Age-related exacerbation in disease-associated olfactory disorders

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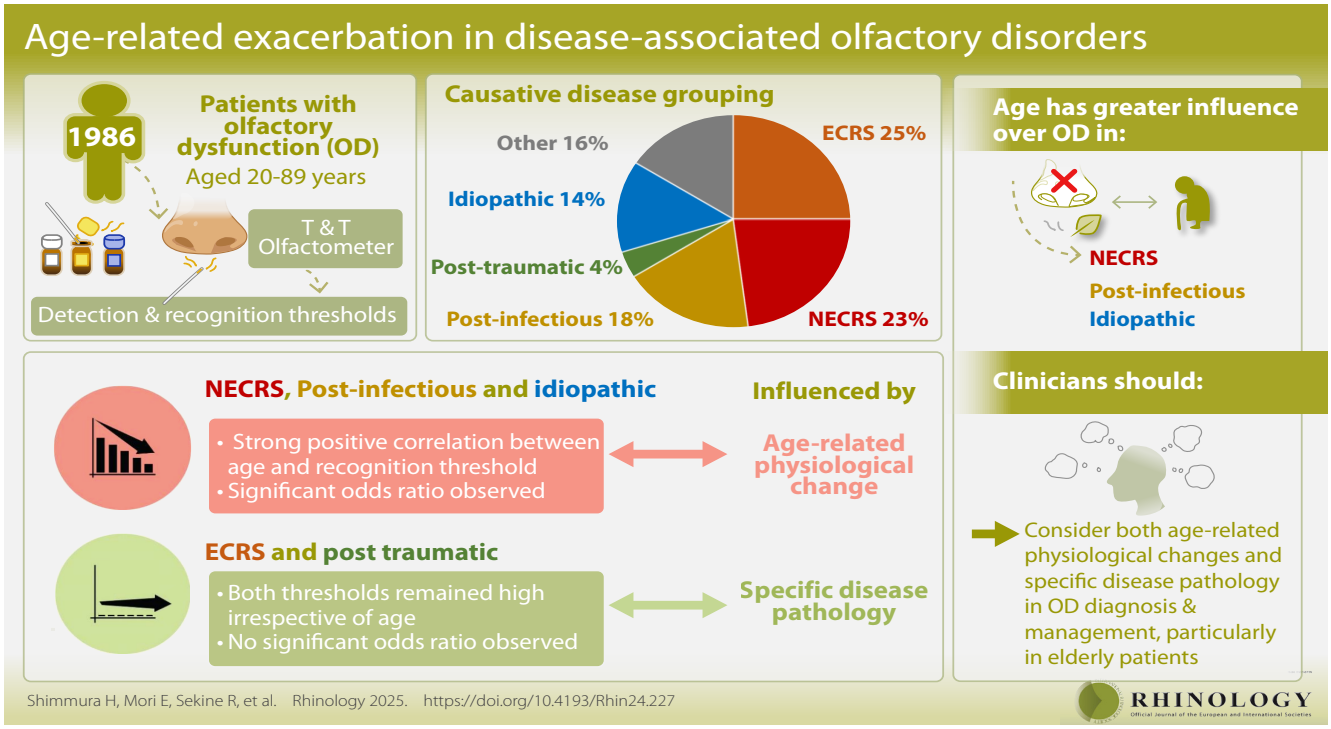

Abstract

Background: Both the physiological degeneration linked to aging and the pathological changes resulting from diseases can impact olfactory function in the patients with olfactory disorder (OD). However, the epidemiological literature addressing the extent of aging's involvement to the diseases which causes OD is limited. Our study aimed to investigate how aging affects olfactory function in major causes of OD by employing psychophysical olfactory sensory testing. **Methodology**: Non-eosinophilic chronic rhinosinusitis (NECRS), eosinophilic chronic rhinosinusitis (ECRS), post-infectious OD (PIOD), post-traumatic OD, and idiopathic OD were identified as major contributors to OD. Retrospective data from 1986 patients were collected from our smell clinic. We utilized T&T olfactometer thresholds to assess quantitative olfactory function. Patients were categorized into age groups spanning every 10 years from their 20s to 80s, and we analyzed potential differences between age groups and diseases. Additionally, the odds ratio of severe OD was analyzed with respect to gender and age, categorizing patients into two groups: <60 and ≥60. **Results**: A significant odds ratio was observed for elevated T&T average threshold with respect to age in the detection and recognition thresholds of patients diagnosed with NECRS, PIOD and idiopathic OD. In contrast, no significant odds ratio was observed in patients with ECRS or post-traumatic OD, regardless of age. **Conclusion**: Analysis of disease-specific OD revealed varying degrees of age-related physiological and disease-pathological across different conditions. These findings underscore the importance for clinicians to consider both age-related physiological changes and the specific disease pathology of the disease when diagnosing and managing OD, particularly in elderly patients.

