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Review

Virus–Associated Olfactory Dysfunction: Mechanistic Insights From Epidemiology and Animal Models

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Abstract

The olfactory system plays a critical role in odor detection, flavor perception, hazard recognition, and social communication. Olfactory dysfunction arises from a range of etiologies, including inflammatory processes, neurodegenerative disorders, and infections, with viral infections representing the most prevalent infectious cause. In this review, we synthesize evidence from epidemiological investigations and animal model studies examining olfactory dysfunction associated with major viral pathogens, including severe acute respiratory syndrome coronavirus 2, influenza A virus, parainfluenza virus type 3, respiratory syncytial virus, human immunodeficiency virus, herpes simplex virus, cytomegalovirus, and Zika virus, to provide an integrated and mechanistic perspective on virus-induced alterations of the olfactory system. In addition, current limitations in the literature are critically evaluated, and key directions for future research on virus–associated olfactory dysfunction are outlined. A comprehensive literature search was conducted using the terms "viral infection", "olfactory dysfunction", "postviral olfactory dysfunction", or "virus-associated olfactory dysfunction" across multiple databases, including PubMed, Web of Science, Google Scholar, and Scopus. Collectively, through this synthesis, we establish a conceptual framework to advance mechanistic understanding and to inform the development of targeted therapeutic strategies for postviral olfactory dysfunction.

Keywords: animal models; epidemiology; olfaction; olfaction disorders; virus infections

1. Introduction

The sense of smell plays a fundamental role in both animal and human physiology, contributing to odor detection, pheromone signaling, hazard recognition, and social communication [1]. Odorant molecules dissolve in the mucus lining the nasal passages and traverse the superior nasal concha within the nasal cavity. These molecules are detected either through diffusion into olfactory sensory neurons (OSNs) or via binding to olfactory receptors located on the dendritic processes of OSNs within the olfactory epithelium (OE) [2]. Olfactory signals are subsequently transmitted along the axons of OSNs, pass through the cribriform plate, and project to the glomeruli located in the outer layer of the olfactory bulb (OB) [3]. Within the OB, input from the glomeruli is transformed into patterned neural activity by mitral and tufted cells in the inner layers [4]. This information is conveyed via the lateral olfactory tract to multiple cerebral regions, including the piriform cortex, anterior olfactory nucleus, and amygdala, where integrated processing supports odor identification, memory, and emotional responses [5]. In parallel, olfactory perception is modulated by both olfactory nerve input and trigeminal chemosensory activation [6]. Chemosensory irritation associated with odor perception, including chemesthetic and nociceptive components, is transmitted through trigeminal afferents in the nasal mucosa to the spinal trigeminal nucleus and subsequently to the somatosensory cortex [7,8]. This integrated processing enables the assessment of odorant pungency, intensity, thermal qualities, and potential harmfulness.

Olfactory dysfunction (OD) is defined as an alteration in the perception of odorants [9]. Relative to other sensory impairments, OD is frequently underrecognized or diagnosed at a later stage [10]. Despite this, OD exerts a substantial negative impact on quality of life by impairing the detection of hazardous odors, diminishing enjoyment of food, and contributing to psychological distress, including depression and social isolation [11]. Approximately 20% of the general population experience OD at some point during their lifetime [12]. Olfactory deficits may arise from dysfunction within the peripheral nasal sensory apparatus or from abnormalities in central sensory processing pathways [13]. Such dysfunction may be induced by a variety of factors, including inflammation, infection, neurodegenerative disease, medication, or idiopathic causes [10,14,15].

Infection represents one of the most common causes of OD, with viruses constituting the predominant etiological agents [16]. Viral infections can cause diverse forms of OD, collectively referred to in this review as virus-associated

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olfactory dysfunction (VAOD) [17,18]. Four distinct clinical categories can be distinguished within this spectrum. Acute infection-associated OD occurs during active viral upper respiratory tract infections (URTIs), such as viral rhinitis, in which inflammation and edema of the nasal mucosa impair the delivery of odorants to olfactory receptors on OSNs [19,20]. Postviral/postinfectious OD persists after the resolution of acute nasal symptoms and may reflect damage to peripheral or central olfactory pathways mediated by inflammatory processes [21]. Developmental virus-associated olfactory impairment results from viral infection during critical periods of olfactory system development, as observed in congenital infections [22]. Central neurological VAOD results from viral involvement of central structures responsible for olfactory processing [23]. Accordingly, the broader term VAOD is used throughout this review to encompass these distinct clinical entities.

Epidemiological studies provide a framework for understanding VAOD by characterizing its clinical patterns and associations, but they cannot establish the underlying pathophysiological mechanisms. For example, the mechanisms underlying the rapid development of OD during acute severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection and its persistence in some patients after the acute phase [24,25], as well as the markedly reduced olfactory involvement associated with the Omicron variant despite transmissibility comparable to earlier variants [26,27,28,29,30], remain unresolved. Experimental animal models provide complementary mechanistic insights that may help explain these clinical observations. Therefore, this narrative review summarizes epidemiological and animal-model studies of VAOD and synthesizes the available evidence to provide an integrated understanding of the mechanisms underlying VAOD and to identify limitations in the current literature and priorities for future research.

2. Data Sources and Search Strategy

Relevant studies published through August 31, 2026, without publication-year restrictions were identified using the keywords “viral infection”, “olfactory dysfunction”, “postviral olfactory dysfunction”, or “virus-associated olfactory dysfunction” across multiple databases, including PubMed, Web of Science, Google Scholar, and Scopus. The literature search included the established term ‘postviral olfactory dysfunction’ because this terminology has been widely used in the published literature. Studies were included if they addressed the epidemiology of virus-associated OD in humans or investigated the underlying olfactory pathology and mechanisms in animal models. Studies unrelated to viral infections or lacking relevant olfactory findings were excluded. Studies were selected based on their relevance to human epidemiological findings and experimental animal research on VAOD, with priority given to studies considered representative and informative for the topics addressed in this narrative review.

3. Epidemiological Studies of OD Associated With Viral Infections

Viral infections are well established as a major cause of postinfectious OD, mediated through mechanisms such as epithelial injury, inflammatory responses, and viral neurotropism. SARS-CoV-2 has received particular attention due to the high prevalence and clinical significance of OD in Coronavirus disease 2019 (COVID-19). In addition, other respiratory and non-respiratory viruses, including influenza virus, parainfluenza virus (PIV), human immunodeficiency virus (HIV), herpes simplex virus (HSV), cytomegalovirus (CMV), and Zika virus (ZIKV), have been implicated in OD through their pathological effects on the peripheral olfactory system or the central nervous system (CNS). This section reviews epidemiological studies of OD associated with SARS-CoV-2 as well as other respiratory and non-respiratory viral infections, with a primary focus on prevalence, risk factors, and observed disease patterns. Although SARS-CoV-2 is a respiratory virus, it is discussed separately because of the large number of available studies and the more detailed mechanistic evidence regarding COVID-19-associated OD. A summary of these epidemiological studies is presented in Table 1 (Ref. [24,26,27,28,29,30,31,32,33,34,35,36,37,38,39,40,41,42,43,44,45,46,47,48,49,50,51,52,53,54,55,56,57,58,59,60,61,62,63,64,65,66,67,68,69,70,71,72,73,74,75,76,77,78,79,80,81,82,83,84,85,86]).

3.1 OD Linked to SARS-CoV-2 Infection

Since the initial reports in 2019 [87], numerous studies have identified OD as a prevalent acute symptom of COVID-19 [24,31,32]. The reported prevalence of OD among patients with COVID-19 has varied considerably, with most studies estimating rates in the range of approximately 40–70% [33,37,88,89]. In contrast to OD associated with common viral rhinitis, which typically improves following resolution of nasal obstruction, approximately 67% of patients with COVID-19–related OD experience anosmia in the absence of nasal obstruction or rhinorrhea [34,90]. These findings suggest that nasal obstruction is unlikely to represent the primary mechanism underlying OD in COVID-19 and indicate the involvement of additional pathological processes.

The prevalence of OD varies substantially across racial, ethnic, and geographic populations. In a European multicenter cohort study of 774 patients with COVID-19, objective psychophysical testing identified olfactory impairment in 62.1% of participants [35]. Observational studies from Asian populations have reported lower prevalence estimates, ranging from 26.1% to 39.5% [36]. Similar regional differences have been observed in pooled analyses. Meta-analyses and systematic review have reported higher reported prevalence rates in European (approximately 54–55%) and North American (approximately 51–56%) populations compared with Asian (approximately 28–31%) and

Table 1. Summary of epidemiological studies of olfactory dysfunction associated with virus infection.

Pathogen	Design	Sample size	Olfactory assessment methods	Comparison of subjective and objective olfactory assessments	Lesion	Reference
SARS-CoV-2	Retrospective cohort study	361	Self-report	-	-	[24]
	Prospective observational study	3525	UPSIT, Self-report	Discrepant	-	[31]
	Prospective multicenter observational cohort study	105	Sniffin' sticks test, self-report	Not compared	-	[32]
	Case-control study	115	Disposable smell kit	-	-	[33]
	Prospective multicenter observational cohort study	417	Self-report	-	-	[34]
	Prospective multicenter observational cohort study	774	Sniffin' sticks test, CCCRC, self-report	Discrepant	-	[35]
	Retrospective cohort study	199	Self-report	-	-	[36]
	Retrospective cohort study	114	Self-report	-	-	[37]
	Cross-sectional study	103	Self-report	-	-	[38]
	Prospective observational study	83	Sniffin' sticks test, self-report	Not compared	-	[39]
	Cross-sectional study	1942	Self-report	-	-	[40]
	Cross-sectional study	20,669	Self-report	-	-	[41]
	Retrospective cohort study	7590	ICD-10-CM	-	-	[42]
	Prospective observational study	3191	Self-report	-	-	[43]
	Prospective observational study	608	Self-report	-	-	[44]
	Retrospective cohort study	169	Self-report, YOF test	Discrepant	-	[45]
	Prospective case-control study	68	Self-report	-	-	[46]
	Retrospective cohort study	128	Self-report	-	-	[47]
	Cross-sectional study	205	Self-report	-	-	[26]
	Cross-sectional study	774	UPSIT	-	-	[27]
	Retrospective cohort study	299,151	Self-report	-	-	[28]
	Retrospective cohort study	732	Self-report	-	-	[29]
	Retrospective cohort study	6053	Self-report	-	-	[30]
	Retrospective comparative study	70	Sniffin' sticks test, Self-report	Not compared	Olfactory cleft	[48]
	Observational case-control study	72	Sniffin' sticks test	-	Olfactory cleft	[49]
	Cross-sectional comparative study	171	BTT, Smell identification test	-	-	[50]
	Case-control study	71	Olfactory-action meter, Self-report	Discrepant	-	[51]
URTIs	Retrospective case series	143	Detection and recognition thresholds	-	OM	[52]
	Cross-sectional study	70	-	-	OM	[53]
	Cross-sectional study	266	T&T olfactometry test, Intravenous olfactory test	-	-	[54]
	Cross-sectional study	48	Sniffin' sticks test	-	OB	[55]
	Retrospective descriptive study	457	Sniffin' sticks test	-	-	[56]
	Retrospective cross-sectional study	26	Sniffin' sticks test	-	OB, Olfactory sulcus	[57]
	Prospective cohort study	24	Questionnaire, CC-SIT	Not compared	-	[58]
	Case-control study	47	CC-SIT	-	-	[59]

Table 1. Continued.

