Neurology Asia 2026; 31(1) : 265 – 273

Olfactory bulb volume changes across Alzheimer's disease stages

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Abstract

Background: Olfactory dysfunction is commonly seen in Alzheimer's disease (AD) and has been reported in many studies. In this study, we measured the olfactory bulb volume (OBV) and olfactory sulcus depth (OSD) by MRI to see if they can help in distinguishing between healthy controls and different stages of Alzheimer's disease (AD). *Methods:* This retrospective cross-sectional study included 125 participants, divided according to clinical stage (Control, Mild AD, Moderate AD, and Severe AD). OBV and OSD were measured by MRI. Welchs ANOVA were used to compare the mean OBV and OSD between the groups. Multiple linear regression was performed to check the relationship of OBV with stage, age, and gender. ROC analysis was used to find the diagnostic cutoff values. *Results:* Mean OBV varied by stage: 81.2±19.2 mm^3 (Controls), 89.1±26.9 mm^3 (Mild AD, vs Controls $p=0.12$), 60.3±19.8 mm^3 (Moderate AD, vs Controls $p<0.001$), and 42.4±17.3 mm^3 (Severe AD, vs Controls $p<0.001$). OSD showed no significant differences ($p>0.05$). Regression analysis indicated a significant association between OBV and AD stage (B=-18.39 for AD vs. controls, $p<0.001$) and a positive association with age (B=0.844, $p=0.008$). ROC analysis for AD (EVRE 3-4 vs. EVRE 1-2) yielded an AUC of 0.706 (95% CI: 0.612–0.800, $p=0.001$), with a cut-off of 56.25 mm^3 providing 96.7% sensitivity and 40.0% specificity.
Conclusions: OBV was significantly lower in moderate and severe AD, which shows that it may have diagnostic value in later stages of the disease. However, there was no significant decrease in Mild AD, meaning it may not be useful for early screening. Long-term studies are needed for understand if OBV can predict the progression to AD.

Keywords: Alzheimer's disease, diagnosis, olfactory bulb volume, olfactory sulcus dept

INTRODUCTION

Alzheimer's disease (AD) is a progressive brain disorder and the most common cause of dementia around the world, affecting millions of people and creating a serious health problem.[1,2] Although there have been many advances in understanding how the disease works, there are still not enough effective treatments. This is because the diagnosis is usually made after many brain cells are already lost.[3,4] Exploring biomarkers in different stages of AD is important to make diagnosis and treatment better.[5-8]

Problems with the olfactory function are seen in different stages of AD, but the frequency changes between studies.[9-13] Research has shown that olfactory dysfuntion can appear in AD, sometimes even before memory loss or other cognitive problems.[14-17] Around 85% of early-stage AD patients may have difficulties with smelling or recognizing odors before cognitive symptoms, which shows a possible diagnostic value, even though it is not always an early sign.[18-21] These results show that smell tests can be a cheap and non-invasive way to help in diagnosis compared to traditional methods.[12]

The olfactory bulb, which is important for the olfactory function, is affected by AD. Studies of postmortem brain tissue have shown that neurofibrillary tangles are present in the entorhinal and transentorhinal areas, the anterior olfactory nucleus, and the olfactory bulb, even in the early stages of AD.[19,22-25] MRI studies have also shown that the olfactory bulb volume (OBV) reduces in AD cases, but the level of change depends on the disease stage.[6, 26] The loss of OBV

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Date of Submission: 31 July 2025; Date of Accpetance: 12 December 2025

https://doi.org/10.54029/2026mdm

is related to amyloid-beta and tau accumulation, and it is also connected with atrophy in the medial temporal lobe.[5,6,27,28]

Olfactory problems have practical benefits as biomarkers. Olfactory tests are easier to perform than invasive or expensive methods like cerebrospinal fluid analysis or PET scans.[13,29,30] Tests that check the ability to identify or discriminate odors show good sensitivity and specificity for AD.[12,31-33] A meta-analysis also highlights that odor identification tests can help identify at-risk individuals.[12]