Key words: olfactory disorder, aging, non-eosinophilic chronic rhinosinusitis, eosinophilic chronic rhinosinusitis, post-infectious olfactory disorder, post-traumatic olfactory disorder, idiopathic olfactory disorder

Introduction

The olfactory system plays an essential role in food intake and hazard perception [1,2]. Furthermore, it is closely linked with the psychological aspect [1], and its association with neurodegenerative diseases, dementia, and prognosis has been reported [3-5]. The ability of olfactory identification increases during childhood and adolescence, plateaus from the age of 20 [6], and declines after the 40s [7] or 50s [8]. Previous studies have reported that the number of individuals affected by olfactory disorder (OD) is much larger than expected. According to reports, the estimated prevalence of OD ranges from 7.2 to 19.4% [9-12], with approximately 40% of individuals over the age of 65 having a history of OD [1, 12]. Aging has been identified as an important factor affecting OD. Owing to physiological changes in the olfactory pathway, the prevalence of OD is thought to increase with age [13-19]. However, the relationship between the severity of OD and age within the context of specific diseases remains inadequately understood. In fact, only a limited number of studies have examined the effects of aging on OD associated with particular diseases [20,21]. Due to its gradual progression, OD is often less noticeable than other symptoms, such as nasal obstruction and rhinorrhea, with patients frequently unaware of when it began. Routine olfactory testing remains uncommon, further complicating the detection of OD during general follow-ups. Additionally, clinicians often prioritize the underlying disease and may overlook the influence of age when assessing patients with OD.
It is reasonable to consider that the severity of OD may be influenced not only by the underlying pathology, but also by age-related changes. Understanding whether age-related changes exacerbate OD in specific causative disease could aid clinicians in offering more accurate prognostic information, guiding expectations for recovery, and tailoring treatment more effectively. Therefore, this study aimed to clarify the association between aging and OD within specific disease contexts.

Materials and methods

Study design and participants

This retrospective observational study included 2444 patients with OD who had visited our smell clinic in the Department of Otorhinolaryngology at the Jikei University Hospital between April 2009 and March 2019. Patients with insufficient data, those who declined participation in the study, and those aged <20 years (more than 20 years old was adult in law at that moment) were excluded. Thus, 1986 patients, comprising 952 men and 1034 women, were included in this study.

Procedure

Data regarding age, history of OD, smoking habits, and presence of complications, were collected from the medical records. General examinations, including nasal endoscopy, were performed on all participants. T and T Olfactometry (T&T) [22] was performed for all patients, and the thresholds (average detection/recognition threshold at the time of the first visit to clinic) were collected. Blood sample collection and computed tomography (CT) examinations were also performed in all patients. Magnetic resonance imaging (MRI) examinations were performed when neurodegenerative diseases or brain tumor was suspected. Additionally, age-specific average values were quoted from previous reports, referencing a study that administered T&T test to 105 healthy individuals [23], and these reference values were compared with our findings. As individual numerical data were not available from previous reports, statistical significance testing was not conducted.

Classification of olfactory disorders

The medical history including OD, age, blood test results, endoscopic findings, sinus CT scan, sinus or head MRI, and olfactory test results were comprehensively analyzed to diagnose and classify OD. The diagnostic guidelines for OD [24] published in 2019 by the Japanese Rhinologic Society and a position paper on OD [1] published in 2023 in Rhinology were used as references. The primary causes of OD included non-eosinophilic chronic rhinosinusitis (NECRS), eosinophilic chronic rhinosinusitis (ECRS), post-infectious OD (PIOD), post-traumatic OD, and idiopathic OD. In accordance with the JESREC Study, ECRS was diagnosed as bilateral lesions observed predominantly in the ethmoid sinus on CT, with eosinophil count of peripheral blood of >2% [25]. Other cases of rhinosinusitis were diagnosed as NECRS.