Pathogen	Design	Sample size	Olfactory assessment methods	Comparison of subjective and objective olfactory assessments	Lesion	Reference
	Cross-sectional study	122	Sniffin' sticks test	-	OB	[60]
	Cross-sectional study	18	BTT, Olfactory identification test	-	Piriform cortex, Amygdala, Parahippocampal area, Insular cortex, Temporal cortex	[61]
	Retrospective cohort study	791	Sniffin' sticks test	-	-	[62]
	Cross-sectional study	38	T&T olfactometry test, Sniffin' sticks test	-	Orbitofrontal cortex, OB	[63]
	Case-control study	70	Questionnaire, Sniffin' sticks test	Not compared	-	[64]
	Case-control study	191	UPSIT	-	-	[65]
	Retrospective cohort study	587	UPSIT	-	-	[66]
	Cross-sectional study	149	Questionnaire	-	-	[67]
	Cross-sectional study	307	T&T olfactometry test, Intravenous olfactory test	-	-	[68]
HIV	Cross-sectional study	79	UPSIT	-	-	[69]
	Cross-sectional study	80	Detection thresholds, Memory tests, Discrimination tests, Identification tasks	-	-	[70]
	Cross-sectional study	49	Ascending, Forced-choice, Two-alternative, Odor threshold test	-	-	[71]
	Prospective cohort study	84	Questionnaire, UPSIT	Not compared	-	[72]
	Cross-sectional study	64	Odorant Confusion Matrix, UPSIT, BTT	-	-	[73]
	Cross-sectional study	74	Sniffin' sticks test	-	-	[74]
	Cross-sectional study	48	Recognition task, Identification task	-	-	[75]
	Case-control study	162	Questionnaire, Sniffin' sticks test	Discrepant	-	[76]
	Cross-sectional study	135	Questionnaire, Sniffin' sticks test	Not compared	-	[77]
	Cross-sectional study	172	Brief smell identification test	-	-	[78]
	Cross-sectional study	74	-	-	OB, Insular gyrus, Corpus amygdala	[79]
HSV	Descriptive pathology study	3	-	-	OM	[80]
	Descriptive pathology study	29	-	-	Temporal lobes, Hippocampus, Amygdaloid nuclei, Olfactory cortex, Insula, Cingulate gyrus	[81]
	Retrospective cohort study	42	-	-	-	[82]
	Retrospective case series	3	Sniffin' sticks test	-	-	[83]
cCMV	Descriptive pathology study	16	-	-	Cortex, Hippocampus, OB	[84]
	Prospective cohort study	88	Sniffin' sticks test	-	-	[85]
ZIKV	Prospective cohort study	28	Sniffin' sticks test	-	-	[86]

Abbreviations: BTT, butanol threshold test; CC-SIT, cross-cultural smell identification test; CCCRC, Connecticut Chemosensory Clinical Research Center test; cCMV, congenital cytomegalovirus; HIV, human immunodeficiency virus; HSV, herpes simplex virus; ICD-10-CM, International Classification of Diseases, Tenth Revision, Clinical Modification; OB, olfactory bulb; OM, olfactory mucosa; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; T&T, Takagi-Toyoda test; UPSIT, University of Pennsylvania Smell Identification Test; URTIs, upper respiratory tract infections; YOF, Yonsei olfactory function test; ZIKV, Zika virus. Comparison of subjective and objective olfactory assessments was classified as follows: discrepant, conflicting findings in olfactory dysfunction (OD) prevalence between subjective and objective assessments; and not compared, both methods were used without direct comparison; a dash (-) indicates that only one assessment method was used or that olfactory testing was not performed.

Australian (approximately 10%) cohorts [91,92]. However, this regional pattern has not been consistently observed across studies. In an Indian cohort of 34 asymptomatic SARS-CoV-2 carriers and 37 healthy controls, objective olfactory assessment identified OD in 82% of the evaluated carriers [51]. These findings indicate substantial heterogeneity in reported OD prevalence within Asian populations, potentially reflecting differences in sample size, clinical symptom status, and olfactory assessment methods, and underscore the need for cautious interpretation of regional differences. Nevertheless, the population-level variation reported in epidemiological studies may reflect both viral and host-related factors [34]. The D614G substitution in the SARS-CoV-2 spike protein has been associated with enhanced viral infectivity and transmissibility [93]. This mutation has also been shown to increase ACE2-binding affinity and cellular entry efficiency [94]. In addition, host-related factors, including genetic background, may influence the prevalence of VAOD across different populations [95]. However, no studies have conclusively identified group-specific gene expression patterns sufficient to explain these epidemiological differences. Further investigation is required to elucidate population-specific host determinants of VAOD.

Disease severity represents another important determinant of OD prevalence in COVID-19. Multiple studies have reported that OD is more frequently observed in mild or ambulatory cases compared with severe or hospitalized patients [44,46,47]. Substantial olfactory impairment has also been reported among asymptomatic individuals with SARS-CoV-2 infection [50,51]. Two primary hypotheses have been proposed to explain this association. The first suggests that OD occurs early in the disease course, as SARS-CoV-2 infects the olfactory mucosa (OM) during the initial phase of infection, with olfactory function potentially recovering by the time of hospitalization [46]. The second hypothesis posits that OD reflects a robust local immune response in URTIs. In this context, localized inflammation within the olfactory cleft may indicate effective viral containment in the upper airway, supported by its inverse association with sputum production, a marker of lower respiratory tract involvement and disease progression [47].

Demographic factors have also been associated with variation in OD prevalence. Multiple studies have reported a higher prevalence of OD in females compared with males among patients with COVID-19 [37,38,39,40,41], as well as a greater likelihood of persistent OD lasting ≥12 months [44]. These sex-related differences may reflect both biological and anatomical factors, including variation in inflammatory responses [96] and reduced pharyngeal resistance in females, which may allow increased airflow interaction with the OM [97]. A meta-analysis has demonstrated that females generally exhibit superior olfactory performance compared with males across multiple functional domains [98]. This higher baseline sensitivity may increase the likelihood of detecting even subtle olfactory changes, contributing to higher rates of self-reported OD. Age-related differences have also been observed, with OD occurring more frequently among younger and middle-aged adults with COVID-19 [42,43]. A nationwide cohort study based on Korean insurance claims data reported a significantly lower median age among patients with COVID-19–related OD (27 years) compared with those without OD (47 years) [42]. Similarly, another large cohort study found that OD occurred predominantly in individuals younger than 60 years, with prolonged anosmia more commonly observed in those aged 20–39 years [43]. These findings are supported by meta-analyses demonstrating increased susceptibility to OD in younger populations [88,90]. Additionally, older individuals may be more likely to under-recognize or under-report OD due to baseline age-related presbyosmia associated with reduced OSN populations and impaired OE stem cell function [99,100,101].

As noted above, substantial variation in OD prevalence has been observed across SARS-CoV-2 variants, with a progressive decline from early strains to later variants [102]. One study reported lower OD prevalence rates in the Alpha (41%) and Delta (48%) variants compared with the ancestral strain (73%) [103]. The Omicron variant has been associated with a marked reduction in OD prevalence [26,27]. Large cohort studies in England have demonstrated a decrease in OD prevalence from 33.7% during the Delta wave to 13.4% during the Omicron wave [28]. Additional studies have reported OD prevalence as low as 1.6% during the Omicron wave in China [29], and a reduction from 52.6% with the original strain to 5.8% with Omicron in Brazil [30]. This decline has been attributed to reduced neurotropism and altered cellular entry mechanisms associated with the Omicron variant. Specifically, Omicron demonstrates a relative shift toward endosomal entry pathways rather than reliance on transmembrane serine protease 2 (TMPRSS2)–mediated membrane fusion, resulting in preferential replication within the respiratory epithelium rather than the TMPRSS2-rich OE and consequently reduced olfactory injury [104,105,106]. Consistent with this reduced OE tropism, a recent hamster study further showed that Omicron infection of the OE is delayed and attenuated relative to earlier variants [107]. These observations indicate that viral evolution influences tissue tropism and cellular entry mechanisms, thereby modulating patterns of OD.

Heterogeneity in COVID-19-associated OD extends beyond prevalence to its clinical phenotype. In addition to the commonly reported quantitative deficits of anosmia and hyposmia, qualitative disturbances, including parosmia and phantosmia, have also been reported in patients with COVID-19 [34,35,45,108,109]. Parosmia and phantosmia can occur with or without concurrent quantitative OD and may also emerge during or after apparent recovery from anosmia or hyposmia [109,110,111]. Proposed peripheral mechanisms include altered odorant processing at the re-

ceptor level [112,113], ephaptic interactions in demyelinated olfactory neurons [114], and inappropriate rewiring of regenerating OSN axons [113,115]. Alterations in central olfactory circuits have also been proposed for both parosmia and phantosmia. In parosmia, impaired integration between peripheral olfactory input and higher brain regions may distort the processing of actual odor signals [115], whereas phantosmia may involve disinhibition within central olfactory pathways, generating odor perception in the absence of external stimuli [111]. Together, these findings suggest that COVID-19-related qualitative OD may involve pathophysiological alterations at multiple levels of the olfactory system, encompassing both peripheral and central mechanisms.