The olfactory system has a close connection with brain regions involved in memory, such as the hippocampus and entorhinal cortex.[19,34] Because the olfactory bulb is easily affected by neurodegeneration, it may be a useful marker that can help understand and diagnose the various stages of AD.[6,19]

While olfactory biomarkers appear promising, challenges remain, such as establishing standards and testing them over time. Our study aims to examine the diagnostic value of OBV and OSD across AD stages (controls, mild, moderate and severe AD) and provide evidence on how well they can distinguish different stages.

METHODS

Study design and participants

This retrospective cross-sectional study included 125 participants, comprising healthy individuals and patients. Participants were stratified into four groups based on clinical assessment: controls (n=28), mild AD (n=33), moderate AD (n=46), and severe AD (n=18).This study was approved by local ethics committee and conducted in accordance with the Helsinki Declaration (Ethics Committee Approval No:2025/34). Participants were recruited based on established 2011 National Institute on Aging (NIA) diagnostic criteria for probable AD, while healthy controls were included if they exhibited normal cognitive function and activities of daily living.

Exclusion criteria included clinical or imaging evidence of stroke, a history of head trauma and any other central nervous system diseases. Additionally, MRI scans with motion artifacts or sinonasal abnormalities were excluded to ensure the reliability of OBV measurements.

Scanning protocol

All MR images were obtained using a head coil on General Electric Signa™ Explorer MR 1.5T closed system scanner (GE Healthcare, Chicago, Illinois, United States). The sequence used for assessment of the olfactory bulb in all patients and control subjects is Coronal T2-weighted fast spin echo (FSE) sequence. Our imaging parameters were 332 × 232 matrix and 22 cm field of view (FOV), repetition time (TR): 6000 ms, echo time (TE): 100 ms, excitation number (NEX): 4. The field of view covered the anterior and middle segment of the base of the skull. Voxel size was about 0.66 mm × 0.95 mm × 5 mm.

Volumetric analysis and image interpretation

Volumetric analyses were independently performed by a radiologist with 9 years of experience in neuroradiology and a neurologist experienced in neuroimaging (ICC: 0.91). Volumetric analysis of the olfactory bulb was performed using a free and open-source imaging package software [three-dimensional (3D) Slicer version 5.2.2 for Mac OS X] (http://www.slicer.org/). Segmentation was conducted in Labelmap (voxel-based) mode using the Segment Editor module without applying interpolation or surface smoothing. Volume values were automatically calculated from the voxel-based labelmaps. All measurements were performed on images in their original DICOM format. The olfactory bulbs were manually delineated. Following the segmentation of all slices containing the regions of interest, a quantification process was performed, yielding the volumetric measurement of the olfactory bulb structure and generating a three-dimensional graphical representation (Figure 1).The depth of the olfactory sulcus was assessed on coronal T2-weighted images by constructing a tangent line along the inferior margins of the gyrus rectus and medial orbital gyrus, followed by measuring the perpendicular distance from this line to the deepest point of the olfactory sulcus (Figure 2).

Statistical methods

The Kolmogorov-Smirnov test confirmed that all variables followed a normal distribution. Continuous variables are presented as mean ± standard deviation (Std) and categorical variables as frequencies and percentages. Because the group sizes were not equal, Welch's ANOVA was used to compare the mean OBV and OSD between groups. Post-hoc comparisons were done with the Games–Howell test. Multiple linear regression analysis was used to study the independent relationships between mean OBV and the variables of stage, age, and sex.