Details of sensory testing

T&T, a standardized olfactory test that is used to measure the severity of OD and evaluate the effect of treatment in Japan (22), was used to evaluate olfaction. T&T is performed using five olfactory substances: β-phenylethyl alcohol (rose, light and sweet), methyl cyclopentenolone (burnt, caramel), isovaleric acid (rotten, old socks, sweat), γ-undecalactone (canned-peach, heavy and sweet), and skatole (feces, rotten vegetable, stinky). Solutions with 7–8 degrees of concentration (-2 to +5 for methylcyclopentenolone and -2 to +6 for the remaining four odorants) were prepared. Each odorant was brought to the patient's nostril from the lowest concentration (-2) to the highest concentration (+5 or +6), and the ability of the patient to detect the odor was evaluated at first, and the lowest concentration was recorded as detection threshold score. Then the ability to recognize the odor was evaluated using same technique as detection threshold score, and the score was recorded as recognition threshold. We regarded as the correct answer either when patient could correctly identify the name of the presented odor or could describe the odor descriptive listed above. Finally, the average thresholds for the five odorants were recorded. Average recognition thresholds of <1.1, 1.1–2.5, 2.6–4.0, 4.1–5.5, and >5.5 were classified as normosmia, mild OD, moderate OD, severe OD, and anosmia,

Table 1. Number of patients, age, T&T average Recognition / Detection threshold and Recognition-Detection threshold difference of the patients who visited the smell and taste clinic in the Department of Otorhinolaryngology at the Jikei University Hospital from April 2009 to March 2019.

	All Patients (N = 1986)	NECRS (N = 458)	ECRS (N = 497)	Post-infectious (N = 358)	Post-traumatic (N = 80)	Idiopathic (N = 318)
Gender						
Male	952	269	251	88	41	146
Female	1034	189	246	270	39	172
Age						
Median (IQR, Min–Max)	55.0 (22, 20–89)	51.0 (20, 20–85)	49.0 (20, 20–86)	58.0 (21, 20–89)	48.0 (21, 21–78)	66.0 (10, 22–88)
20–29 years	73	23	27	9	7	7
30–39 years	205	67	92	21	10	15
40–49 years	368	110	138	70	25	25
50–59 years	381	113	116	94	13	45
60–69 years	365	93	83	81	18	90
70–79 years	248	45	38	68	7	90
80–89 years	71	7	3	15	0	46
T&T						
Median Detection Threshold (IQR, Min–Max)	4.4 (3.8, -2.0–5.8)	4.4 (4.1, -2.0–5.8)	5.6 (2.8, -2.0–5.8)	4.2 (3.0, -2.0–5.8)	5.6 (2.2, -1.8–5.8)	4.6 (3.4, -2.0–5.8)
Median Recognition Threshold (IQR, Min–Max)	5.2 (3.0, -2.0–5.8)	5.1 (3.6, -2.0–5.8)	5.8 (2.0, -2.0–5.8)	4.8 (2.8, -1.4–5.8)	5.8 (1.0, -0.4–5.8)	5.4 (2.3, -1.6–5.8)
Median Recognition-Detection Threshold Difference (IQR, Min–Max)	0.2 (0.8, -1.4–6.2)	0.2 (0.6, -0.6–4.6)	0.0 (0.4, -1.4–6.0)	0.2 (0.8, -0.4–5.8)	0.0 (0.8, -0.2–2.8)	0.2 (1.0, -1.2–6.2)

NECRS; non-eosinophilic chronic rhinosinusitis, ECRS; eosinophilic chronic rhinosinusitis.

respectively [24].

Statistical analysis

All statistical analyses were performed using GraphPad PRISM ver. 9 (La Jolla, CA, USA). Statistical significance was set at $p < 0.05$. First, we summarized the T&T average threshold for each diagnosed disease group and each age group. Next, the correlation coefficient analyses were performed using Spearman's correlation coefficient test for non-normally distributed data. The correlation coefficient ρ-score was analyzed to determine the correlation between the average detection and recognition thresholds of the T&T test and age. Third, within each disease group, the patients were divided into two groups: those with a T&T average recognition threshold < 4.1 (the normal and mild-to-moderate OD group) and those with a T&T average threshold > or = 4.1 (the severe OD group and the anosmia group). The odds ratio for having a T&T average recognition threshold > or = 4.1 with respect to gender and age groups was analyzed using logistic regression analysis. Age groups consisted of patients under 60 years old and those 60 years and older.

Ethics statement

This study was approved by the Ethics Committee of the Jikei University School of Medicine (33-155(10770)). Information regarding the study was posted on the university website and was open to the public.

