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RESEARCH ARTICLE

Olfactory function, neurofilament light chain, and cognitive trajectory: A 12-year follow-up of the Shanghai Aging Study

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Abstract

This study aimed to determine whether blood neurofilament light chain (NfL) modifies the association of olfactory dysfunction (OD) with long-term cognitive decline. A total of 1125 non-demented older adults in the Shanghai Aging Study were evaluated for baseline olfaction (12-item Sniffin' Sticks Smell Test) and cognitive trajectory by a 12-year follow-up. Baseline blood NfL was quantified using Single Molecular Array assay, and dichotomized into low and high levels based on the median value of concentration. The Mini-Mental State Examination (MMSE) and Telephone Interview for Cognitive Status-40 were used to assess participants' cognitive function. Cognitive decline was ascertained when dementia was diagnosed or documented in the medical record during follow-up, or the MMSE declining rate (slope) was 1.0 SD larger than the group mean. OD participants presented a steeper trajectory of MMSE score (p interaction = 0.004) and a high risk of cognitive decline (adjusted HR [95% CI], 1.82 [1.11, 2.98]) only in those with high NfL. Participants with combined OD and high NfL showed the highest risk of cognitive decline (adjusted HR, 2.43 [1.20, 4.92]). OD, especially in combination with high blood NfL concentration, may be able to identify individuals who later incur cognitive deterioration.

KEYWORDS
cognitive decline, cognitive trajectory, cohort, neurofilament light chain, olfactory dysfunction

1 | BACKGROUND

Olfactory dysfunction (OD) is an age-related condition in older populations, with a prevalence from 17% in their sixties to 62% in their eighties.[1] However, less than a quarter of individuals with OD would be aware of their olfactory deficits unless objective testing is performed.[2] Notably, OD has been recognized as an early indicator of neurodegenerative diseases, such as Alzheimer's disease (AD) and Parkinson's disease.[2] Previous cohort studies demonstrated the association of poorer olfactory performance with cognitive decline,[3–7] incident mild cognitive impairment (MCI),[8–10] and incident dementia.[5,9,11–13] A few studies revealed a linkage between OD and imaging features of degeneration, including brain atrophy (eg, entorhinal cortex, hippocampus, and temporal lobe) [6,14–18] and hypometabolism.[19] However, the role of neurodegeneration in the olfaction–cognitive impairment association is still unclear.

Neurofilament light chain (NfL) is a sensitive indicator of axonal injury or degeneration.[20] Recent studies demonstrate that NfL in blood strongly correlates with that in cerebrospinal fluid (CSF) and could reflect neurodegeneration in both the central and peripheral nervous systems.[21] One cross-sectional study found that higher plasma NfL was associated with anosmia.[18] Longitudinal studies exploring the interactive effect of blood NfL and olfactory function with cognitive impairment are still lacking.

Here, we proposed the hypothesis that blood NfL, a neurodegenerative biomarker, may modify the association of OD with long-term cognitive decline. We analyzed the baseline and 12-year longitudinal data from a cohort with community-dwelling older adults to verify this hypothesis.

RESEARCH IN CONTEXT

1. **Systematic Review**: We searched and reviewed the literature in PubMed using the following terms: "(olfact*) OR (anosmia) OR (hyposmia)," "(cogniti*) OR (mild cognitive impairment) OR (MCI) OR (Alzheimer*) OR (AD)," "(neurofilament light chain) OR (NfL)."Previous studies demonstrated that olfactory dysfunction (OD) was associated with cognitive impairment and longitudinal cognitive decline. However, the role of neurodegeneration in this relationship is poorly understood.
2. **Interpretation**: Our findings indicated that blood NfL modifies the association of OD with long-term cognitive decline in community-dwelling older adults. Combining baseline OD and high NfL may better predict future cognitive deterioration.
3. **Future Directions**: Multi-ethnic large-sampled studies should be conducted to validate the robustness of the results. Whether OD and higher NfL contributed to cognitive decline through different pathways deserves further exploration.

2 | METHODS

2.1 | Study design and participants

The Shanghai Aging Study (SAS) is a population-based cohort study that aims to explore the prevalence, incidence, and risk factors of dementia and MCI among older community residents in downtown Shanghai, China.[22] The study recruited participants at baseline in 2010 and 2011[22] and conducted the 5-year follow-up interview between 2014 and 2016.[23] From 2018, participants were contacted annually for further follow-ups. The current study included dementia-free participants aged ≥ 60 years at baseline, who completed the olfactory assessment at baseline, and had at least one follow-up interview during the prospective stage. We excluded individuals at baseline who (1) had undergone maxillofacial surgery; (2) had histories of rhinal or paranasal sinuses diseases; (3) had chronic obstructive pulmonary disease, asthma, chronic sinusitis, or acute upper respiratory tract infection within the past 7 days; or (4) had a history of alcohol or drug abuse.

