Olfactory Dysfunction in Alzheimer's Disease: The Clinical Characteristics and Cortical Thickness Alterations

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Abstract

Background Olfactory dysfunction (OD) is reported as a useful predictor for Alzheimer's disease (AD). There are three sub-domains of olfaction: olfactory threshold, discrimination and identification. In AD patients, whether the performance of three sub-domains has different influential factors or relates to specific brain magnetic resonance imaging (MRI) change is not clear.

Methods We recruited 105 typical AD patients, assessed patients' cognitive function, neuropsychiatric symptoms and activity of daily living by related scales, evaluated patients' olfactory function by Sniffin' Sticks test and measured patients' cortical thicknesses by MRI.

Results Olfactory threshold negatively correlated with AD patients' age and positively related to cognitive function; olfactory discrimination positively related to patients' cognitive function and cortical thickness of left lateral orbitofrontal gyrus; olfactory identification positively related to patients' cognitive function and cortical thicknesses of left medial orbitofrontal gyrus, left middle temporal gyrus and bilateral superior temporal gyrus.

Conclusions The three sub-domains of olfaction in AD patients have different influential factors: age influences olfactory threshold and cognitive function influences all three olfactory sub-domains. The performance of olfactory discrimination and identification in AD patients was associated with the cortical thickness of orbitofrontal gyrus and temporal lobe.

Background

Alzheimer's disease (AD) is neurodegenerative disease with a very insidious onset and progressive deterioration, making a big challenge to its early diagnosis. Several methods have been proposed for early prediction of AD, including neuropsychological tests, measurements of β amyloid and tau in cerebrospinal fluid and positron emission tomography (PET). However, the invasiveness cerebrospinal fluid collection by lumbar puncture and the expensive cost of PET makes them difficult to be widely used in the clinical practice.

Olfactory dysfunction (OD) is very common in AD patients and relates to the pathogenesis of AD [1–3]. Longitudinal studies showed that OD was able to predict cognitive decline at early stage of disease[2–5]. Therefore, OD was considered as a useful biomarker for AD. Olfactory function includes three sub-domains as olfactory threshold, olfactory identification and olfactory discrimination[6]. Although the association between OD and cognitive impairment was reported in the previous studies[2–5], rare studies focused on the relation between OD and neuropsychiatric symptoms in AD patients. The performance of each olfactory sub-domain in AD patients may have different influential factors, which could be age, disease duration, disease severity, et al. The impairment of different olfactory sub-domain in AD may be the results of different brain regions impaired. For now, few studies focused on the influential factors or brain areas impaired for each olfactory sub-domain in AD patients. The aim of this research is to explore the relation between OD and neuropsychiatric symptoms of AD and clarify whether the three sub-

domains of olfaction in AD patients have different influential factors or relate to specific brain MRI change, such as cortical thickness.

Methods

The protocol of this study was approved by the Beijing Tiantan Hospital review board (KY2013-003-02). Written informed consents were obtained from all participants. The methods were similar to our prior publications[7, 8].

Subjects

This is a cross-sectional study. Total 105 AD patients were consecutively recruited from April 2014 to April 2017. All patients were diagnosed typical AD phenotype according to the International Working Group-2 criteria [9]. Auditory verbal learning test[10] was used to evaluate episodic memory and in-vivo evidence of Alzheimer's pathology was obtained from amyloid PET. Patients recruited were newly diagnosed AD and did not take any medication for AD and mental illness. Patients with the history of sinus surgery, nasal fracture and other diseases that may affect olfactory function, such as rhinitis, sinusitis, nasal polyps, nasal tumors, brain tumors, head trauma and substance use/drug abuse, et al, were excluded. Among 105 AD patients, 40 cases (38.1%) were male, age from 45 to 93 with an average of 68 years old; 65 cases (61.9%) were female and age from 42 to 88 with an average of 68 years old. Patients' demographic information, including gender, age, disease duration, educational level and smoking condition, was collected. Disease duration was based on the retrospective clinical information of the illness timeline.

Evaluation of olfactory function

Olfactory function of AD patients was evaluated by Sniffin' Sticks test. Sniffin' Sticks were bought from Burghart Messtenik Company, German (product number: LA-13-00005). There was total 112 sticks, 48 sticks, 48 sticks and 16 sticks were used for testing olfactory threshold, discrimination and identification, respectively. Olfactory stimulations were delivered monorhinally and randomly.