Results

Patients

Among the 1986 patients who visited the clinic within the research period, 458 (23%), 497 (25%), 358 (18%), 90 (4%), 318 (14%), and 275 (14%) patients were diagnosed with NECRS, ECRS, PIOD, post-traumatic OD, idiopathic OD, and other diseases (Table 1). The median age of the study cohort was 55.0 years (interquartile range: IQR=22.0, minimum–maximum 20.0–89.0). The median ages of the patients with NECRS, ECRS, PIOD, post-traumatic OD, and idiopathic OD were 51.0 years (IQR=20.0, 20.0–85.0), 49.0 years (IQR=20.0, 20.0–86.0), 58.0 years (IQR=21.0, 20.0–89.0), 48.0 years (IQR=21.0, 21.0–78.0), and 66.0 years (IQR=10.0, 22.0–88.0), respectively (Table 1).

T&T average detection/recognition threshold

Age-specific average values for healthy individuals, as reported

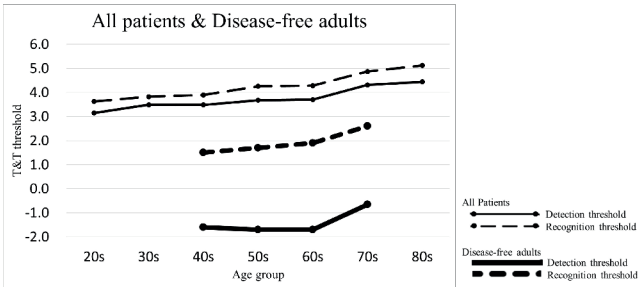

Figure 1. The relationship between the average detection/ recognition threshold and age in all patients in this study with healthy individuals in another report [23]. The thin solid line represents the average detection threshold of all patients, while the thin dotted line represents the average recognition threshold of all patients. The thick solid line represents the average detection threshold of healthy individuals, while the thick dotted line represents the average recognition threshold of healthy individuals. The vertical axis represents the T&T average threshold. Lower T&T average thresholds indicated better olfactory function, whereas higher average thresholds indicated worse olfactory function. The horizontal axis represents the age groups every 10 years. The age groups are defined as follows: the 20s represent ages 20 to 29, the 30s represent ages 30 to 39, the 40s represent ages 40 to 49, the 50s represent ages 50 to 59, the 60s represent ages 60 to 69, the 70s represent ages 70 to 79, and the 80s represent ages 80 to 89.

Table 2. Spearman's rank correlation coefficient between average detection/recognition thresholds in each patient group and age.

Cause of olfactory dysfunction	Number of Patients	Correlation coefficient ρ-value	p-value
Detection threshold			
All patients	1986	0.23	<.001*
NECRS	458	0.14	<.001*
ECRS	497	0.1	<.001*
Post-infectious	358	0.31	<.001*
Post-traumatic	80	0.08	0,28
Idiopathic	318	0.22	<.001*
Recognition threshold			
All patients	1986	0.23	<.001*
NECRS	458	0.2	<.001*
ECRS	497	0.1	<.001*
Post-infectious	358	0.36	<.001*
Post-traumatic	80	0.05	0.18
Idiopathic	318	0.28	<.001*

NECRS; non-eosinophilic chronic rhinosinusitis, ECRS; eosinophilic chronic rhinosinusitis.

in previous studies [23], were compared with the age-specific average T&T results of all patients in this study. The comparison is illustrated in Figure 1.

The T&T average detection/recognition threshold for all patients was 4.4 (IQR=3.8, -2.0–5.8)/5.2 (IQR=3.0, -2.0–5.8). The T&T average detection/recognition thresholds for the patients with NECRS, ECRS, PIOD, post-traumatic OD, and idiopathic OD and median recognition-detection threshold difference are shown in Table 1. The T&T average detection/recognition threshold for each age group, ranging from the 20s to the 80s are shown in Figure 2. The age groups are defined as follows: the 20s represent ages 20 to 29, the 30s represent ages 30 to 39, the 40s represent ages 40 to 49, the 50s represent ages 50 to 59, the 60s represent ages 60 to 69, the 70s represent ages 70 to 79, and the 80s represent ages 80 to 89. The number of patients in each age group is indicated below the age group labels.

