

# Olfactory Decline in Elderly at High Altitudes: A Narrative Review

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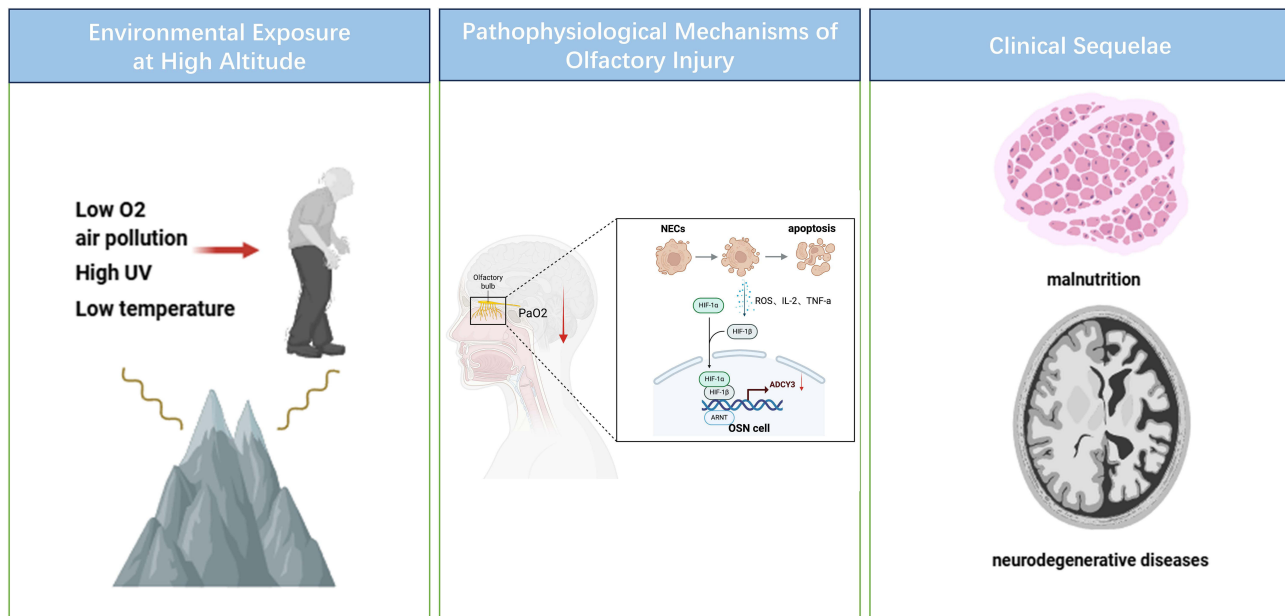
**Abstract:** Olfactory dysfunction is highly prevalent in the elderly population, severely affecting nutritional status, environmental safety perception, and quality of life, and is recognized as an early warning marker of neurodegenerative diseases. Compared with populations living at low altitudes, residents at high altitudes are chronically exposed to combined extreme environmental conditions including hypoxia, low temperature, and low humidity, which may lead to more complex and severe degenerative changes in the olfactory system. However, existing evidence remains fragmented, and a systematic synthesis is lacking. This narrative review aims to systematically integrate the epidemiological characteristics, pathophysiological mechanisms, diagnostic assessment tools, intervention strategies, and health risks associated with olfactory decline in elderly residents at high altitudes. Epidemiological evidence shows a significant negative correlation between altitude and olfactory function, and the effects of aging are substantially amplified under high-altitude conditions. The underlying mechanisms primarily involve chronic hypoxia interacting with aging and genetic susceptibility through damage to olfactory ensheathing cells, suppression of olfactory neurogenesis, and remodeling of synaptic plasticity in olfactory-related brain regions. Olfactory behavioral testing combined with functional magnetic resonance imaging and emerging biomarkers provides multidimensional tools for early diagnostic stratification. Although oxygen therapy, olfactory training, and environmental management have shown potential efficacy, evidence-based data specific to this population remain limited. The core value of this review lies in adopting an integrated perspective of “environment-aging” interactions to systematically elucidate the combined effects of high-altitude stress and age-related degenerative changes on the olfactory system, revealing the unique patterns and intervention targets for olfactory dysfunction in this vulnerable population. Future research urgently needs large-scale longitudinal cohort studies, establishment of altitude-specific normative olfactory assessment tools, and development of precision interventions targeting hypoxic injury to improve overall health outcomes in this population.

**Keywords:** high-altitude, olfactory decline, elderly, hypoxia, review

## Background

Olfaction is a crucial sensory function for detecting chemical signals, playing essential roles in food identification, environmental hazard perception, emotional regulation, and memory formation. With advancing age, the olfactory system undergoes degenerative changes, leading to a significant increase in the prevalence of olfactory dysfunction among older adults. Due to its insidious onset and slow progression, olfactory impairment has long been underappreciated. However, accumulating evidence suggests that olfactory decline not only affects nutritional intake, safety perception, and quality of life in the elderly but also serves as an early clinical marker for neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease.<sup>1</sup>

Currently, research on olfactory decline in the elderly has predominantly focused on normoxic, low-altitude regions, whereas evidence regarding older populations residing in high-altitude environments ( $\geq 2500$  m) remains limited. High-altitude regions are characterized by chronic hypoxia, hypobaria, low temperature, and low humidity,<sup>2</sup> constituting a sustained composite environmental stress. Chronic hypoxia in this context refers to sustained hypobaric hypoxic exposure resulting from continuous residence at altitudes  $\geq 2500$  m for months to years, with clinical reference thresholds such as  $\text{PaO}_2 < 60$  mmHg or arterial oxygen saturation  $< 90\%$  serving as indicators.<sup>3</sup> Under such conditions,



