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Nasal microbiome in relation to olfactory dysfunction and cognitive decline in older adults

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Emerging evidence has highlighted that olfactory dysfunction, a common feature of aging, is increasingly linked to cognitive decline in older adults. However, research on the underlying mechanism, particularly the role of nasal microbiome, remains limited. In this study, we investigated the associations between olfactory function, the nasal microbiome, and cognition among 510 older adults with an average age of 77.9 years. Olfactory function was assessed using the brief Chinese Smell Identification Test, and cognitive assessments were conducted via the Mini-Mental State Examination and the Revised Hasegawa Dementia Scale. Nasal microbiome profiles were generated through 16S RNA gene sequencing. We observed that olfactory dysfunction (i.e., hyposmia) was associated with a higher richness of nasal bacteria, and such observation was replicated in an external dataset. A total of 18 nasal bacterial genera were identified to be associated with olfactory function, with eight genera such as *Acidovorax* and *Morganella* being enriched in the hyposmic group. A composite microbial index of nasal olfactory function significantly improved the reclassification accuracy of traditional risk model in distinguishing hyposmic from normosmic participants ($P = 0.008$). Furthermore, participants with a nasal biotype dominated by *Corynebacterium* had a lower prevalence of mild cognitive impairment compared to those dominated by *Dolosigranulum* or *Moraxella*. Our findings suggested that the nasal microbiome may play a role in the association of olfactory function with cognition in older adults, providing new insights into the microbial mechanisms underlying hyposmia and cognitive decline.

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INTRODUCTION

Cognitive decline, commonly associated with aging, represents a rapidly growing public health challenge. The global population of dementia patients is projected to increase from 55 million in 2019 to an estimated 139 million by 2050 [1]. The detection rate of cognitive decline is relatively low, indicating the need to develop universal and accurate detection biomarkers. Epidemiological studies have demonstrated a significant association between impaired olfactory function and cognitive decline [2, 3]. However, this relationship may not be causal and could instead result from share underlying mechanisms, such as aging or neurodegenerative processes. One hypothesis was that changes in the olfactory system might lead to neuronal death in various brain regions, suggesting that olfactory dysfunction could be an early sign of neurodegenerative diseases [4]. Notably, human olfactory function naturally diminishes with age, resulting in a high prevalence of olfactory dysfunctions in older adults [5]. Research further suggests that olfactory dysfunction was also a significant predictor of mortality risk in older adults, emphasizing its importance as a focal point for early diagnostic strategies [6–9].

The nasal microbial ecosystem, essential for the normal development of the olfactory epithelium [10], plays a crucial role in this context. While research on the nasal microbiome and olfactory function is still in its early stages, emerging studies suggest that nasal microbes contribute to maintaining a healthy microenvironment by limiting pathogenic invasions and modulating immune responses to respiratory infections [11, 12]. Most previous research has focused on the gut-brain axis in the context of neurological diseases [13, 14]; however, the potential association of nasal microbiota with olfactory and cognitive functions warrants further exploration [10, 15]. Understanding these interactions could help provide new insights into the mechanisms of cognitive decline and open novel preventative and therapeutic avenues targeting the nasal microbiome.

In this study, we aimed to explore the potential role of the nasal microbiome underlying the association between olfactory dysfunction and mild cognitive impairment (MCI). By analyzing nasal microbiome data, along with olfactory and cognitive functions measurements from approximately 500 older adults aged 66 to 95 years, we investigated the intricate relationships between

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olfactory function, the nasal microbiome, and cognitive decline in older adults. Our findings suggest a microbial mechanism that may contribute to the link between hyposmia and cognitive decline in older adults.

MATERIALS AND METHODS

Study populations

This cross-sectional analysis was performed based on participants from the Rugao Longitudinal Ageing Study (RLAS). Detailed information about the study design and inclusion and exclusion criteria in RLAS has been previously described [16]. In the fourth follow-up examination conducted from December 2019 to January 2020, a total of 2200 participants were recruited, and 510 participants who provided nasal swab samples were included in the current analysis. Among them, 457 participants completed cognition screening using the Mini-Mental State Examination (MMSE) and the Revised Hasegawa Dementia Scale (HDS-R), and 430 participants completed olfactory function assessment using the brief version of the Chinese Smell Identification Test (B-CSIT) [17] (Supplementary Fig. 1).

To replicate the nasal microbial associations with olfactory function, we performed the same analysis in an external population [15]. The replication population included 67 participants (50 women) with an average age (standard deviation) of 27 (6.8) years and an average body mass index (BMI) (standard deviation) of 22.7 (3.8) kg/m^2, and they provided complete nasal microbial 16S rRNA gene amplicon (V4) sequencing data and olfactory function measurement using the Sniffin' Sticks.

Assessment of olfactory function

Olfactory function was assessed using the B-CSIT designed based on local dietary culture [9], comprising 14 validated odors [18] and four locally relevant odors (vinegar, Florida water, longyan, and milk). The B-CSIT score for each participant, ranging from 0 to 18, was determined by the number of correct answers. Participants with a B-CSIT score of ≤3 were classified as hyposmic, while those above this threshold were considered normosmic based on previous definition criteria (10%) using the Sniffin' Sticks [19].

Assessment of cognitive function

Cognitive performance was measured using the MMSE [20] and HDS-R [21]. MCI was defined as an MMSE score of ≤17 for illiterate individuals, ≤20 for those with 1–6 years of education, and ≤24 for individuals with more than 6 years of education [20], or an HDS-R score of ≤21.5 [22].

Measurement of nasal microbiome

Nasal samples were obtained from both nares with nasal swabs (CY-98000, HCY Technology, China) according to a pre-defined protocol [23].

DNA was processed using high-thought Illumina amplicon sequencing of the V4 variable region of the microbial 16S rRNA gene according to established protocols [23]. A total of 104.83 million sequences were obtained, with an average of 210,750 reads per sample, ranging from 10,794 to 772,196 reads. Samples with <10,000 16S rRNA gene sequencing reads ($n = 14$) were considered of low quality and removed from the following analysis.