Significant correlations were identified between average detection and recognition thresholds and age across all patient groups, including those with ECRS, NECRS, PIOD, and idiopathic OD. However, no correlation was observed between age and average detection thresholds in patients with post-traumatic OD (Table 2). Logistic regression analysis further revealed that the odds ratios for a T&T average recognition threshold ≥ 4.1 were not significant with respect to gender (Table 3). In contrast, when comparing age groups, the odds ratio for a T&T average recognition threshold ≥ 4.1 was significantly elevated in elderly patients across the overall patient cohort, as well as in those with NECRS, PIOD, and idiopathic OD. Notably, no significant association was found in the ECRS and post-traumatic OD groups (Table 3).

Discussion

The findings of this study suggest that OD severity tends to increase with age among patients with NECRS, PIOD and idiopathic OD, highlighting the importance of considering age-related impacts on OD. In contrast, OD associated with ECRS and post-traumatic OD did not follow this trend; these conditions are linked with severe disorders regardless of the patient's age. Although it might be expected that OD severity would generally increase with age across causative diseases, our result reveal that this relationship varies by underlying cause. This insight may provide valuable prognostic information, helping clinician to select options with greater precision and proactive consideration.

Age and disease-induced OD

The relative contributions of aging and disease pathology to the development and severity of OD vary across different disease conditions [21, 26]. Our findings suggest that distinguishing