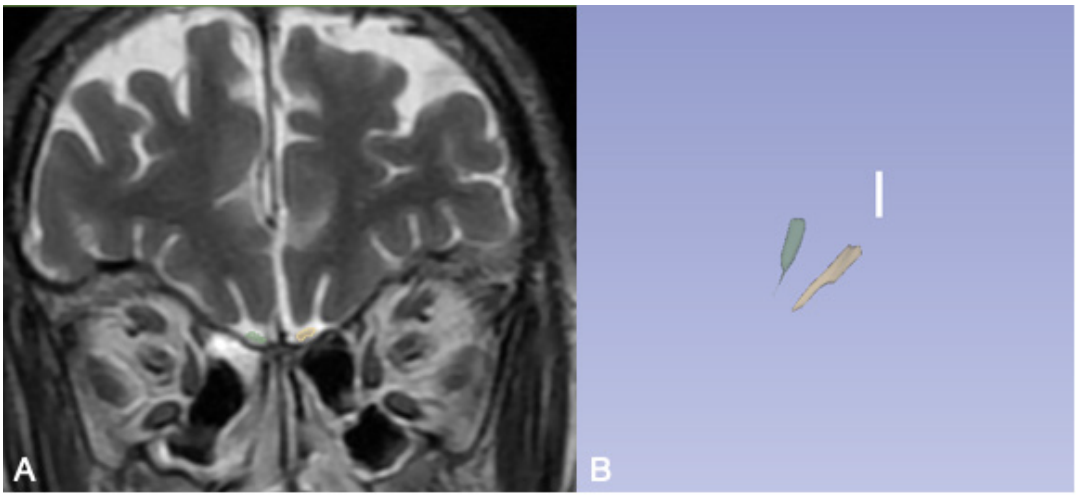

Figure 1. Olfactory bulb structure and three-dimensional graphical representation

Collinearity was checked with tolerance and VIF values. The diagnostic performance of mean OBV was evaluated using receiver operating characteristic (ROC) analysis, with the Youden index to determine the optimal cut-off value. All analyses were conducted using the mean OBV and mean OSD, which was calculated by averaging the right and left OBV and OSD. Statistical significance was set at $p<0.05$ for all analyses. All statistical analyses were performed using SPSS version 16 (SPSS Inc., Armonk, NY). The sample size and statistical power were calculated using G*Power software (version 3.1, Universität Düsseldorf, Düsseldorf, Germany) to ensure an adequate power level of 0.80 for detecting significant differences among groups with an alpha level of 0.05.

RESULTS

A total of 125 participants were included in the study, consisting of 30 controls, 31 patients with mild AD, 46 with moderate AD, and 18 with severe AD. Descriptive analyses of demographic and imaging variables are presented in (Table 1**)**. The distribution of gender across disease stages did not differ significantly according to the chi-square test ($\chi^2= 2.44$, $p = 0.485$)

There was a significant difference in the mean OBV between the groups ($F(3, 56.22) = 25.37$, $p < 0.001$). However, no significant difference was found in OSD ($F(3, 55.41) = 0.48$, $p = 0.697$). According to the Games–Howell test, the mean OBV was lower in the moderate and severe Alzheimer's disease groups compared with the

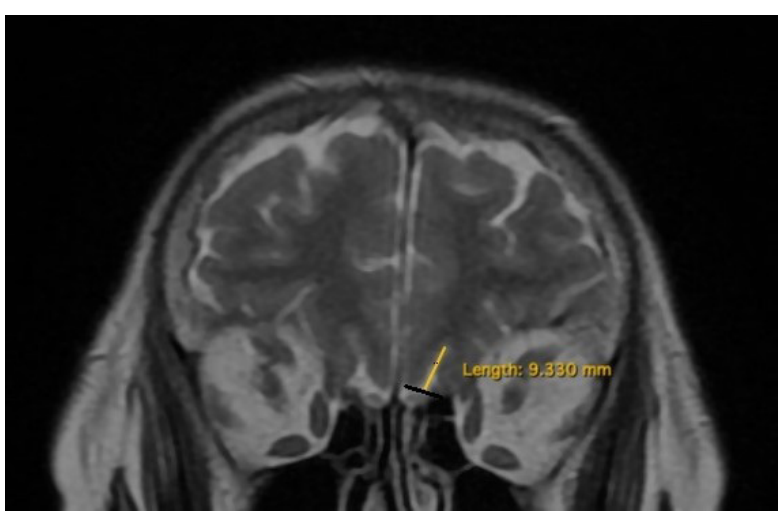

Figure 2. Olfactory sulcus measurement.