This study was approved by the Medical Ethics Committee of Huashan Hospital, Fudan University. All participants and/or their legal representatives signed the written informed consent.

2.2 | Baseline interview

Demographics and lifestyle characteristics, including age, sex, years of formal education, and cigarette smoking status of each participant, were collected through an interviewer-administered questionnaire.[22] DNA was extracted from the blood or saliva sample and was used to detect the apolipoprotein E (*APOE*) ε4 allele using the TaqMan SNP method. Participants with one or two ε4 alleles were regarded as *APOE* ε4 carriers.[24] Neurologists from Huashan Hospital interviewed each participant, conducted neurological examinations, and collected medical histories of hypertension and type II diabetes confirmed with medical records. Participants' cognitive functions were evaluated through a battery of neuropsychological tests administered by certified psychometrists.[25] A consensus diagnosis was reached by a panel of neurologists and neuropsychologists based on the aforementioned examinations. The diagnosis of dementia was determined based on the DSM-IV criteria,[26] and those who did not meet the criteria for dementia were regarded as non-demented.

2.3 | Assessment of olfactory function

A Sniffin' Sticks Smell Test-12 (SSST-12) test kit was used to assess the olfactory identification function, including detection, recognition, recall, and naming of an odor.[27] The SSST-12 kit is a portable and rapid olfaction screening tool adapted from the original "16-item Sniffin Sticks."[28] It contains 12 felt-tip sticks in 12 different odors (orange, leather, cinnamon, peppermint, banana, lemon, licorice, coffee, cloves, pineapple, rose, and fish). Participants were required to sniff each opened stick for 3 to 4 s and to choose the correct odor from four alternative options. The total of the SSST-12 score ranges from 0 to 12. The detailed administration procedure and normative data in the SAS cohort have been reported previously.[29] In the current study, OD was defined as a score 1.0 standard deviation (SD) below the mean normative SSST-12 score stratified by age group, according to previously reported data,[29] that is, SSST-12 scores of <7, 6, and 5 in participants aged 60 to 69, 70 to 79, and 80 years or older, respectively (Table S1 in supporting information).

2.4 | Blood NfL measurement

At baseline, plasma and serum samples were centrifuged, aliquoted, and stored at −80°C. Blood NfL was quantified using ultra-sensitive single-molecule array (Simoa) technology (Quanterix) on the automated Simoa HD-X platform (GBIO), following the manufacturer's instructions. The NfL assay kit was purchased from Quanterix and used according to the manufacturer's instructions. Plasma or serum samples were diluted at a 1:4 ratio for the assay. Calibrators and quality controls were measured in duplicate. Sample measurement was performed on a single-run basis using kits with the same lot numbers. Operators were blind to participants' characteristics.

2.5 | Cognitive evaluation

The Mini-Mental State Examination (MMSE) has been widely used for evaluating global cognitive function. A validated Chinese version of the MMSE was used at baseline and each follow-up interview before 2022.[30] Due to the coronavirus disease 2019 (COVID-19) epidemic, the Telephone Interview for Cognitive Status-40 (TICS-40) was used in 2022 for cognition assessment. The TICS-40 comprises 9 items with a maximum score of 40 and has shown high sensitivity and specificity in detecting AD.[31] TICS-40 scores were converted to MMSE scores using equipercentile equating, which has been constructed and validated to provide crosswalks between the TICS-40 and MMSE.[32]

Incident "cognitive decline" during the follow-up period was determined if any of the following criteria were met: (1) incident dementia diagnosed using the same procedure and diagnostic criteria as baseline; (2) newly diagnosed dementia documented in the medical record by other hospitals; or (3) an MMSE declining rate (slope) 1.0 SD faster than the mean value, that is, slope (b) ≤ −1.06 (derived from individual-level linear regression models, with time as a predictor of multi-point MMSE).[33]

2.6 | Statistical analysis

The Mann-Whitney *U* test and Pearson's chi-square test were used to compare the continuous and categorical characteristics between participants with OD and normal olfaction, respectively. A multivariate linear regression model was used to evaluate the association between the baseline SSST-12 score and MMSE after adjusting for baseline age, sex, educational years, *APOE* ε4, smoking, hypertension, and diabetes. To depict the MMSE trajectories in participants with normal olfaction and OD, a linear mixed-effects model was constructed by including the interaction item of categorical olfactory function and follow-up year, adjusting for the same confounders mentioned above. In this model, person-specific random intercept and random slope were taken into consideration. Cox regression models were used to calculate the hazard ratio (HR) of incident cognitive decline in participants with OD compared to those with normal olfaction. Follow-up time was defined as the time from baseline to the diagnosis of dementia or to the last follow-up visit. Model 1 was the univariate model. Model 2 adjusted for baseline age, sex, educational years, and baseline MMSE. Model 3 further adjusted for *APOE* ε4, smoking, hypertension, and diabetes, as compared to Model 2. Model 4 was a model for the competing risk of death (Fine and Gray) adjusting for the same covariates as Model 3.