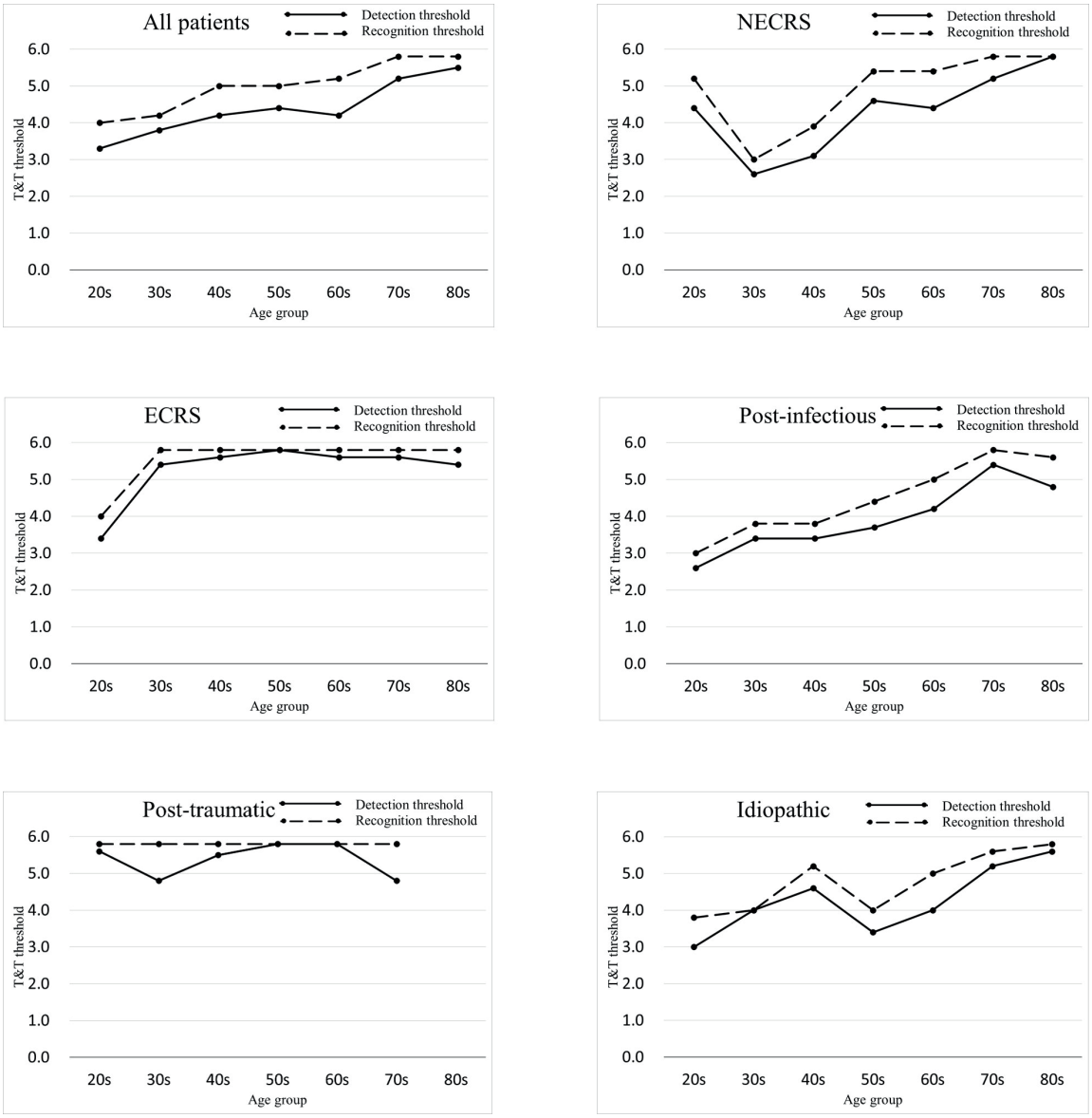

Figure 2. The relationship between the T&T average detection/ recognition threshold and age in all patients with NECRS, ECRS, and PIOD, as well as post-traumatic and idiopathic cases. The solid line represents the average detection threshold, while the dotted line represents the average recognition threshold. The age groups are defined as follows: the 20s represent ages 20 to 29, the 30s represent ages 30 to 39, the 40s represent ages 40 to 49, the 50s represent ages 50 to 59, the 60s represent ages 60 to 69, the 70s represent ages 70 to 79, and the 80s represent ages 80 to 89. NECRS; non-eosinophilic chronic rhinosinusitis, ECRS; eosinophilic chronic rhinosinusitis.

between the effects of physiological aging and disease-related changes is particularly complex in conditions such as NECRS and PIOD. In cases where disease-related changes are minimal, age-related physiological alterations may exert a more pronounced influence on olfactory function. Conversely, as the severity of the disease pathology increases, the impact of age-related changes may be less significant. This dynamic interplay between aging and disease pathology complicates the clinical diagnosis of OD, especially in older patients, where differentiating between age-related and disease-induced OD becomes increasingly challenging [21, 26].

Pathological alteration of the olfactory neuroepithelium

The results of this study illustrate the intricate relationship between aging and disease pathology in the development of OD.

In NECRS, primarily caused by bacterial infections, inflammation in the nasal and olfactory membranes leads to edema and increased nasal secretions, obstructing odor molecules from reaching the olfactory membrane [27, 28]. While short-term inflammation may cause reversible OD, chronic inflammation can lead to irreversible injury to both the olfactory membrane and bulb.

Table 3. Result of logistic regression analysis in each patient group.

1. Relationship between sex or age and average detection thresholds in each disease.

Sex (Male : Female)					
Detection threshold	**Detection threshold < 4.1 (Male : Female)**	**Detection threshold > or = 4.1 (Male : Female)**	**p-value**	**Odds ratio**	**95% Confidence Interval**
All patients	437 : 486	515 : 548	0.62	1.05	0.88 - 1.25
NECRS	130 : 90	139 : 99	0.88	0.97	0.67 - 1.41
ECRS	86 : 82	165 : 164	0.83	0.96	0.66 - 1.39
Post-infectious	42 : 135	46 : 135	0.71	1.10	0.68 - 1.77
Post-traumatic	14 : 12	27 : 27	0.75	0.86	0.34 - 2.19
Idiopathic	58 : 86	88 : 86	0.07	1.52	0.97 - 2.37
Age (<60 : ≥60)					
Detection threshold	**Detection threshold < 4.1 (< 60 : > or = 60)**	**Detection threshold > or = 4.1 (< 60 : > or = 60)**	**p-value**	**Odds ratio**	**95% Confidence Interval**
All patients	321 : 602	469 : 594	0.01*	1.28	1.06 - 1.56
NECRS	164 : 56	149 : 89	<0.01*	1.75	1.17 - 2.61
ECRS	132 : 36	240 : 89	0,17	1.36	0.87 - 2.11
Post-infectious	117 : 60	76 : 105	<0.01*	2.69	1.75 - 4.14
Post-traumatic	20 : 6	35 : 19	0.28	1.81	0.62 - 5.27
Idiopathic	50 : 94	42 : 132	0.04*	1.67	1.03 - 2.72

