-density lipoprotein cholesterol.[5] This atherogenic lipid profile is thought to contribute to the development of subclinical atherosclerosis in migraine patients. Studies demonstrating increased carotid intima–media thickness and a greater atherosclerotic burden in individuals with migraine support this notion.[6]

Furthermore, the interaction between oxidative stress, inflammatory markers, and lipid metabolism in the pathogenesis of migraine has been identified as an important component of vascular injury.[7] Recent meta-analyses

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have shown that serum lipid abnormalities are more frequent in patients with migraine than in healthy controls.[8] In light of these findings, a comparative evaluation of lipid profiles and atherogenic indices in migraine with and without aura may contribute to a better understanding of migraine-associated vascular risk.

Although the chronic course and variable clinical manifestations of migraine are often explained by triggering factors, endogenous mechanisms—particularly atherogenic burden—may be related to vascular mechanisms; however, the relationship with disease duration remains unclear and requires cautious interpretation. Accordingly, the present study aimed to compare serum atherogenic index of plasma (AIP) among patients with migraine with aura, migraine without aura, and healthy controls, and to identify potential differences in atherogenic risk related to migraine subtypes and disease duration.

## METHODS

This retrospective cross-sectional study was conducted in a tertiary referral neurology outpatient clinic of Sakarya University Training and Research Hospital and included consecutive patients diagnosed with migraine with aura (n = 99) and migraine without aura (n = 104) according to the International Classification of Headache Disorders, 3rd edition criteria. In addition, 100 age- and sex-matched healthy control individuals were enrolled.

Individuals with a history of coronary artery disease, cerebrovascular disease, peripheral arterial disease, diabetes mellitus, chronic kidney disease, active infection or systemic inflammatory disease, thyroid disorders, pregnancy, or the use of lipid-lowering medications were excluded.

Demographic and clinical data, including age, sex, smoking status, duration of migraine, monthly attack frequency, Visual Analog Scale scores, and Migraine Disability Assessment scores, were retrospectively obtained from medical records. Migraine subtype was determined based on clinical history and neurological evaluation.

Medical records were reviewed retrospectively, and fasting serum lipid profiles—including total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol—were recorded. Biochemical analyses were performed in the hospital's central laboratory using standard enzymatic methods.

The primary outcome measure of the study was the AIP, calculated as the logarithmic ratio of triglycerides to high-density lipoprotein cholesterol. The AIP values were compared among the migraine with aura, migraine without aura, and healthy control groups, and their relationships with migraine subtype and disease duration were evaluated.

Additionally, age was dichotomized at 35 years to perform subgroup analyses based on previous epidemiological studies suggesting increased vascular risk beyond this threshold; however, this approach was exploratory and may not fully distinguish aging effects from disease duration.

### *Statistical analysis*

Statistical analyses were performed using SPSS version 21.0. The normality of variables was assessed using skewness and kurtosis coefficients. Continuous variables were expressed as mean ± standard deviation or median and interquartile range as appropriate, whereas categorical variables were presented as frequency and percentage.

Comparisons of categorical variables between groups were performed using the Pearson chi-square test or the Fisher–Freeman–Halton exact test when appropriate. Continuous variables were compared using Student's t-test or the Mann–Whitney U test for two-group comparisons and one-way analysis of variance or the Kruskal–Wallis test for three-group comparisons. Post-hoc analyses were conducted using Tukey HSD or Tamhane's T2 tests when required.

The diagnostic performance of the AIP in predicting migraine with aura was evaluated using receiver operating characteristic curve analysis. The area under the curve with 95% confidence intervals was reported. Pearson correlation analysis was used to evaluate the relationships between AIP, disease duration, and age. Additionally, partial correlation analyses were performed to evaluate the association between AIP and disease duration after adjusting for age, sex, and migraine severity (VAS and MIDAS scores). Confidence intervals were obtained using bootstrap resampling (1000 samples, bias-corrected and accelerated method). Scatter plots were generated to visually assess the relationship between AIP and disease duration in migraine subgroups. Multinomial logistic regression analysis was performed to assess the independent association between the

AIP and migraine subtype after adjustment for age and sex. A p value < 0.05 was considered statistically significant.

## RESULTS

No statistically significant differences were observed among the episodic migraine without aura (n = 104), migraine with aura (n = 99), and healthy control (n = 100) groups in terms of age, sex distribution, or smoking status (p > 0.05 for all).

When the migraine subgroups were compared, the visual analog scale score during attacks was significantly higher in the migraine with aura group than in the migraine without aura group (p = 0.002), whereas Migraine Disability Assessment scores did not differ significantly between the two subtypes (p = 0.229).