**Figure 1** Technical roadmap of the present review on olfactory decline in elderly residents at high altitudes. The figure outlines the research framework and analytical modules of this review. Module 1 (Environmental Exposure): elderly populations in high-altitude regions are chronically exposed to multiple factors including hypoxia, air pollution, high ultraviolet radiation, and low temperature. Module 2 (Pathophysiological Mechanisms): chronic hypoxia and aging affect olfactory neurons and the olfactory bulb, with alterations including decreased expression of olfactory marker protein (OMP) and ADCY3, as well as increased reactive oxygen species (ROS) generation. Module 3 (Clinical Consequences): olfactory decline may contribute to malnutrition and neurodegenerative diseases, thereby affecting the quality of life in the elderly.

environmental factors—particularly chronic hypoxia—may interact with the aging process, further impairing neurogenesis, synaptic plasticity, and regenerative capacity of the olfactory system, thereby exacerbating olfactory dysfunction.

However, current knowledge regarding the interplay among high-altitude environments, aging, and olfactory dysfunction remains fragmented, lacking systematic synthesis and integration. Therefore, this review focuses on olfactory dysfunction in elderly residents at high altitudes, systematically summarizing epidemiological characteristics, underlying mechanisms, diagnostic approaches, intervention strategies, and associated health risks, with the aim of providing a theoretical basis and practical reference for early identification and precise management of this vulnerable population, as illustrated in Figure 1.

## Epidemiological Characteristics of Olfactory Decline in Elderly Populations at High Altitude

### Current Status of Epidemiological Investigations on Olfactory Decline in Elderly Populations at High Altitude

Although epidemiological studies specifically focusing on olfactory decline in the elderly population residing at high altitudes remain limited, independent research on the effects of high-altitude-related factors and aging provides important insights.

Multiple cross-sectional studies indicate a direct association between high-altitude exposure and decreased olfactory function. A controlled study conducted by Altundağ et al in Turkey recruited 41 healthy adult volunteers, excluding confounding factors such as chronic sinusitis or nasal polyps<sup>4</sup>. The study assessed participants' odor threshold and identification abilities using the "Sniffin Sticks" test in both a high-altitude environment at 2200 meters and at sea level. The results showed a significant decline in olfactory function under high-altitude conditions, with the odor threshold decreasing from  $10.3 \pm 2.0$  at sea level to  $7.8 \pm 2.2$ , and the odor identification score decreasing from  $13.6 \pm 1.5$  to  $12.4 \pm 1.5$ , both differences being statistically significant ( $p < 0.001$ ). Correlation analysis revealed a significant negative correlation between altitude and olfactory scores (threshold:  $r = 0.49$ ; identification:  $r = 0.39$ ). No significant association was found between changes in

threshold and changes in identification ability, suggesting that high altitude may affect olfactory sensitivity and discrimination through different mechanisms. Furthermore, high-altitude exposure acutely impairs olfactory function by affecting nasal physiology and sensory conduction. A study by Cemal Cingi et al found<sup>2</sup> that mountaineers experienced a 27.43% decrease in peak nasal inspiratory flow ( $p < 0.001$ ) and an 8.94% decrease in peak nasal expiratory flow ( $p < 0.05$ ), alongside significant declines in odor detection and identification abilities ( $p < 0.05$ ).<sup>5</sup>

Regarding age-related effects, a U.S. population-based analysis using the NHANES database reported that olfactory dysfunction increases significantly with age based on both subjective self-report and objective odor identification testing.<sup>6</sup> The risk ratio for olfactory decline in individuals over 80 years old is 9.288 (7.265–11.873) based on objective testing.<sup>6</sup> Of note, discrepancies between self-reported and objective measures of olfactory function have been documented, highlighting the importance of specifying the measurement method when interpreting prevalence estimates.<sup>6</sup> A population-based study reported that the prevalence of olfactory impairment in older adults is 24.5%, with rates increasing to 62.5% among those aged 80 to 97 years.<sup>7</sup> Olfactory dysfunction is more pronounced in the context of disease. Dan et al found that selective odor discrimination loss is the initial change in olfactory behavior with aging, followed by declines in odor sensitivity and detection ability, while odor habituation typically persists for a longer duration. Compared to behavioral changes related to cognitive and motor functions, OD is considered one of the earliest biomarkers of aging and an independent risk factor for mortality.<sup>8,9</sup> Additionally, a larger longitudinal cohort study involving 1556 elderly individuals assessed olfactory function using the San Diego Odor Identification Test over a follow-up period of 5 to 10 years. The 5-year incidence of olfactory impairment was 12.5%, with the incidence steadily increasing with age. Multivariate analysis identified several risk factors significantly associated with an increased likelihood of olfactory impairment: age (OR = 1.79 per 5-year increase [95% CI: 1.61–2.00]).<sup>10</sup> These studies collectively suggest a potential association between aging and olfactory decline.