Collectively, these epidemiological findings indicate that OD in COVID-19 can manifest as different clinical phenotypes and is influenced by multiple factors, including racial and geographic background, disease severity, demographic characteristics, and viral variants (Fig. 1, Ref. [26,27,28,29,30,35,36,37,38,39,40,41,42,43,44,46,47,54,56,57,59,60,64,66,76,82,83,85,86,91,92]). Recognition of this multifactorial basis underscores the importance of integrating epidemiological observations with mechanistic investigations of host and viral determinants to advance understanding of the pathophysiology of COVID-19–associated OD.

3.2 OD Linked to Other Respiratory Viral Infections

URTIs, excluding SARS-CoV-2, represent one of the most commonly identified causes of OD, accounting for approximately 20–30% of reported cases [116]. Many affected individuals describe their symptoms as a loss of taste, reflecting common linguistic usage; however, more than 80% of these patients demonstrate isolated olfactory impairment with preserved gustatory function [117]. Consequently, the true incidence of VAOD following respiratory viral infections is likely underestimated in the literature. The earliest report describing OD following viral URTIs was published by Henkin et al. [52], who documented pathological findings including pale nasal mucosa, elevated odor identification thresholds, and chronic inflammatory cell infiltration within the upper lamina propria. Subsequent investigations have sought to identify the viral etiologies of VAOD, implicating several common cold viruses, including influenza virus, parainfluenza virus, respiratory syncytial virus (RSV), adenovirus, rhinovirus, coronavirus, and Epstein–Barr virus [54,56,58,59,64,66]. Environmental influences, including seasonal variation in viral transmissibility, have been proposed to contribute to differences in VAOD prevalence associated with specific viral pathogens [66]. Several studies have reported that VAOD incidence exhibits two peak periods, between January and March and between March and July, with variation across geographic regions, rather than a consistent predominance during winter months [54,56,59,66]. These observations suggest that certain respiratory viruses may play disproportionately prominent roles in VAOD pathogenesis. Seasonal patterns have been attributed primarily to influenza virus between January and March and to parainfluenza virus type 3 (PIV3) between March and July, based on virus-specific clinical features, transmission dynamics, serologic antibody profiles, and direct identification of PIV3 in inferior turbinate epithelial cells [54,56,59,66]. However, the precise viral etiologies underlying seasonal VAOD remain uncertain. Notably, PIV3 accounts for only approximately 5% of URTI cases [118], which appears insufficient to explain the overall burden of VAOD. An additional limitation is that many patients with VAOD present for clinical evaluation long after symptom onset, further complicating pathogen identification. Collectively, these factors contribute to the difficulty in establishing definitive viral etiologies in VAOD.

The pathophysiology of VAOD associated with URTIs remains incompletely characterized; however, evidence suggests that mechanisms beyond simple mechanical obstruction are involved in the development of OD. Notably, OD may persist following resolution of nasal obstruction or may occur in the absence of overt obstructive symptoms [58]. Histopathological analyses of OE biopsies from patients with VAOD have demonstrated direct injury to OSNs, including degeneration and loss of olfactory receptors, reduced numbers of olfactory nerve bundles, and squamous metaplasia of the OE [53]. Neuroimaging studies have consistently shown a reduction in OB volume in patients with VAOD, which correlates with both the duration of olfactory impairment and psychophysical measures of OD assessed using orthonasal and retronasal testing [57,60,63]. Although the mechanisms underlying reduced OB volume remain uncertain, it is likely attributable to diminished peripheral sensory input, as OB volume is thought to correlate with the number of OSNs within the OE [55,119]. In addition to peripheral mechanisms, trigeminal sensory pathways in the non-olfactory nasal mucosa may also be affected. Olfactory event-related potentials (oERPs) are detectable in approximately one-third of patients with VAOD, whereas intranasal trigeminal event-related potentials (tERPs) are observed in the majority of cases [60]. Further studies have demonstrated elevated carbon dioxide trigeminal thresholds, prolonged tERP latencies, and reduced tERP amplitudes in patients with VAOD [120]. Beyond peripheral involvement, central olfactory pathways may also be implicated. Functional imaging studies have identified reduced metabolic activity in the piriform cortex, as well as in secondary olfactory regions including the amygdala and parahippocampal gyrus [61]. Whole-brain magnetic resonance imaging analyses have demonstrated reduced gray matter volume in the right orbitofrontal cortex, a region associated with odor evaluation, with these changes correlating with the duration of OD [63]. These

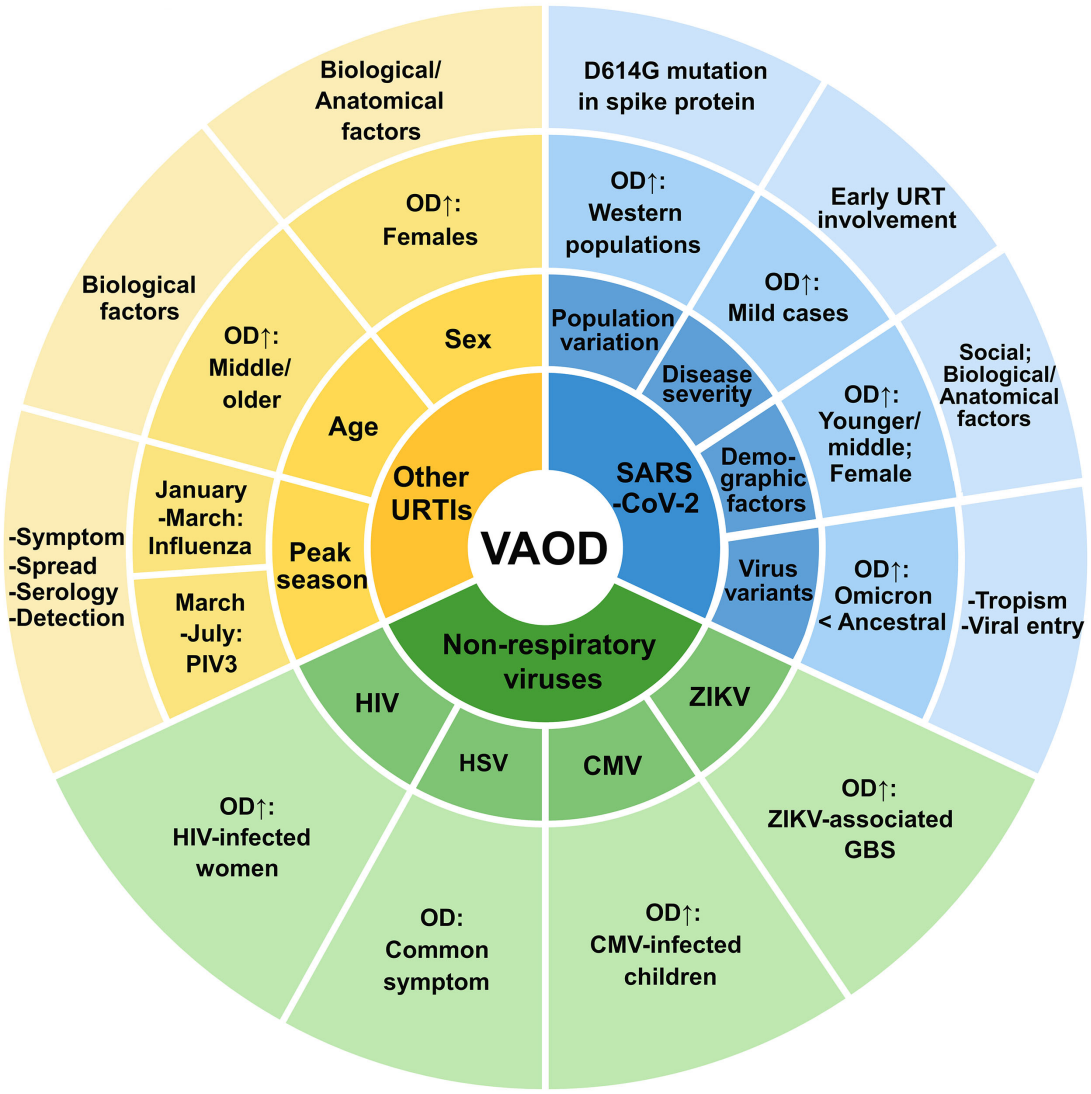


Fig. 1. Epidemiological overview of virus-associated olfactory dysfunction (VAOD). The sunburst diagram summarizes epidemiological factors and patterns related to OD across different viral infections, including SARS-CoV-2, other URTIs, and non-respiratory viruses. Data were synthesized from references [26,27,28,29,30,35,36,37,38,39,40,41,42,43,44,46,47,54,56,57,59,60,64,66,76,82,83,85,86,91,92]. SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; OD, olfactory dysfunction; URT, upper respiratory tract; URTIs, upper respiratory tract infections; PIV3, parainfluenza virus type 3; HIV, human immunodeficiency virus; HSV, herpes simplex virus; CMV, cytomegalovirus; ZIKV, Zika virus; GBS, Guillain–Barré syndrome. The upward arrow (↑) indicates a higher prevalence of OD.

findings indicate that both peripheral and central structural and functional alterations contribute to OD following URTIs.

The incidence and clinical characteristics of VAOD associated with respiratory viral infections may also be influenced by host-related factors, including age and sex. OD related to respiratory viral infections is more commonly observed in females, accounting for approximately 63–86% of cases, and typically presents at older ages, with a mean or median age ranging from 46 to 58 years [54,56,57,60,64]. The increased prevalence of VAOD among middle-aged and older women may reflect age-related or postmenopausal changes in olfactory function, as reductions in estrogen levels have been proposed to influence olfactory sensitivity [121,122].

OD associated with respiratory viral infections may demonstrate gradual recovery over time. Among studies evaluating recovery outcomes in VAOD, the longest follow-up study (3 years) reported the highest improvement rate, reaching 90% [123]. However, given the limited sample size in that study, findings from a larger retrospective cohort of 791 patients provide additional insight. In this cohort, with a mean follow-up duration of 1.94 years, recovery rates were 46% among patients with anosmia and 35% among

those with hyposmia [62]. Prognostic outcomes in VAOD are influenced by several factors reflecting residual or recoverable olfactory function [60,62,124,125,126]. These include electrophysiological measures such as oERPs and tERPs, as well as psychophysical parameters including odor threshold, discrimination, and identification scores, in addition to OB volume and patient age. Collectively, these measures may serve as indicators of the functional status of OSNs within the OE and as important predictors of recovery.

Consequently, OD in other URTIs is affected by various factors, including sex, age, and seasonality (Fig. 1). In contrast to COVID-19–associated OD, epidemiological data on VAOD related to other respiratory viral infections remain limited, largely due to the involvement of multiple viral pathogens and the absence of systematic surveillance. To address these limitations, future studies should prioritize prospective cohort designs incorporating precise viral identification, standardized olfactory assessment, and longitudinal follow-up.

