European Review for Medical and Pharmacological Sciences 2022; 26: 7734-7741

Classification of Alzheimer's disease stage using machine learning for left and right oxygenation difference signals in the prefrontal cortex: a patient-level, single-group, diagnostic interventional trial

J. KIM[1], S.C. KIM[2], D. KANG[2], D.K. YON[3,4], J.G. KIM[1]

[1]Department of Biomedical Science and Engineering, Gwangju Institute of Science and Technology, Gwangju, South Korea
[2]Institute for Artificial Intelligence, N.CER, Gwangju, South Korea
[3]Centre for Digital Health, Medical Science Research Institute, Kyung Hee University Medical Center, Kyung Hee University College of Medicine, Seoul, South Korea
[4]Department of Data Science, Sejong University College of Software Convergence, Seoul, South Korea

Abstract. – OBJECTIVE: Recent evidence shows that indicators testing conventional olfactory function have a high degree of similarity to cognitive function tests and the potential to diagnose early-stage Alzheimer's disease (AD). In this study, the efficacy of functional near-infrared spectroscopy time-series data obtained through olfactory stimulation was investigated as an early diagnostic tool for mild cognitive impairment in AD using random forest, a machine learning algorithm.

PATIENTS AND METHODS: We conducted a patient-level, single-group, diagnostic interventional trial using near-infrared signals measured during olfactory stimulation in the prefrontal cortex of 178 older adults ranging from normal to participants with AD as markers to discriminate AD stages. We first divided the participants into normal older adults, AD mild cognitive impairment, and AD groups using dementia diagnostic criteria such as the Mini-Mental State Examination and Seoul Neuropsychological Screening Battery. We compared the left and right oxygenation difference by calculating the relative oxygenation difference from the change in relative oxygen concentration.

RESULTS: A total of 168 participants met the eligibility criteria: 70 (41.6%) had normal cognitive function; 42 (25%) mild cognitive impairment; 21 (12.5%) mild AD; and 35 (20.8%) moderate AD. A random forest machine learning model was developed to predict the AD stage, with an area under the receiver operating characteristic curve of 90.7% for mild cognitive impairment and AD, 90.99% for mild cognitive impairment, and 93.34% for AD only.

CONCLUSIONS: Based on the classification of the oxygenation difference index of the left and right prefrontal cortices during olfactory stimulation through machine learning, we found that it was possible to detect early-stage mild cognitive impairment in AD. Our results highlight the potential for early AD diagnosis using near-infrared signals from the prefrontal cortex obtained upon olfactory stimulation. Moreover, the results showed high similarity to the existing cognitive function tests and high accuracy in AD stage classification.

Key Words:
Cognitive impairment, Alzheimer's disease, fNIRS, Mild cognitive impairment, Random forest classifier.

Introduction

Alzheimer's disease (AD) is the leading cause of dementia worldwide[1-3]. The worldwide prevalence is 5-6 per 1000 people, and this number is expected to rise further in the future[1,2]. It is a disease in which beta-amyloid entanglement and tau protein block nerve signals and induce neuronal cell death, leading to cognitive impairment[1,2]. Therefore, it must be detected at an early stage when cognitive decline begins[4]. Previous studies have reported a decrease in olfactory function when cognitive function declines[5,6]. Olfactory function is also correlated with cognitive func-

Corresponding Authors: Dong Keon Yon, MD, FACAAI; e-mail: yonkkang@gmail.com
Jae Gwan Kim, Ph.D; e-mail: jaekim@gist.ac.kr

tion tests[7,8]. In animal and human autopsy studies, beta-amyloid entanglement and tau protein toxicity have been reported to affect one of the thin cranial nerves, the posterior nerve. In animal models of AD and studies with humans, when the olfactory nerve is affected by the causative agent of AD, the ability to identify olfactory sense is reduced[9-11].

Many studies have used positron emission tomography (PET) and magnetic resonance imaging (MRI) to quantify brain responses to olfactory stimuli and identify activated regions[12]. The results confirmed that activation occurred more frequently in the right orbital frontal cortex (OFC) than in the left eye[13,14]. In addition, studies have shown that the left OFC is activated more by unpleasant scents, and the right OFC is activated by familiar or pleasant smells[15]. Using these characteristics, if there is a difference between healthy older adults and patients with AD, it can be expected that the disease can be detected at the stage of mild cognitive impairment[14,16].