Raw sequence data for each sample were processed consistent with procedures described in previous articles published in our laboratory [24]. Briefly, to analyze the microbial community structure and taxonomic diversity, raw reads were processed using QIIME2 (version 2022.8) [25]. Paired-end sequencing reads were quality-filtered, trimmed, de-noised, and merged using the DADA2 software [26], then summarized into amplicon sequence variants (ASVs) in a feature table. Taxonomic assignments were made using the Naïve Bayes classifier trained on the SILVA 138 database [27], and functional profiles of the microbial communities were predicted by using PICRUSt2 [28]. Three α diversity indices were calculated based on the ASV level: ACE index, Chao1 index, and Shannon index. The microbial composition β-diversity was calculated based on ASV-level Bray-Curtis dissimilarity metrics and visualized via principal coordinate analysis (PCoA). Microbial genera with a relative abundance <0.01% in over 90% of samples and pathways with a relative abundance <0.001% in over 90% of samples were excluded from the downstream analyses. Eventually, a total of 87 genera and 355 pathways were included. Based on methods described for human gut microbiome enterotypes [29], we also performed the clustering of the nasal microbiome. Samples were clustered using the Partitioning Around Medoids algorithm with Jensen-Shannon Divergence distance, implemented in the "cluster" R package (version 2.1.4). The optimal number of clusters was determined using the Calinski-Harabasz.

Nasal olfactory index

The nasal olfactory index (NOI) was calculated regarding to the calculation of the gut aging index [30]. The olfactory-associated nasal genera were grouped into two sets M_P and M_N, where M_P was the set of nasal genera positively associated with olfactory function and vice versa for M_N. The NOI for each sample was defined as:

$$NOI = \log 10\left(\frac{R_{M_{P,i}}}{|M_P|}\sum\nolimits_{j\in M_P} x_{j,i} \Big/ \frac{R_{M_{N,i}}}{|M_N|}\sum\nolimits_{j\in M_N} x_{j,i}\right)$$

where $R_{M_{P,i}}$ denotes the prevalence of M_P (or the number of present genera of M_P in sample i) in sample i, $|M_P|$ is the size of set M_P (or the overall number of genera in M_P), $x_{j,i}$ denotes the relative abundance of genera j in sample i and the same for $R_{M_{N,i}}$ and $|M_N|$. The calculation integrated both the prevalence and relative abundance of olfactory-associated nasal genera. For each sample, the NOI balanced these two factors by incorporating the average relative abundance of relevant genera, weighted by their prevalence within M_P and M_N. This approach ensured that the NOI reflected not only the composition but also the prevalence of nasal genera associated with olfactory function. The logarithmic transformation emphasized proportional differences between M_P and M_N. A higher NOI indicates a nasal microbiota composition more favorable to olfactory function.

Statistical analysis

Differences in demographic factors and characteristics between the hyposmic and normosmic participants were examined using t-test or Wilcoxon rank-sum test for continuous variables and chi-square-test for categorical variables. Linear regression models were used to measure the associations between olfactory and cognitive functions, with both MMSE or HDS-R scores being standardized in the models. Differences in α-diversity indices between the two groups were examined using the Wilcoxon rank-sum test. Differences in microbial composition across different groups were determined using permutational multivariate analysis of variance (PERMANOVA) with 9999 permutations, implemented in the R package "vegan" (version 2.6–4). Multivariate analysis by linear models (MaAsLin, version 1.12.0) [31] was used to examine the associations of bacterial genera and pathways with olfactory function. The relative abundance of bacterial genera and pathways was transformed by centered log-ratio (CLR) before association analysis with adjustments of age and sex. Significance was established using a false discovery rate (FDR) of <0.05. To address potential confounding by age and sex, we conducted a sensitivity analysis using propensity score matching (PSM). Participants in the hyposmic and normosmic groups were matched at a 1:1 ratio based on their age and sex. Spearman correlation coefficients were used to measure correlations between genera and pathways. Logistic regression models were used to conduct comparisons between different biotypes.

The classification performance of NOI and traditional risk factors (such as sex, age, BMI, and smoking status) on hyposmia were estimated using logistic regression and visualized by the receiver operating characteristic (ROC) area under the curve (AUC). The significance of the difference between model performances was evaluated using the Delong test, implemented via the "roc. test" function of the R package "pROC" (version 1.18.0).

Mediation analyses examined the potential mediation effects of microbial structure on the associations between olfactory function and cognitive function. The first two eigenvalues from PCoA, which jointly explained approximately 50% of the microbial community variation, were used to represent the overall nasal microbial structure in the mediation models. Mediation analysis was performed using the R package "mediation" (version 4.5.0).

All statistical analyses were performed using R version 4.2.3, and a P-value < 0.05 was considered statistically significant unless otherwise specified.

RESULTS

Olfactory function correlated significantly with cognitive function

Among the 1381 participants (aged 65–95 years) with complete B-CSIT data and cognitive function measurements (Table S1), the

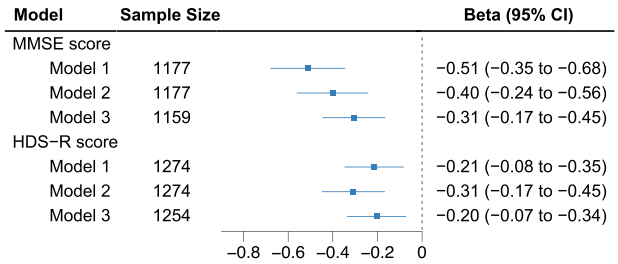


Fig. 1 Association between olfactory function and cognitive scores in the RLAS cohort. Model 1 adjusted for no covariable; Model 2 adjusted for sex, age, and BMI; Model 3 further adjusted for lifestyle factors including smoking, drinking, and marital status. Cognitive measures included the Mini-Mental State Examination (MMSE) and the Hasegawa Dementia Scale-Revised (HDS-R). Sample sizes and beta coefficients with 95% confidence intervals (CIs) were displayed for each model. The beta values represented the extent of cognitive decline in the hyposmic group compared to the normosmic group, quantified in standard deviations of cognitive scores in the population.

cognitive function measured by either MMSE or HDS-R was significantly reduced in the hyposmic group (B-CSIT ≤ 3) compared to those with normal olfactory function. With further adjustments of age, sex, and BMI, hyposmia remained significantly associated with inferior cognitive function as assessed by HDS-R or MMSE (both $P < 0.05$, Fig. 1). With further adjustments of lifestyle factors, including smoking status, drinking status, and marital status, the hyposmic group showed a decline of 0.31 standard deviation (SD) in MMSE scores and 0.20 SD in HDS-R scores compared to the normosmic group (Fig. 1).

Microbial community composition differs between the normosmic and hyposmic groups

Among the 430 participants (aged 66–95 years) with both nasal microbiome data and olfactory function measurements, 386 participants were categorized as normosmic and 44 as hyposmic (B-CSIT ≤ 3; Table 1). Compared to the normosmic group, hyposmic participants were more likely to be older and ever smokers ($P < 0.05$) and tended to have a higher BMI ($P = 0.07$).