2. Relationship between sex or age and average recognition thresholds in each disease.

Sex (Male : Female)					
Recognition threshold	**Recognition threshold < 4.1 (Male : Female)**	**Recognition threshold > or = 4.1 (Male : Female)**	**p-value**	**Odds ratio**	**95% Confidence Interval**
All patients	355 : 393	597 : 641	0,74	1.03	0.86 - 1.24
NECRS	107 : 80	162 : 109	0,58	1.11	0.76 - 1.62
ECRS	70 : 65	181 : 181	0,71	0.93	0.63 - 1.38
Post-infectious	37 : 109	51 : 161	0,78	0.93	0.57 - 1.52
Post-traumatic	7 : 9	34 : 30	0,5	1.46	0.48 - 4.39
Idiopathic	39 : 62	107 : 110	0,08	1.55	0.96 - 2.50
Age (<60 : ≥60)					
Recognition threshold	**Recognition threshold < 4.1 (< 60 : > or = 60)**	**Recognition threshold > or = 4.1 (< 60 : > or = 60)**	**p-value**	**Odds ratio**	**95% Confidence Interval**
All patients	227 : 521	563 : 675	<0.01*	1.48	1.22 - 1.80
NECRS	142 : 45	171 : 100	<0.01*	1.85	1.22 - 2.80
ECRS	109 : 26	263 : 99	0,07	1.58	0.97 - 2.57
Post-infectious	101 : 45	92 : 120	<0.01*	2.93	1.88 - 4.56
Post-traumatic	14 : 2	41 : 23	0,09	3.93	0.82 - 18.82
Idiopathic	46 : 55	46 : 171	<0.01*	3.11	1.87 - 5.17

NECRS; non-eosinophilic chronic rhinosinusitis, ECRS; eosinophilic chronic rhinosinusitis.

With aging and cumulative nasal membrane damage, the regenerative capacity of olfactory sensory neurons (OSNs) diminishes, particularly in older patients, intensifying OD severity. The study's findings likely reflect this combination of pathological and age-related changes.

ECRS is marked by eosinophilic infiltration and nasal polyp formation, closely associated with severe OD [27–32]. Primary lesions in ECRS are often found in the ethmoidal sinus and olfactory

cleft, where the olfactory neuroepithelium is located. OD in ECRS patients likely results from multiple factors, including obstruction of odor transmission pathways to the olfactory cleft, mucosal edema, and nasal polyps at the olfactory cleft [33]. In this study, the odds ratio for severe OD in ECRS was not significantly different between older and younger patients, suggesting that OD severity in ECRS is independent of age. Nonetheless, the T&T average recognition thresholds tended to increase with age, possibly because ECRS generally develops in adulthood, with progressive polyp formation compounding olfactory dysfunction over time [25].

PIOD, more common in women, usually has an acute onset often triggered by viral infections [34, 35]. Physiological aging contributes to PIOD progression [36]. Although PIOD patients often recover more quickly than those with other OD types, middle-aged and older patients frequently experience incomplete recovery [37, 38], likely due to the age-related decline in OSN regeneration. This may result in accumulated mucosal damage and, consequently, more severe and irreversible OD. This study observed that PIOD patients had significantly higher odds ratios for severe OD, with T&T average thresholds increasing with age.

Post-traumatic OD may stem from peripheral, central, or combined damage. Trauma can block odor transmission to the olfactory neuroepithelium or sever olfactory nerve fibers, especially where the nerve traverses the cribriform plate to reach the olfactory bulb [39]. Central injuries, such as cerebral contusions, hemorrhages, or delayed cortical edema, can also contribute to post-traumatic OD [40, 41]. This study showed that post-traumatic OD had the lowest, non-significant odds ratios for severe OD across age groups, with consistently higher T&T average thresholds. This suggests that trauma-induced damage is often more profound than age-related effects, resulting in severe, irreversible OD from the onset.

Idiopathic OD is diagnosed when no identifiable cause is determined through clinical or diagnostic methods. In this study, older patients constituted most idiopathic OD cases, with odds ratios indicating that OD severity increased with age. Some idiopathic cases may, in fact, be age-related OD, potentially affecting the study outcomes.

Detection threshold and recognition threshold

In healthy subjects, the recognition threshold is defined as the ability of the olfactory nerve to detect which odor molecules bind to olfactory receptors. It has a relatively low range value and a high T&T score [1]. The detection threshold, on the other hand, represents the responsiveness of olfactory receptors to the presence of odor molecules. It has a relatively high range value and a low T&T score [1]. Furthermore, the recognition threshold is more significantly affected by aging than the detection threshold, with higher T&T values [42]. Therefore, the greater the influence of age on olfactory dysfunction, the more the T&T numerical difference between the recognition threshold and the detection threshold opens.