Functional near-infrared spectroscopy (fNIRS) is a technology that can measure oxygenation difference in tissues by delivering near-infrared wavelength light to organs. This technology can track reduced oxygen-haemoglobin and reduced deoxy-haemoglobin[17]. Proper processing of the fNIRS signal can be used to measure cortical oxygenation difference, similar to PET-computed tomography (CT). These methods are being actively used in neuropsychiatric research[18,19]. In AD, attempts have been made to diagnose and detect brain fNIRS signals by providing memorisation and behavioural tasks to participants. The fNIRS diagnostic method has a good advantage over existing examination methods in that it can increase the accuracy using deep or machine learning[19,20].

In this context, fNIRS has several advantages over other imaging devices, making it more suitable for the diagnosis of AD[17]. fNIRS can be used to measure the change in oxygenation difference in the cerebral cortex in small hospitals that do not conduct neuropsychological tests or in small hospitals without large hospital-level facilities such as MRI or CT[17]. Since fNIRS is a light-based technology, patients are not exposed to risks such as radiation and do not have to lie down for an extended period as with MRI; therefore, there are fewer restrictions for older adults. However, fNIRS-based studies have not included all stages of AD, have a relatively low-evidence study design with a 10-patient/control comparison, and included only some patients with normal and AD among normal, mild cognitive impairment, and AD[21]. Observations of the mechanisms by which the brain activity changes are also limited[19,20].

In this study, the efficacy of fNIRS time-series data obtained through olfactory stimulation was investigated as an early diagnostic tool for mild cognitive impairment in AD using random forest, a machine learning algorithm.

Patients and Methods

Study Design

This study included volunteers aged ≥60 years in the community of Gwangju Metropolitan City, South Korea, from 2 March 2021 to 1 March 2022[22,23]. Participants with malignant tumours, head trauma, cerebral haemorrhagic stroke, anatomical problems such as loss of smell after brain surgery, and mental disorders such as major depression, schizophrenia, and bipolar disorder were excluded. In addition, those who had musculoskeletal disorders to the extent that they were unable to proceed with the examination or were uncooperative, were excluded.

Written consent was obtained from each participant and legal guardian at the time of patient registration. Research protocols such as olfactory stimulation and neuropsychological testing were approved by the Gwangju Institute of Science and Technology Institutional Review Committee (20210115-HR-58-01-02). The trial was registered with the Clinical Research Information Service of the Republic of Korea (CRIS number, KCT0007589). The study adhered to the tenets of the Declaration of Helsinki.

Participants

A total of 178 volunteers aged ≥60 years were recruited. The participants were 73 older adults with normal cognitive function, 45 with mild cognitive impairment due to AD, and 60 with mild to moderate AD dementia. In the final sample, 168 older adults were included. Three participants from the normal group, three with mild cognitive impairment, and four with dementia were excluded because of poor signal quality and failure to follow the test protocol. Since people with moderate dementia cannot undergo tests over an extended period, only the Mini-Mental State Examination (MMSE)[24] and olfactory tests were conducted.

Cognitive function tests were conducted using the MMSE and Seoul Neuropsychological Screening Battery. The diagnostic criteria for each AD

group were based on the 2011 National Institute on Aging recommendations[25].

The normal group included participants whose cognitive function test results were normal. The AD mild cognitive impairment group had a standardised uptake value of 1.1 or higher on PET-CT at Chonnam National University Hospital (Gwangju, South Korea) before the cognitive function test among those with amyloid-beta plaque to confirm AD. Participants were classified with mild cognitive impairment if the comprehensive Jak/Bondi classification criteria were met[25]. In this classification, five diagnostic methods for mild cognitive impairment are presented based on cognitive function indicators[17]. The comprehensive criteria we used defined the cognitive function test scores as being in the lower 5% of the standard normal distribution in domain 2. Participants with AD dementia were defined as those diagnosed with AD at a hospital and had a clinical dementia grade of 1 or higher[17].