The nasal microbial profile of these participants was dominated by phyla Firmicutes (43.7%), Actinobacteria (41.1%), and Proteobacteria (12.8%) (Supplementary Fig. 2). Participants in the hyposmic group exhibited a trend toward higher richness of nasal bacteria, as indicated by the ACE and Chao1 indices ($P < 0.05$, Fig. 2a), and such association became borderline significant with adjustment of sex, age, BMI and smoking status (Supplementary Table 2). Significant differences in β diversity between hyposmic and normosmic groups were observed, and such differences persisted significantly even with adjustment for sex, age, BMI, and smoking status ($P < 0.05$, Fig. 2b). The nasal microbial composition explained 1.25% of the variation in olfactory function, ranking only lower than age and education, but higher than BMI, lifestyle factors such as smoking status, and diseases (Fig. 2c). In the MaAsLin analysis, incorporating adjustments of age, sex, BMI, and smoking status, 41 of the 87 analyzed genera from eight phyla were identified to be associated with the olfactory function (FDR < 0.05, Fig. 2d), with 18 genera exhibiting particularly significant associations (FDR < 0.01, Supplementary Fig. 3). For example, *Acidovorax*, a well-established bacterial biomarker for lung cancer [32], has been demonstrated to promote inflammation [33]. Furthermore, 15 predicted microbial pathways had different abundances between the hyposmic and normosmic groups (FDR < 0.05, Supplementary Fig. 4). Notably, all the differential pathways were more abundant in the hyposmic group, primarily including pathways of aromatic compound degradation, and biosynthesis of cofactors, carriers, and vitamins.

Table 1. Basic characteristics of participants.

	Olfactory Function Group[a]		*P*-value
	hyposmic *N* = 44	normosmic *N* = 386	
Male	23 (52.3)	177 (45.9)	0.52
Age, mean (SD), y	79.70 (5.83)	77.60 (4.60)	0.005
BMI[b], mean (SD), (kg/m^2)	23.26 (3.53)	24.27 (3.50)	0.07
Illiterate	22 (52.4)	184 (49.1)	0.81
Married	26 (63.4)	244 (65.4)	0.93
Smoker	16 (40.0)	85 (23.0)	0.03
Drinker	19 (47.5)	140 (37.7)	0.30
Stroke	0 (0.0)	24 (6.2)	0.18
Diabetes	6 (13.6)	57 (14.8)	0.99
Hypertension	20 (45.5)	165 (42.7)	0.86
Glucose, mean (SD), mmol/l	5.46 (1.84)	5.76 (1.67)	0.25
B-CSIT score, mean (SD)	0.48 (0.95)	13.30 (2.82)	<0.001
MMSE, mean (SD)	20.24 (6.96)	21.56 (5.62)	0.21
HDS-R, mean (SD)	20.15 (6.06)	20.76 (5.32)	0.51
Cognitive Impairment	18 (48.6)	184 (51.4)	0.88

[a]Data are expressed as No. (%) unless otherwise indicated.
[b]The body mass index is the weight in kilograms divided by the square of the height in meters.

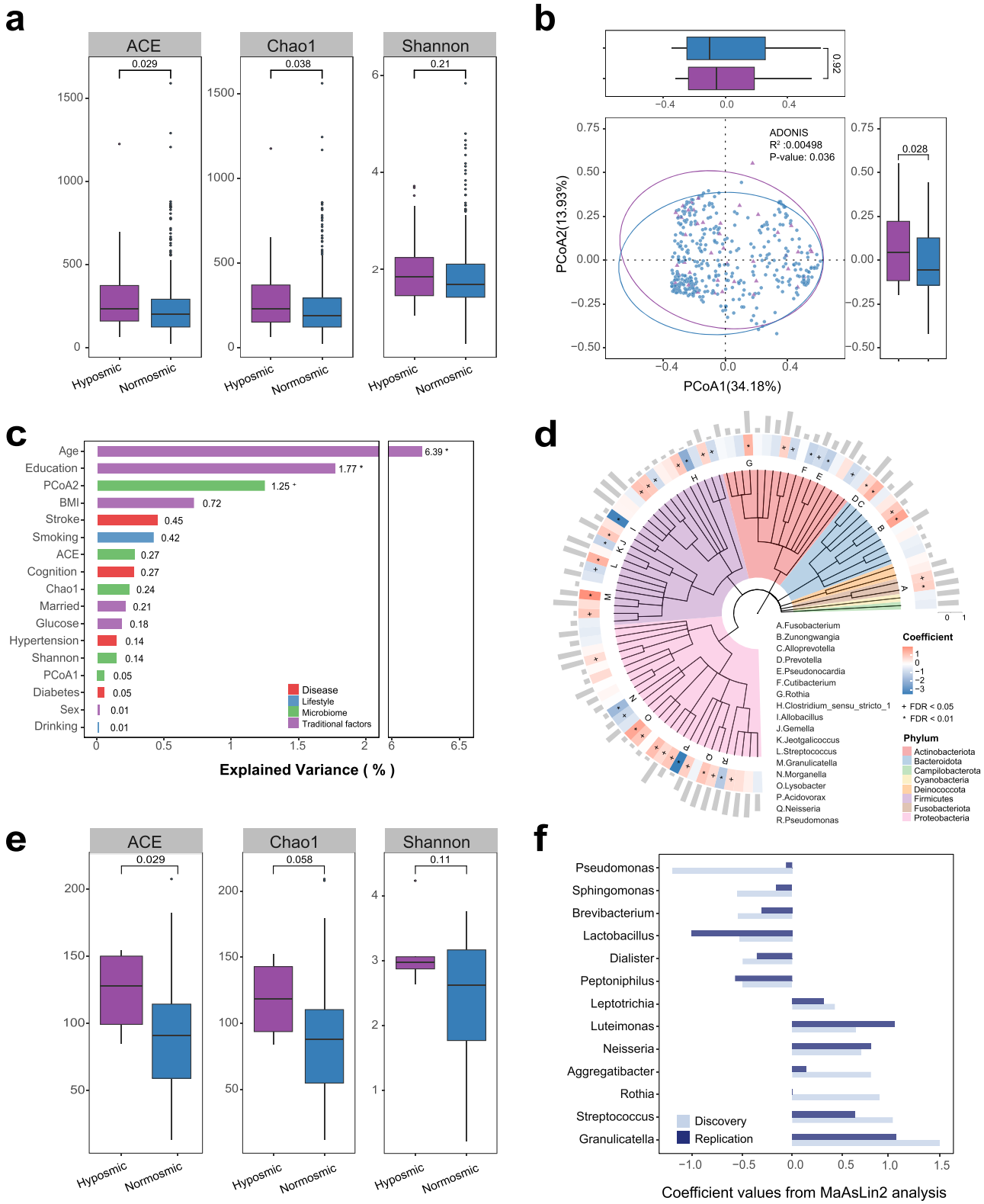
To corroborate our findings, we performed external replication using an independent dataset. The differences and trends in the richness of nasal bacteria between the normosmic and hyposmic groups were consistently observed in the external replication set (Fig. 2e). Moreover, after adjusting sex, age and BMI, we observed a significantly decreased microbial richness in the normosmic group using the replication dataset, (Supplementary Table 2). Notably, 25 out of the 41 genera identified in our study were detected in the external replication set, with 13 genera demonstrating consistent associations with olfactory function (Fig. 2f).