Blood NfL was categorized into low (≤16.0 pg/mL) and high (>16.0 pg/mL) levels based on the median value of concentration. To explore whether blood NfL modifies the association between OD and cognitive decline, the interaction term of dichotomized NfL level and SSST-12 was included in the linear model, and stratification analyses were conducted in the linear mixed-effects model and Models 1-4. Finally, the additive effects of NfL and olfaction on MMSE trajectories and cognitive decline were examined in participants with four categorized levels, that is, "normal olfaction and low NfL," "OD and low NfL," "normal olfaction and high NfL," and "OD and high NfL."

A two-tailed *p*-value less than 0.05 was considered statistically significant. The forest plot was created using GraphPad Prism version 8.0.0 for Windows (GraphPad Software, San Diego, California, USA). Other data analyses and graphical representations were conducted in R Software v.4.0.4 (R Foundation for Statistical Computing, Vienna, Austria).[34]

3 | RESULTS

3.1 | Characteristics of the study participants

Among 1125 participants included in this study, 296 (26.3%) were defined as having OD at baseline. Participants with OD showed statistically significantly fewer educational years ($p < 0.001$), lower scores for the SSST-12 ($p < 0.001$) and MMSE ($p < 0.001$), and a higher proportion carrying the *APOE* ε4 allele ($p = 0.004$) compared to those with

TABLE 1 Characteristics of study participants.

	All ($N = 1125$)	Normal olfaction ($N = 829$)	Olfactory dysfunction ($N = 296$)	p-value*
Baseline				
Age, years, median (Q1, Q3)	69.2 (63.9, 75.9)	69.0 (63.6, 75.8)	69.7 (64.6, 76.1)	0.42
Sex, male, *n* (%)	506 (45.0)	380 (45.8)	126 (42.6)	0.33
Education, years, median (Q1, Q3)	12.0 (9.0, 15.0)	12.0 (12.0, 15.0)	12.0 (9.0, 15.0)	<0.001
APOE ε4 allele, positive, *n* (%)	188 (17.1)	123 (15.1)	65 (22.6)	0.004
Cigarette smoking, *n* (%)	124 (11.0)	87 (10.5)	37 (12.5)	0.34
Hypertension, *n* (%)	595 (52.9)	440 (53.1)	155 (52.4)	0.83
Type II diabetes, *n* (%)	145 (12.9)	108 (13.0)	37 (12.5)	0.82
SSST-12 score, median (Q1, Q3)	8.0 (7.0, 9.0)	9.0 (8.0, 10.0)	6.0 (5.0, 6.0)	<0.001
MMSE, median (Q1, Q3)	29.0 (28.0, 30.0)	29.0 (28.0, 30.0)	28.0 (27.0, 29.0)	<0.001
Blood NfL, pg/mL, median (Q1, Q3)[b]	16.0 (12.1, 21.7)	15.9 (12.1, 21.1)	16.2 (12.2, 23.6)	0.42
Low (< = 16.0 pg/mL), *n* (%)	505 (50)	380 (50.5)	125 (48.6)	
High (> 16.0 pg/mL), *n* (%)	505 (50)	373 (49.5)	132 (51.4)	
Follow-up				
Follow-up years, median (Min, Max)	9.4 (0.9, 12.5)	9.8 (0.9, 12.5)	8.3 (0.9, 12.4)	0.12
MMSE at the final interview, median (Q1, Q3)	27.0 (25.0, 29.0)	27.0 (25.0, 29.0)	26.3 (23.0, 28.5)	<0.001
Incident cognitive decline, *n* (%)[c]	102 (9.1)	61 (7.4)	41 (13.9)	<0.001

Abbreviations: *APOE*, apolipoprotein E; Max, maximum; Min, minimum; MMSE, Mini-Mental State Examination; NfL, neurofilament light chain; Q1, lower quartile; Q3, upper quartile; SSST-12, Sniffin' Sticks Screening Test.

[a]Continuous variables were compared with the Mann-Whitney *U* test, and categorical variables were compared with Pearson's chi-squared test.

[b]A total of 1010 blood samples were tested with NfL.