Olfactory threshold: Participants need to find the n-butyl alcohol stick among three sticks in each group, with the other two sticks are blank. Total six-teen groups were provided to participants, with the concentration of n-butyl alcohol from the lowest to the highest. The score was the number of correct answers. The lower the score, the worse the olfactory threshold.

Olfactory discrimination: Participants were asked to distinguish the stick that smelled differently from the other two in each group. Total six-teen groups were provided to participants. The score was the number of correct answers. The lower the score, the worse the olfactory discrimination.

Olfactory identification: Participants were required to identify the odor of sticks and choose the correct answer in four given options. Total six-teen sticks were provided to participants. The score was the number of correct answers. The lower the score, the worse the olfactory identification.

Global olfactory function was reflected by summing up the scores of olfactory threshold, discrimination and identification, which was abbreviated as TDI. OD was diagnosed following the criteria from a cross-sectional study in 3282 people[11]: for participants from 36 to 55 years old, OD was diagnosed when TDI score was ≤ 24 points in the male and ≤ 28 points in the female; for participants >55 years old, no matter male or female, OD was diagnosed when TDI score ≤ 19 points. According to the results of TDI, patients were divided into AD-OD group AD with no OD (AD-NOD) group.

Assessments of clinical features

Global cognitive function was assessed by Mini-Mental State Examination (MMSE) [12]. There were 30 questions about orientation, memory, attention, calculation, language and visuospatial ability. The lower the MMSE score, the worse the global cognitive function. Neuropsychiatric Inventory (NPI) [13] was used to assess the global neuropsychiatric symptoms of AD patients. NPI evaluates 12 common neuropsychiatric symptoms, including hallucinations, delusions, agitation/aggression, dysphoria/depression, anxiety, irritability, disinhibition, euphoria, apathy, aberrant motor behavior, sleep and night-time behavior change and appetite and eating change. Each symptom was scored according to its frequency, severity and caregiver burden. The higher the NPI score, the worse the overall neuropsychiatric symptoms. Activities of daily living (ADL) [14] scale was used, which contains questions about bathing, dressing, toilet use, transferring, eating, use of the telephone, traveling via car or public transportation, food or clothes shopping, meal preparation, housework, handyman work, laundry, medication use and management of money. ADL was graded by the level of dependence. The higher the score, the lower the ADL.

Image's collection and processing

3.0T magnetic resonance imaging system from the Siemens (Siemens, Germany) was used. The T1-weighted three-dimensional magnetization gradient echo sequence was used to get transverse brain images from the cranial dome to the foramen magnum. The repetition time was 2300 milliseconds, echo time was 2.3 milliseconds, inversion time was 900 milliseconds, the scanning field was 240 mm x 240 mm, the matrix was 256 x 256, the layer thickness was 1 mm and the interlayer spacing was 1 mm.

Two researchers who had no idea about patients' clinical information were independently responsible for reading and evaluating patients' brain images to exclude other neurological diseases. The consensus agreements were reached by discussion if there were disagreements between them.

Cortical reconstruction and volumetric segmentation were performed by the Freesurfer image analysis suite (version 6.0), which was freely available for download online (<http://surfer.nmr.mgh.harvard.edu/>). We measured the cortical thicknesses of latera orbitofrontal gyrus, medial orbitofrontal gyrus, entorhinal gyrus, para hippocampus gyrus, superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus, fusiform and insula, which might play a role in olfaction processing [15, 16]. The technical details were described in prior publications [17, 18].

Data Analyses

Statistical analyses were performed with SPSS Statistics 20.0 (IBM Corporation, New York, USA). We compared the demographic information, olfactory function, cognitive function, neuropsychiatric symptoms, activity of daily living and cortical thickness between AD-OD and AD-NOD groups. Continuous variables were presented as mean $\pm$ standard deviations and compared by 2-tailed t test if they were normally distributed; or presented as median (quartile) and compared by nonparametric test when they were not normally distributed. Discrete variables were compared by Chi square test. Bonferroni correction was performed. Then, Spearman correlation analyses and multiple linear analyses were performed between each olfactory sub-domain and potential influential factors, including age, MMSE and cortical thickness (latera orbitofrontal gyrus, medial orbitofrontal gyrus, entorhinal gyrus, para hippocampus gyrus, superior temporal gyrus, middle temporal gyrus, inferior temporal gyrus, fusiform and insula). P value was significant when it was less than 0.05.