In this study, a greater difference between recognition and detection thresholds was observed in patients with PIOD, NECRS, and idiopathic OD than in patients with ECRS and post-traumatic OD (Table 1). This result may be because the former diseases are more strongly influenced by aging than the pathological conditions as a cause of olfactory dysfunction. Although age-related changes can affect any pathology, the effect of T&T on the gap between detection and recognition thresholds suggests that aging may be a more significant cause of olfactory dysfunction in patients with PIOD, NECRS, and idiopathic OD. Particularly in idiopathic cases, this pattern of relatively preserved peripheral olfactory sensitivity (detection threshold) with more impaired central olfactory functions (recognition threshold) is noteworthy, as similar patterns have been observed in neurodegenerative diseases [43-45]. This suggests a potential link between idiopathic olfactory loss and neurodegenerative processes, where higher-order olfactory functions are predominantly affected while peripheral olfaction remains relatively intact.

Characteristics of OD in elderly patients

Diagnosing OD in older adults is challenging due to low self-reporting rates. Studies indicate that only 9.5% of older adult's self-report OD, with the accuracy of self-reports declining with age [46]. Gradual OD progression is less noticeable than vision or hearing loss, and many patients only become aware of it once the condition has significantly deteriorated, often without recalling its onset. Promoting early clinical intervention through routine olfactory assessments or patient education on the impact of OD on quality of life is essential. Treatment strategies for age-related OD, such as olfactory training, have shown promising effects [47], likely due to their role in regulating interneuron populations in the olfactory bulb and generating new olfactory receptor neurons in response to odor stimulation when neuroplasticity remains.

ECRS and post-traumatic OD in younger patients

While OD prevalence is generally higher among older adults, younger patients may also experience significant OD, particularly in conditions such as ECRS and post-traumatic OD. In these cases, the aggressive eosinophilic inflammation associated with ECRS and the substantial neural damage commonly linked to trauma can lead to more severe OD. Recognizing the potential severity of OD in younger patients is essential, as olfactory impairment can considerably impact quality of life and social interactions. For these individuals, an early and accurate diagnosis is crucial to facilitate timely intervention. Treatment strategies, including surgical intervention with topical corticosteroids for ECRS or olfactory training following trauma, may help reduce OD severity and promote olfactory recovery.

Limitation

This study has some limitations. First, this study did not take into account the duration of the disease. The duration of the disease can be an important factor affecting its pathophysiology. Second, while the sample size is large enough to run most of the analyses, it is clearly limited in the case of post-traumatic patients. Analyses conducted for this specific group might be underpowered and findings on post-traumatic OD should be interpreted more cautiously. However, our study analyzed approximately 2000 cases over a 10-year period, which we consider to be large enough to make statistical analyses.

Conclusion

Our study demonstrated that aging has a more pronounced effect on NECRS, PIOD, and idiopathic OD, with less influence observed in ECRS and post-traumatic OD. While OD is shaped by both underlying disease pathology and age-related physiological changes, the relative impact of each factor varies by disease. These findings may encourage a shift in clinical perspective, as clinicians often prioritize underlying disease pathology over age-related changes. Optimal management should therefore be tailored to the specific cause and age of the patient, with clinicians addressing not only the primary disease but also recognizing age as a significant contributing factor to olfactory disorder.

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Authorship contribution

HS, EM designed the study, the main conceptual ideas, and the proof outline. HS collected and analyzed the data. EM and NO supervised the project. HS wrote the manuscript with support from RS and MT. All authors discussed the results and commented on the manuscript.

Conflict of interest

The authors declare no conflicts of interest associated with this manuscript.

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SUPPLEMENTARY MATERIAL

Supplementary Material 1. Questionnaire sheet.

Age: Sex: Male/Female Occupation:

1. How bad is your sense of smell?
   1. not at all
   2. almost no smell, faintly noticeable when approached
   3. strong smell, mostly noticeable when approached
   4. a little weak
   5. normal odour
   6. too sensitive, too strong

2. Do you have fluctuating symptoms of olfactory disorder?
   1. none
   2. gradually getting worse
   3. gradually getting better
   4. changing (intraday, daily)

3. Do you have any allergies?
   1. no
   2. asthma (pediatric asthma, bronchial asthma, aspirin asthma, other)
   3. allergic rhinitis, pollen allergy
   4. other ( )

4. Do you have any taste disorder?
   ☐ No ☐ Yes

5. Do you smell differently from before?
   ☐ No ☐ Yes

6. Do you smell, even when there is no odour?
   ☐ No ☐ Yes