3.3 OD Linked to Non-Respiratory Viral Infections

Among non-respiratory viruses, several neurotropic viruses, including HIV, HSV, CMV, and ZIKV, have been reported to affect olfactory function and provide evidence of potential mechanisms beyond peripheral OE damage, including involvement of central olfactory pathways and virus-associated neuropathological changes [79,84,127,128]. HIV profoundly impairs immune function through its primary targeting of CD4+ T cells [129]. In addition, HIV can directly or indirectly invade the CNS, leading to neurological complications in approximately 40–60% of affected individuals, including neurocognitive disorders, peripheral neuropathy, and meningoencephalitis [130]. OD has been documented in individuals living with HIV and likely reflects both peripheral and central nervous system involvement. The prevalence of hyposmia was significantly higher in HIV-infected women (39.8%) than in HIV-uninfected women (12.7%) [76]. Furthermore, HIV-infected women receiving highly active antiretroviral therapy (HAART) were reported to have higher odds of hyposmia than HIV-uninfected controls (OR = 2.13, 95% CI: 1.597–2.828) [76]. A longer duration of HAART use was also associated with higher odds of hyposmia, although this association does not establish causality [76]. Patients with HIV exhibit heterogeneous patterns of OD, including deficits in odor detection, discrimination, recognition, and identification, which vary according to disease stage and degree of immunosuppression. Evidence indicates that impairments in odor detection tend to occur early in HIV infection and are primarily associated with peripheral olfactory damage, often secondary to opportunistic nasal and upper respiratory infections commonly observed in this population [70,74]. In contrast, deficits in odor discrimination, recognition, and identification are associated with declining CD4+ T cell counts and increasing severity of HIV-associated neurocognitive disorders, suggesting involvement of central olfactory processing in regions such as the piriform cortex, amygdala, and hippocampus [69,70,75]. However, further investigation is required to delineate the specific peripheral and central mechanisms underlying OD in HIV infection.

HSV has the capacity to infect multiple organ systems; however, its invasion of the CNS can result in herpes simplex encephalitis (HSE), one of the most severe and life-threatening complications of HSV infection [131]. Although the introduction of acyclovir has substantially reduced mortality, neurological sequelae remain common among survivors. McGrath et al. [82] reported that anosmia occurred in 65% of individuals surviving HSV infection, representing the second most common symptom after short-term memory impairment, which was observed in 70% of cases. Retrospective analyses of HSE survivors indicate that OD varies depending on the anatomical regions affected by HSV, with impairments observed in odor threshold detection and/or odor identification, often persisting for follow-up periods exceeding 3 years [83]. Autopsy studies have demonstrated pathological lesions in the OM, OB, hippocampus, and insula [80,127]. In addition, the olfactory and trigeminal nerves have been proposed as principal pathways for neurotropic viral entry into the CNS [132,133]. OD following HSV infection is therefore common among survivors of HSE and is frequently persistent [83], with clinical manifestations likely reflecting the extent and regional distribution of damage to peripheral and central olfactory structures.

Congenital CMV (cCMV) infection may result in clinical manifestations such as hepatomegaly, splenomegaly, sensorineural hearing loss, microcephaly, and a range of neurological abnormalities in approximately 10–15% of infected infants at birth [134,135]. CMV exhibits marked neurotropism for neural stem cells within the fetal OB, suggesting the potential for structural and functional lesions in this region [84]. However, current understanding of OD in CMV-infected children remains limited, largely due to challenges in reliably assessing olfactory function in pediatric populations. Recently, Lazarini et al. [85] reported that OD was significantly more prevalent in CMV-infected children who were symptomatic at birth and older than 6 years, as assessed using rapid odor discrimination tasks designed to minimize cognitive and linguistic demands. Given the lack of validated, age-appropriate olfactory assessments and the limited clinical data available, large-scale cohort studies employing standardized methodologies are needed to better define the prevalence and clinical implications of OD in cCMV infection.

ZIKV infection may occasionally lead to neurological complications, including congenital Zika syndrome in fetuses and Guillain–Barré syndrome (GBS), a postinfectious autoimmune peripheral neuropathy, in adults [136].

OD is not commonly reported in ZIKV infection; however, a limited number of cases have been described [137]. Experimental studies have demonstrated that human OE cells, olfactory ensheathing cells, and glial cells of the peripheral olfactory system are susceptible to ZIKV infection and replication, suggesting potential involvement of the olfactory system in ZIKV pathogenesis [128,138]. To date, however, no clinical studies have directly established an association between ZIKV infection and OD, apart from reports describing olfactory impairment in patients with GBS following ZIKV infection. Lazarini et al. [86] demonstrated that the prevalence of hyposmia was higher in patients with GBS associated with ZIKV infection (68.4%) compared with those with GBS unrelated to ZIKV (22.2%), with impairments observed in both odor threshold detection and identification. These findings may not be generalizable to the broader population of individuals with ZIKV infection, underscoring the need for further investigation to clarify this relationship.

Overall, several neurotropic viruses have been implicated in the development of OD; however, epidemiological evidence remains limited compared with that for respiratory virus–associated OD (Fig. 1). This limitation likely reflects factors such as the relatively small number of surviving patients following severe neurological complications, the lower frequency of centrally mediated OD, and the underrecognition of olfactory symptoms in the context of acute neurological disease. Accordingly, large-scale, multinational cohort studies incorporating standardized olfactory assessments are required to overcome sample size limitations and to enable systematic evaluation of olfactory involvement in neurotropic viral infections.

3.4 Perspectives and Limitations of Epidemiological Studies

Epidemiological research has played a central role in identifying viral pathogens, risk factors, clinical patterns, and outcomes associated with VAOD (Fig. 1). However, interpretation of these findings is constrained by several methodological and conceptual limitations. A major concern is the frequent reliance on self-reported olfactory symptoms in the absence of validated psychophysical testing, particularly during the COVID-19 pandemic [90]. Studies that applied both subjective and objective assessments often reported discrepancies in OD prevalence between the two methods, although the direction of these differences varied across studies [35,45,51,76]. Such discrepancies may lead to under- or overestimation of OD prevalence, underscoring the need for standardized, objective olfactory assessment methods to improve the reliability of prevalence estimates. Another limitation arises from geographic and demographic imbalances. The majority of cohorts have been conducted in Europe and Asia, with limited representation from Africa, the Middle East, and South America [102,139]. This restricted diversity limits the generalizability of findings and constrains robust subgroup analyses. Large, multinational, and demographically balanced cohorts are required to more accurately characterize the global burden of VAOD. In addition, most epidemiological investigations have focused predominantly on respiratory viruses, particularly SARS-CoV-2, whereas other viruses implicated in OD have received comparatively limited attention. A broader scope of investigation is therefore necessary to capture the full epidemiological and clinical spectrum of VAOD associated with diverse viral pathogens. Moreover, longitudinal study designs remain limited, and most investigations lack integration with mechanistic or translational approaches, leaving disease patterns, long-term outcomes, and underlying pathophysiology insufficiently characterized.

Future research should prioritize the use of standardized psychophysical testing, adopt prospective cohort designs with greater population diversity, and incorporate longitudinal follow-up to better define trajectories of recovery or persistence. Integration of epidemiological observations with mechanistic data, including biological biomarkers, neuroimaging findings, and experimental evidence, will be essential for elucidating underlying mechanisms, characterizing disease progression, and identifying predictors of clinical outcomes. Such comprehensive approaches will enhance the accuracy and interpretability of epidemiological findings and provide a more robust foundation for understanding the pathophysiology and management of VAOD.

4. Animal Model Studies for VAOD

OD is a common consequence of viral infections; however, its underlying pathophysiological mechanisms remain incompletely understood. Given the inherent limitations of mechanistic investigations in human subjects, animal models provide valuable opportunities to examine aspects of disease that are difficult to study clinically, including viral tropism, neuroinflammatory processes, and olfactory recovery under controlled experimental conditions. This section focuses on recent findings from animal studies that elucidate the mechanisms underlying virus-induced OD. Table 2 (Ref. [22,86,107,128,140,141,142,143,144,145,146,147,148,149,150,151,152,153,154,155,156,157,158,159,160,161,162,163,164,165,166,167,168,169,170,171,172,173,174,175]) presents a summary of animal studies related to VAOD.

4.1 Animal Models of SARS-CoV-2-Induced OD

OD is a prevalent feature of SARS-CoV-2 infection; accordingly, investigations into its underlying mechanisms have increasingly relied on animal models. A range of experimental systems has been utilized to study SARS-CoV-2 infection, each offering distinct advantages for elucidating mechanisms of COVID-19–associated OD. Transgenic (Tg) mice expressing human ACE2 (hACE2) have been extensively employed to

Table 2. Summary of animal studies of olfactory dysfunction associated with virus infection.

Pathogen (variant/strain)	Experimental model	Route of inoculation	Examined region	Affected lesions/Cells	Olfactory assessment	OD evidence level	Reference
SARS-CoV-2 (USA-WA1/2019)	K18-hACE2 Tg mice	Intranasal	Lung, RE, OE, OB, Other brain region (Cerebral cortex, Caudate/Putamen, Thalamus, Hypothalamus, Ventral striatum, Brainstem), Heart, Liver, Kidney, Spleen, Intestine	Lung, RE, OE, OB, Other brain region (Cerebral cortex, Caudate/Putamen, Thalamus, Hypothalamus, Ventral striatum, Brainstem), Liver	BFT, SSDT	A	[140]
(hCOV-19/USA-WA1/2020)	K18-hACE2 Tg mice	Intranasal	OE, OB, Other brain region (PC, TuS)	OE (SC), OB, Other brain region (PC, TuS)	-	B	[141]
(NCCP 43326)	K18-hACE2 Tg mice	Intranasal	Lung, OE, Lamina propria, OB, Other brain region (cerebrum, cerebellum)	Lung, OE (SC, OSN), Lamina propria, OB, Other brain region (cerebrum, cerebellum)	-	B	[142]
(Spain/CT-2020030095/2020)	K18-hACE2 Tg mice	Intranasal	OE, OB, Other brain region (Cortex, Hippocampus, Striatum, Thalamus, Hypothalamus, Mesencephalon, Pons, Medulla oblongata, Cerebellum)	OE, OB, Other brain region (Cortex, Hippocampus, Striatum, Thalamus, Hypothalamus, Mesencephalon, Pons, Medulla oblongata)	-	B	[143]
(NCCP 43326, S-type variant)	K18-hACE2 Tg mice	Intranasal	Lung, Nasal conchae, Spleen, Small intestine, Brain tissues	Lung, Nasal conchae, Spleen, Small intestine, Brain tissues	-	C	[144]
(WH-09/human/2020/CHN)	K18-hACE2 Tg mice, hACE2 Tg mice, Golden Syrian hamster	Intranasal	Lung, OE, RE, Lamina propria, OB, Other brain region (Cerebrum, Cortex, Brainstem, Hippocampus, Cerebellum)	Lung, OE (OSN, BC, SC), RE, Lamina propria, OB, Other brain region (Cerebrum, Cortex, Brainstem, Hippocampus, Cerebellum)	-	B	[145]
(USA-WA1/2020)	K18-hACE2 Tg mice	Intranasal	NT, Lung, Brain (Cortex, Hippocampus, Choroid plexus, Meninges), Spleen, Trachea, Heart, Kidney, Liver, Intestine	NT, Lung, Brain (Cortex, Hippocampus, Choroid plexus, Meninges), Kidney, Liver, Intestine	-	C	[146]

Table 2. Continued.