## Altitude Distribution Characteristics of Populations with Olfactory Decline

The impact of varying altitudes on olfactory decline is increasingly drawing attention in the academic field. Emerging evidence suggests that changes in altitude can affect neural structures and gene expression related to olfactory function.<sup>11–13</sup>

In a study involving individuals with long-term exposure in different altitude environments, healthcare workers residing at high altitudes (eg., 4300 meters) scored significantly lower on multiple cognitive assessments compared to those at low altitudes (eg., 1700 meters). These assessments included the Montreal Cognitive Assessment (MoCA), Digit Span Test (DST), Verbal Fluency Test (VFT), Rey Auditory Verbal Learning Test (RAVLT), and Trail Making Test (TMT). Structural MRI data further revealed reductions in gray matter density, particularly in regions such as the left olfactory cortex, indicating that prolonged exposure to hypoxic environments may lead to widespread cognitive impairment and region-specific neurodegeneration potentially linked to olfactory dysfunction.<sup>14</sup>

## Gender and Age Distribution Characteristics of Olfactory Decline Populations

Among elderly residents in high-altitude regions, the distribution of olfactory decline exhibits distinct age-related patterns, whereas evidence regarding gender differences remains less clear.<sup>15–17</sup>

Age is a primary determinant of olfactory dysfunction.<sup>18,19</sup> Multiple studies consistently report that the incidence of olfactory decline increases with advancing age.<sup>19–21</sup> For example, research on community-dwelling older adults shows that the risk of olfactory impairment significantly rises with every five-year increase in age.<sup>10</sup>

The role of gender is ambiguous. In a study examining older adults with obstructive lung disease (OLD) (including 98 OLD patients [mean age 71.2 years, 59.2% female] and 1,036 non-OLD individuals [mean age 69.5 years, 58.9% female]), decline in odor identification ability was associated with frailty in OLD patients. However, after adjusting for demographic variables, alcohol consumption, smoking, and comorbidities, this association was not observed in the non-OLD group. Longitudinal data from a nationally representative sample of older U.S. adults (aged 57–85 years) demonstrate that the rate of olfactory decline increases with age and is significantly greater in men than in women, with men making 0.17 additional errors per 5 years compared with women after adjusting for psychosocial and health factors ( $p = 0.005$ ).<sup>22</sup> To date, early studies have also noted that females outperform males in odor identification tasks, with males exhibiting olfactory decline from a younger age. Even after adjusting for psychosocial factors and underlying

health conditions, results indicate a more rapid decline in olfactory function among males compared to females, at a rate of  $-0.15$  percentage points (95% CI:  $-0.25$ ,  $-0.04$ ,  $p=0.007$ ).<sup>22</sup>

Notably, no significant gender-based differences were detected in the relationship between olfactory decline and frailty.<sup>23</sup>

Similarly, a retrospective analysis of patients with olfactory dysfunction found no significant gender differences in the etiological distribution of olfactory decline. However, the proportion of idiopathic olfactory impairment was notably higher among older adults compared to younger cohorts.<sup>24</sup>

Overall, current evidence suggests that age is a consistent predictor of olfactory decline, whereas gender differences remain inconclusive. Research specifically targeting elderly residents in high-altitude environments is still limited, and further studies are needed to clarify potential sex-specific influences in this population.

## Evidence from In vivo and In vitro Studies on the Impact of High Altitude on Olfaction in the Elderly Population

### Effect of High-Altitude Hypoxia on Olfactory Neurons

The hypoxic environment characteristic of high altitude exerts multifaceted and profound effects on olfactory neurons. Evidence suggests that hypoxia disrupts the metabolism and functional integrity of these neurons.<sup>25–27</sup>

At the animal level, mice subjected to chronic high-altitude hypoxia (5,000 m, 12 weeks) displayed learning and memory impairments associated with hippocampal dysfunction, alongside reduced expression levels of synaptic proteins such as synaptophysin (SYP) and spinophilin (SPH) in the olfactory cortex. These findings indicate that neural and synaptic integrity in olfactory-related brain regions may be compromised under chronic high-altitude exposure, potentially contributing to olfactory decline.<sup>28</sup> Furthermore, genetic studies of high-altitude-adapted animals (eg., yaks) have identified significant differences in the number and composition of olfactory receptor (OR) genes compared to low-altitude bovine species.<sup>29,30</sup> These genetic adaptations may influence olfactory performance and further suggest that long-term altitude exposure can drive evolutionary changes in olfactory function.<sup>31</sup>

At the cellular level, in vitro studies on olfactory ensheathing cells (OECs) isolated from the olfactory bulbs of neonatal rats have demonstrated that hypoxia induces significant cellular damage.<sup>32</sup> Since OECs play a critical role in axonal growth and myelination of olfactory neurons, their dysfunction may compromise neuronal survival and regenerative capacity. Interestingly, curcumin has been shown to enhance OECs viability under hypoxic conditions, suggesting its potential neuroprotective role in mitigating hypoxia-induced olfactory deficits.<sup>32</sup>