Table 1: Descriptive analyses

	Control Mean±Std	Mild AD Mean±Std	Moderate AD Mean±Std	Severe AD Mean±Std
Age, Year	73.5±6.6	78.1±7.0	75.8±6.6	72.6±8.8
Right Olfactor Bulb Volume (mm^3)	84.2±22.7	89.3±27.2	60.3±20.7	44.0±19.3
Left Olfactor Bulb Volume (mm^3)	82.2±22.8	86.0±28.1	60.2±21.7	40.7±17.5
Right Olfactor Sulcus Dept (mm)	9.1±1.2	8.4±1.1	8.5±1.4	8.8±1.6
Left Olfactor Sulcus Dept (mm)	8.5±1.3	8.7±1.1	8.4±1.1	8.6±0.8
Mean Olfactor Bulb Volume (mm^3)	83.2±21.6	87.64±26.0	60.26±19.8	42.35±17.3
Mean Olfactor Sulcus Dept (mm)	8.8±1.2	8.6±1.1	8.4±1.2	8.7±1.1
	N (%)	**N (%)**	**N (%)**	**N (%)**
Gender, Female	15 (50)	18 (58)	31 (67)	10 (56)
Sample size	30 (24)	31 (25)	46 (37)	18 (15)

control and mild AD groups (all $p < 0.01$) (Table 2, Figure 3.).

Statistics showed a significant difference in age between the groups ($F(3, 52.85) = 2.98$, $p = 0.039$). But Post-hoc analysis using the Games–Howell test revealed that participants in the mild Alzheimer's disease group were significantly older than those in the control group ($p = 0.047$). No other significant differences were found among the other groups (all $p > 0.05$) (Table 3.).

ROC analysis was conducted to assess the diagnostic performance of the variable mean OBV. AUC was calculated as 0.706 (95% CI: 0.612–0.800, p = 0.001). Based on the Youden index, the optimal cut-off value was determined as 56.25, which provided a sensitivity of 96.7% and a specificity of 40.0% (Figure 4).

Regression model was statistically significant ($F(3,121)=21.84$, $p<0.001$) and explained approximately 35% of the variance in OBV (R^2=0.351, adjusted R^2=0.335). Controls and AD stages showed the strongest and significant negative association with OBV (β=–0.529, $p<0.001$). Both age (β=0.171, p=0.021) and sex (β =–0.153, p=0.040) also contributed significantly to the model. Collinearity diagnostics indicated no multicollinearity problems (VIF values≈1.0; tolerance>0.99). The standardized residuals ranged between –1.83 and 2.70 (Table 4.).

DISCUSSION

Previous studies in the literature have demonstrated that olfactory dysfunction can serve as an biomarker for AD.[5,21,31,35-37] Traditional smell tests often depend on the patient's response. They also change due to differences in nasal anatomy. But MRI is now used more widely and this allows doctors to diagnose more objectively. Our study aimed to add new objective test method for AD

Table 2: Welch ANOVA and Games–Howell post-hoc comparisons for mean OBV

	MD (mm^3)	SE	p	95% CI
Control vs Mild	-4.45	6.12	0.886	-20.63 – 11.73
Control vs Moderate	22.93	4.91	**<0.001**	9.94 – 35.91
Control vs Severe	40.84	5.68	**<0.001**	25.65 – 56.02
Mild vs Moderate	27.38	5.51	**<0.001**	12.77 – 41.99
Mild vs Severe	45.29	6.20	**<0.001**	28.76 – 61.82
Moderate vs Severe	17.91	5.02	**0.006**	4.39 – 31.43
	df1	**df2**	**F**	**p**
Welch ANOVA- OBV	3	56.22	25.37	**<0.001**
Welch ANOVA- OSD	3	55.41	0.481	0.697