Among the 88 sex- and age-matched participants (Supplementary Table 3), alpha diversity indices remained significantly lower in the normosmic group than the hyposmic group (Supplementary Fig. S5a), while beta diversity did not differ significantly, likely due to the reduced sample size (Supplementary Fig. S5b). Among the 18 genera used to construct the NOI, significant differences between groups remained even after adjusting for sex, age, BMI, and smoking status (all FDR < 0.05, Supplementary Fig. S5c).

The nasal microbiome-based signature effectively discriminated between the hyposmic and normosmic groups

To generate a composite indicator reflecting the olfactory function-related nasal bacterial profile, we calculated the NOI from the above-identified 18 differential genera. As expected, the normosmic group exhibited a significantly higher NOI compared to the hyposmic group, females had higher NOI scores compared to males, while there were no significant differences in NOI scores across participants of different age, BMI, and smoking status (Fig. 3a). In general, the correlation among differential genera was not high, and the average correlation coefficient was 0.31. *Clostridium_sensu_stricto_1* had the highest number of significant correlations with other differential genera. *Prevotella* has the highest average correlation coefficient with other differential genera, reaching 0.46. (Fig. 3b).

The reclassification model based on NOI demonstrated comparable performance to that of the model based on traditional risk



factors (i.e., sex, age, BMI, and smoking status) in distinguishing hyposmic participants from normosmic ones (AUC [95%CI] 0.88 [0.80–1.00] vs. 0.75 [0.63–0.90], $P = 0.09$, Fig. 3c). Notably, the addition of NOI into traditional risk factors significantly enhanced the model's discriminatory power (AUC improved from 0.75 [0.63–0.90] to 0.93 [0.89–1.00], P for difference = 0.008, Fig. 3c).

The nasal bacterial biotypes were associated with mild cognitive impairment

Given the observed associations of olfactory function with both nasal microbiome and cognitive function, we conducted investigations to explore the connection between nasal microbiome and cognitive function. Although there was no significant difference

Fig. 2 Differences in nasal microbiome between the hyposmic and normosmic groups. a Boxplots illustrated α diversity indices (ACE, Chao1, and Shannon) in the hyposmic and normosmic groups, with statistical significance indicated by P-values. **b** Principal Coordinates Analysis (PCoA) plot based on Bray–Curtis distance visualized differences in microbial community structure between groups. Results from PERMANOVA (Adonis R^2 and *P*-value) were displayed. **c** Bar graph showed the proportion of variance in olfactory function explained by nasal microbiome composition, lifestyle factors, and other covariates, with significant contributors marked by '+' ($P < 0.05$) and '*' ($P < 0.01$). **d** Phylogenetic tree of nasal microbiome, highlighted genera differentially abundant between groups, with coefficient values from MaAsLin analysis: blue for higher abundance in the hyposmic group and red for lower. The outermost ring indicated the prevalence of each genus in the subjects. Significant genera were flagged with '+' (FDR < 0.05) or '*' (FDR < 0.01). **e** Boxplots of α diversity in the replication dataset with *P*-values. **f** Bar graph displayed the MaAsLin analysis coefficients for 13 genera that showed consistent associations with olfactory function between the discovery and replication datasets.