[c]Defined as incident dementia, documented dementia diagnosis on the medical record, or MMSE slope ≤ −1.06.

normal olfaction (Table 1). In 1010 (89.8%) participants with blood NfL measured, no statistically significant difference in NfL concentrations was detected between those with normal olfaction and OD ($p = 0.42$). However, the baseline SSST-12 score exhibited a statistically significant correlation with the baseline NfL (Spearman's rank correlation rho = −0.15; $p < 0.001$).

During the median of 9.4 (range 0.9, 12.5) years of follow-up, 102 (9.1%) participants progressed to cognitive decline, and 109 (9.7%) participants died before the incident occurred. Participants with OD at baseline performed worse on the MMSE at the last interview ($p < 0.001$) and had a higher proportion of cognitive decline ($p < 0.001$) during the follow-ups compared to those with normal olfaction (Table 1).

3.2 | Association between olfactory dysfunction and cognitive decline

At baseline, a significant linear correlation between scores of the SSST-12 and MMSE (adjusted b [95% CI], 0.10 [0.05, 0.14]; $p < 0.001$; Figure 1A) was found in all participants. During the 12-year follow-up, a decreasing SSST-12 score showed a correlative trend with a steeper decline in the MMSE score, but this correlation was insignificant after adjusting for confounders (adjusted b, 0.01 [−0.01, 0.03]; $p = 0.30$; Figure 1C). Participants with OD exhibited a faster decline in MMSE score compared to those with normal olfaction (p for interaction = 0.01; Figure 2D and Table S2). A higher risk of cognitive decline was observed in OD participants (Model 3 adjusted HR [95% CI], 1.59 [1.05, 2.41]; $p = 0.03$; Table 2). However, after considering the competing risk of death, this association was no longer significant (Model 4 adjusted HR, 1.50 [0.98, 2.30]; $p = 0.06$; Table 2).

3.3 | NfL modified the association of olfactory dysfunction with cognitive decline

At baseline, no significant difference was found in the correlation between scores of the SSST-12 and MMSE (p for interaction = 0.84; Figure 1B) among participants with low or high NfL. Intriguingly, during the follow-up, a decreasing SSST-12 score was correlated with a faster decline of the MMSE score in participants with high NfL, but not in those with low NfL (p for interaction = 0.003; Figure 1D and Table S3). Meanwhile, participants with normal olfactory and those with OD showed diverse deteriorating trajectories of the MMSE score in participants with high NfL (p for interaction = 0.004; Figure 2F), but not in those with low NfL (p for interaction = 0.92; Figure 2E and Table S2). OD was associated with a higher risk of cognitive decline in the high NfL group (Model 3 HR, 1.82 [1.11, 2.98]; $p = 0.02$), but not in the low NfL group (Model 3 HR, 1.09 [0.35, 3.43]; $p = 0.88$; Table 2). This association was robust even considering the competing risk of death (Model