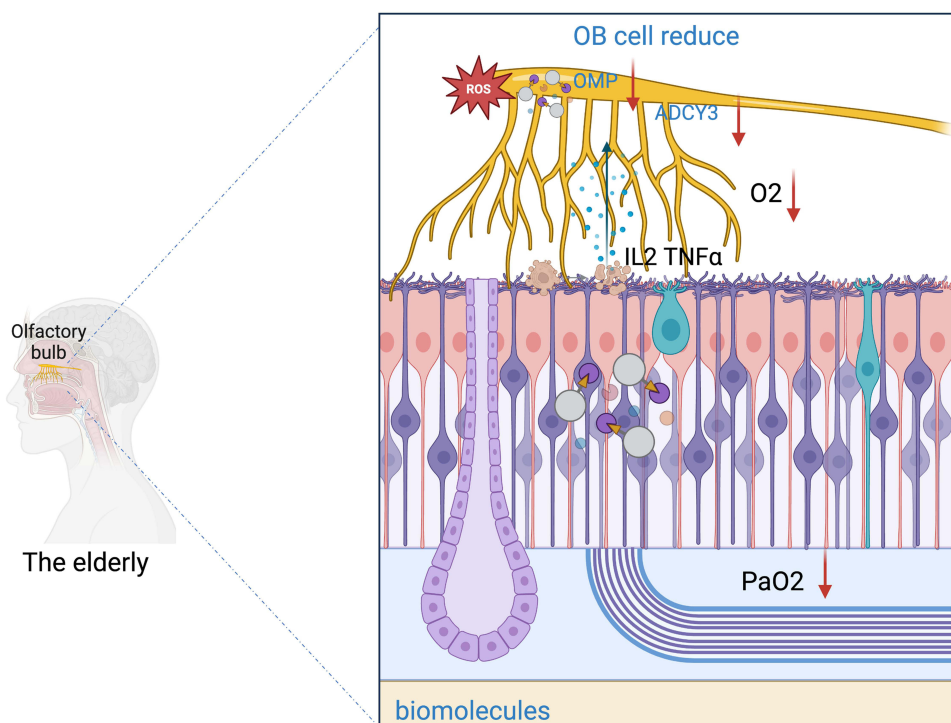
At the molecular level, hypoxia also alters gene expression patterns related to neurogenesis and neuronal function.<sup>33,34</sup> In mouse models, chronic intermittent hypoxia (CIH) has been shown to downregulate the mRNA levels of olfactory marker protein (OMP), *Olf1507*, *ADCY3*, and *GNAL* within the olfactory epithelium.<sup>35</sup> Conversely, it upregulates transcripts associated with neurogenesis and neuronal stress responses, including *NGFR*, *CNPase*, *NGFRAP1*, *NeuN*, and *MAP-2*. These changes indicate CIH disrupts olfactory neurogenesis and cellular function through broad transcriptional reprogramming (Figure 2).<sup>36</sup>

In addition, hypoxia may impair neurotransmitter signaling and synaptic plasticity in olfactory pathways, exacerbating dysfunction and accelerating decline.<sup>37</sup> Nonetheless, the precise molecular and cellular mechanisms underlying these alterations remain incompletely understood and warrant further investigation.

### Impairment of Olfactory Function by Pollutants in High-Altitude Environments

Research specifically addressing the impairment of pollutants on olfactory function in high-altitude environments remains limited. Nonetheless, existing evidence suggests that pollutants common to such regions—including industrial emissions, airborne dust particles, and storm-related particulate matter—may adversely affect the olfactory system.<sup>38,39</sup>

Indirect studies indicate that environmental pollutants can enter the human body via the respiratory tract, alter the nasal microenvironment and olfactory epithelium, and consequently impair olfactory performance.<sup>40,41</sup> Epidemiological observations have shown that in areas with severe air pollution, the prevalence of both respiratory diseases and olfactory dysfunction is elevated, implying a detrimental role of pollutants in olfactory health.<sup>42</sup>



**Figure 2** Schematic diagram of the mechanisms underlying high-altitude hypoxia-induced damage to the olfactory nervous system in the elderly. Long-term residence at altitudes  $\geq 2500$  m leads to chronic hypoxia ( $\text{PaO}_2 \downarrow$ ) combined with compounded environmental stressors including high ultraviolet radiation, air pollution, and low temperature. Hypoxia reduces the expression of olfactory marker protein (OMP) and ADCY3, while increasing reactive oxygen species (ROS) generation, resulting in damage and apoptosis of olfactory epithelial cells. Impairment of olfactory neurons further affects the number of fibers projecting to the olfactory bulb (OB) and synaptic stability, reducing neural circuit plasticity. Hypoxia activates the HIF pathway, but adaptive capacity declines with aging; concurrently, increased inflammatory markers and oxidative stress inhibit olfactory stem cell differentiation and survival of newly generated neurons. Blue arrows: pro-inflammatory cytokine (IL-2, TNF- $\alpha$ ) damage/interference to olfactory neurons. Red arrows: inhibition of signaling pathways (e.g., OMP, ADCY3);  $\text{O}_2 \downarrow$ ,  $\text{PaO}_2 \downarrow$ : local hypoxic state.

Dust storms, which are frequent in certain high-altitude regions, represent another potential risk factor.<sup>43</sup> Particulate matter carried in dust can adsorb toxic compounds and directly irritate the olfactory mucosa.<sup>44</sup> In addition, dust exposure can trigger inflammatory responses that disrupt the structural and functional integrity of olfactory receptor neurons.<sup>45,46</sup> These mechanisms collectively contribute to olfactory impairment.

Despite these insights, specific mechanisms and related studies on olfactory impairment caused by particular pollutants in high-altitude regions remain scarce. Further targeted research is needed to clarify the relationship between environmental pollutants in high-altitude areas and olfactory decline.

## The Impact of High-Altitude Related Disorders on Olfactory Function

High-altitude illness refers to a series of pathological conditions caused by rapid ascent or prolonged residence in a hypoxic environment.<sup>47</sup> Emerging evidence suggests a possible association between olfactory decline and high-altitude illness,<sup>48</sup> though the underlying mechanisms remain incompletely understood.