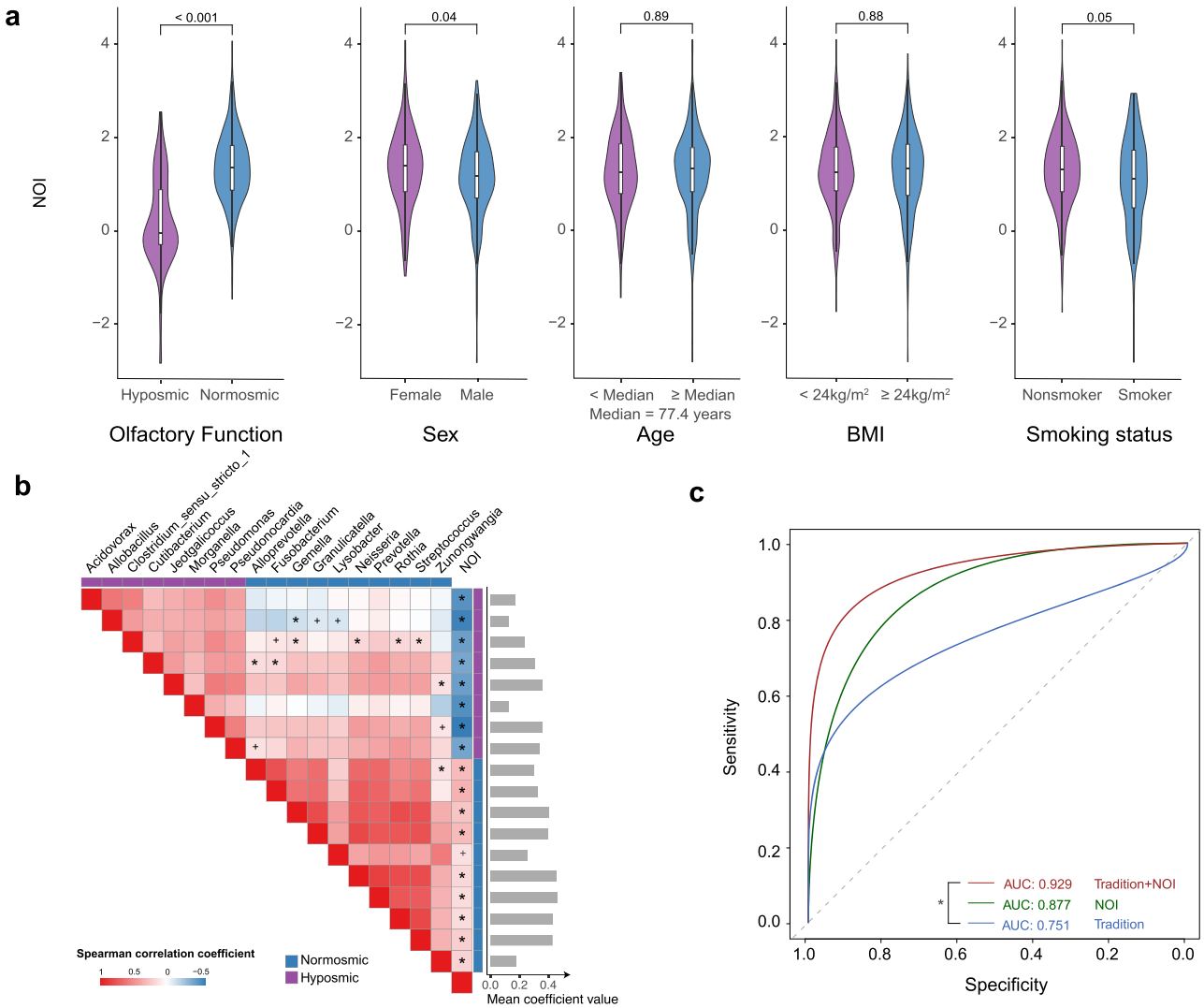


Fig. 3 Differences in the nasal olfactory index (NOI) between hyposmic and normosmic groups and its performance in reclassification accuracy of olfactory dysfunction. a Violin plots depicted the distribution of the NOI across various different demographic and behavioral factors, with *P*-values indicating statical differences. **b** Heatmap illustrated the Spearman correlation coefficients between differentially abundant nasal genera and NOI. Significant correlations were marked with '+' (FDR < 0.05) or '*' (FDR < 0.01). **c** Receiver Operating Characteristic (ROC) curves demonstrated the enhancement in reclassification accuracy for hyposmia by incorporating the NOI alongside traditional factors (sex, age, BMI, and smoking status). Area under the curve (AUC) values for each model were provided, with statistically significant differences indicated by '*' ($P < 0.01$).

between the groups in terms of community richness represented by ACE and Chao1 indices, significant differences were observed between the two groups in the Shannon index, which combines richness and evenness of the community (Fig. 4a), and in the bacterial compositional structure ($P = 0.001$, Fig. 4b). After clustering the participants based on the nasal microbial community characteristics at the genus level, we observed significant differences in the prevalence of MCI among different nasal biotypes ($P < 0.05$, chi-square-test, Fig. 4c). For example, the participants who were dominated by the genus *Corynebacterium* exhibited a lower prevalence of MCI compared to clusters dominated by the genera *Dolosigranulum* and *Moraxella* ($P < 0.05$, Fig. 4d). This significance remained even after adjusting for sex, age, and BMI.

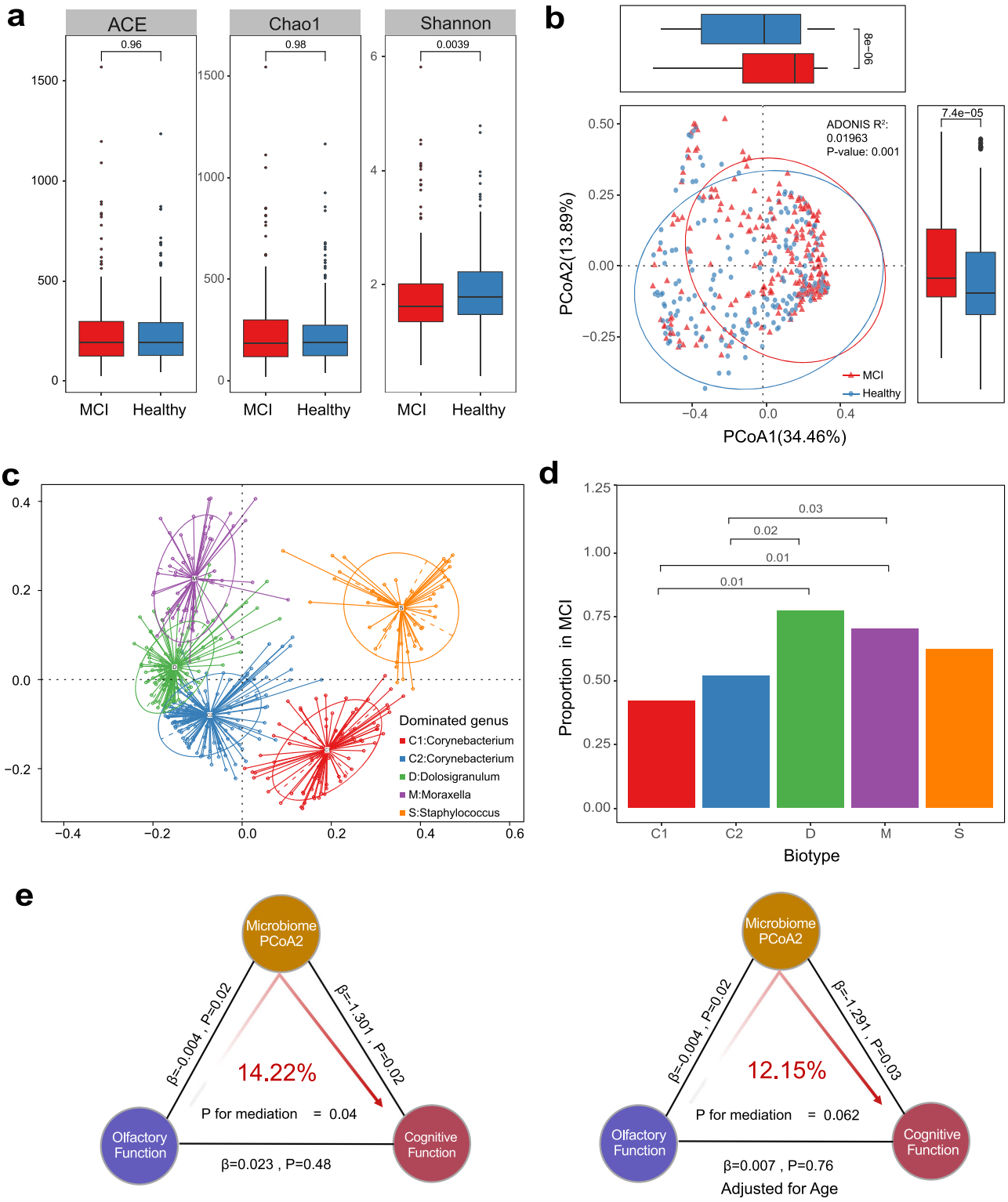


Fig. 4 Differences in the nasal microbiome between mild cognitive impairment (MCI) and cognitively healthy groups. a Boxplots illustrated α diversity indices (ACE, Chao1, and Shannon) in MCI and cognitive healthy groups, with statistical significance indicated by P-values. **b** Principal Coordinates Analysis (PCoA) plot based on Bray–Curtis distance visualizes differences in microbial community structure between groups. Results from PERMANOVA (Adonis R^2 and *P*-value) were displayed. **c** Cluster analysis of the nasal microbiome biotypes, depicted in different colors (C1 in red, C2 in blue, D in green, M in purple, and S in orange), with key genera characterizing each biotype. **d** Bar graph compared the prevalence of MCI across different nasal microbiome biotypes, with statistical significance denoted by P-values. **e** Mediation analysis diagram demonstrated the mediating effects of the nasal microbiome on the associations between olfactory and cognitive functions, quantified by β coefficients and *P*-values.