Results

In this study, 44 of 105 (41.9%) AD patients had OD. AD-OD patients had worse olfactory threshold, olfactory discrimination, olfactory identification, global olfactory function, cognitive function and ADL than AD-NOD group (Table 1). Gender, age, disease duration, educational level, smoking condition and neuropsychiatric symptoms were not significantly different between the two groups (Table 1).

Table 1
Comparison of demographic variables of AD-OD¹ and AD-NOD² groups

Demographic variables	AD-OD group	AD-NOD group	P value
Olfactory threshold	2.5(1.0 ~ 4.8)	6.0(4.0 ~ 6.0)	0.000*
Olfactory discrimination	5.0(3.3 ~ 7.0)	10.0(8.0 ~ 12.0)	0.000*
Olfactory identification	6.0(3.3 ~ 8.0)	11.0(9.0 ~ 13.0)	0.000*
Olfactory TDI ³	14.5(11.0 ~ 17.8)	26.0(22.0 ~ 29.5)	0.000*
Sex			0.105
Male [case (%)]	21(47.7%)	19(31.1%)	
Female [case (%)]	23(52.3%)	42(68.9%)	
Age [year, median (quartile)]	69.5 (61.0 ~ 77.8)	64.0(59.5 ~ 75.0)	0.232
Smoking condition			0.141
Smoking [case (%)]	32(72.7%)	9(14.8%)	
Non-smoking [case (%)]	12(27.3%)	52(85.2%)	
Disease duration [year, median (quartile)]	3.0 (2.0 ~ 5.0)	3.0(1.0 ~ 5.0)	0.519
MMSE ⁴ [scores, median (quartile)]	19.0(13.0 ~ 26.0)	26.0(23.5 ~ 28.0)	0.000*
NPI ⁵ [scores, median (quartile)]	1.0(0 ~ 9.5)	1.5(0 ~ 5.0)	0.841
ADL ⁶ [scores, median (quartile)]	25.0(20.0 ~ 38.0)	20.0(20.0 ~ 22.0)	0.000*
*: P < 0.004 after Bonferroni correction. ¹ AD-OD: Alzheimer disease patient with olfactory dysfunctions, ² AD-NOD: Alzheimer disease with no olfactory dysfunctions, ³ the sum of olfactory threshold, discrimination and identification, ⁴ Mini-Mental State Examination, ⁵ Neuropsychiatric Inventory, ⁶ Activity of Daily Livings.			

Correlation analyses between olfactory functions and potential influential factors in the AD patients showed that, olfactory threshold, discrimination, identification and TDI negatively correlated with age ($r=-0.258$, $P = 0.008$; $r=-0.256$, $P = 0.008$, $r=-0.239$, $P = 0.013$ and $r=-0.283$, $P = 0.003$, respectively) and positively correlated with the score of MMSE ($r = 0.335$, $P = 0.000$; $r = 0.501$, $P = 0.000$, $r = 0.482$, $P = 0.000$ and $r = 0.516$, $P = 0.000$, respectively). Further multiple linear analyses demonstrated that olfactory threshold was independently associated with age and MMSE score; olfactory discrimination and identification were independently associated with MMSE score ($P < 0.05$) (Table 2).

Table 2
Multiple linear regression analyses between olfactory sub-domains and related factors

Factors	Included variables	Excluded variables	P value	ΔR^2	Adjusted R^2
Olfactory threshold ¹	Age		0.000*	0.156	0.139
	MMSE				
Olfactory discrimination ²	MMSE	Age	0.000*	0.333	0.326
Olfactory identification ³	MMSE	Age	0.000*	0.332	0.310
*: P < 0.05.					