Stimulus and Experimental Design

For olfactory stimulation[17], a total of five scents (unscented, downy, peppermint, leather, and unscented) were presented using a sniff stick. For each stimulus, participants were asked to smell the scent 5–10 cm away from the nose for 20 seconds. At this time, they were allowed to smell naturally, without closing their eyes or blocking one nostril. A 40-second break was permitted between each scent stimulus. The total experiment duration time was approximately 5 minutes.

Data Pre-Processing

Data for measuring oxygenation difference were collected using N.CER N2 fNIRS equipment (N.CER Co., Gwangju, South Korea) with wavelengths of 730 and 850 nm. The NIRS probe consists of two emitters, three left and right emitters, and one detector for skin signal detection. The probe was placed between the eyebrows, where it most likely records oxygenation difference in the prefrontal cortex. Before the probe was attached, the skin was wiped with an alcohol swab.

For fNIRS measurement, the raw data sampled at 10 Hz and stored as CSV were signal-processed using Python (ver 3.9)[26,27]. To remove physiological signals such as cardiac and respiration signals from the original signal, wavelet processing and a low-pass filter (cutoff 3 Hz) were performed to remove the high frequencies. Subsequently, the concentrations of oxidised haemoglobin and reduced haemoglobin were calculated using the modified Beer-Lambert law, and the skin signal was removed to extract the pure brain signal using the same detector, and corrected NIRS (C-NIRS) data were obtained.

By subtracting the reduction graph value from the obtained C-NIRS oxidised haemoglobin graph, the relative oxygenation difference (oxygen consumption) separated from red blood cells was measured and obtained. Using the difference in oxygen consumption between the left and right prefrontal lobes, we created a graph of the difference in oxygen consumption between the two prefrontal lobes (LR oxygenation difference; **Supplementary Figure 1**).

Machine Learning Analysis and Sample Size Calculation

We checked the characteristics of the LR oxygenation difference graph to determine whether it was possible to classify the stages of AD using a random forest classifier, a machine learning algorithm. In addition, the accuracy and other indicators of this machine learning algorithm were calculated using the average value of the five hyperparameters to prevent overfitting.

Statistical Analysis

We compared the sample sizes required to use data applicable to real participants with near-infrared spectroscopy. Statistically, 17 participants in each group needed to have 90% power at the 10% significance level for the normal, mild cognitive impairment, and AD groups. We included 70 participants with CN, 42 with MCI, and 56 with AD. Therefore, even with the hyperparameters modified, the test set was averaged by running 10 tests, maintaining the test set size of 34 participants. A two-sided *p*-value below 0.05 was considered statistically significant.

Results

Baseline Characteristics

A total of 178 older adult individuals were screened. Of these, 168 met the eligibility criteria. Four participants with nasal obstruction and acute respiratory disease, and six participants who refused cognitive function tests were excluded. Of the 168 participants, 70 (41.6%) had normal cognitive function (73.9 ± 5.7 years), 42 (25.0%) mild cognitive impairment due to AD (73.0 ± 6.0 years), and 21 (12.5%) AD (75.6 ± 7.6 years), while 35 (20.8%) had moderate dementia (83.6 ± 5.4 years) (Table I).

Table I. Participant baseline characteristics at enrolment (n=168).

	Total	CN	MCI†	AD‡	Moderate AD‡
Number (%)	168 (100.0)	70 (41.6)	42 (25)	21 (12.5)	35 (20.8)
Age, years, mean	75.9 ± 7.2	73.9 ± 5.7	73.0 ± 6.0	75.6 ± 7.6	83.6 ± 5.4
Sex, female (%)	96 (57.1)	34 (48.6)	22 (52.4)	12 (57.1)	28 (80.0)
Education, years, median (IQR)	10.5 ± 4.5	10.9 ± 4.3	10.4 ± 4.8	9.4 ± 4.9	-
APOE4 carrier, n (%)	84 (63.6)	37	34	13	-
Mini-Mental State Examination, median (IQR)	23.5 ± 6.3	28.0 ± 1.3	25.8 ± 2.4	19.2 ± 4.3	14.4 ± 5.0
Cognitive measures (composite z score), mean (SD)					
SNSB attention	-0.3 ± 1.0	0.0 ± 0.9	-0.6 ± 0.8	-0.9 ± 1.0	-
SNSB language and related function	0.1 ± 1.5	0.6 ± 0.7	-0.0 ± 1.1	-2.0 ± 2.9	-
SNSB visuospatial function	0.2 ± 2.3	1.0 ± 0.7	0.2 ± 1.6	-2.4 ± 4.6	-
SNSB memory	-0.4 ± 1.7	0.7 ± 1.0	-0.9 ± 1.5	-2.7 ± 1.2	-
SNSB frontal/executive function	-0.3 ± 1.4	0.5 ± 0.8	-0.6 ± 1.1	-2.3 ± 1.4	-
Amyloid PET-CT positive (%)	90 (67.7)	28 (40.0)	42 (100)	21 (100)	-