No significant differences were found among the migraine groups and the healthy controls in terms of total cholesterol, low-density lipoprotein cholesterol, or high-density lipoprotein cholesterol levels (p > 0.05 for all). In contrast, triglyceride levels were significantly higher in the migraine with aura group compared with the migraine without aura and control groups (p = 0.029).

The primary outcome measure, the AIP, was significantly elevated in patients with migraine with aura compared with those with migraine without aura and healthy controls (p = 0.004). Demographic characteristics and laboratory parameters of the study population are summarized in Table 1.

In subgroup analyses, AIP showed a significant positive correlation with disease duration in both migraine without aura (r=0.860, p<0.001) and migraine with aura (r=0.751, p<0.001).

Receiver operating characteristic curve analysis demonstrated that the AIP had a significant diagnostic value in discriminating migraine with aura. In the comparison between the migraine with aura and control groups, the area under the curve was 0.630 (95% confidence interval: 0.552–0.707; p = 0.002). When patients with migraine with aura were compared with those without aura, the area under the curve was 0.600 (95% confidence interval: 0.522–0.678; p = 0.014). However, the diagnostic performance of AIP was not maintained after adjustment for age and sex in the multinomial logistic regression analysis. The results of the receiver operating characteristic analyses are presented in Table 2 and Figure 1.

A significant positive correlation was observed between AIP and disease duration in both migraine subgroups. Additionally, disease duration was moderately correlated with age in the migraine with aura group, while the correlation between AIP and age was weak. The results of the correlation analysis between AIP, disease duration and age in migraine subgroups

**Table 1: Demographic characteristics and laboratory parameters**

| Variable | Migraine without Aura (n=104) | Migraine with Aura (n=99) | Control Group (n=100) | P value |
|---|---|---|---|---|
| Age (years), mean ± SD | 34.16 ± 6.17 | 35.22 ± 7.35 | 34.99 ± 8.53 | 0.499 |
| Female, n (%) | 91 (87.5) | 83 (83.8) | 81 (81.0) | 0.364 |
| Male, n (%) | 13 (12.5) | 16 (16.2) | 19 (19.0) | |
| Smoking, n (%) | 23 (22.1) | 23 (23.2) | 21 (21.0) | 0.910 |
| VAS score, mean ± SD | 6.68 ± 1.10 | 7.29 ± 0.96 | – | 0.002 |
| MIDAS score, mean ± SD | 12.18 ± 5.16 | 13.02 ± 5.06 | – | 0.229 |
| Total cholesterol (mg/dL), mean ± SD | 181.55 ± 31.41 | 190.83 ± 43.90 | 187.71 ± 39.95 | 0.179 |
| LDL cholesterol (mg/dL), mean ± SD | 114.94 ± 22.95 | 119.86 ± 32.63 | 117.09 ± 32.57 | 0.463 |
| HDL cholesterol (mg/dL), mean ± SD | 48.69 ± 9.70 | 50.37 ± 13.62 | 51.07 ± 11.26 | 0.231 |
| Triglycerides (mg/dL), mean ± SD | 129.63 ± 74.67 | 149.70 ± 66.49 | 124.70 ± 68.11 | 0.029 |
| AIP, mean ± SD | 0.378 ± 0.25 | 0.451 ± 0.23 | 0.340 ± 0.26 | 0.004 |

**Table 2: Receiver operating characteristic analysis of the AIP for predicting migraine subtypes**

| Comparison | AUC | Standard Error | P value | 95% Confidence Interval | Cut-off | Sensitivity (%) | Specificity (%) |
|---|---|---|---|---|---|---|---|
| Migraine with Aura – Control | 0.630 | 0.040 | 0.002 | 0.552–0.707 | 0.282 | 76.8 | 47.5 |
| Migraine without Aura – Control | 0.534 | 0.040 | 0.396 | 0.455–0.613 | – | – | – |
| Migraine with Aura – Migraine without Aura | 0.600 | 0.040 | 0.014 | 0.522–0.678 | 0.374 | – | – |

are presented in Table 3.

Furthermore, partial correlation analysis adjusted for age, sex, and migraine severity (VAS and MIDAS score) demonstrated that the positive association between AIP and disease duration remained significant in both migraine subgroups. The results of the partial correlation between AIP and disease duration adjusted for age, sex and migraine severity (VAS and MIDAS score) in migraine subgroups are presented in Table 4.

The scatter plot demonstrates the relationship between the atherogenic index of plasma (AIP) and disease duration in patients with migraine with aura and without aura. The results of the scatter plot showing the relationship between AIP and disease duration in migraine subgroups are presented in Figure 2.