Acute Mountain Sickness (AMS) is among the most common conditions in high-altitude regions.<sup>49</sup> Studies have reported that individuals with AMS may exhibit impaired olfactory function, manifested as elevated odor thresholds and reduced odor discrimination and identification abilities.<sup>50,51</sup> While the specific mechanisms remain unclear, these changes may be related to systemic hypoxia, neuroinflammation, and neurological dysfunction associated with AMS.<sup>52,53</sup>

In contrast, chronic high-altitude illnesses—such as Chronic Mountain Sickness (CMS)—resulting from long-term exposure to high-altitude environments, may indirectly affect the olfactory system.<sup>54</sup> CMS is often characterized by hematological abnormalities, including polycythemia and increased blood viscosity, which can impair cerebral blood flow.<sup>54</sup> Reduced perfusion of olfactory centers in the brain may compromise neuronal function and contribute to olfactory decline.<sup>55</sup>

Despite these observations, research directly linking olfactory impairment with high-altitude illnesses is still limited and largely preliminary. More clinical and experimental studies are required to elucidate the intrinsic relationship between a high-altitude illness and olfactory dysfunction, as well as to uncover the molecular and physiological mechanisms involved.

## Potential Interactive Mechanisms of Olfactory System Dysfunction in the Context of High Altitude and Aging

### Combined Effects of Environmental Factors at High Altitude

The high-altitude environment is characterized by hypoxia, low temperature, reduced humidity, and enhanced ultraviolet radiation, all of which can adversely affect the olfactory system.<sup>56</sup> Among these factors, hypoxia has been identified as a primary contributor to olfactory dysfunction.<sup>57</sup>

Clinical evidence suggests that hypoxia associated with Obstructive Sleep Apnea Syndrome (OSAS) may impair olfactory performance.<sup>58,59</sup> A cross-sectional study involving 69 snoring patients (divided into mild [Apnea-Hypopnea Index (AHI) <15] and moderate-to-severe [AHI ≥15] groups), significant differences were observed in body mass index, mean oxygen saturation (SaO<sub>2</sub>), minimum SaO<sub>2</sub>, mean snoring duration, and olfactory function tests (using the Korean version of the Sniffin' Sticks test I and II). AHI values significantly correlated with odor threshold scores, whereas mean SaO<sub>2</sub> correlated with odor discrimination scores. These findings suggest that hypoxia and reduced nasal airflow may jointly contribute to olfactory impairment.<sup>60</sup> Furthermore, high-altitude hypoxia may impair the development and function of olfactory neurons.<sup>51</sup> Olfactory ensheathing cells (OECs) exhibit enhanced migratory capacity in response to brain-derived neurotrophic factor (BDNF) via TRPC channel activation, thereby promoting axonal regeneration and neuronal support in the olfactory system.<sup>61</sup> However, hypoxic conditions impair OECs and affect their function. High-altitude hypoxia may disrupt olfactory function by damaging OECs.<sup>32</sup>

Beyond hypoxia, low temperatures may reduce enzymatic activity in the olfactory mucosa and slow the diffusion rate of odorant molecules;<sup>62</sup> low humidity predisposes the nasal mucosa to dryness and ciliary dyskinesia, affecting the effective adsorption and transport of odorant molecules;<sup>63</sup> intense ultraviolet radiation may indirectly damage olfactory epithelial cells by inducing oxidative stress.<sup>64</sup> These factors often coexist in high-altitude environments, potentially producing additive or synergistic effects that collectively exacerbate the functional load on the olfactory system.

## Mechanisms of Aging Effects on the Olfactory System

Olfactory function gradually declines with age, a process associated with various physiological and molecular changes.<sup>18,20,65</sup>

From a neurological perspective, studies have demonstrated a close link between type 2 diabetes (T2D) and olfactory dysfunction. In aged T2D rat models, the piriform cortex exhibits pathological alterations, including changes in NeuN-positive neurons and Calbindin-D28k-positive interneurons. These changes are accompanied by elevated cellular stress, as evidenced by c-Jun N-terminal kinase (JNK) phosphorylation, although no apoptosis is observed.<sup>66</sup>

From a genetic perspective, interindividual differences in olfactory sensitivity may be related to polymorphisms in genes associated with odorant-binding proteins (OBPs).<sup>67-69</sup> A study of OBPIIa gene polymorphism (rs2590498) in 69 subjects found that individuals with the AA genotype had significantly higher odor threshold scores compared to those with GG or heterozygous genotypes. The AA genotype and A allele were associated with normal olfactory function, whereas the GG genotype and G allele were linked to hyposmia. These findings suggest that OBPIIa gene polymorphism may contribute to age-related differences in olfactory performance.<sup>70</sup> Additionally, age-related changes in the olfactory epithelium also lead to functional decline. During aging, horizontal basal cells (HBCs), crucial for olfactory neuron regeneration, become activated. This is often accompanied by dysfunction in retinoic acid metabolism, resulting in diminished olfactory neuron regenerative capacity and increased respiratory epithelial metaplasia, both of which impair olfactory function.<sup>71</sup>

## Interactive Effects of Genetic Variants Related to High-Altitude Adaptation and Olfactory Aging

Genetic factors play a crucial role in both olfactory decline and physiological adaptation to high-altitude environments, particularly for elderly residents of plateau regions.<sup>71–74</sup>

A notable example is the olfactory receptor gene *Olfir78*, which has been identified as functionally significant in both olfaction and hypoxia sensing.<sup>75</sup> *Olfir78* is highly and selectively expressed in oxygen-sensitive glomus cells of the carotid body. Studies on *Olfir78*-deficient mice show that these animals fail to increase ventilation in response to hypoxia, although their response to hypercapnia remains intact. This indicates that *Olfir78* not only functions in olfactory perception but also acts as a lactate-sensitive hypoxia sensor, modulating the respiratory response to hypoxic conditions.<sup>76</sup>