†AD: Alzheimer's disease; APOE4: apolipoprotein E 4; CN: cognitively normal; IQR: interquartile range; MCI: mild cognitive impairment; SD: standard deviation; SNSB: Seoul Neuropsychological Screening Battery; PET-CT: positron emission tomography-computed tomography. †The diagnostic criteria for MCI were based on the Jak/Bondi comprehensive criteria.

Left and Right Oxygenation Difference Graphs for Each Group and Important Sections Considered in the Random Forest Model

The left and right haemoglobin-oxyhaemoglobin graphs for the normal, mild cognitive impairment, AD, and moderate dementia of the participants in each group are shown in Figure 1.

Prediction Results of Cognitive Dysfunction Due to Alzheimer's Disease

The LR oxygenation difference signal, calculated from the difference between the oxidised haemoglobin and reduced haemoglobin signals using the fNIRS signal, was applied to the random forest model. The averages obtained using 10 hyperparameters are listed in Table II. The training

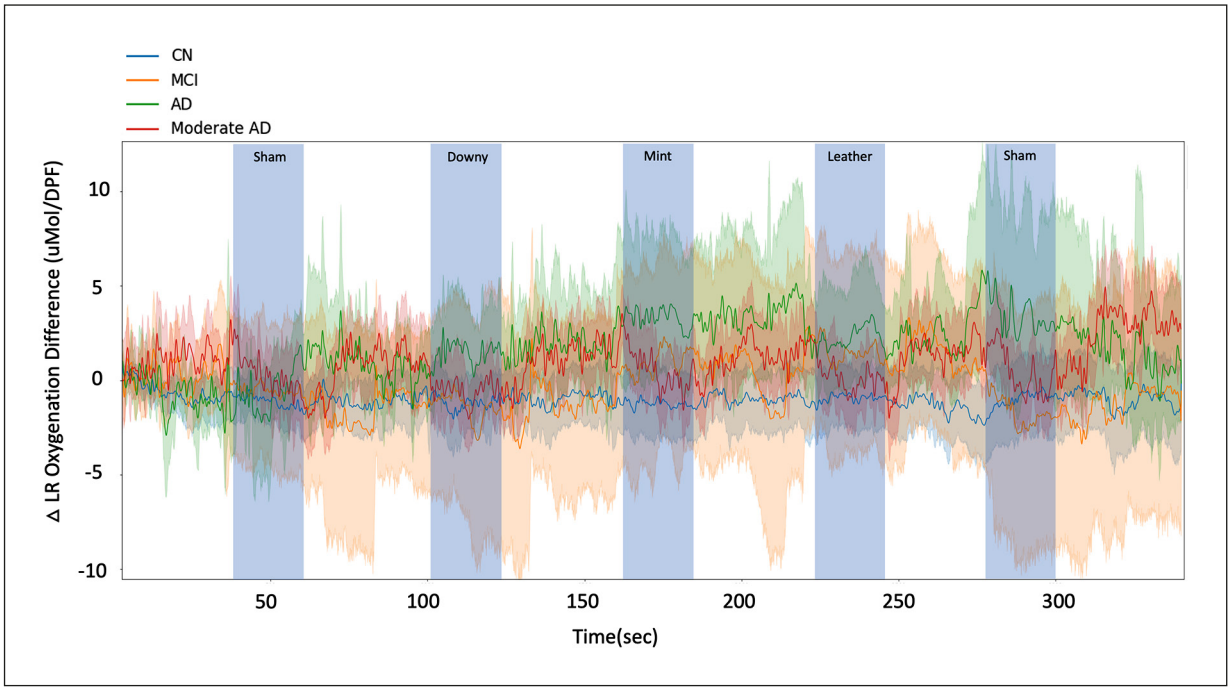

Figure 1. Graph of left and right oxygenation difference for each group. CN: cognitively normal; MCI: mild cognitive impairment; AD: Alzheimer's disease; LR: Left/Right; DPF: Differential pathlength factor. ‡Mild dementia and moderate dementia were integrated into the dementia stages and trained on the model.