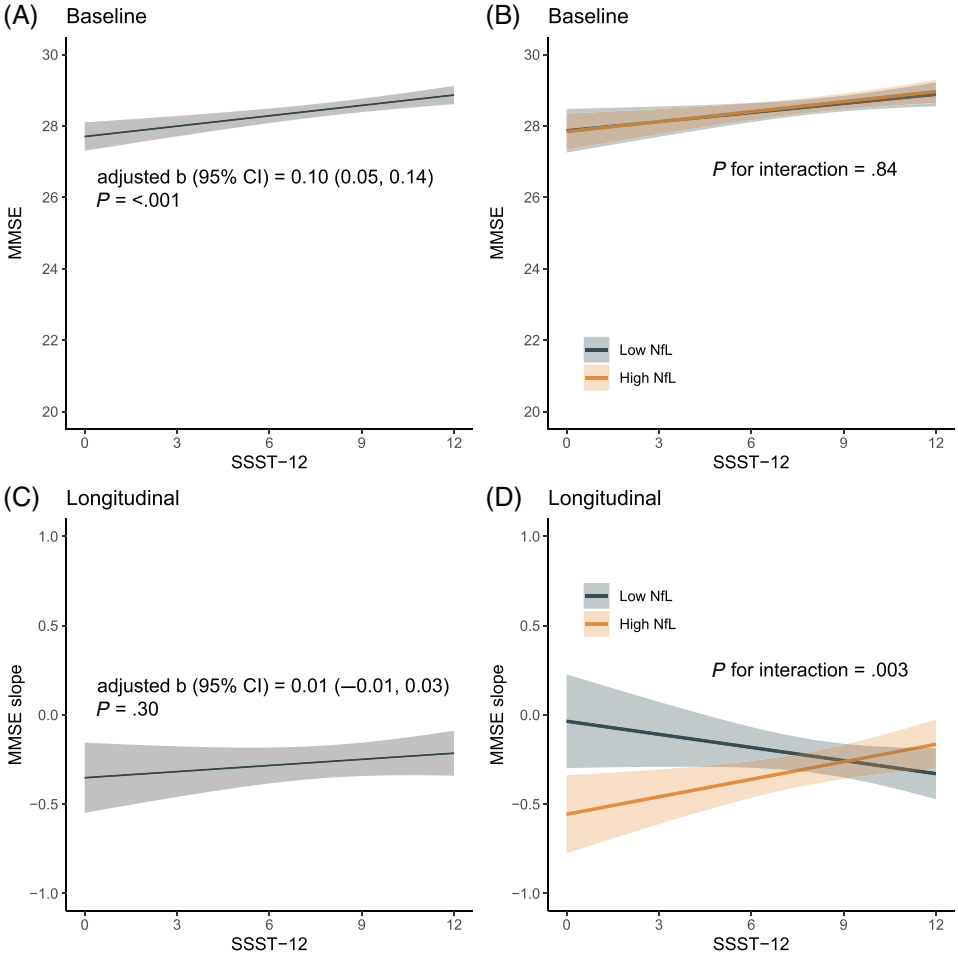

FIGURE 1 Correlations between the baseline SSST-12 score and baseline MMSE score or MMSE slopes during follow-up. Higher SSST-12 scores indicate better olfactory function. (A,B) Correlation between the baseline SSST-12 score and MMSE score in all participants (A), and in low/high NfL groups with SSST-12 × NfL interaction (B). (C,D) Correlation between the baseline SSST-12 score and MMSE score slopes during follow-up in all participants (C), and in low/high NfL groups with SSST-12 × NfL interaction (D). CI, confidence interval; MMSE, Mini-Mental State Examination; NfL, neurofilament light chain; SSST-12, Sniffin' Sticks Screening Test.

TABLE 2 Hazard ratios of cognitive decline during follow-up in participants stratified by NfL levels.

		Model 1		Model 2		Model 3		Model 4	
	Events/N	HR (95% CI)	*p*-value	HR (95% CI)	*p*-value	HR (95% CI)	*p* value	HR (95% CI)	*p*-value
All									
Normal olfaction	61/829	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
Olfactory dysfunction	41/296	2.01 (1.35, 2.99)	<0.001	1.65 (1.10, 2.47)	0.02	1.59 (1.05, 2.41)	0.03	1.50 (0.98, 2.30)	0.06
Low NfL									
Normal olfaction	12/380	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
Olfactory dysfunction	7/125	1.82 (0.72, 4.61)	0.21	1.24 (0.42, 3.65)	0.70	1.09 (0.35, 3.43)	0.88	1.05 (0.42, 2.63)	0.92
High NfL									
Normal olfaction	39/373	1 [Reference]		1 [Reference]		1 [Reference]		1 [Reference]	
Olfactory dysfunction	30/132	2.27 (1.41, 3.65)	<0.001	1.83 (1.13, 2.97)	0.01	1.82 (1.11, 2.98)	0.02	1.89 (1.13, 3.15)	0.02

Note. Cox regression models were used in Models 1-3. Model 1 is a univariate model; Model 2 is a multivariate model adjusted for baseline age, sex, educational years, and baseline MMSE; Model 3 is a multivariate model further adjusted for APOE ε4, smoking, hypertension, and diabetes; and Model 4 is a Fine and Gray death competing risk model adjusting for the same confounders as Model 3. Abbreviations: HR, hazard ratio; CI, confidence interval; NfL, neurofilament light chain.