In the subgroup of patients younger than 35 years, triglyceride, high-density lipoprotein cholesterol, and AIP values did not differ significantly between migraine subtypes ($p > 0.05$ for all). In contrast, in patients aged 35 years or older, triglyceride levels and AIP values were significantly higher in those with migraine with aura compared with those without aura ($p < 0.05$ for both). The demographic and laboratory characteristics of participants stratified by age group are presented in Table 5.

Multinomial logistic regression analysis adjusted for age and sex revealed that AIP was not independently associated with migraine with aura (OR=2.89, 95% CI: 0.91–9.21, p=0.073) or migraine without aura (OR=0.41, 95% CI: 0.13–1.32, p=0.136) when compared to controls.

The results of the regression analysis evaluating the effects of AIP, age and sex on migraine subtypes are presented in Table 6.

## DISCUSSION

In this study, the AIP was significantly higher in patients with migraine with aura compared with both patients with migraine without aura and healthy controls. This finding suggests a possible association between migraine with aura and a higher atherogenic and vascular risk profile.

Age-stratified analyses demonstrated that this association was predominantly observed in individuals aged 35 years or older. While no significant differences in lipid-related parameters were detected between migraine subtypes in younger patients, triglyceride levels and the AIP were significantly higher in patients with migraine with aura in the older age group. This pattern may reflect an association between migraine and vascular risk profile; however, given the cross-sectional design, no causal inference can be made. The age cut-off of 35 years should be interpreted cautiously, as it may not fully disentangle aging effects from disease duration.

Previous population-based studies have shown that migraine, particularly migraine with aura, is associated with an increased risk of cardiovascular diseases and mortality.[9,10] Our findings provide biochemical support for these observations by demonstrating a higher atherogenic lipid burden in patients with migraine with aura. Although conventional lipid parameters were comparable between groups, the elevated AIP suggests that lipid ratios may better reflect migraine-related vascular risk than individual lipid components alone.[11]

In addition, subgroup analyses demonstrated a significant positive correlation between AIP and disease duration in both migraine without aura and migraine with aura. Longer disease duration showed a statistical association with AIP levels; however, no causal inference can be

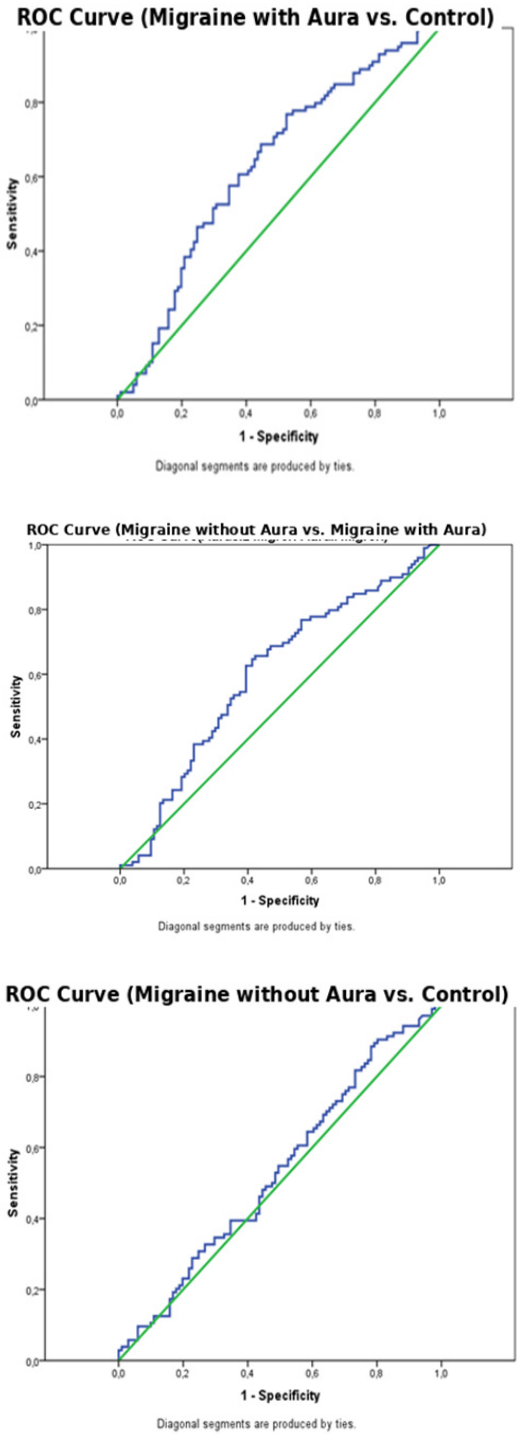


Figure 1. ROC curves of the AIP for discriminating migraine subtypes

made due to the cross-sectional design. Although a strong correlation was observed, AIP did not remain an independent predictor in multivariable analysis, suggesting that this relationship may be mediated by other clinical factors. Although partial correlation analysis adjusting for age, sex, and migraine severity confirmed the persistence of the association, residual confounding cannot be excluded. The very high correlation coefficients observed should be interpreted cautiously, as they may reflect shared variance or overestimation rather than a true strong independent relationship.