Table II. Ten hyperparameter average results of random forest machine learning.

Test Set Performance (%, best performance)	Results					
	Accuracy	Precision	Recall	F1 score	ROC_AUC	PR_AUC
Prediction model as AD and MCI using machine learning algorithm	91.159 ± 1.39 (94.1)	91.5 ± 1.9 (95.5)	90.7 ± 1.6 (92.9)	90.9 ± 1.4 (93.8)	90.7 ± 1.6 (92.9)	84.6 ± 3.3 (91.6)
Prediction model as only MCI using machine learning algorithm	92.06 ± 2.36 (95.80)	92.66 ± 3.17 (96.80)	90.99 ± 2.40 (94.40)	91.42 ± 2.46 (95.40)	90.99 ± 2.40 (94.40)	90.98 ± 2.58 (93.70)
Prediction model as only AD using machine learning algorithm	94.00 ± 3.40 (100)	94.86 ± 2.36 (100)	93.33 ± 4.51 (100)	93.56 ± 3.78 (100)	93.34 ± 4.52 (100)	92.79 ± 5.54 (100)

ROC: receiver operating characteristic; AUC: are under the curve; PR_AUC: area under the precision-recall curve; MCI: mild cognitive impairment; AD: Alzheimer's disease.

data and test data were classified as 8:2, and the training set accuracy of the best model, sensitivity, and specificity were 96%, 95%, and 96%, respectively; the F1 score, and recall were 95% and 95%, respectively. The accuracy, sensitivity, and specificity of the test dataset were 94%, 90%, and 100%, respectively; the F1 score, and recall were 94% and 93%, respectively (Figure 2).

Discussion

Previous studies have confirmed that olfactory function is associated with cognitive decline in patients with AD. A random forest machine learning model was developed to predict the stage of AD, with an area under the receiver operating characteristic curve of 90.7% for AD mild cognitive impairment and AD, 90.99% for mild cognitive impairment, and 93.34% for AD only. It showed excellent predictive performance.

Previous studies have shown that olfactory function tests using the Brief Smell Identification Test or University of Pennsylvania Smell Identification Test were predictive for AD, and olfactory function decreased with similarity to various parts of the cognitive function evaluation index[5]. This is due to the fact that when using a linear mixed effect model, similarity is shown in memory, executive ability, language, and global cogni-