Pathogen (variant/strain)	Experimental model	Route of inoculation	Examined region	Affected lesions/Cells	Olfactory assessment	OD evidence level	Reference
(England/Liverpool_REMRQ0001/2020, Alpha [B.1.1.7], Beta [B.1.351], Delta [B.1.617.2], Omicron [B.1.1.529])	K18-hACE2 Tg mice	Intranasal	Lung, Nasal cavity, OE, Cribriform plate, OB, Other brain region (Cortex, Hippocampus, Thalamus, Hypothalamus, Midbrain, Brainstem, Striatum, Amygdala, Cerebellum), Spinal cord, Inner ear, Capillary endothelial cells	Lung, Nasal cavity, OE (OSN, BC), Cribriform plate, OB (Glomerular layer, Mitral cell layer, Inner plexiform layer, Outer plexiform layer, Granule cell layer, Olfactory nerve layer), Other brain region (Cortex, Hippocampus, Thalamus, Hypothalamus, Midbrain, Brainstem, Striatum, Amygdala, Cerebellum), Spinal cord, Capillary endothelial cells	-	B	[147]
(USA-WA1/2020)	K18-hACE2 Tg mice	Intranasal	Nasal cavity, Lung, OB, Other brain region (Anterior olfactory nucleus, Cerebral cortex, Hippocampus, Subcortical structure, Brainstem, Nucleus accumbens, Thalamic nuclei, Midbrain, Pons, Medulla oblongata, Ependyma/Choroid plexus), Spinal cord, GI (Stomach, Intestine), Kidney, Heart, Retina (Retinal ganglion cell)	Nasal cavity, Lung, OB (Mitral cell layer, Glomerular layer, External plexiform layer, Granule cell layer), Other brain region (Anterior olfactory nucleus, Cerebral cortex, Hippocampus, Subcortical structure, Brainstem, Nucleus accumbens, Thalamic nuclei, Midbrain, Pons), Spinal cord	-	B	[148]
(USA-WA1/2020)	K18-hACE2 Tg mice	Intranasal	NT, Lung, OB, Other brain region (Cortex, Cerebellum, Hippocampus), Eye, Kidney, Spleen, Pancreas, Heart, Liver	NT, Lung, OB, Other brain region (Cortex, Cerebellum, Hippocampus)	-	C	[149]
(BetaCoV/France/IDF/200107/2020, D614G, hCoV-19/Netherlands/NH-RIVM-72291/2021, Omicron [B.1.1.529])	Golden Syrian hamster	Intranasal	RE, OE	RE, OE (OSN)	BFT	A	[107]
(HKU-001a)	Golden Syrian hamster	Intranasal	NT, OE, OB, Other brain region	NT, OE (OSN, BC, SC)	-	B	[150]

Table 2. Continued.

Pathogen (variant/strain)	Experimental model	Route of inoculation	Examined region	Affected lesions/Cells	Olfactory assessment	OD evidence level	Reference
(BetaCoV/Hong Kong/VM20001061/2020)	Golden Syrian hamster	Intranasal	NT, OE, Lungs, Brain, Duodenum, Heart, Liver, Spleen, Kidney	NT, OE (OSN), Lung, Duodenum	-	C	[151]
(UCN1, UCN19)	Golden Syrian hamster	Intranasal	Nasal cavity, OE, Lamina propria, VNO, Steno's gland, OB, Other brain regions (Cortex, Hypothalamus, Hippocampus, Brainstem)	Nasal cavity lumen, OE (OSN, SC), Lamina propria, VNO, Steno's gland	-	B	[152]
(WA-1, Alpha [B.1.1.7], Beta [B.1.351], Gamma [P.1], Delta [B.1.617.2], Omicron [B.1.1.529])	Golden Syrian hamster	Intranasal	NT (S, MT, DT, LT), Lung	NT (S, MT, DT, LT), Lung	BFT	A	[153]
(BetaCoV/France/IDF00372/2020, hCoV-19/Japan/TY7-501/2021, Delta [B.1.617.2], Omicron [B.1.1.529])	Golden Syrian hamster	Intranasal	NT, OE, Lung, OB, Other brain region	NT, OE, Lung, OB	BFT	A	[154]
hCoV-19/Japan/TY11-927/2021, Delta [B.1.617.2]	Golden Syrian hamster	Intranasal	Lung, NT, OB, Other whole brain region	Lung, NT, OB, Hippocampus	Smell test (TMT avoidance)	A	[155]
(USA/WA1/2020)	Golden Syrian hamster	Intranasal	OE, Lung	OE, Lung	-	B	[156]
(BetaCoV/France/IDF/200107/2020, D614G)	Golden Syrian hamster	Intranasal	RE, VNO, OE	RE, OE (OSN, BC, SC)	BFT	A	[157]
IAV (R404BP)	C57BL/6 mice	Intranasal	OE, OB, Other brain region (Anterior olfactory nucleus, Diagonal band, Hypothalamus, Amygdala, Substantia nigra, Dorsal raphe)	OE (OSN)	-	B	[158]

Table 2. Continued.

Pathogen (variant/strain)	Experimental model	Route of inoculation	Examined region	Affected lesions/Cells	Olfactory assessment	OD evidence level	Reference
(A/PR/8/34 [PR8])	C57BL/6 mice	Intranasal	OB, Other brain region (Piriform cortex, Olfactory tubercle, Somatosensory cortex, Amygdala, Hypothalamus)	OB (Olfactory nerve layer, Glomerular layer External plexiform layer, Molecular layer), Other brain region (Piriform cortex, Olfactory tubercle, Central amygdala, Hypothalamus)	-	B	[159]
Sendai virus (52)	C57BL/6 mice	Intranasal	OB, OE	OB, OE (Basal layer)	BFT	A	[160]
(Nagoya)	C3H/HeJ mice	Intranasal	OE, OB, Lung, PBMC, RBC, Plasma	OE (OSN), OB (Glomerulus), Lung, PBMC, RBC, Plasma	-	C	[161]
RSV (line 19)	BALB/c mice	Intranasal	Nasal mucosa (OE), OB	Nasal mucosa (OE [OSN progenitor]), OB	-	B	[162]
(N.S.)	BALB/c mice	Intranasal	Endoturbinate (OE, RE), OB, Steno's gland, Other brain region (Cerebellum)	Endoturbinate (OE [OSN, SC]), OB (Glomerular layer, Olfactory nerve layer), Steno's gland	-	B	[163]
HSV-1 (N.S.)	BALB/c mice	Intranasal, intracorneal	TG, OB, Other brain region (Thalamus, Hypothalamus, Cerebellum, Anterior olfactory nucleus, Lateral olfactory tract, Septal nuclei, Hippocampus, Cingulate cortex, Piriform cortex, Medial septal nucleus)	TG, OB (Mitral neuron), Other brain region (Thalamus, Hypothalamus, Cerebellum, Anterior olfactory nucleus, Lateral olfactory tract, Septal nuclei, Hippocampus, Cingulate cortex, Piriform cortex, Medial septal nucleus)	-	C	[164]
(McKrae)	C57BL/6 mice	Intranasal	RE, OE, OB, Other brain region (Brainstem nuclei, Diencephalon nuclei, Hippocampus)	RE, OE, OB, Other brain region (Brainstem nuclei [XIIN, DMX, SPVC, NoST, AP, RaN, LC, Gi, MRNv, MVN, LRN, IRTA], Diencephalon nuclei [LH, DMH, PVN])	-	B	[165]
(SC16)	BALB/c, C57BL/6, ROSA26R mice	Intranasal, oral, whisker pad	Skin, TG, OB, Nasal septum, NT, OE, RE	Skin, TG, OB, Nasal septum, NT, OE, RE	-	C	[166]

Table 2. Continued.

Pathogen (variant/strain)	Experimental model	Route of inoculation	Examined region	Affected lesions/Cells	Olfactory assessment	OD evidence level	Reference
(McKrae)	C57BL/6, gBT-I.1 mice	Intracorneal	Nasal cavity, Cornea, TG, OB, Other brain region (Brainstem)	Nasal cavity, Cornea, TG, OB, Other brain region (Brainstem)	-	B	[167]
HSV-2 (186)	BALB/c mice	Intranasal	OE, VNO, OB, Brain section	OE (OSN), VNO (Chemosensory neuron), OB, Other brain region (Olfactory cortex, Anterior olfactory nucleus, Cerebral cortex, Medial amygdala)	-	B	[168]
(333)	BALB/c mice	Intranasal	Nasal cavity, Olfactory nerve, VNO, Skin, Iris, TG, Cribriform plate, OB, Other brain region (Brainstem, Cerebellum)	Nasal cavity (RE, Squamous epithelium, OE), Olfactory nerve, VNO, Skin, Iris, TG, Cribriform plate, OB, Other brain region (Brainstem [Pons, Ventrolateral medulla], Cerebellum)	-	C	[169]
mCMV (K181, Smith)	BALB/c mice	Intranasal, Oral	Lung, Heart, Liver, Kidney, Salivary gland, Spleen, Skull, Intestine, Tongue, Nose, Skin, Muscle, Fat, Cervical lymph node, Rib, Omentum, Serum	Lung, Heart, Liver, Kidney, Salivary gland, Spleen, Skull, Intestine, Tongue, Nose (OE), Skin, Muscle, Fat, Cervical lymph node, Serum	-	C	[170]
(Smith)	OF1 mice	Intraplacental	OE, OB, Other brain region (SVZ, RMS)	OB (Dopaminergic neurons, Calbindin interneurons, Granule cell layer, Glomerular layer), Other brain region (SVZ, RMS)	BFT, Go/no-go discrimination task, Odorant detection threshold, Odor discrimination task, Long-term memory test	A	[171]
ZIKV (PRVABC59)	Ifnar−/− mice	Footpad	Taste tissue, OE, OB	OE (OSN), OB (OSN)	-	C	[128]
(FG15)	AG129 mice	Intranasal	Plasma, OE, OB, Other brain region (Cortex, Brainstem, Cerebellum)	Plasma, OE, OB (Granule cell layer, external plexiform layer), Other brain region (Cortex, Brainstem, Cerebellum)	BFT	A	[86]

Table 2. Continued.