CI: Confidence Interval, df: Degrees of Freedom, MD: Mean Difference, OBV: Olfactory Bulb Volume, OSD: Olfactory Sulcus Dept, SE: Standart Error,

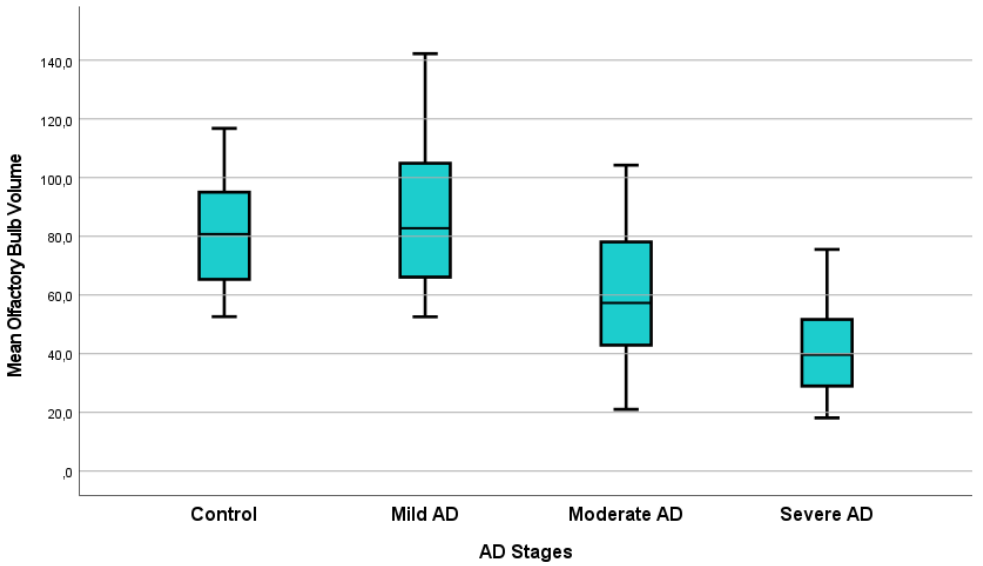

Figure 3. Box plot showing mean olfactory bulb volumes in control subjects and patients with mild, moderate, and severe Alzheimer's disease (AD)

to the current literature. The results show that OBV can be used as an objective imaging test in Alzheimer's disease. By comparing OBV in different stages, we suggest that OBV may help to distinguish patients with AD from healthy individuals.

We found significant OBV reductions in both moderate and severe AD groups compared to controls. A study showed clear atrophy in the olfactory bulb and tract in AD patients, with signs of neurodegeneration already present at the MCI stage In contrast, we did not find a significant difference between the mild AD group and the controls. However, a longitudinal study is necessary to assess the ability of OBV to distinguish between individuals with MCI and mild AD who will progress to severe AD and those who will not. Since our study is cross-sectional, we did not include MCI patients to directly evaluate the applicability of OBV in individuals with a confirmed Alzheimer's diagnosis.