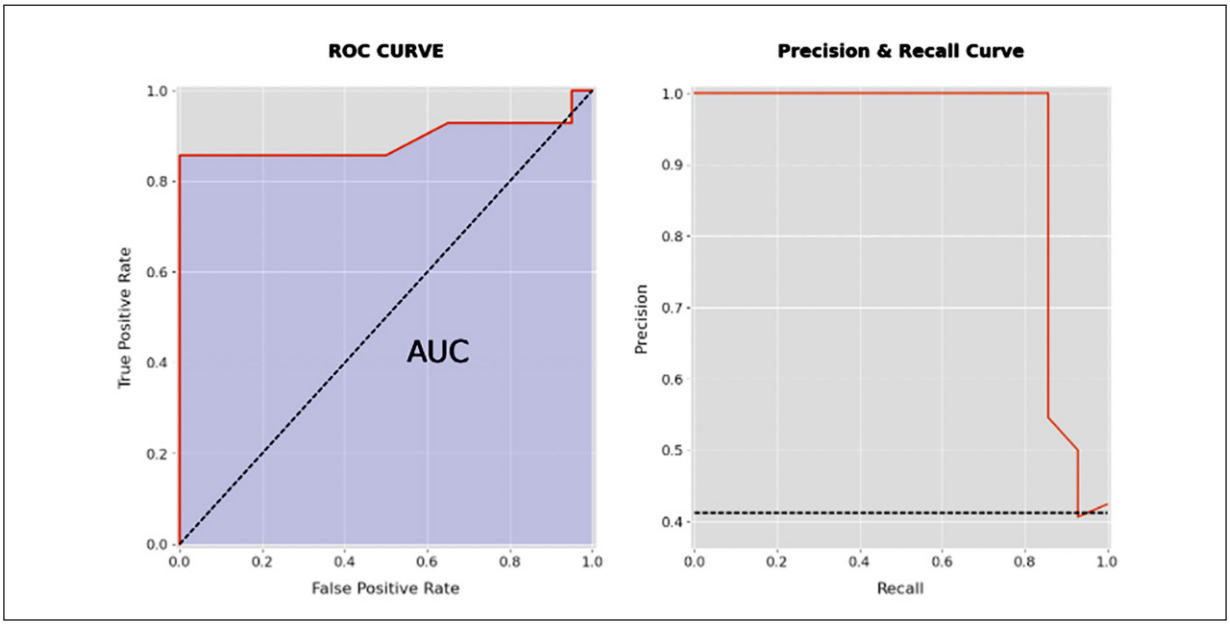

Figure 2. Receiver operating characteristic curve and precision/recall curve for the best performance of the random forest diagnostic model from normal older adult patients with Alzheimer's disease (receiver operating characteristic curve 0.941, area under the precision-recall curve 0.915). ROC: receiver operating characteristic; AUC: area under the curve.

tive function in normal participants and memory, language, and global cognitive functions have been statistically significantly correlated with olfactory function in patients with mild cognitive impairment[28,29]. As in the cohort study for a duration 5 years, when the olfactory function deteriorated in patients with mild cognitive impairment, the progression to AD was strongly predicted[30]. Decreased olfactory function has also been associated with all mild cognitive impairment types but not with non-amnestic mild cognitive impairment, with memory retention[30].

This study had several limitations. In order to reduce the experimental time for participants with dementia with limited concentration, participants with AD were exposed to only three fragrances, providing a more limited olfactory response than would be observed through stimulation with a greater variety of fragrances. However, machine learning yielded satisfactory results, and they can be used to predict cognitive function test results and disease stage in people with AD. In addition, to utilise the fNIRS technology used in this study as a biomarker for AD, it is necessary to confirm the relationship between fNIRS markers through repeated individual evaluations and longitudinal studies.

Even though limitations as mentioned above, this study has several advantages due to the fact that it was conducted to investigate the entire AD spectrum from normal to AD, not just two groups of participants with normal and mild cognitive impairment or normal and AD. In addition, the study was conducted using the fNIRS technology, which is smaller and more portable than large instruments used such as MRI or CT.

Conclusions

This work confirmed the possibility of early detection for AD mild cognitive impairment and AD using a machine learning algorithm by measuring the difference in the left and right relative cerebral metabolic rates during olfactory stimulation with fNIRS. A random forest machine learning model was developed to predict the AD stage, with an area under the receiver operating characteristic curve of 90.7% for AD mild cognitive impairment and AD, 90.99% for mild cognitive impairment, and 93.34% for AD only. We found that the results of the machine learning processing for the fNIRS signals were diagnostically useful. As a result, it is expected that AD can be detected at an early stage.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Funding

This work was supported by a grant from the MD-PhD/Medical Scientist Training Program through the Korea Health Industry Development Institute (KHIDI) funded by the Ministry of Health.

Authors' Contribution

Jae Gwan Kim and Dong Keon Yon had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. All authors approved the final version before submission. Study concept and design: Jae Gwan Kim and Jaewon Kim; acquisition, analysis, or interpretation of data: Donghuk Kang and SungChul Kim; drafting of the manuscript: Jaewon Kim; critical revision of the manuscript for important intellectual content: Jaewon Kim, SungChul Kim, Donghuk Kang, Dong Keon Yon, and Jae Gwan Kim; statistical analyses: Jaewon Kim; study supervision: Jae Gwan Kim and Dong Keon Yon. The corresponding authors attest that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Informed Consent

Written consent was obtained from each participant and legal guardian at the time of patient registration.