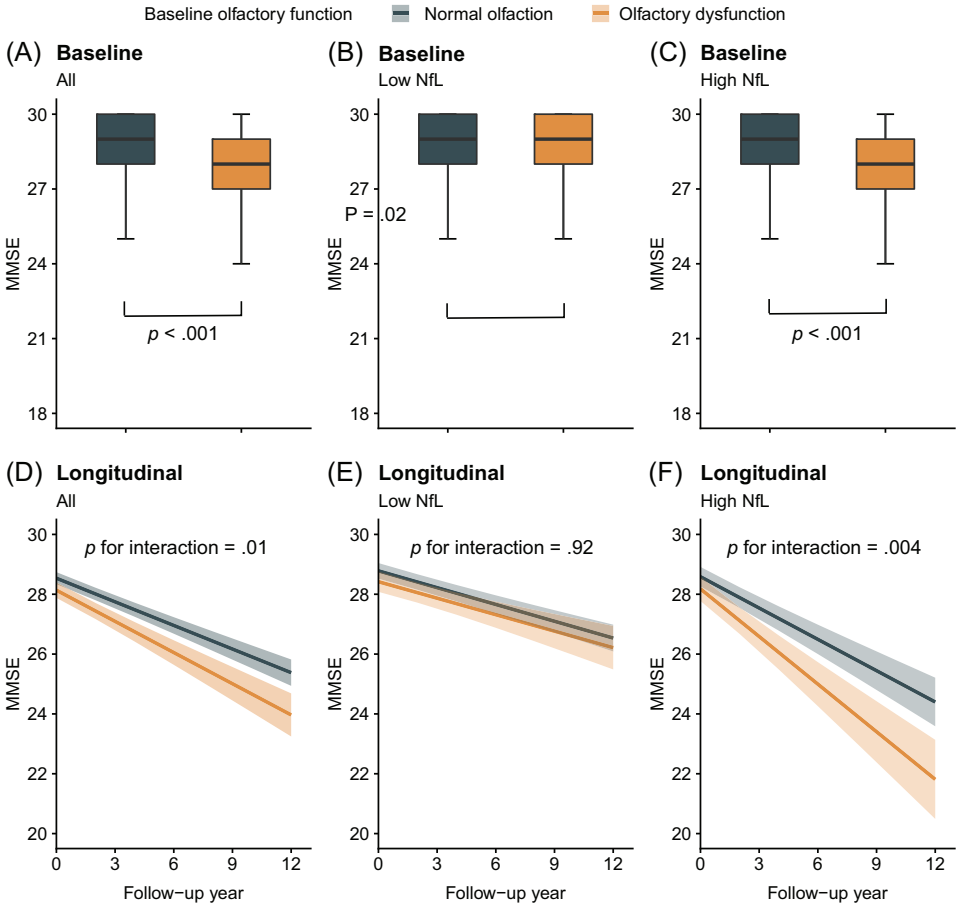

FIGURE 2 Baseline MMSE score and longitudinal MMSE trajectories in participants with normal olfaction and olfactory dysfunction stratified by NfL levels. (A–C) Comparison of baseline MMSE scores between individuals with normal olfaction and olfactory dysfunction in all participants (A), low NfL group (B), and high NfL group (C). (D–F) Comparison of longitudinal MMSE trajectories between individuals with normal olfaction and olfactory dysfunction, with the interaction of olfactory function and follow-up year, in all participants (D), low NfL group (E), and high NfL group (F). MMSE, Mini-Mental State Examination; NfL, neurofilament light chain.

4 HR for high NfL, 1.89 [1.13, 3.15]; $p = 0.02$; low NfL, 1.05 [0.42, 2.63]; $p = 0.92$).

3.4 | Additive effect of NfL and olfaction on cognitive decline

As shown in Figure 3, participants with combined OD and high NfL demonstrated the fastest decline in MMSE scores compared to other groups (all $p < 0.001$, Table S4 in supporting information), and this subgroup of participants had a twofold higher risk of cognitive decline compared to those with combined normal olfaction and low NfL (Model 3 HR, 2.43 [1.20, 4.92]; $p = 0.01$; Model 4 HR, 2.33 [1.20, 4.50]; $p = 0.01$). Participants with combined normal olfaction and high NfL also demonstrated a faster decline in MMSE scores compared to the two low NfL groups (all $p < 0.01$; Table S4). No statistically significant difference in MMSE trajectories was found between subgroups with "normal olfaction and low NfL" and "OD and low NfL" ($p = 0.96$; Table S4).

4 | DISCUSSION

In this population-based cohort study, older adults with OD demonstrated a steeper trajectory of MMSE score and a higher risk of incident cognitive decline, particularly in individuals with high blood NfL concentration at baseline. Additionally, olfaction and blood NfL showed an additive effect on incident cognitive decline during the 12-year follow-up. Our results contribute to the growing body of evidence supporting the potential role of blood NfL, an easily accessible indicator of neural degeneration, in the longitudinal relationship between olfactory function and cognitive decline in community-dwelling older adults.

Previous cross-sectional studies have found that poor olfaction is a risk factor for cognitive impairment.[35,36] Longitudinal cohort studies have further revealed that OD is an independent indicator of incident cognitive decline. A Japanese-American community cohort study with non-demented participants reported that lower olfactory scores were associated with a higher risk of cognitive decline during a 2-year follow-up.[3] A series studies from the Rush Memory and Aging Project (MAP) also demonstrated that poor olfactory identification function