Considering that only microbial composition but not individual genera (all FDR > 0.05, Supplementary Table 4) was linked to cognitive function in our population, we explored the potential role of the overall nasal microbial structure indicated by PCoA as a mediator in the association between olfactory function and cognitive function. Of note, the microbial structure PCoA2 potentially mediated approximately 14% of the association of olfactory dysfunction with MCI ($P = 0.04$), although further adjustment of age attenuated such mediation (Fig. 4e).

DISCUSSION

Among community-based older adults, we observed distinct microbial structural compositions and abundances of bacterial genera between the hyposmic and normosmic groups. In addition, we identified five nasal biotypes, and the biotype dominated by *Corynebacterium* was associated with lower odds of MCI compared to the biotypes dominated by the genera *Dolosigranulum* and *Moraxella*. Moreover, our results indicated a potential association between olfactory function and nasal microbiome composition in older adults, with the nasal microbiome potentially mediating the association of olfactory function with cognitive function.

Given that 75–95% of early neurodegenerative patients exhibit impaired olfactory function [34, 35], the molecular mechanisms linking olfactory function to neurodegenerative progression warrant further investigation. The nasal cavity, a portal for pathogens and toxins, hosts a diverse microbiota. In our study, significant differences in 41 genera between the two olfactory groups were primarily found in the phyla Firmicutes (*Streptococcus, Granulicatella*), and Proteobacteria (*Pseudomonas, Acidovorax*), aligning with results from a smaller study ($n = 67$) [15]. The composite NOI significantly enhanced the performance of the model with traditional risk factors to reclassify olfactory function groups among older adults, further supporting the importance of nasal microbiota in maintaining healthy olfactory function.

Furthermore, previous studies indicated that the nasal microbiome, particularly in the nasopharynx and oropharynx, plays a crucial role in neuro-regulation [36, 37]. In older adults, immune senescence and weakened immune responses may facilitate the upward spread of nasal bacteria, escalating proinflammatory markers and diminishing immune stress management [38]. Additionally, microorganism-human tissue interactions are mediated by microbial metabolites, such as short-chain and branched-chain amino acids, and hormone-like molecules [39–41]. Over the past decade, evidence has shown that microbiota could affect the central nervous system's physiology and neurochemistry [42, 43]. When pathogenic microbiota penetrates the brain via the nasal cavity, they can significantly alter cerebral metabolism and endocrine signaling pathways [44, 45]. Therefore, the nasal microbiome's composition, changes, and interactions are crucial for cognitive functions [46].

Similar to the enterotypes [47], biotypes using the nasal microbiome data may also have health implications. Our study observed that the biotype dominated by *Corynebacterium* was positively associated with cognition, and prior evidence suggested that immunoregulatory mechanisms might underlie such an association. For example, *Corynebacterium accolens* has been shown to modulate dermal γδ T cell populations, especially the IL-17A-producing Vγ4 + γδ T cells [48]. IL-17A plays a vital role in enhancing host immune responses by interacting with various immune cells [49], and it is crucial for maintaining systemic energy homeostasis and emerges as a significant factor in neuroimmunometabolism [50]. Moreover, *Corynebacterium pseudodiphtheriticum*, a commensal found in the human nasopharyngeal mucosa, has been recognized for its immunomodulatory properties that confer health benefits [51, 52], including increased resistance to bacterial and viral pathogens [53]. These mechanisms might help explain the observed beneficial cognitive associations with biotype dominated by *Corynebacterium*.

Previous evidence suggested that nasal microbiomes can enter the brain via the olfactory pathway, potentially damaging neurons and contributing to neurodegenerative diseases [46, 54]. The nasal microbiome originates at the cribriform plate, extends through the olfactory epithelium, and then spreads to other brain regions, impacting brain metabolism and neuronal physiology [55, 56]. Previous studies have linked nasal pathogenic flora to Alzheimer's and Parkinson's diseases, affecting central nervous and immune systems [57, 58]. Thus, differences in nasal microbiomes could be a putative microbial mechanism explaining differences in cognitive abilities among older adults. The inconsistencies in study results arise from variations in nasal swab collection methods, as well as small, culturally diverse study populations [34, 58, 59].

To our knowledge, this study is among the largest to explore the association of nasal microbiome's diversity and structure with olfactory function, and the first study to explore the underlying role of the nasal microbiome in the association between olfactory and cognitive functions. However, due to its observational design, our study cannot establish a causal link among these associations. While we observed significant associations, the specific underlying mechanisms of these relationships remain unclear. Additionally, the cross-sectional design is subject to residual confounding, even after adjustments for key covariates. Longitudinal studies are needed to establish temporal sequences and causal links. Future research incorporating longitudinal cohorts could provide deeper insights into the dynamics of nasal microbiome, olfactory function and cognitive function. Furthermore, our method for assessing olfactory function was not the gold standard, specifically the comprehensive Sniffin' Sticks test. However, the questionnaire employed was validated for reliability and validity, demonstrating a high correlation with gold standard scores has proved to be cost-effective for use in large population-based studies [60]. Additionally, we only sampled the anterior nostril for microbiome analysis, and our microbiome data may not be generalized to the overall nasal microbiome.

CONCLUSION

This study provides evidence for a potential link between olfactory function and the nasal microbiome, suggesting a microbial mechanism associated with hyposmia and MCI in older adults. Clustering analysis reveals significant differences in the prevalence of MCI among older adults with different biotypes. Furthermore, the results support further study into the role of the nasal microbiome in mediating the association between olfactory and cognitive functions.

DATA AND MATERIALS AVAILABILITY

Sequencing data during the current study can be viewed in NODE database (https://www.biosino.org/node/project/detail/OEP005489) and are available upon acceptance of the publication, and code will be made available upon reasonable request.