Ethical Approval

Research protocols such as olfactory stimulation and neuropsychological testing were approved by the Gwangju Institute of Science and Technology Institutional Review Committee (20210115-HR-58-01-02). The trial was registered with the Clinical Research Information Service of the Republic of Korea (CRIS number, KCT0007589). The study adhered to the tenets of the Declaration of Helsinki.

Data Availability

The authors confirm that data supporting the findings of this study are available upon reasonable request.

References

1) Baek MS, Kim HK, Han K, Kwon HS, Na HK, Lyoo CH, Cho H. Annual Trends in the Incidence and Prevalence of Alzheimer's Disease in South Korea: A Nationwide Cohort Study. Front Neurol 2022; 13: 883549.
2) Young CB, Winer JR, Younes K, Cody KA, Betthauser TJ, Johnson SC, Schultz A, Sperling RA, Greicius MD, Cobos I, Poston KL, Mormino EC. Divergent Cortical Tau Positron Emission Tomog-

raphy Patterns Among Patients With Preclinical Alzheimer Disease. JAMA Neurol 2022; 79: 592-603.

3) Smith L, Shin JI, Hwang SY, Tizaoui K, Dragioti E, Jacob L, Kostev K, Lee SW, Koyanagi A. Global Burden of Disease study at the World Health Organization: research methods for the most comprehensive global study of disease and underlying health policies. Life Cycle 2022; 2: e8.
4) Rasmussen J, Langerman H. Alzheimer's Disease - Why We Need Early Diagnosis. Degener Neurol Neuromuscul Dis 2019; 9: 123-130.
5) Roberts RO, Christianson TJ, Kremers WK, Mielke MM, Machulda MM, Vassilaki M, Alhurani RE, Geda YE, Knopman DS, Petersen RC. Association Between Olfactory Dysfunction and Amnestic Mild Cognitive Impairment and Alzheimer Disease Dementia. JAMA Neurol 2016; 73: 93-101.
6) Petersen ML, Bresolin M, Monteiro AM. 521 - The link between olfactory dysfunction and dementia: the road so far. Int Psychoger 2021; 33: 69-70.
7) Heath PT, Galiza EP, Baxter DN, Boffito M, Browne D, Burns F, Chadwick DR, Clark R, Cosgrove C, Galloway J, Goodman AL, Heer A, Higham A, Iyengar S, Jamal A, Jeanes C, Kalra PA, Kyriakidou C, McAuley DF, Meyrick A, Minassian AM, Minton J, Moore P, Munsoor I, Nicholls H, Osanlou O, Packham J, Pretswell CH, San Francisco Ramos A, Saralaya D, Sheridan RP, Smith R, Soiza RL, Swift PA, Thomson EC, Turner J, Viljoen ME, Albert G, Cho I, Dubovsky F, Glenn G, Rivers J, Robertson A, Smith K, Toback S. Safety and Efficacy of NVX-CoV2373 Covid-19 Vaccine. N Engl J Med 2021; 385: 1172-1183.
8) Dintica CS, Marseglia A, Rizzuto D, Wang R, Seubert J, Arfanakis K, Bennett DA, Xu W. Impaired olfaction is associated with cognitive decline and neurodegeneration in the brain. Neurology 2019; 92: e700-e709.
9) Schonfeld E, Schonfeld E, Aman C, Gill N, Kim D, Rabin S, Shamshuddin B, Sealey L, Senno RG. Lateralized Deficits in Motor, Sensory, and Olfactory Domains in Dementia. J Alzheimers Dis 2021; 79: 1033-1040.
10) Wesson DW, Levy E, Nixon RA, Wilson DA. Olfactory dysfunction correlates with amyloid-beta burden in an Alzheimer's disease mouse model. J Neurosci 2010; 30: 505-514.
11) Fladby T, Bryhn G, Halvorsen O, Rosé I, Wahlund M, Wiig P, Wetterberg L. Olfactory response in the temporal cortex of the elderly measured with near-infrared spectroscopy: a preliminary feasibility study. J Cereb Blood Flow Metab 2004; 24: 677-680.
12) Brand G, Millot JL, Henquell D. Complexity of olfactory lateralization processes revealed by functional imaging: a review. Neurosci Biobehav Rev 2001; 25: 159-166.