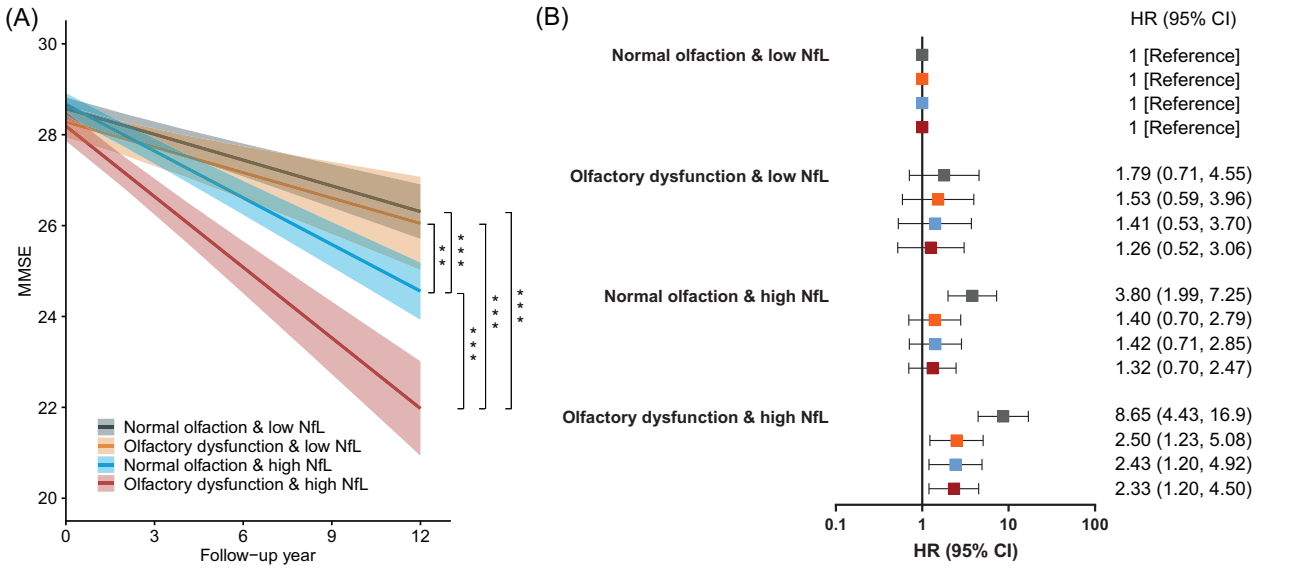

FIGURE 3 Additive effect of baseline NfL and olfaction on cognitive decline during follow-up. (A) Comparisons of the MMSE trajectories of four subgroups with combined different levels of NfL and olfaction. (B) Forrest plots for hazard ratios of incident cognitive decline in four subgroups, as calculated with different Cox regression models: Model 1 (black square), univariate model; Model 2 (orange square), multivariate model adjusted for baseline age, sex, educational years, and baseline MMSE; Model 3 (blue square), multivariate model further adjusted for *APOE* ε4, smoking, hypertension, and diabetes; Model 4 (purple square), Fine and Gray death competing risk model adjusting for the same confounders in Model 3. CI, confidence interval; HR, hazard ratio; MMSE, Mini-Mental State Examination; NfL, neurofilament light chain. $^{**}p < 0.01$, $^{***}p < 0.001$.

was related to more rapid cognitive decline, an increased risk of incident MCI, and motoric cognitive risk syndrome.[6,37,38] Recent evidence from MAP further indicated that faster olfactory decline during normal cognition could predict a higher incidence of MCI or dementia.[9] The Mayo Clinic Study of Aging followed 1430 cognitively normal participants for 3.5 years and indicated that lower olfactory scores were associated with an increased risk of amnestic MCI and progression from that condition to AD dementia.[8] Other longitudinal cohort studies also showed that poor olfactory function was associated with a higher risk of cognitive decline,[5,39] MCI,[10] and dementia.[5,12,13] Our results reconfirmed that OD was an indicator of cognitive decline independent of potential confounders over a long timescale.

Pathological and basic studies have provided clues to explain the link between OD and cognitive impairment. Neurofibrillary tangles, one of the core pathologies of AD, occur very early in the regions related to olfactory information processing and have been found associated with olfactory impairment and future cognitive decline.[27,40,41] The damaged forebrain neurotransmitter and neuromodulator circuits might be the fundamental cause of OD in neurodegenerative diseases.[42] Disentangling the molecular mechanisms of neurotransmitter dysregulation in OD could have implications for the pathophysiology of neurodegenerative diseases.