Comparative genetic studies on yaks, which have evolutionarily adapted to high-altitude habitats, further highlight the role of genetic variation in olfactory function.<sup>77,78</sup> Yaks possess a significantly lower number of olfactory receptor (OR) genes compared to low-altitude cattle species and lack receptors associated with compounds such as  $\beta$ -ionone and isovaleric acid (IVA). This may reflect an evolutionary adaptation to the reduced plant diversity in alpine environments and the underdeveloped sweat glands of yaks, both of which diminish the need for a highly diversified olfactory repertoire.<sup>31</sup>

In humans, genetic variants associated with high-altitude adaptation—such as those involved in oxygen transport, erythropoiesis, and vascular regulation—also influence the development and function of the nervous system, including olfactory pathways.<sup>73,79</sup> While direct links between these variants and olfactory function remain underexplored, emerging evidence suggests that genetic adaptations to high altitude may indirectly affect sensory performance in the elderly population.<sup>72</sup> Further research is needed to clarify these mechanisms and their implications for age-related olfactory decline.

## Diagnostic Techniques for Olfactory Dysfunction in Elderly Residents at High Altitudes

### Application of Olfactory Function Testing

Olfactory function testing serves as a critical tool for assessing olfactory decline in elderly populations residing at high altitudes. Standardized olfactory tests commonly used in the general population remain applicable in these environments.<sup>80</sup> For example, the Sniffin' Sticks test, a widely utilized clinical assessment, evaluates three key domains of olfactory performance: threshold, discrimination, and odor identification.<sup>81</sup> Studies involving elderly high-altitude residents have confirmed its effectiveness in determining olfactory functional status.<sup>82</sup>

In addition to conventional methods, simplified screening approaches are being developed to facilitate easier screening of olfactory decline in elderly populations, particularly in resource-limited or high-altitude settings.<sup>83,84</sup> One such tool is the 4-item Concise Olfactory Screening Test for the Elderly (4-CAST), which predicts olfactory dysfunction by incorporating variables such as age, type II diabetes status, overall olfactory visual analog scale (VAS) score, and safety-impact VAS score related to olfaction.<sup>85</sup> In the development cohort, the 4-CAST model demonstrated strong predictive validity, with an area under the curve (AUC) of 0.805 ( $p < 0.001$ ) for identifying individuals in the lowest 25th percentile of the Sniffin' Sticks test. Validation results showed similar level of accuracy, correctly classifying 83.8% of participants. These findings highlight the potential clinical utility of 4-CAST as a rapid and reliable screening tool for olfactory decline among elderly high-altitude residents.<sup>85</sup>

### Imaging Diagnosis

Imaging techniques provide valuable objective evidence for diagnosing olfactory decline in elderly residents of high-altitude regions.<sup>86</sup> Structural magnetic resonance imaging (MRI) enables the assessment of morphological and volumetric changes in brain regions associated with olfaction.<sup>87</sup> Studies in older adults with dementia but without cognitive impairment have demonstrated that impaired olfactory function is correlated with reduced volume in the hippocampus, entorhinal cortex, fusiform gyrus, and middle temporal cortex. These findings suggest that structural degeneration in these regions may be linked to olfactory dysfunction.<sup>88</sup> In high-altitude environments, chronic hypoxia may accelerate degeneration in these regions. Thus, MRI examinations may assist in the early detection of structural alterations with olfactory decline-related brain.

Functional MRI (fMRI) provides complementary insights by detecting brain activity in response to olfactory stimuli.<sup>89</sup> In patients with olfactory dysfunction, fMRI has revealed alteration activation patterns within primary olfactory cortices and the hippocampus, with changes correlating to behavioral measures. Among elderly high-altitude residents, fMRI offers the potential to uncover functional abnormalities in olfactory-related networks, thereby providing more precise diagnostic and prognostic information.<sup>90</sup>

However, high-altitude conditions pose imaging challenges. Environmental factors such as hypobaric hypoxia and technical limitations in MRI equipment performance may affect both image quality and diagnostic accuracy. Therefore, further methodological optimization and development of altitude-adapted imaging protocols are required to enhance the reliability of MRI-based diagnostics in these settings.

## Research on Biomarkers

The identification of biomarkers for olfactory decline holds significance for the early diagnosis and timely intervention of olfactory impairment in elderly populations residing at high altitudes. Insights from studies on neurodegenerative and metabolic diseases suggest potential candidates that may also be relevant in this context.

In Alzheimer's disease (AD), both structural and functional alterations in the primary olfactory cortex (POC) have been proposed as biomarkers of olfactory decline and disease progression.<sup>91</sup> In one study including 27 cognitively normal (CN), 21 mild cognitive impairment (MCI), and 15 AD subjects, revealed significant atrophy of the POC and hippocampus was observed in MCI and AD groups, correlating with behavioral olfactory measures. Importantly, reductions in olfactory activation volume within the POC and hippocampus were more pronounced in the MCI patients than the degree of tissue atrophy, resembling the pattern observed in the AD. These findings suggest that olfactory functional magnetic resonance imaging (fMRI) may provide an earlier and more sensitive biomarker of neurodegeneration compared to structural imaging alone in AD and MCI patients.<sup>92</sup>

Beyond neuroimaging, genetic and protein biomarkers have also attracted attention. In studies of patients with type 2 diabetes mellitus (T2DM), a panel of biomarkers-including plasma  $\beta$ -amyloid ( $A\beta$ ), platelet glycogen synthase kinase-3 $\beta$  (GSK-3 $\beta$ ), apolipoprotein E (ApoE) genotype, and olfactory function measures-proved effective in diagnosing MCI. Among these, decline in olfactory function emerged as a key predictive indicator, highlighting the potential utility of combining olfactory testing with molecular biomarkers for early detection of cognitive decline in metabolic disorders.<sup>93</sup> For elderly populations at high altitudes, chronic hypoxia may modulate these biomarkers through pathways involving inflammatory responses, oxidative stress, and hypoxia-inducible factors (HIFs). Although direct evidence in high-altitude cohorts remains limited, these candidate biomarkers are potentially feasible to measure and warrant investigation in future studies targeting olfactory decline in this population.