Pathogen (variant/strain)	Experimental model	Route of inoculation	Examined region	Affected lesions/Cells	Olfactory assessment	OD evidence level	Reference
(GZ01)	ICR, AG6, A129 mice	Intracranial, Intranasal	OM, OB, Brain, Serum, Lung, RM	OM (OE [OEC, OSN], OT [OEC, OSN]), OB (OEC, OSN, Outer nerve layer), Brain, Serum, Lung, RM	BFT	A	[22]
(CAM/2010, VEN/2016)	ICR mice	Intracranial	Other brain region (Cortex, Hippocampus, Cerebellum)	Other brain region (Cortex, Hippocampus, Cerebellum)	-	C	[172]
(MR766, Paraiba)	C57BL/6J, Ifnar−/− mice	Intraperitoneal	OB, Other brain region (SVZ, Hippocampus, Cortex, Striatum), Testis	OB, Other brain region (SVZ, Hippocampus [Dentate gyrus], Cortex, Striatum)	-	B	[173]
LCMV (E350, WE2.2, Clone 13)	Lewis rats	Intracranial	OB, Other brain region (Cerebellum), Spleen	OB, Other brain region (Cerebellum [Molecular layer, Granular layer, Purkinje cell layer]), Spleen	Olfaction discrimination test	A	[174]
VSV (Indiana, New Jersey)	C57BL/6J, OT-I, $Stop^{fl/fl}$ TdTomato, Confetti, GREAT	Intranasal	OM, NT	OM (OE [OSN], Basal lamina, Lamina propria), NT	BFT	A	[175]

Abbreviations: AP, area postrema; BC, basal cell; BFT, buried food test; DMH, dorsomedial hypothalamus; DMX, dorsal motor nucleus of the vagus nerve; DT, dorsal turbinate; GI, gastrointestinal tract; Gi, gigantocellular medullary reticular nucleus; hACE2, human angiotensin-converting enzyme 2; HSV, herpes simplex virus; IAV, influenza A virus; IRTA, intermediate reticular nucleus; LC, locus coeruleus; LCMV, lymphocytic choriomeningitis virus; LH, lateral hypothalamus; mCMV, murine cytomegalovirus; MRNv, ventral medullary nucleus; MT, medial turbinate; MVN, medial vestibular nucleus; NoST, nucleus of the solitary tract; N.S., not specified; LRN, lateral reticular nucleus; LT, lateral turbinate; NT, nasal turbinate; OB, olfactory bulb; OE, olfactory epithelium; OEC, olfactory ensheathing cell; OM, olfactory mucosa; OSN, olfactory sensory neuron; OT, olfactory tract; PC, piriform cortex; PBMC, peripheral blood mononuclear cell; PVN, paraventricular nucleus; RaN, raphe nucleus; RBC, red blood cell; RE, respiratory epithelium; RM, respiratory mucosa; RMS, rostral migratory stream; RSV, respiratory syncytial virus; S, nasal septa; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SC, sustentacular cell; SPVC, spinal trigeminal nucleus; SSDT, social scent discrimination test; SVZ, subventricular zone; TG, trigeminal nerve ganglia; Tg, transgenic; TMT, 2,4,5-trimethyl-3-thiazoline; TuS, Tubular Striatum; VNO, vomeronasal organ; VSV, vesicular stomatitis virus; XIIN, hypoglossal nucleus; ZIKV, Zika virus. OD evidence level was classified as follows: A, direct functional evidence based on behavioral assessment; B, structural or pathological alterations in olfactory-related tissues without direct functional assessment; and C, viral presence in olfactory-related tissues without structural or pathological changes.

investigate the pathogenesis of SARS-CoV-2 and its associated outcomes [140,141,142,145] (Fig. 2, Ref. [22,128,132,133,140,141,142,145,150,151,152,153,154, 155,158,159,160,161,162,163,164,165,166,169,170,171, 173]). Wild-type mice exhibit resistance to SARS-CoV-2, largely due to incompatibility between murine ACE2 and the viral spike protein [140]. In contrast, K18-hACE2 Tg mice permit viral entry and subsequently develop rapidly progressive and often lethal infection following intranasal inoculation [143,144,176,177]. Viral antigens have been detected in both the respiratory mucosa and OM as early as 2 days post-infection (dpi) following intranasal exposure [140]. Infection predominantly targets ACE2-expressing sustentacular cells (SCs) within the OE, with anosmia arising primarily from indirect dysfunction of OSNs rather than direct neuronal infection [140,141,142]. Histopathological alterations include focal epithelial necrosis, loss of the ciliary layer, and infiltration of immune cells into the lamina propria [145]. Behavioral assessments, including the social scent discrimination test and the buried food test, demonstrate marked olfactory deficits by 2–3 dpi [140], indicating that early OD is predominantly driven by local epithelial injury and inflammation. Viral antigens have also been identified in nerve bundles beneath the OE and in vascular endothelial cells, supporting potential neuroinvasion via the olfactory nerve [140]. The virus has been proposed to subsequently disseminate to the OB and multiple brain regions, including the cerebral cortex, hippocampus, and brainstem, potentially contributing to CNS pathology such as encephalitis, which may further impair olfactory function in severe cases [143,145,146,147,148,149].

While K18-hACE2 mice provide evidence supporting both peripheral and central mechanisms of OD, studies of SARS-CoV-2–associated olfactory impairment in Golden Syrian hamsters offer complementary insights, particularly regarding peripheral epithelial pathology with comparatively limited CNS involvement. These animals exhibit high viral replication rates and an ACE2 expression profile similar to that of humans [150,151,178,179], resulting in substantial viral RNA burden in the lungs and the development of severe, reproducible respiratory disease [145]. Importantly, consistent involvement of the OE has been observed following intranasal inoculation [150,151,152], enabling detailed characterization of peripheral olfactory pathology associated with SARS-CoV-2 infection [153]. Following intranasal exposure, damage is predominantly localized to SCs, whereas OSNs are largely preserved. Infection induces extensive epithelial destruction and desquamation driven by intense immune cell infiltration, leading to substantial loss of OSN cilia [152]. This acute epithelial injury is evident as early as 2 dpi and peaks around 4 dpi, consistent with mechanisms underlying the transient anosmia frequently reported in patients with COVID-19 [152]. Recent studies have also demonstrated that SARS-CoV-2 can exhibit neuroinvasive potential in this model, including infection of OB neurons [154]. Nevertheless, the onset and severity of OD appear to be primarily associated with peripheral epithelial injury rather than CNS involvement [145,152,154,155]. Partial regeneration of the OE occurs by 14–21 dpi; however, histological recovery varies across epithelial regions, with some areas demonstrating persistent damage [156]. These region-specific differences in epithelial recovery suggest that, in addition to direct cytopathic effects, impaired epithelial repair and reduced olfactory input may contribute to prolonged OD beyond the acute phase [156,157].

Collectively, findings from K18-hACE2 mice and Golden Syrian hamster models indicate that SARS-CoV-2–induced OD is primarily initiated by infection of non-neuronal SCs within the OE [140,142,152], resulting in structural disruption and impaired olfactory signal transduction. Given that SARS-CoV-2 infection may downregulate ACE2 expression and impair its normal catalytic activity [180,181], an ACE2 knockout study examined the potential contribution of ACE2 deletion to olfactory function. ACE2 knockout mice exhibited reduced OSN layer thickness, structural alterations in the OB, and impaired odor discrimination and identification, suggesting that ACE2 loss itself, in the absence of SARS-CoV-2 infection, may contribute to olfactory abnormalities [181]. Collectively, these models advance understanding of the pathogenesis of SARS-CoV-2-associated OD, spanning acute epithelial injury, partial recovery, and ACE2 loss-related alterations, and highlight shared and distinct mechanisms that may inform the development of targeted therapeutic strategies.

4.2 Animal Models of OD Induced by Other Viral Infections

In this section, OD associated with viral infections other than SARS-CoV-2 is discussed, including both respiratory and non-respiratory viruses. While SARS-CoV-2–associated OD has been extensively investigated in animal models due to its prominent clinical manifestation during the COVID-19 pandemic, mechanistic studies of OD induced by other viruses remain comparatively limited. This disparity likely reflects differences in the clinical frequency of OD as well as research priorities that have historically emphasized severe CNS pathology rather than peripheral olfactory deficits. Accordingly, this section also incorporates studies that do not directly evaluate olfactory function but describe virus-induced pathology within peripheral or central olfactory structures, which may nonetheless suggest a potential contribution to OD (Fig. 2).

Studies using influenza virus models have demonstrated that different influenza strains exhibit distinct patterns of involvement within the olfactory system. In a recombinant neurovirulent influenza A R404BP strain, early induction of apoptosis in OSNs through activation of the Fas/FasL and c-Jun N-terminal kinase pathways appeared to limit viral neuroinvasion from the OE to the CNS [158].