Previous studies have suggested that migraine without aura may be more strongly associated with AIP compared to migraine with aura. This discrepancy may be related to differences in study populations and cardiovascular risk profiles, as well as variations in study design and lipid parameters evaluated.

Endothelial dysfunction has been reported in patients with migraine even during interictal periods and has been linked to increased carotid intima–media thickness and subclinical atherosclerosis.[12,13] Considering the close relationship between endothelial impairment and atherogenic lipid profiles, the elevated AIP observed in patients with migraine with aura in the present study may reflect an underlying vascular dysfunction associated with this subtype.

Consistent with previous reports linking the AIP to subclinical cerebral vascular changes in migraine[14], the higher values observed in patients with migraine with aura—particularly among those aged 35 years or older— support a possible association between migraine and vascular risk profile, particularly in patients with longer disease duration.

Several limitations of this study should be acknowledged. The retrospective and single-center design limits causal inference. In addition, inflammatory markers, indices of insulin resistance, and direct measures of endothelial function were not evaluated. The absence of long-term cardiovascular outcome data also precludes assessment of the prognostic value of the AIP. The lack of adjustment for key metabolic confounders such as BMI, physical activity, dietary habits, insulin resistance, and blood pressure represents a major limitation and may have significantly influenced the observed associations. Therefore, the observed relationships should be interpreted with caution.

In conclusion, the present study demonstrates

**Table 3: Correlation analysis between AIP, disease duration and age in migraine subgroups**

| Variable | MwoA (n=104) r (p value) | MwA (n=99) r (p value) |
|---|---|---|
| Disease duration – AIP | 0.860 (<0.001) | 0.751 (<0.001) |
| Disease duration – Age | 0.147 (0.137) | 0.413 (<0.001) |
| AIP – Age | 0.032 (0.748) | 0.213 (0.034) |

**Table 4: Partial correlation between disease duration and AIP adjusted for age, sex and migraine severity (VAS, MIDAS) in migraine subgroups**

| Variable | MwoA (n=104) r (p value), 95% CI | MwA (n=99) r (p value), 95% CI |
|---|---|---|
| Disease duration – AIP | 0.867 (<0.001), (0.797–0.913) | 0.734 (<0.001), (0.635–0.818) |

Abbreviations: AIP, atherogenic index of plasma; MwoA, migraine without aura; MwA, migraine with aura. Partial correlation analyses were performed adjusting for age, sex and migraine severity (VAS and MIDAS score). Confidence intervals were obtained using bootstrap resampling (1000 samples, bias-corrected and accelerated method). A p value < 0.05 was considered statistically significant.

that the AIP is elevated in patients with migraine with aura, particularly in those aged 35 years or older. AIP may be associated with migraine subtype and disease duration; however, this association was not independent after adjustment for confounding variables. Therefore, its independent predictive value appears limited.

## DISCLOSURE

Ethics: The study protocol was approved by the Sakarya University Clinical Research Ethics Committee (Date: 19.01.2026, Decision No: 552465-09) and conducted in accordance with the Declaration of Helsinki. Due to the retrospective design of the study, the requirement for written informed consent was waived by the ethics committee.

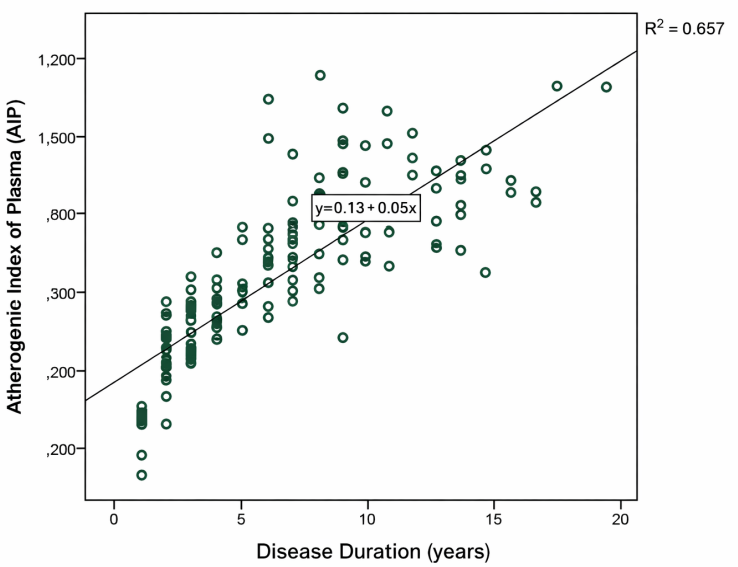


Figure 2. Scatter plot showing the relationship between AIP and disease duration in migraine subgroups