13) Wang J, Eslinger PJ, Doty RL, Zimmerman EK, Grunfeld R, Sun X, Meadowcroft MD, Connor JR, Price JL, Smith MB, Yang QX. Olfactory deficit detected by fMRI in early Alzheimer's disease. Brain Res 2010; 1357: 184-194.
14) Zatorre RJ, Jones-Gotman M, Evans AC, Meyer E. Functional localization and lateralization of human olfactory cortex. Nature 1992; 360: 339-340.
15) Son G, Steinbusch HWM, López-Iglesias C, Moon C, Jahanshahi A. Severe histomorphological alterations in post-mortem olfactory glomeruli in Alzheimer's disease. Brain Pathol 2022; 32: e13033.
16) Yang QX, Dardzinski BJ, Li S, Eslinger PJ, Smith MB. Multi-gradient echo with susceptibility inhomogeneity compensation (MGESIC): demonstration of fMRI in the olfactory cortex at 3.0 T. Magn Reson Med 1997; 37: 331-335.
17) Kim J, Yon DK, Choi KY, Lee JJ, Kim N, Lee KH, Kim JG. Novel diagnostic tools for identifying cognitive impairment using olfactory-stimulated functional near-infrared spectroscopy: patient-level, single-group, diagnostic trial. Alzheimers Res Ther 2022; 14: 39.
18) Kim M, Lee S, Dan I, Tak S. A deep convolutional neural network for estimating hemodynamic response function with reduction of motion artifacts in fNIRS. J Neural Eng 2022; 19: 55.
19) Fernandez Rojas R, Huang X, Ou KL. A Machine Learning Approach for the Identification of a Biomarker of Human Pain using fNIRS. Sci Rep 2019; 9: 5645.
20) Yeung MK, Chan AS. Functional near-infrared spectroscopy reveals decreased resting oxygenation levels and task-related oxygenation changes in mild cognitive impairment and dementia: A systematic review. J Psychiatr Res 2020; 124: 58-76.
21) Doi T, Makizako H, Shimada H, Park H, Tsutsumimoto K, Uemura K, Suzuki T. Brain activation during dual-task walking and executive function among older adults with mild cognitive impairment: a fNIRS study. Aging Clin Exp Res 2013; 25: 539-544.
22) Kim SY. Nationwide COVID-19 vaccination coverage and COVID-19 incidence in South Korea, January 2022: a national official report. Life Cycle 2022; 2: e2.
23) Yoo IK, Marshall DC, Cho JY, Yoo HW, Lee SW. N-Nitrosodimethylamine-contaminated ranitidine and risk of cancer in South Korea: a nationwide cohort study. Life Cycle 2021; 1: e1.
24) Myrberg K, Hydén LC, Samuelsson C. The mini-mental state examination (MMSE) from a language perspective: an analysis of test interaction. Clin Linguist Phon 2020; 34: 652-670.
25) Jack CR, Jr., Albert MS, Knopman DS, McKhann GM, Sperling RA, Carrillo MC, Thies B, Phelps CH. Introduction to the recommendations from the National Institute on Aging-Alzheimer's Association workgroups on diagnostic guidelines for Alzheimer's disease. Alzheimers Dement 2011; 7: 257-262.
26) Lee SW. Methods for testing statistical differences between groups in medical research: statisti-

cal standard and guideline of Life Cycle Committee. Life Cycle 2022; 2: e1.

27) Lee SW. Regression analysis for continuous independent variables in medical research: statistical standard and guideline of Life Cycle Committee. Life Cycle 2022; 2: e3.

28) Murphy C. Olfactory and other sensory impairments in Alzheimer disease. Nat Rev Neurol 2019; 15: 11-24.

29) Leso V, Caturano A, Vetrani I, Iavicoli I. Shift or night shift work and dementia risk: a systematic review. Eur Rev Med Pharmacol Sci 2021; 25: 222-232.

30) Adams DR, Kern DW, Wroblewski KE, McClintock MK, Dale W, Pinto JM. Olfactory Dysfunction Predicts Subsequent Dementia in Older U.S. Adults. J Am Geriatr Soc 2018; 66: 140-144.