Previous studies also found significant relationships between olfaction and neurodegenerative indicators, such as brain atrophy and hypometabolism, total tau protein (t-tau), and NfL. Olfactory scores were found to be associated with magnetic resonance imaging-measured volumes, mainly in AD-signature regions, such as hippocampal, temporal lobe, entorhinal regions, and amygdala.[6,14–17,43] In addition, hypometabolism in olfactory regions, measured by fluorodeoxyglucose positron emission tomography, was also shown to have a significant association with odor identification scores.[15] Longitudinally, higher olfactory scores were related to slower brain atrophy in the entorhinal cortex and hippocampus.[7] Faster olfactory decline could predict smaller olfaction- and AD-associated brain regions.[9] Of note, one cross-sectional study measured plasma t-tau and NfL in 1054 participants and found a linear relationship between olfactory impairment and higher levels of t-tau and NfL.[18] However, thus far, few studies have tried to disentangle the relationships among olfaction, neurodegeneration, and cognition. Reijs et al. did not find that CSF t-tau modified the association between olfaction and cognitive function.[44] Similarly, in our study, blood NfL did not show any interaction with the correlation between the olfactory identification score and baseline MMSE score. However, we found that the association of OD and longitudinal cognitive decline was only significant in participants with high NfL. Our findings highlighted the importance of stratifying individuals upon differences in neurodegenerative burden when using the olfactory test to screen participants who have a high risk of developing cognitive decline in the community.

Furthermore, only participants with combined OD and high NfL demonstrated a significant risk of cognitive decline regardless of confounding factors or competing risk of death, indicating that both OD and higher NfL may contribute to cognitive decline through different pathways or mechanisms and reflect the consequences of upstream neurodegeneration, regardless of specific pathologies.[42] Olfaction and NfL could also be affected by various other factors. For instance, trauma, xenobiotics, and viruses could affect olfactory function,[42] and both central and peripheral axonal injuries could cause an increase in blood NfL.[21] Thus, combining olfaction and NfL may be able to

better detect the degenerative process in the brain. Neurodegeneration has been regarded as the last biological event before cognitive impairment.[45] The combination of both poor olfaction and higher NfL may signify a more severe neurodegenerative change and a closer pathophysiological status to cognitive impairment.

Results of this study should be interpreted after considering potential limitations. First, the study outcomes included all-cause dementia and cognitive decline but lacked pathological information. Thus, we were unable to explore the relationships between olfaction and the incidence of the specific neurodegenerative diseases. Also, we combined dementia and faster MMSE decline as the main outcome, because participants with telephone interviews lacked a clinical evaluation due to the COVID-19 epidemic. However, using long-term cognitive decline as the outcome may generalize our results to the general older population and have significant implications in clinical practice. Second, 193 (17.2%) participants were evaluated using the TICS-40 at follow-ups due to the COVID-19 epidemic. Pooling different tests may cause discrepancies in the determination of cognitive decline. However, we used published crosswalks[32] to unite the two tests and minimize bias. Third, since there is no acknowledged cutoff value of blood NfL to determine the definite neurodegenerative status as yet,[46] we chose the statistical median value to categorize participants with low and high neurodegenerative burden. This cutoff value was only applicable to the current cohort of dementia-free individuals, and the high NfL defined in our study may not reflect severe neurodegeneration. However, we still observed a significant association in our study even by using this relatively arbitrary cutoff value of NfL. Fourth, we only examined the plasma biomarker NfL, a neurodegenerative biomarker, according to the hypothesis of our study. Other AD-specific biomarker measurements in not only cross-sectional but also longitudinal samples should also be considered in the context of OD and cognitive deterioration. A previous cross-sectional study examined the associations of OD with plasma Aβ42, Aβ40, the Aβ42/Aβ40 ratio, t-tau, and NfL, and found significant results with only t-tau and NfL.[18] Whether AD pathology plays a role in the relationship of OD and cognitive deterioration deserves further investigation. Fifth, we did not take Parkinson's disease (PD) or α-synuclein pathology into consideration when analyzing the relationship of OD, NfL, and cognitive decline. Since OD is an early clinical sign in PD, which affects 90% of PD patients,[47] it is worth exploring whether PD or α-synuclein pathology plays a role in the relationship between OD and cognitive decline in the future. Sixth, COVID-19 was reported to be associated with both OD and dementia.[48] However, accurate information on whether participants had ever had COVID-19 was not available in the current study through the pandemic. Therefore, our results could be influenced by this factor, but the extent was hard to estimate. Finally, participants in this study were recruited from a developed metropolis in China, and therefore, our findings might not be generalizable to other older populations. In the future, multi-ethnic large-sampled studies with longer follow-ups should be conducted to validate the robustness of our results.

In conclusion, blood NfL modifies the association of OD with long-term cognitive decline in community-dwelling older adults. OD, especially in combination with high blood NfL concentration, may identify individuals incurring later cognitive deterioration.

AUTHOR CONTRIBUTIONS

D.D. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. D.D. designed the original study. W.W., Z.X., X.L., and X.M. collected data. Z.X., W.W., and J.W. collected and processed blood samples. Z.X. analyzed the data and Y.C. corroborated the data analysis. Z.X. and D.D. drafted the manuscript. All co-authors reviewed and revised the manuscript critically.

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CONFLICT OF INTEREST STATEMENT

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CONSENT STATEMENT

All participants and/or their legal representatives signed the written informed consent.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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