**Table 5: Demographic and laboratory parameters of participants stratified by age group (<35 vs. ≥35 Years)**

| Variable | <35 Migraine without Aura (n=59) | <35 Migraine with Aura (n=53) | <35 Control (n=54) | P value | ≥35 Migraine without Aura (n=45) | ≥35 Migraine with Aura (n=46) | ≥35 Control (n=47) | P value |
|---|---|---|---|---|---|---|---|---|
| Age (years), mean ± SD | 29.69 ± 3.94 | 29.42 ± 4.80 | 28.37 ± 5.53 | 0.348 | 40.02 ± 2.61 | 41.91 ± 2.34 | 42.60 ± 3.54 | <0.001 |
| Female, n (%) | 51 (86.4) | 43 (81.1) | 38 (70.4) | 0.100 | 40 (88.9) | 40 (87.0) | 43 (91.5) | 0.792 |
| Male, n (%) | 8 (13.6) | 10 (18.9) | 16 (29.6) | | 5 (11.1) | 6 (13.0) | 4 (8.5) | |
| VAS score, mean ± SD | 6.71 ± 1.15 | 7.28 ± 0.89 | – | 0.002 | 7.11 ± 1.01 | 7.30 ± 1.05 | – | 0.227 |
| MIDAS score, mean ± SD | 12.10 ± 5.38 | 12.23 ± 5.04 | – | 0.757 | 12.30 ± 4.90 | 13.93 ± 4.97 | – | 0.115 |
| Total cholesterol (mg/dL), mean ± SD | 175.29 ± 26.67 | 194.66 ± 49.68 | 183.96 ± 41.10 | 0.013 | 189.76 ± 35.36 | 186.41 ± 36.16 | 192.02 ± 38.56 | 0.519 |
| LDL cholesterol (mg/dL), mean ± SD | 108.73 ± 19.18 | 118.68 ± 35.49 | 114.24 ± 33.36 | 0.330 | 123.09 ± 25.08 | 121.22 ± 29.31 | 120.36 ± 31.69 | 0.899 |
| HDL cholesterol (mg/dL), mean ± SD | 47.68 ± 9.53 | 52.92 ± 15.78 | 50.37 ± 10.54 | 0.087 | 50.02 ± 9.86 | 47.43 ± 9.98 | 51.87 ± 12.10 | 0.137 |
| Triglycerides (mg/dL), mean ± SD | 125.64 ± 63.60 | 147.23 ± 79.95 | 114.41 ± 58.72 | 0.030 | 134.87 ± 87.59 | 152.54 ± 47.16 | 136.53 ± 76.45 | 0.008 |
| AIP, mean ± SD | 0.38 ± 0.25 | 0.42 ± 0.25 | 0.31 ± 0.27 | 0.113 | 0.37 ± 0.26 | 0.49 ± 0.18 | 0.38 ± 0.25 | 0.020 |

**Table 6: Regression analysis of the effects of AIP, age and sex on migraine subtypes**

| Group | Variable | β | Standard Error | P value | Exp(β) | 95% CI for Exp(β) |
|---|---|---|---|---|---|---|
| Migraine without Aura | Intercept | 0.434 | 0.678 | 0.523 | – | – |
| | AIP | -0.89 | 0.585 | 0.136 | 0.41 | 0.13–1.32 |
| | Age | -0.019 | 0.019 | 0.323 | 0.981 | 0.945–1.019 |
| | Sex | 0.284 | 0.412 | 0.491 | 1.33 | 0.59–2.97 |
| Migraine with Aura | Intercept | -0.557 | 0.715 | 0.436 | – | – |
| | AIP | 1.06 | 0.598 | 0.073 | 2.89 | 0.91–9.21 |
| | Age | -0.005 | 0.020 | 0.794 | 0.995 | 0.957–1.034 |
| | Sex | 0.315 | 0.427 | 0.458 | 1.37 | 0.59–3.16 |

Note: Multinomial logistic regression was performed with the control group as the reference category and adjusted for age and sex. Exp(β) represents the odds ratio (OR), and CI denotes the confidence interval.

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