REFERENCES

1. Long S, Benoist C, Weidner W World Alzheimer report 2023: reducing dementia risk: never too early, never too late. 2023; https://www.alzint.org/u/World-Alzheimer-Report-2023.pdf
2. Yaffe K, Freimer D, Chen H, Asao K, Rosso A, Rubin S, et al. Olfaction and risk of dementia in a biracial cohort of older adults. Neurology. 2017;88:456–62.
3. Roberts RO, Christianson TJ, Kremers WK, Mielke MM, Machulda MM, Vassilaki M, et al. Association between olfactory dysfunction and amnestic mild cognitive impairment and Alzheimer disease dementia. JAMA Neurology. 2016;73:93–101.
4. Franco R, Garrigos C, Lillo J. The olfactory trail of neurodegenerative diseases. Cells. 2024;13:615.

5. Dong J, Pinto JM, Guo X, Alonso A, Tranah G, Cauley JA, et al. The prevalence of anosmia and associated factors among U.S. Black and white older adults. J Gerontol A Biol Sci Med Sci. 2017;72:1080–6.
6. Doty RL, Hawkes CH. Chemosensory dysfunction in neurodegenerative diseases. Handb Clin Neurol. 2019;164:325–60.
7. Park H, Kim H, Kim S, Cha H. The association between olfactory function and cognitive impairment in older persons with cognitive impairments: a Cross-Sectional Study. Healthcare. 2021;9:399.
8. Ekström I, Sjölund S, Nordin S, Nordin Adolfsson A, Adolfsson R, Nilsson LG, et al. Smell loss predicts mortality risk regardless of dementia conversion. J Am Geriatr Soc. 2017;65:1238–43.
9. Yang X, Si J, Lin S, Zhou X, Zhang H, Sun Z, et al. Olfactory function, genetic predisposition, and cognitive performance in chinese adults. Curr Alzheimer Res. 2021;18:1093–103.
10. François A, Grebert D, Rhimi M, Mariadassou M, Naudon L, Rabot S, et al. Olfactory epithelium changes in germfree mice. Sci Rep. 2016;6:24687.
11. Bomar L, Brugger SD, Lemon KP. Bacterial microbiota of the nasal passages across the span of human life. Curr Opin Microbiol. 2018;41:8–14.
12. Thangaleela S, Sivamaruthi BS, Kesika P, Bharathi M, Chaiyasut C. Nasal microbiota, olfactory health, neurological disorders and aging-a review. Microorganisms. 2022;10:1405.
13. Mayer EA, Nance K, Chen S. The gut-brain axis. Annu Rev Med. 2022;73:439–53.
14. Esteves AR, Munoz-Pinto MF, Nunes-Costa D, Candeias E, Silva DF, Magalhães JD, et al. Footprints of a microbial toxin from the gut microbiome to mesencephalic mitochondria. Gut. 2023;72:73–89.
15. Koskinen K, Reichert JL, Hoier S, Schachenreiter J, Duller S, Moissl-Eichinger C, et al. The nasal microbiome mirrors and potentially shapes olfactory function. Sci Rep. 2018;8:1296.
16. Liu Z, Wang Y, Zhang Y, Chu X, Wang Z, Qian D, et al. Cohort profile: the Rugao Longevity and Ageing study (RuLAS). Int J Epidemiol. 2016;45:1064–73.
17. Feng G, Zhuang Y, Yao F, Ye Y, Wan Q, Zhou W. Development of the Chinese smell identification test. Chem Senses. 2019;44:189–95.
18. Shu CH, Yuan BC. Assessment of odor identification function in Asia using a modified "Sniffin' Stick" odor identification test. Eur Arch Otorhinolaryngol. 2008;265:787–90.
19. Oleszkiewicz A, Schriever VA, Croy I, Hahner A, Hummel T. Updated Sniffin' Sticks normative data based on an extended sample of 9139 subjects. Eur Arch Otorhinolaryngol. 2019;276:719–28.
20. Li H, Jia J, Yang Z. Mini-mental state examination in elderly chinese: a Population-Based Normative Study. J Alzheimer's Dis. 2016;53:487–96.
21. Liu H, Lu X, Li C, Bai L, Dong X. Studying on relationship between Hasegawa dementia scale and nursing care of senile dementia patients. Mod Nurs. 2001;7:1–2.
22. Kashiwase H, Watanabe M, Suda E, Tachibana S, Kinuya M, Ohtakeno S, et al. Affective and cognitive symptoms in the aged in a Japanese nursing home. Dementia. 1991;2:112–5.
23. Wang Y, Zhang R, Pu Y, Wang D, Wang Y, Wu X, et al. Sample collection, DNA extraction, and library construction protocols of the human microbiome studies in the international human phenome project. Phenomics. 2023;3:300–8.
24. Wang Y, Yue H, Jiang Y, Huang Q, Shen J, Hailili G, et al. Oral microbiota linking associations of dietary factors with recurrent oral ulcer. Nutrients. 2024;16:1519.
25. Bolyen E, Rideout JR, Dillon MR, Bokulich NA, Abnet CC, Al-Ghalith GA, et al. Reproducible, interactive, scalable and extensible microbiome data science using QIIME 2. Nat Biotechnol. 2019;37:852–7.
26. Callahan BJ, McMurdie PJ, Rosen MJ, Han AW, Johnson AJ, Holmes SP. DADA2: high-resolution sample inference from Illumina amplicon data. Nat Methods. 2016;13:581–3.
27. Quast C, Pruesse E, Yilmaz P, Gerken J, Schweer T, Yarza P, et al. The SILVA ribosomal RNA gene database project: improved data processing and web-based tools. Nucleic Acids Res. 2013;41:D590–6.
28. Douglas GM, Maffei VJ, Zaneveld JR, Yurgel SN, Brown JR, Taylor CM, et al. PICRUSt2 for prediction of metagenome functions. Nat Biotechnol. 2020;38:685–8.
29. Arumugam M, Raes J, Pelletier E, Le Paslier D, Yamada T, Mende DR, et al. Enterotypes of the human gut microbiome. Nature. 2011;473:174–80.
30. Lai S, Yan Y, Pu Y, Lin S, Qiu JG, Jiang BH, et al. Enterotypes of the human gut mycobiome. Microbiome. 2023;11:179.
31. Mallick H, Rahnavard A, McIver LJ, Ma S, Zhang Y, Nguyen LH, et al. Multivariable association discovery in population-scale meta-omics studies. PLoS Comput Biol. 2021;17:e1009442.
32. Dong H, Tan Q, Xu Y, Zhu Y, Yao Y, Wang Y, et al. Convergent alteration of lung tissue microbiota and tumor cells in lung cancer. iScience. 2022;25:103638.
33. Stone JK, von Muhlinen N, Zhang C, Robles AI, Flis AL, Vega-Valle E, et al. Acidovorax temperans skews neutrophil maturation and polarizes Th17 cells to promote lung adenocarcinoma development. Oncogenesis. 2024;13:13.