Olfactory dysfunction is seen as a strong early indicator for progression to Alzheimer's, with around 10% of affected individuals eventually developing the disease.[38] But the widespread smell loss linked to COVID-19 might weaken the usefulness of olfactory tests in distinguishing at-risk cases.[39-41] Assessing OBV could improve diagnostic precision. According to a study OBV is significantly reduced in AD patients compared to healthy controls, a finding that is not observed in Parkinson's disease (PD) or frontotemporal dementia (FTD).[42] This finding suggests that

Table 3: Welch ANOVA and Games–Howell post-hoc comparisons for mean age

	MD (mm³)	**SE**	**p**	**95% CI**
Control vs Mild	-4.66	1.75	**0.047**	-9.29 – -0.04
Control vs Moderate	-2.32	1.55	0.446	-6.40 – 1.77
Control vs Severe	0.86	2.40	0.984	-5.69 – 7.40
Mild vs Moderate	2.35	1.59	0.459	-1.86 – 6.55
Mild vs Severe	5.52	2.43	0.128	-1.09 – 12.12
Moderate vs Severe	3.17	2.29	0.519	-3.12 – 9.47
	df1	**df2**	**F**	**p**
Welch ANOVA- Age	3	52.846	2.984	**0.039**

CI: Confidence Interval, df: Degrees of Freedom, MD: Mean Difference, SE: Standart Error,

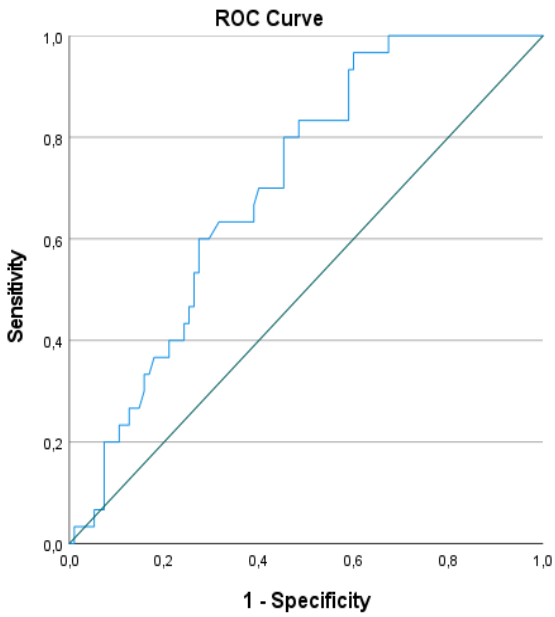

Figure 4. ROC curve for mean olfactory bulb volume control vs AD.

OBV measurement may help not only in early AD diagnosis but also in telling it apart from other neurodegenerative diseases. It provides more specific information than tests affected by nasal anatomy or unrelated pathologies. OBV reduction is strongly linked to amyloid-β and tau accumulation, which supports its value as a possible preclinical marker.[18,28,43,44] Postmortem studies show that the anterior olfactory nucleus (AON), key for smell processing, is one of the first regions where Aβ and tau appear.[27,45]

The olfactory system's role in AD goes beyond structural atrophy. Tau pathology is found in almost all OB samples from AD patients. Aβ appears later, starting around Thal phase 3. This pattern seems to match Braak stages and disease severity.[45] Dopaminergic changes in the OB have also been reported. AD patients show more dopaminergic periglomerular neurons, possibly as a response to early damage. This upregulation might help counteract the toxic effects of tau, Aβ, and α-synuclein, which interfere with smell and neural signaling.[42]

Functional imaging shows that olfactory cortex atrophy often runs parallel with hippocampal degeneration. This supports the idea that memory and smell networks are closely linked.[18] Other studies suggest the olfactory nerve itself develops tau deposits as dementia progresses.[44] All this points to a direct role of olfactory dysfunction in AD, rather than it being a side effect.

Some researchers believe that OB atrophy, combined with smell tests, could work as a non-invasive marker for early AD.[18, 28] Still, there are obstacles. Standardizing OBV measurements is not easy, and it's difficult to separate OB changes in AD from those in other brain diseases.