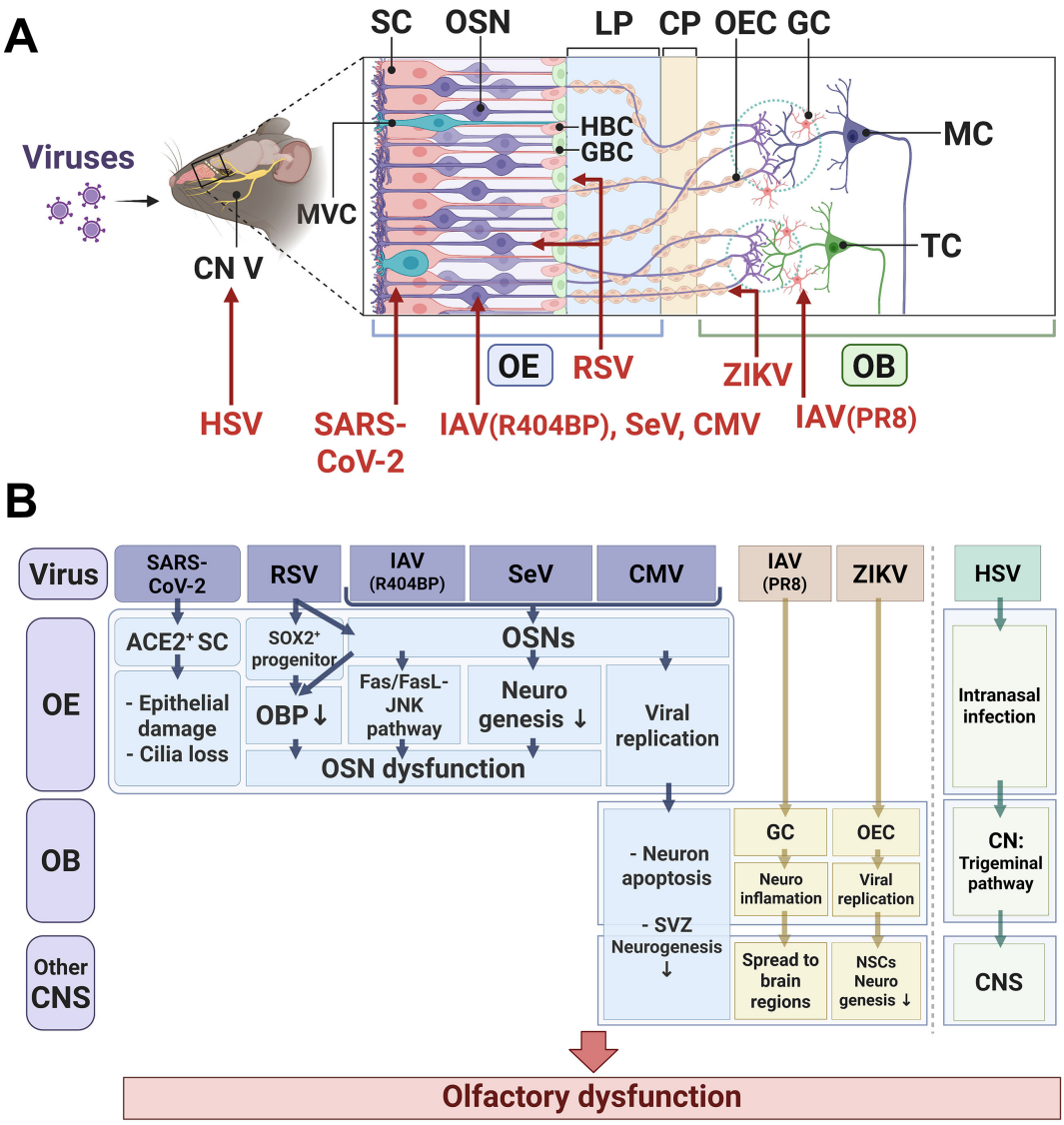


Fig. 2. Schematic representation of virus-specific invasion pathways and mechanisms underlying OD. (A) An illustration depicting virus-specific invasion pathways in the olfactory system. Arrows indicate the major target sites of each virus. (B) An illustration depicting virus-specific mechanisms underlying OD. Arrows indicate the sequential progression of virus-induced pathological mechanisms. This figure was developed based on findings reported in references [22,128,132,133,140,141,142,145,150,151,152,153,154,155,158,159,160,161,162,163,164,165,166,169,170,171,173]. Background colors distinguish the proposed mechanistic routes: SARS-CoV-2, RSV, IAV (R404BP), SeV, and CMV enter through the OE; IAV (PR8) and ZIKV act directly within the OB; and HSV follows a distinct trigeminal route to the CNS. Fig. 2A: Created in BioRender. Veterinary, A. (2026) https://BioRender.com/dzosqph; Fig. 2B: Created in BioRender. Veterinary, A. (2026) https://BioRender.com/olgtfar. CNS, central nervous system; CN V, trigeminal nerve; CP, cribriform plate; GC, glomerular cell; GBC, globose basal cell; HBC, horizontal basal cell; LP, lamina propria; MC, mitral cell; MVC, microvillar cell; NM, nasal mucosa; NSCs, neural stem cells; OB, olfactory bulb; OBP, odorant-binding protein; OEC, olfactory ensheathing cell; OE, olfactory epithelium; OSN, olfactory sensory neuron; RSV, respiratory syncytial virus; SC, sustentacular cell; SeV, Sendai virus; SVZ, subventricular zone; TC, tufted cell.

In mice infected with the influenza A/Puerto Rico/8/34 (H1N1) strain, the virus localized primarily to glial cells within the olfactory nerve layer and glomerular layer of the OB, while inflammatory cytokines were widely detected in the OB, olfactory cortex, somatosensory cortex, and regions of the central autonomic nervous system [159]. These findings suggest that, when present, OD may reflect strain-dependent heterogeneity in the pathophysiological effects of influenza viruses on the olfactory system.

Sendai virus is frequently utilized as a murine model to investigate mechanisms relevant to human PIV3–associated OD, which has been implicated as an etiological factor in seasonally occurring VAOD in humans, despite its closer virological relationship to human PIV1. In mice infected with Sendai virus, OD peaked at 15 dpi and persisted for at least 2 months in approximately one-third of animals. Viral copies were detected in the OM and OB for durations ranging from 60 to 168 dpi, suggesting that Sendai virus may inhibit apoptosis of OSNs [160,161]. Furthermore, in OSNs primarily infected with Sendai virus, calcium signaling responses to odorants were impaired when stimulated with mixed odorants [160]. These findings indicate that Sendai virus–induced OD may arise from impaired neuronal regeneration and functional deficits in OSNs.

Evidence indicates that RSV is implicated in OD. Intranasal infection with RSV in mice reduced the number of SRY-box transcription factor 2–positive OSN progenitors [162]. Bryche et al. [163] reported that RSV infects and replicates within OSNs, correlating with reduced expression of olfactory binding proteins, which are essential for odorant detection, in Steno's gland. These findings suggest that RSV may impair olfactory function by disrupting peripheral olfactory structures and associated secretory glands involved in odorant processing.

Numerous animal studies of HSV have primarily focused on pathways of viral entry into the CNS, whereas involvement in OD has received comparatively limited attention. Clinical and pathological observations in HSV–infected patients suggest that both olfactory and trigeminal pathways may contribute to viral neuroinvasion [132,133]. However, experimental evidence increasingly supports a predominant role for trigeminal fibers in CNS entry. In adult mice infected with HSV, involvement of the olfactory pathway within the OB was infrequent; when present, it was primarily observed in severely infected juvenile mice and followed a delayed and less consistent pattern relative to trigeminal spread [164,166,169]. Niemeyer et al. [165] reported that intranasal HSV type 1 infection produced lesions in the OE and in brain regions associated with trigeminal pathways, including the locus coeruleus, raphe nucleus, and hypothalamus, while involvement of the OB remained limited. These findings suggest that HSV–associated OD, particularly when accompanied by central pathology, is more likely related to trigeminal rather than olfactory pathway involvement.

Murine CMV (mCMV), used as a model for human CMV, infects OSNs through binding to heparan sulfate predominantly localized on the apical surface of the OE, similar to human CMV [170]. Following nasal and oral inoculation, mCMV preferentially infects via the nasal route, particularly targeting OSNs, rather than via the oral route [170]. cCMV exhibits selective tropism for neural stem cells within the olfactory system during early neurodevelopment [84]. However, the functional consequences of this tropism for olfactory function remain incompletely understood. Lazarini et al. [171] demonstrated that olfactory perception and discrimination of binary odorant mixtures were impaired at postnatal day 6 following in utero mCMV inoculation. No changes were observed in OSN density or innervation of the OB. However, neuronal apoptosis associated with increased autophagy in the OB, together with reduced neurogenesis in the subventricular zone, may contribute to neuronal loss in the OB and subsequent OD [171]. These findings suggest that OD may serve as a sensitive indicator of neuronal alterations following cCMV infection.

Adult wild-type mice are resistant to ZIKV infection; therefore, interferon (IFN) receptor–deficient models, including A129 and ifnar−/− mice (IFN-α/β receptor knockout) and AG6 mice (IFN-α/β and IFN-γ receptor knockout), have been widely employed in ZIKV research [128]. Ozdener et al. [128] demonstrated that ZIKV exhibits preferential tropism for olfactory tissue over gustatory tissue, with evidence of infection and replication in the OM and OB, while no infection was observed in taste papilla cells in ifnar−/− mice. Intranasal Zika virus infection resulted in viral lesions primarily affecting olfactory ensheathing cells in the OB, with minimal involvement of OSNs, SCs, and horizontal basal cells within the OE of AG6 immunodeficient mice [22]. ZIKV depletes neural stem cells in the CNS by promoting viral replication through regulation of macroautophagy and Fanconi anemia protein pathways, effectively infecting brain regions such as the hippocampus and OB [173]. In neonatal ICR mice infected intracerebrally with ZIKV, viral copies and host immune responses were observed in both the OE and OB. These mice exhibited transient OD in the buried food test upon reaching puberty [22]. These findings indicate that viral pathogenesis, influenced by tropism for olfactory structures, may contribute to clinical manifestations of OD.

Although OD associated with some viruses has not been clearly documented in humans, several animal models have utilized these pathogens to investigate mechanisms relevant to VAOD. Lymphocytic choriomeningitis virus is associated with aseptic meningitis, encephalitis, and meningoencephalitis in humans; however, a definitive association with OD has not been established [182]. Plume et al. [174] demonstrated significant reduction in OB volume and inflammation following infection with the lymphocytic choriomeningitis virus E350 strain, accompanied by impaired olfactory discrimination as assessed by nest-seeking behavior. Vesicular stomatitis virus, which rarely infects humans and typically causes mild influenza-like illness, has been used as a model of olfactotropic viral infection [183]. Vesicular stomatitis virus induces early loss of OSNs and inflammatory responses within the OM, followed by persistent immune cell infiltration and metaplastic transformation of the OM into respiratory mucosa after viral clearance, resulting in functional hyposmia [175]. Collectively, these findings suggest that, although not directly linked to hu-

man VAOD, virus-induced structural alterations of olfactory tissues and sustained immune activation observed in animal models may provide important insights into mechanisms underlying VAOD.