34. Pal G, Ramirez V, Engen PA, Naqib A, Forsyth CB, Green SJ, et al. Deep nasal sinus cavity microbiota dysbiosis in Parkinson's disease. NPJ Parkinson's Dis. 2021;7:111.
35. Lazarini F, Roze E, Lannuzel A, Lledo PM. The microbiome-nose-brain axis in health and disease. Trends Neurosci. 2022;45:718–21.
36. He W, Ma Y, Zhou L, Hao X. The role of microbiome in respiratory disease. Chin. J. Lab. Med. 2016;39:322–325.
37. Gevers D, Kugathasan S, Denson LA, Vázquez-Baeza Y, Van Treuren W, Ren B, et al. The treatment-naive microbiome in new-onset Crohn's disease. Cell Host Microbe. 2014;15:382–92.
38. Franceschi C, Bonafè M, Valensin S, Olivieri F, De Luca M, Ottaviani E, et al. Inflamm-aging. An evolutionary perspective on immunosenescence. Ann N Y Acad Sci. 2000;908:244–54.
39. Grenham S, Clarke G, Cryan JF, Dinan TG. Brain-gut-microbe communication in health and disease. Front Physiol. 2011;2:94.
40. Hughes DT, Sperandio V. Inter-kingdom signalling: communication between bacteria and their hosts. Nat Rev Microbiol. 2008;6:111–20.
41. Wilson MT, Hamilos DL. The nasal and sinus microbiome in health and disease. Curr Allergy Asthma Rep. 2014;14:485.
42. Fox M, Knorr DA, Haptonstall KM. Alzheimer's disease and symbiotic microbiota: an evolutionary medicine perspective. Ann N Y Acad Sci. 2019;1449:3–24.
43. Bell JS, Spencer JI, Yates RL, Yee SA, Jacobs BM, DeLuca GC. Invited review: from nose to gut - the role of the microbiome in neurological disease. Neuropathol Appl Neurobiol. 2019;45:195–215.
44. Konovalovas A, Armalytė J, Klimkaitė L, Liveikis T, Jonaitytė B, Danila E, et al. Human nasal microbiota shifts in healthy and chronic respiratory disease conditions. BMC Microbiol. 2024;24:150.
45. Xie J, Tian S, Liu J, Cao R, Yue P, Cai X, et al. Dual role of the nasal microbiota in neurological diseases-An unignorable risk factor or a potential therapy carrier. Pharmacol Res. 2022;179:106189.
46. Harrass S, Yi C, Chen H. Chronic rhinosinusitis and Alzheimer's disease-A possible role for the nasal microbiome in causing neurodegeneration in the elderly. Int J Mol Sci. 2021;22:11207.
47. Costea PI, Hildebrand F, Arumugam M, Bäckhed F, Blaser MJ, Bushman FD, et al. Enterotypes in the landscape of gut microbial community composition. Nat Microbiol. 2018;3:8–16.
48. Ridaura VK, Bouladoux N, Claesen J, Chen YE, Byrd AL, Constantinides MG, et al. Contextual control of skin immunity and inflammation by corynebacterium. J Exp Med. 2018;215:785–99.
49. Fu JJ, Huang Y, Bao T, Liu CC, Liu X, Chen XP. The role of Th17 cells/IL-17A in AD, PD, ALS and the strategic therapy targeting on IL-17A. J Neuroinflamm. 2022;19:98.
50. Douglas A, Stevens B, Lynch L. Interleukin-17 as a key player in neuroimmunometabolism. Nat Metab. 2023;5:1088–1100.
51. Andrade BGN, Cuadrat RRC, Tonetti FR, Kitazawa H, Villena J. The role of respiratory microbiota in the protection against viral diseases: respiratory commensal bacteria as next-generation probiotics for COVID-19. Biosci Microb Food H. 2022;41:94–102.
52. Piters WAAD, Binkowska J, Bogaert D. Early life microbiota and respiratory tract infections. Cell Host Microbe. 2020;28:223–32.
53. Moyano RO, Tonetti FR, Fukuyama K, Elean M, Tomokiyo M, Suda Y, et al. The respiratory commensal bacterium as a mucosal adjuvant for nasal vaccines. Vaccines-Basel. 2023;11:611.
54. Mattson MP, Duan W, Pedersen WA, Culmsee C. Neurodegenerative disorders and ischemic brain diseases. Apoptosis. 2001;6:69–81.
55. Phillips AT, Stauft CB, Aboellail TA, Toth AM, Jarvis DL, Powers AM, et al. Bioluminescent imaging and histopathologic characterization of WEEV neuroinvasion in outbred CD-1 mice. PLoS ONE. 2013;8:e53462.
56. Tai J, Han MS, Kwak J, Kim TH. Association between microbiota and nasal mucosal diseases in terms of immunity. Int J Mol Sci. 2021;22:4744.
57. Little CS, Bowe A, Lin R, Litsky J, Fogel RM, Balin BJ, et al. Age alterations in extent and severity of experimental intranasal infection with chlamydophila pneumoniae in BALB/c mice. Infect Immun. 2005;73:1723–34.
58. Heintz-Buschart A, Pandey U, Wicke T, Sixel-Döring F, Janzen A, Sittig-Wiegand E, et al. The nasal and gut microbiome in Parkinson's disease and idiopathic rapid eye movement sleep behavior disorder. Mov Disord. 2018;33:88–98.
59. Li Z, Lu G, Luo E, Wu B, Li Z, Guo J, et al. Oral, nasal, and gut microbiota in parkinson's disease. Neuroscience. 2022;480:65–78.
60. Su BH, Wu DW, Wei YX. Development of Chinese odor identification test. Ann Transl Med. 2021;9:499.

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AUTHOR CONTRIBUTIONS

HS, ZS and YP collected and conducted wet lab portion of the experiments and data. HS analyzed 16S rRNA sequencing data. HS and JZ interpreted the results and wrote the manuscript. YZ, XG, XW, CY, QL, WQ and LS provided critically important revisions to the manuscripts. All authors revised the manuscripts, approved the final version of the manuscript, and the submission of the manuscript. YZ is the guarantor of this work and, as such, has full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

ETHICAL APPROVAL

The study was conducted with the approval of the Human Ethics Committee of the School of Life Sciences of Fudan University (No: BE1815). Written informed consent was provided by all study participants. All methods were performed in accordance with the relevant guidelines and regulations.

COMPETING INTERESTS

The authors declare no competing interest.

ADDITIONAL INFORMATION

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