Comparison of cortical thickness between the two groups showed that bilateral middle temporal gyrus and right entorhinal gyrus in AD-OD group were thinner than AD-NOD group (Table 3). Spearman correlation analyses between olfactory functions and cortical thickness in AD patients showed that, olfactory threshold positively correlated with left para hippocampus ($r = 0.365$, $P = 0.040$), left fusiform ($r = 0.386$, $P = 0.029$), left middle temporal gyrus ($r = 0.394$, $P = 0.026$), left superior temporal gyrus ($r = 0.479$, $P = 0.006$), right fusiform ($r = 0.352$, $P = 0.048$) and right superior temporal gyrus ($r = 0.376$, $P = 0.034$); olfactory discrimination positively correlated with left lateral orbitofrontal gyrus ($r = 0.457$, $P = 0.008$), left inferior temporal gyrus ($r = 0.374$, $P = 0.032$), left middle temporal gyrus ($r = 0.405$, $P = 0.019$) and right middle temporal gyrus ($r = 0.464$, $P = 0.007$); olfactory identification positively correlated with left lateral orbitofrontal gyrus ($r = 0.361$, $P = 0.039$), left medial orbitofrontal gyrus ($r = 0.348$, $P = 0.047$), left fusiform ($r = 0.452$, $P = 0.008$), left inferior temporal gyrus ($r = 0.363$, $P = 0.038$), left middle temporal gyrus ($r = 0.482$, $P = 0.005$), left superior temporal gyrus ($r = 0.475$, $P = 0.005$) and right superior temporal gyrus ($r = 0.458$, $P = 0.007$).

Table 3
Comparison of cortical thickness of AD-OD¹ and AD-NOD² groups

Cortical thickness	AD-OD group	AD-NOD group	P value
Left hemisphere			
Lateral orbitofrontal gyrus	2.484(2.402 ~ 2.639)	2.575(2.535 ~ 2.641)	0.110
Medial orbitofrontal gyrus	2.337(2.190 ~ 2.426)	2.356(2.301 ~ 2.448)	0.311
Entorhinal gyrus	3.303(2.841 ~ 3.582)	3.386(3.161 ~ 3.698)	0.276
Parahippocampi gyrus	2.473(2.338 ~ 2.748)	2.644(2.452 ~ 2.899)	0.228
Superior temporal gyrus	2.446(2.335 ~ 2.768)	2.636(2.544 ~ 2.777)	0.049
Middle temporal gyrus	2.664(2.429 ~ 2.812)	2.831(2.752 ~ 2.930)	0.010*
Inferior temporal gyrus	2.705(2.608 ~ 2.786)	2.810(2.689 ~ 2.861)	0.039
Fusiform	2.648(2.505 ~ 2.738)	2.730(2.687 ~ 2.802)	0.049
Insula	2.8030(2.748 ~ 2.909)	2.847(2.787 ~ 2.984)	0.311
Right hemisphere			
Lateral orbitofrontal gyrus	2.458(2.332 ~ 2.679)	2.594(2.484 ~ 2.624)	0.599
Medial orbitofrontal gyrus	2.391(2.195 ~ 2.479)	2.367(2.304 ~ 2.448)	0.726
Entorhinal gyrus	3.394(2.745 ~ 3.640)	3.692(3.435 ~ 3.859)	0.020*
Parahippocampi	2.559(2.034 ~ 2.773)	2.616(2.474 ~ 2.777)	0.330
Superior temporal gyrus	2.554(2.421 ~ 2.704)	2.726(2.595 ~ 2.824)	0.036
Middle temporal gyrus	2.668(2.505 ~ 2.828)	2.847(2.737 ~ 2.896)	0.011*
Inferior temporal gyrus	2.730(2.516 ~ 2.855)	2.746(2.686 ~ 2.822)	0.586
Fusiform	2.648(2.505 ~ 2.738)	2.730(2.687 ~ 2.802)	0.049
Insula	2.752(2.502 ~ 2.925)	2.920(2.825 ~ 3.020)	0.047
*: P < 0.025 after Bonferroni correction. ¹ AD-OD: Alzheimer disease patient with olfactory dysfunctions, ² AD-NOD: Alzheimer disease with no olfactory dysfunctions			

In further multiple linear regression analyses, with age, disease duration and MMSE score as confound factors, none of above cortical thickness independently correlated with olfactory threshold ($P > 0.05$); however, left lateral orbitofrontal gyrus was independently associated with olfactory discrimination (Table 4, $P < 0.05$) and left medial orbitofrontal gyrus, left middle temporal gyrus and bilateral superior frontal gyrus independently related to olfactory identification ($P < 0.05$, Table 5).

Table 4

Multiple linear regression analyses between cortical thickness and olfactory discrimination¹

Cortical thickness	Included variables	Excluded variables	P value	ΔR^2	Adjusted R^2
Left lateral orbitofrontal gyrus	Olfactory discrimination [†]	Age MMSE ¹	0.003*	0.247	0.223
*: P < 0.05, ¹ Mini-Mental State Examination.					