Further research into these established biomarkers, along with the discovery of novel molecular and imaging biomarkers specific to high-altitude elderly populations, are essential. Such efforts will enhance the precision and timeliness of diagnosing olfactory decline and may ultimately contribute to improved strategies for prevention and intervention.

Several limitations of current diagnostic approaches should be acknowledged. First, most olfactory tests, imaging modalities, and biomarkers have been validated primarily in low-altitude populations, and their applicability to elderly residents at high altitudes remains to be established. Second, the feasibility of advanced imaging techniques such as fMRI in high-altitude settings may be affected by equipment stability and the lack of altitude-specific protocols. Third, although biomarkers associated with hypoxic stress have been identified, their specificity for olfactory decline requires further validation in high-altitude cohorts.

## Treatment Strategies for Olfactory Dysfunction in Elderly High-Altitude Residents

### Intervention Measures for Olfactory Decline in High-Altitude Environments

Targeted interventions are essential for addressing olfactory decline associated with high-altitude environments. One major strategy involves mitigating hypoxia stress. The use of oxygen delivery devices to improve systemic oxygenation in elderly high-altitude residents has been shown to alleviate hypoxia-induced neuronal damage, thereby improving olfactory function. In some medical institutions located in high-altitude regions, oxygen therapy is routinely offered to

elderly patients.<sup>94</sup> Clinical observations indicate that certain individuals experience partial improvements in olfactory performance following oxygen supplementation, although outcomes vary depending on individual physiological and health factors.<sup>95</sup>

Another commonly employed intervention is nasal irrigation, aimed at reducing the harmful effects of dust, pollutants, and other irritants frequently encountered in high-altitude settings.<sup>96,97</sup> Regular irrigation can help cleanse the nasal cavity, minimize direct stimulation of the olfactory epithelium by harmful substances, and alleviate inflammatory responses, thus contributing to the maintenance of olfactory function.<sup>97</sup> Evidence from clinical studies suggests that irrigation with saline or specialized solutions can improve the nasal microenvironment and provide symptomatic relief for some patients experiencing olfactory decline.<sup>97</sup>

Beyond direct clinical interventions, environmental management plays a critical preventive role. Strategies such as reducing pollutant emissions, strengthening dust control, and improving overall air quality in high-altitude regions are vital for protecting nasal and olfactory health. By combining individual-level interventions with population-level environmental measures, a more comprehensive approach to the prevention and treatment of olfactory decline in elderly high-altitude residents can be achieved.

## Application of Pharmacotherapy in Elderly High-Altitude Residents

Pharmacotherapy may provide therapeutic benefits in managing olfactory decline among elderly residents living at high altitudes. Several pharmacological approaches have shown potential in supporting neuronal survival and mitigating hypoxia-related damage.<sup>98,99</sup>

Brain-derived neurotrophic factor (BDNF) plays a crucial role in neural development, plasticity, and functional maintenance.<sup>100</sup> It is theorized that BDNF could promote the survival and regeneration of olfactory neurons, thereby counteracting hypoxia-induced decline.<sup>101</sup> While large-scale clinical studies investigating BDNF specifically for olfactory impairment in elderly high-altitude populations are currently lacking, evidence from basic research and studies on other neurological conditions suggests positive effects on neural repair and regeneration, indicating its potential therapeutic value in this context.<sup>100</sup>

In addition, antioxidant therapies may counteract the oxidative stress associated with chronic hypoxia in high-altitude environments. Curcumin, for instance, has demonstrated the ability to protect olfactory ensheathing cells (OECs) under hypoxic conditions and to mitigate oxidative damage in olfactory neurons.<sup>32</sup> Results from *in vitro* experiments and small-scale human studies indicate that curcumin possesses both antioxidant and neuroprotective effects, although its specific efficacy in elderly high-altitude residents remains to be confirmed through larger clinical trials.<sup>32</sup>

Pharmacotherapy in this population faces significant challenges, including altered drug metabolism, potential side effects, and variability in treatment response. Future research is needed to determine the most appropriate pharmacological agents, optimize dosage regimens, and evaluate long-term safety and efficacy for elderly high-altitude residents experiencing olfactory decline.

## Olfactory Training and Rehabilitation Methods

Olfactory training has emerged as a promising non-pharmacological intervention for olfactory decline and may hold particular value for elderly residents in high-altitude environments. Multiple studies have demonstrated its effectiveness in improving olfactory function.<sup>102,103</sup> A systematic review and meta-analysis involving 639 patients reported statistically significant improvements in threshold, discrimination, and identification (TDI) scores (mean difference [MD] 3.77; 95% confidence interval [CI], 2.28–5.26), as well as in odor discrimination (MD 1.92; 95% CI, 1.13–2.71) and odor identification (MD 1.61; 95% CI, 0.55–2.68). No significant improvement was observed in odor threshold (MD –0.01; 95% CI, –0.42–0.39), indicating that olfactory training primarily enhances discrimination and identification rather than sensitivity.<sup>104</sup>

Further evidence comes from research on COVID-19-related olfactory dysfunction. In a prospective study, 57 COVID-19 patients underwent standardized olfactory training, and those who adhered to the regimen showed greater mid-term improvement in psychophysical olfactory scores compared to non-adherent individuals. These findings support

broader applicability of olfactory training across etiologies, including in populations vulnerable to hypoxia-induced olfactory decline such as elderly high-altitude residents.<sup>105</sup>

In addition, emerging multimodal rehabilitation approaches—such as combining olfactory training with visual or cognitive stimuli—may further enhance treatment outcomes. However, optimal training protocols, duration, and integration with adjunctive therapies remain areas requiring further clinical investigation.