4.3 Perspectives and Limitations of Animal Model Studies

Animal models represent indispensable tools for elucidating virus-induced OD, particularly for mechanistic aspects that are challenging to assess directly in humans. They enable detailed investigation of underlying pathophysiological processes, including viral tropism, host immune responses, and alterations in olfactory function, under controlled experimental conditions, thereby facilitating exploration of potential therapeutic strategies (Fig. 2). However, these findings should be interpreted with caution when extrapolated to human disease. First, interspecies differences in anatomy and physiology result in divergent host responses to the same virus. In the extreme case of HIV, such differences, including human-specific entry receptors, intracellular host factors, and immune microenvironments, preclude productive infection in non-human species, highlighting fundamental limitations of animal models [184]. Additionally, Tg mouse models expressing hACE2 have been widely used in SARS-CoV-2 research; however, their rapid disease progression and high lethality do not reflect the typical clinical course observed in humans [185]. The regenerative capacity of the OE may also differ substantially between species; rodents exhibit robust and continuous neurogenesis within the OE, whereas the extent and persistence of olfactory regeneration in humans remain incompletely defined [186,187,188], thereby complicating the translation of outcome findings into clinical application. As a second limitation, most animal models rely on a single intranasal inoculation using high viral titers and focus predominantly on the acute phase of infection, emphasizing early OE injury and inflammatory responses. In contrast, VAOD in humans is more likely to arise from heterogeneous exposure conditions, including variable viral doses, and may persist beyond the acute phase [189,190,191]. Consequently, these experimental conditions may amplify acute pathological features, including viral tropism, lesion distribution, and disease severity, while offering limited insight into long-term outcomes. Finally, olfactory function in animal models is frequently assessed using a single behavioral paradigm, most commonly the buried food test based on food-finding latency [22,86,154,160,175], although some studies have used alternative approaches, including go/no-go discrimination and odorant detection threshold testing [181], to provide complementary measures of olfactory performance. However, this measure can be influenced by factors unrelated to olfaction, including motivation, environmental stress, and locomotor activity [192,193], potentially providing an incomplete representation of qualitative dimensions of olfactory function.

To address these limitations, future studies would benefit from the adoption of complementary modeling strategies that integrate animal models with human-relevant experimental systems, including human OE cultures and organoid platforms, to enhance translational relevance across species. In addition, the implementation of more physiologically relevant infection paradigms, such as low-dose or repeated exposures, together with longitudinal analyses extending into the chronic phase, may better reflect the clinical trajectory of human VAOD. Furthermore, reducing reliance on a single behavioral paradigm and incorporating multiple olfactory assessment approaches may improve evaluation of diverse qualitative aspects of olfactory function. Collectively, these strategies are expected to strengthen the interpretability and translational value of animal model findings in the study of VAOD.

5. Integrating Epidemiological and Animal Model Evidence

This section integrates epidemiological findings in humans with mechanistic evidence from animal models to examine the extent to which experimentally identified mechanisms correspond to the clinical features of VAOD. Among the viruses reviewed, SARS-CoV-2 provides the most extensive basis for such comparison because of the relatively large body of both clinical and experimental evidence. Mechanistic studies using K18-hACE2 mice and golden Syrian hamsters, two commonly used models of SARS-CoV-2 infection, have identified several findings that may help explain corresponding clinical manifestations. In mice, SARS-CoV-2 preferentially targets ACE2-expressing SCs, with olfactory deficits developing rapidly after infection [140]. Similarly, hamsters exhibit extensive epithelial destruction and desquamation associated with immune-cell infiltration within days of infection [152]. These acute peripheral alterations may contribute to the rapid onset of OD observed in patients with COVID-19 [44,46,47]. During recovery, epithelial regeneration may remain incomplete and regionally variable [156], providing a potential structural basis for persistent OD in some patients [44,46,47]. The prevalence of OD also varies among SARS-CoV-2 variants [26,27]. The Omicron variant exhibits altered tissue tropism, with relatively greater involvement of the respiratory epithelium than of the OE, which may contribute to the lower prevalence of OD observed with this variant [104,105,106]. However, direct mechanistic evidence explaining other epidemiological features of SARS-CoV-2-associated OD, including variation across populations, differences according to disease severity, and demographic associations, remains limited, although several host- and virus-related factors have been proposed to account for these patterns.

Epidemiological evidence for the other respiratory and non-respiratory viruses reviewed here is less extensive. For other respiratory viruses, experimental studies

Table 3. Mechanistic links between clinical phenotypes and experimental findings in VAOD.

Pathogen	Major human phenotype	Human evidence	Key animal findings	Proposed mechanistic link	Human-animal concordance
SARS-CoV-2	Acute OD, occasional persistence	Strong	OE injury (SC infection)	Peripheral epithelial dysfunction, impaired OE repair	High
Influenza	Acute OD	Low	OSN/glial injury	Strain-dependent peripheral or central olfactory injury	Partial
PIV3	Acute OD	Low	-	-	-
Sendai virus	-	-	OSN injury	Impaired peripheral olfactory signaling and OE regeneration	-
RSV	Limited	Limited	OSN progenitor injury, reduced odorant-binding protein expression (Steno's gland)	Impaired OE regeneration, glandular dysfunction affecting odorant detection	Uncertain
HIV	Hyposmia with peripheral and central olfactory deficits	Moderate	-	-	-
HSV	Persistent anosmia in HSE survivors	Moderate in HSE survivors	OE lesions with limited OB involvement	Peripheral epithelial injury and route-dependent central involvement	Partial
CMV	Developmental OD	Low	OSN infection, OB neuronal loss, reduced SVZ neurogenesis	Developmental disruption of central olfactory circuits	Partial
ZIKV	Limited	Limited	OB lesions with limited OE involvement	Central olfactory injury	Uncertain

Abbreviations: CMV, cytomegalovirus; HIV, human immunodeficiency virus; HSE, herpes simplex encephalitis; HSV, herpes simplex virus; OB, olfactory bulb; OD, olfactory dysfunction; OE, olfactory epithelium; OSN, olfactory sensory neuron; PIV3, parainfluenza virus type 3; RSV, respiratory syncytial virus; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SC, sustentacular cell; SVZ, subventricular zone; VAOD, virus-associated olfactory dysfunction; ZIKV, Zika virus; -, insufficient evidence for assessment. Evidence strength in "Human evidence" column was qualitatively categorized as strong, moderate, low, or limited based on the amount, consistency, and directness of the available evidence. Human–animal concordance was qualitatively categorized as high, partial, or uncertain based on the consistency between clinical phenotypes observed in humans and corresponding functional or pathological findings in animal models. These categorizations represent qualitative assessments rather than formal grading systems.

have identified several virus- and strain-specific mechanisms [158,159,160,161] that broadly parallel the peripheral and central alterations reported in patients with VAOD [53,61]. In particular, influenza models illustrate strain-dependent variations in the anatomical extent of olfactory-system involvement. In R404BP infection, apoptosis of infected OSNs appears to restrict viral spread from the OE into the CNS [158], whereas PR8 infection involves glial cells in the OB and elicits inflammatory responses in the OB and other olfactory and central regions [159]. Although direct clinical correspondence remains uncertain, these findings suggest that the extent of viral spread may contribute to differences in the clinical course and manifestations of OD. For non-respiratory viruses, several animal studies have directly assessed olfactory function and investigated mechanisms underlying CMV- and ZIKV-associated OD [22,86,171], whereas the available human clinical evidence is more extensive for HIV and HSV [69,70,75,76,82,83]. Because human and experimental studies have often focused on different viruses, definitive human–animal concordance cannot yet be established for many of these pathogens. Nevertheless, HSV may provide an opportunity to relate experimental evidence of neuroinvasion to clinical olfactory outcomes. Animal studies have implicated both olfactory and trigeminal routes of viral entry into the CNS, although their relative contributions remain unresolved [132,133,164,165,166,169]. The persistent OD reported in survivors of HSE [83] suggests the possibility of central involvement. Collectively, these findings broaden the mechanistic framework of VAOD by providing insights beyond those derived primarily from respiratory viral infections, particularly with respect to central mechanisms of OD. Table 3 summarizes the human and animal evidence, proposed mechanistic links, and degree of concordance across the viral pathogens reviewed.

6. Conclusion and Future Directions

This review synthesizes epidemiological and animal model studies of OD associated with major viral pathogens, including SARS-CoV-2, influenza A virus, PIV3, RSV, HIV, HSV, cCMV, and ZIKV. Epidemiological evidence consistently demonstrates substantial heterogeneity in OD patterns according to viral etiology and host-related factors, while animal model studies provide mechanistic insights implicating viral tropism, host inflammatory responses, and the regenerative capacity of the OE. Integration of epidemiological observations with mechanistic data derived from animal models enables a more comprehensive characterization of disease heterogeneity. However, variability in study design, differences in olfactory assessment methodologies, and species-specific biological responses continue to limit direct translation of animal findings to human OD. Accordingly, future research should prioritize longitudinal human studies incorporating standardized olfactory assessments alongside mechanistic investigations and standardized olfactory testing in animal models. We propose the testable hypothesis that persistent and distinct clinical phenotypes of VAOD reflect different combinations of impaired epithelial regeneration and peripheral and central olfactory alterations. This hypothesis could be evaluated by relating longitudinal quantitative and qualitative olfactory phenotypes to peripheral and central biomarkers. Such studies may clarify why recovery differs among patients, identify biomarkers predictive of recovery, and support the development of targeted therapeutic approaches.

Author Contributions

CM conceived the review topic. HJ, SL, BJ, CJ, and JSK performed the literature search and synthesized the literature. HJ, SL, and CM drafted and revised the manuscript. CM supervised the study. All authors contributed to editorial changes in the manuscript. All authors read and approved the final manuscript. All authors have participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Ethics Approval and Consent to Participate

Not applicable.

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Conflicts of Interest

The authors declare no conflicts of interest. Given his role as the Editorial Board member and the Guest Editor, Changjong Moon had no involvement in the peer review of this article and has no access to information regarding its peer review. Full responsibility for the editorial process for this article was delegated to Bettina Platt.

Declaration of AI and AI-Assisted Technologies in the Writing Process

AI-based tools were used solely for language and grammar checking during manuscript preparation. No AI tool was used to generate, analyze, or interpret data, or to create or select references; all scientific contents were written and verified by the authors.

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