Table 5

Multiple linear regression analyses between cortical thickness and olfactory identification[†]

Factors	Included variables	Excluded variables	P value	ΔR^2	Adjusted R^2
Left medial orbitofrontal gyrus	Olfactory identification	Age	0.018*	0.167	0.140
		MMSE ¹			
Left middle temporal gyrus	MMSE	Age	0.000*	0.440	0.422
	Olfactory identification				
Left superior temporal gyrus	Age		0.000*	0.669	0.634
	MMSE				
	Olfactory identification				
Right superior temporal gyrus	Age		0.000*	0.503	0.452
	MMSE				
	Olfactory identification				
*: P < 0.05, ¹ Mini-Mental State Examination.					

Discussions

OD is a very common symptom in AD patients. In this study, 44 of 105 (41.9%) AD patients had OD. Olfactory threshold, identification and discrimination were all worse in AD-OD group. We compared the clinical features and MRI images between AD-OD and AD-NOD groups and explored potential influential factors and MRI image changes for the three sub-domains of OD in AD patients.

Sex was not significantly different between AD-OD group and AD-NOD group in this study (Table 1). A meta-analysis including 5065 women and 3783 men found that women generally outperformed men in olfactory function, however, the effect size was weak [19]. This study showed that sex was not the main factor for the discrepancy of olfactory function between two groups. Although age was not significantly different between AD-OD group and AD-NOD group, AD-OD group tends to be older than AD-NOD group. Furthermore, olfactory threshold, discrimination and identification in AD patients all negatively correlated with age. Olfactory dysfunction is very common in the older population. Multiple conditions could contribute to the age-related olfactory loss, such as nasal engorgement, cumulative damage of the olfactory epithelium from environmental insults, a reduction in mucosal metabolizing enzymes, sensory loss of receptor cells to odorants and changes in neurotransmitter and neuromodulator systems. Structural and functional abnormalities of the olfactory epithelium, olfactory bulb, olfactory cortex and basic olfactory circuitry resulted in olfactory impairment with aging [20]. However, in this study, multiple regression analyses showed that age had no independent influence on olfactory discrimination and identification, except threshold (Table 2). It was consistent with a previous study that age-related OD was mainly identified by detecting threshold rather than other olfactory sub-domains [2].

This study didn't found OD was related to the current smoking condition in AD patients. Current smoking was previously reported to be associated with increased risk of OD, however, the effect of smoking on olfaction could be reversible [21]. We suspect that current smoking is not the main influential factor for olfactory deficits in AD patients. A previous study reported that olfactory deficits in AD patients significantly correlated with the severity of apathy, but not with depression or other neuropsychiatric symptoms [22]. This study did not find the association between OD and neuropsychiatric symptoms, which may be because multiple neuropsychiatric symptoms was evaluated together in the NPI scale. Compared with AD-NOD group, the ADL in AD-OD group was significantly compromised. OD could significantly influence nutritional status as well as physical well-being [20], therefore, is associated with poor ADL.

In this study, disease duration was not significantly different between two groups, but cognitive impairment was more severe in AD-OD group, which indicated that the deterioration of cognitive function was more rapid in AD-OD group. Moreover, MMSE score was found to be an independent influential factor for olfactory threshold, discrimination and identification in this study, suggested that deterioration of cognitive function and olfaction was synchronous. There may be a common pathological mechanism underlying cognitive impairment and olfactory dysfunction, for example, olfactory identification was associated with neurofibrillary tangles in the entorhinal cortex of AD brains [4] [23]. The synchronous change between olfactory dysfunction and cognitive impairment might due to the impaired neuroanatomical structures responsible for the two symptoms were adjacent [21]. Besides, cognitive function such as semantic memory, is involved in olfactory identification and discrimination [24–26], therefore, damage of brain areas responsible for memory, such as temporal lobe, hippocampus, para hippocampus gyrus, could lead to olfactory dysfunction [15, 27] [4]. In this study, we confirmed that the dysfunction of olfactory identification was associated with the damage of left middle temporal gyrus and bilateral superior temporal gyri.