The evidence supporting current therapeutic strategies in elderly high-altitude populations remains limited. Most interventions have been evaluated in small-scale studies with heterogeneous outcome measures and short follow-up durations. Moreover, the pharmacokinetic and pharmacodynamic profiles of pharmacological agents may be altered by chronic hypoxia and age-related changes in hepatic and renal function, yet systematic studies in this population are lacking. Olfactory training, while non-invasive, requires standardized protocols tailored to this specific population. Future randomized controlled trials with adequate statistical power are needed to establish evidence-based guidelines.

## **Health Risks and Future Perspectives of Olfactory Decline in Elderly Residents at High Altitudes**

### **Impact of Olfactory Decline on the Quality of Life of Elderly Residents at High Altitudes**

Olfactory decline exerts wide-ranging adverse effects on the quality of life of elderly individuals living in high-altitude areas.

Firstly, olfactory function is closely related to dietary experience and nutrition.<sup>106</sup> A diminished sense of smell reduces the ability to perceive food odors, which can negatively affect appetite, food preference, and overall dietary intake and nutritional intake.

Secondly, olfactory impairment affects social interactions and psychological well-being. The sense of smell contributes to recognizing familiar scents, perceiving interpersonal cues such as body odor, and maintaining social connectedness. Loss of this ability may lead to discomfort, self-consciousness, and avoidance of social activities. This can foster social isolation, loneliness, and adverse mental health outcomes in elderly populations.

Finally, olfactory dysfunction poses safety risks by reducing the ability to detect hazardous environmental odors, such as smoke from fires, or gas leaks. This diminished hazard perception may significantly increase vulnerability in elderly high-altitude residents, further compromising quality of life and safety.

### **Relationship Between Olfactory Decline and Malnutrition in Elderly Residents at High Altitudes**

A bidirectional relationship likely exists between olfactory decline and malnutrition among elderly residents in high-altitude regions.

On one hand, olfactory impairment reduces the perception of food odors, which can diminish appetite and decrease overall food intake.<sup>107</sup> This effect is particularly pronounced for nutrient-rich foods with subtle aromas, leading to an increased risk of malnutrition.<sup>108</sup> Studies have shown that individuals with olfactory dysfunction are more prone to protein-energy malnutrition and may also exhibit inadequate intake of essential vitamins and minerals.<sup>109,110</sup>

On the other hand, malnutrition itself may exacerbate olfactory dysfunction.<sup>111</sup> Deficiencies in nutrients critical for olfactory function, such as vitamin A and zinc, can impair neuronal metabolism and compromise the structural and functional integrity of olfactory neurons, thereby worsening olfactory performance.<sup>111</sup>

Food diversity, and dietary habits already contribute to unbalanced nutrient intake among elderly residents.<sup>112,113</sup> Olfactory decline may further aggravate these issues, creating a vicious cycle in which impaired olfaction and malnutrition perpetuate one another.

Therefore, comprehensive interventions that address both olfactory function and nutritional status are crucial for improving the overall well-being of elderly high-altitude populations.

## Conclusions and Future Directions

Olfactory decline in elderly residents at high altitudes significantly affects quality of life, nutritional status, social participation, and safety awareness. Although existing studies provide preliminary evidence for early identification, diagnosis, and intervention, many unknowns remain regarding the pathological mechanisms, epidemiological characteristics, and comprehensive intervention strategies for olfactory decline in this population under high-altitude conditions.

Future research should strengthen longitudinal cohort and large-scale multicenter investigations to systematically evaluate the long-term effects of high-altitude exposure, aging processes, and genetic adaptability on olfactory function, and to establish reliable risk prediction models. At the same time, integrated diagnostic tools combining structural and functional imaging with molecular and protein biomarkers should be developed to enable early detection and disease monitoring. Regarding intervention strategies, the pharmacokinetic and pharmacodynamic profiles of elderly high-altitude populations warrant careful consideration. Polypharmacy, age-related decline in hepatic and renal function, and the hypoxic environment may alter drug absorption, distribution, metabolism, and elimination, directly affecting treatment efficacy and safety. Therefore, tailored strategies should be developed for pharmacological interventions and clinical management. Moreover, multimodal comprehensive interventions remain key to improving olfactory health in elderly high-altitude residents, including medical management, nutritional support, psychological intervention, environmental optimization, and olfactory training. Notably, incorporating health education into the intervention framework can enhance residents' awareness and self-management capacity regarding olfactory function, nutritional status, environmental exposure risks, and daily safety, thereby improving the sustainability and overall effectiveness of interventions. Personalized strategies based on individual genetic background, altitude exposure level, and health status will help maximize efficacy and minimize risks.

By integrating basic research, epidemiological investigations, and multidisciplinary intervention strategies, future research and practice are expected to provide more scientific, effective, and sustainable olfactory health management solutions for elderly residents in high-altitude regions, thereby improving their quality of life and overall health, and providing an evidence base for public health policy development.

## Ethics Statement

As this is a narrative review based on published literature, ethical approval and informed consent are not applicable.

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## Disclosure

The authors have no conflicts of interest to declare.

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