In our study, OBV showed a weak positive

Table 4: Multiple linear regression analysis

Variable	B	SE	β	t	p	Tolerance	VIF
(Constant)	69.33	22.11		3.14	**0.002**		
Control, AD Stages	–14.09	1.96	–0.529	–7.20	**<0.001**	0.992	1.008
Age	0.64	0.27	0.171	2.34	**0.021**	0.999	1.001
Sex	–8.31	4.00	–0.153	–2.08	**0.040**	0.993	1.007
	R	**R^2**	**Adjusted R^2**	**RMSE**	**p**		
Model Statistics	0.593	0.351	0.335	21.91	**0.001**		

relationship with age. This result is different from most other studies, which usually show that OBV decreases with age.[46] This may be explained by the age difference between the groups in our study. The mild AD group was slightly older than the control group, and this imbalance might have affected the regression results, while there was no age difference between the moderate, severe, and control groups. Also, the effect of AD itself on OBV may be stronger than the effect of age, which could make the age-related decline less visible.

Altogether, these findings support the idea that OB degeneration plays a key role in AD. It also strengthens the case for using OBV as an early diagnostic marker. The presence of tau, Aβ, inflammation, and dopaminergic changes in the OB suggests that smell loss in AD reflects wider disease mechanisms.

Another important result from this study was the diagnostic cut-off for OBV: 56.25 mm^3. At this threshold, sensitivity reached 96.7%, but specificity was lower at 40.0%. The AUC was 0.706. These values show that OBV could be useful in clinical diagnosis. Earlier studies also reported good diagnostic performance for OB and tract (OBT) volumes, with sensitivity and accuracy around 78% and 79%, respectively.[6] This supports including OBV in multimodal diagnostic models for AD.

While OBV was clearly reduced compared to controls, we did not find significant differences in OSD between groups. This suggests that OSD may have limited value as a diagnostic marker. OB is directly involved in smell processing and is among the first regions affected in AD. But OSD mostly reflects cortical folding, shaped early in development. It might not show the same kind of atrophy seen in OB. Technical factors could also explain the lack of significant results. OSD measurement on MRI depends heavily on image quality, segmentation accuracy, and individual anatomical variation. These can introduce noise and reduce sensitivity. Still, OSD has been considered in Parkinson's disease. Some studies report reduction there, possibly related to dopamine-linked degeneration, which may affect olfactory regions differently than in AD.[47-49]

OBV measurement offers a non-invasive and low-cost alternative to current diagnostic tools like amyloid PET and CSF analysis. PET scans are expensive and not always available. CSF testing, on the other hand, needs a lumbar puncture, which is invasive. In contrast, OBV can be measured using standard MRI, making it more practical, especially where resources are limited. Combining OBV with smell tests could further improve early detection in such settings.

Although OBV shows strong potential for AD screening, some challenges remain. Since this was a cross-sectional study, we couldn't track OBV changes over time or evaluate its predictive value for disease progression. One major issue is the lack of standardized measurement methods. Different techniques are used across studies, which makes comparisons difficult. There's a clear need for consensus in imaging protocols to improve consistency and reliability.

In this study, OBV was measured manually. This could introduce some variability. Automated methods might improve both reliability and clinical use. Still, long-term studies are needed to test how well OBV can predict progression or separate AD from other dementias and healthy aging.

Another limitation was the imbalance in group sizes. There were more AD patients than controls. Although we used Welch's ANOVA to adjust for unequal samples, this difference could still influence the results.

In conclusion, this study points to the potential of OBV in diagnosing AD. Combining OBV with smell tests and other markers could support its strenght. Future studies should focus on standardizing imaging protocols and following patients over time to clarify how OBV can be used in clinical practice.

ACKNOWLEDGEMENTS

The authors would like to express their sincere gratitude to the volunteers.

DISCLOSURE

Ethics: The study was approved by Ethical Committee of Bolu Abant Izzet Baysal University (No: 2023/89).

Data availability: The data supporting the findings of this study are available from the corresponding author upon reasonable request. Due to ethical reasons certain data is not publicly accessible.

Artificial intelligence (AI) tools, such as ChatGPT, were only used for grammar correction and language refinement in this manuscript.

Financial support: None

Conflict of interest: None

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