Olfactory discrimination was associated with the left lateral orbitofrontal gyrus, and olfactory identification was related to the left medial orbitofrontal gyrus in this study, which were not reported previously. Orbitofrontal cortex contains the secondary and tertiary olfactory cortical areas, in which information about the identity of odors is represented[28], thus, orbitofrontal gyrus is related to olfactory identification. A study investigating the responses of neurons in the orbitofrontal cortex and surrounding areas during the performance of an olfactory discrimination task, showed that 65% neurons in the orbitofrontal cortex had different selectivity for the stimuli based on the odor quality, which were responsible for olfactory discrimination [29]. Furthermore, another study detecting the neurons' response to eight different odor stimuli in monkey found that 50% of the cells in the orbitofrontal olfactory area responded to only one odor; the cells which responded to two, three, and four odors decreased in this order, and no cell responded to more than five odors. These cells never responded to light or sound. Using three very similar odors and five very different odors, it was apparent that the ability to discriminate odors of the same category was far more advanced in the orbitofrontal olfactory area than in the lower olfactory areas (such as olfactory bulb, anterior pyriform cortex and the medial portion of the amygdala); and, in contrast, the lower olfactory areas played a significant role on the discrimination of odors which belonged to different categories. It was concluded that the capacity for odor discrimination definitely improved along the olfactory nervous system from the lower to the higher areas. It was highly probable that a fine and specific discrimination of odors was performed in the orbitofrontal olfactory area. According to our clinical observation, the impairment of odors discrimination in AD patients is usually fine and specific, which could explain the relevance between orbitofrontal gyrus and olfactory discrimination[30].

Olfactory processes were reported to be lateralized. One study found that patients with left temporal lobe epilepsy judged odors as less pleasant and had more difficulty with identification than patients with right temporal lobe epilepsy, underlining a privileged role of the left hemisphere in the emotional and semantic processing of odors. They also found a tendency towards a right-nostril advantage for judging odor familiarity, in agreement with a prominent role of the right hemisphere in odor memory processing. Therefore, both hemispheres were involved in the process of olfactory identification and discrimination and played different roles on the process.

In this investigation, no relation was found between olfactory threshold and cortical thickness. A study in a total of 170 men and women (30 to 87 years of age) showed that all of the cognitive factors covering executive function, semantic memory and episodic memory proved unrelated to the performance of olfactory threshold test[26], which revealed that the dysfunction of olfactory threshold might be associated with the impairment of peripheral rather than the central olfactory system.

In summary, OD is a very common symptom of AD. It is associated with the impairments of cognition and ADL, but not neuropsychiatric symptoms. The three sub-domains of olfaction in AD patients have different influential factors. Olfactory threshold relates to age and cognitive function, olfactory discrimination and identification relate to cognitive function. Cortical thickness of orbitofrontal gyrus and temporal lobe is associated with olfactory discrimination and identification in AD patients. Findings from

this study may reveal some potential mechanisms of AD-OD. This research has a limitation that age matched control subjects are not included, which needs to be included in future studies.

List Of Abbreviations

AD	Alzheimer disease
OD	Olfactory disorder
AD-OD	Alzheimer disease patient with olfactory dysfunctions
AD-NOD	Alzheimer disease with no olfactory dysfunctions
TDI	Sum of olfactory threshold, discrimination and identification
MRI	Magnetic resonance imaging
PET	Positron emission tomography
MMSE	Mini-Mental State Examination
NPI	The Neuropsychiatric Inventory
ADL	Activity of daily living

Declarations

Ethics approval and consent to participate

All subjects, or their legal representatives if patients were not capable of providing ethical consent for their participation due to cognitive decline, gave their written informed consent for inclusion before participating in the study. The study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the Beijing Tiantan Hospital review board (KY2013-003-02).

Consent for publication

All authors have seen and agreed with the contents of the manuscript.

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Authors' Contributions

Conceptualization, W.Z. and X.W.; methodology, W.Z., S.L. and Y.L.; formal analysis, S.Y.; investigation, S.Y., W.Z., T.L., P.G., D.D., D.L., L.L., H.Z., L.Z., Y.H., Z.J., R.W., J.G. and R.Z., writing-original draft preparation, S.Y.; writing-review and editing, S.Y., W.Z., T.L., P.G., D.D., D.L., L.L., H.Z., L.Z., Y.H., Z.J., R.W., J.G., R.Z. AND W.Z. All authors have read and approved the final version of this manuscript.

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