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RESEARCH PAPER

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COVID-19-related chemosensory changes: Findings from a prospective national database

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Abstract

Objective: The aim of this study was to review findings from a large prospective national database of chemosensory disturbances associated with coronavirus disease 2019 (COVID-19) infection.

Data Sources: The Virginia Commonwealth University Smell and Taste Center national database of COVID-19 chemosensory disturbances.

Methods: A series of online surveys, first opened on April 10, 2020, was made accessible nationwide to any adult with sudden chemosensory dysfunction since January 2020. Participants received subsequent follow-up surveys 14 days, 1 month, 3 months, and 6 months after enrollment. An additional survey was sent to all participants on May 28, 2022 to assess long-term outcomes. Information pertaining to demographics, symptoms, comorbidities, treatments, and life impact was collected.

Results: Of 363 participants who reported complete smell recovery, 51.2% recovered within 1 month, 70% within 3 months, and 79% within 6 months, while 8.8% took over 1 year to completely recover. Among all participants, 7.5% had no smell recovery. Positive predictors of recovery included age <40, male gender, and the presence of nasal congestion. Negative predictors included difficulty breathing and prior head injury. Many participants reported a decrease in quality of life and the presence of potential safety hazards associated with decreased smell loss.

Conclusions: Most subjects with COVID-19-related chemosensory dysfunction recover, with the majority noting complete recovery within weeks of infection. Those aged over 40 years and female gender were associated with lower rates of recovery. A considerable number of participants reported significant impact on quality of life and safety.

KEYWORDS
anosmia, COVID-19, smell

Key points

- This study aims to summarize the findings of Virginia Commonwealth University Medical Center for Smell and Taste into a single report.
- Most with coronavirus disease 2019 (COVID-19)-related smell loss recover quickly.

- Positive predictors of recovery: age <40, male sex and presence of nasal congestion.
- Negative predictors of recovery: Difficulty breathing and prior head injury.
- Persistent COVID-19-related smell loss leads to decreased quality of life and patient safety concerns.

INTRODUCTION

Chemosensory disturbance has long been recognized as a cardinal symptom of coronavirus disease 2019 (COVID-19) infection. Since the first reports of COVID-19-associated smell and taste changes in early 2020,[1,2] the number of publications regarding this highly prevalent phenomenon has soared. By March 2020 the Centers for Disease Control and World Health Organization had officially declared these symptoms as disease-defining symptoms.[3] In the first months of the pandemic, before readily accessible and reliable tests for active COVID-19 infection,[4] clinicians had to rely primarily on a constellation of symptoms as indicators of disease. Although chemosensory dysfunction was recognized as a hallmark of disease, very little was known about epidemiology, presentation, risk factors, prognosis, consequences, or treatment. To assess these aspects of the disease, the Smell and Taste Center at Virginia Commonwealth University Medical Center created a web-based survey for those with chemosensory changes to report their experiences. Now, over 3 years later, it remains one of the largest prospective longitudinal cohort studies of COVID-19 chemosensory dysfunction, consisting of over 1200 subjects, each queried at multiple timepoints resulting in nearly one million data points.

What follows is a summary of the novel findings that resulted from these accumulated data, with particular attention to rates of recovery, predictors of recovery, quality of life, and safety concerns in this unique study population.

MATERIAL AND METHODS

An online survey was opened to individuals over the age of 18 with sudden changes in smell or taste since January 2020. Recruitment began on April 10, 2020 through social media platforms. Participants completed an enrollment survey and received subsequent follow-up surveys 14 days, 1 month, 3 months, and 6 months after date of enrollment. An additional survey was sent to all participants on May 28, 2022 to further examine the long-term effects of their COVID-19 infection. Participants were asked to rate their sense of smell as "very good," "good," "poor," "very poor," or "absent" at different time points (including before January 1, 2020—considered the pre-COVID-19 baseline). Within the surveys, there were questions regarding demographics (age, race, sex, smoking history, body mass index, and blood type), symptoms during COVID-19 (dyspnea, cough, fever, weakness/fatigue, myalgias, diarrhea, nasal congestion, runny nose, and headaches), pre-existing medical comorbidities (including diabetes, cardiovascular disease, seasonal allergies, chronic sinusitis, nasal polyposis, chronic respiratory diseases, neurologic disorders, or history of head trauma), outpatient COVID-19-directed medication treatments, quality of life, and adverse safety events. Data were collected and managed using the REDCap electronic data capture tool.[5] The study was approved by the Virginia Commonwealth University Institutional Review Board (HM20019186).

RESULTS AND DISCUSSION

Rate of recovery

By June 23, 2022, 945 participants had been enrolled for ≥3 months, 809 for ≥1 year, and 267 for ≥2 years. Table 1 displays the recovery rates as stratified by time since diagnosis. Of the 363 participants who demonstrated complete subjective smell recovery, 51.2% recovered within 1 month, 70% within 3 months, and 8.8% took over 1 year to completely recover (Figure 1).

Other studies have corroborated these findings, indicating that a significant proportion of individuals experiencing COVID-19-related smell loss regain their olfactory function relatively rapidly.[6–10] A study of polymerase chain reaction-tested participants from France demonstrated that 98% experienced complete subjective smell recovery within 28 days, with a mean duration of anosmia of approximately 9 days.[7] Similarly, a Korean study using daily phone surveys of almost 500 newly diagnosed COVID-19 patients showed a median duration of anosmia or ageusia of 7 days, and almost all recovering within 3 weeks.[11] In a survey study conducted in the United Kingdom, 80% reported partial recovery at 1 week, while 17% remained anosmic. Importantly, a recovery "plateau" was noted after

TABLE 1 Recovery status by duration of loss.

Group	Time since COVID+	Percentage (count)		
		Complete recovery	Partial recovery	No recovery at all
A (*n* = 945)	≥3 months	38.7% (366)	51.0% (482)	10.3% (97)
B (*n* = 809)	≥1 year	38.9% (315)	51.4% (416)	9.6% (78)
C (*n* = 267)	≥2 years	38.2% (102)	54.3% (145)	7.5% (20)

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Abbreviation: COVID-19, coronavirus disease 2019.

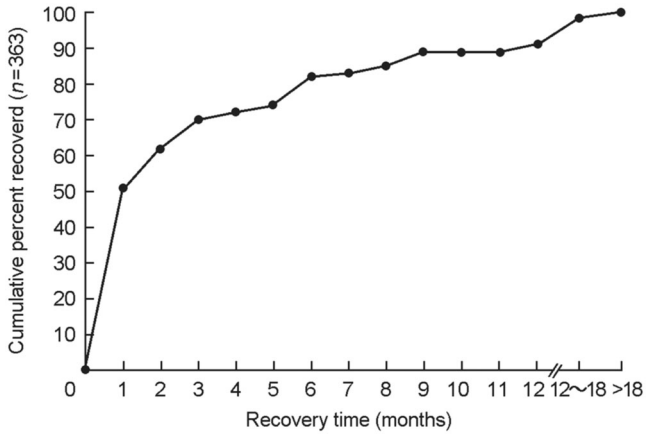

FIGURE 1 Time to recovery to baseline smell function for 363 subjects who reported complete recovery. Reprinted from McWilliams MP, Coelho DH, Reiter ER, Costanzo RM. Recovery from Covid-19 smell loss: 2-years follow-up, 43, 103239. Copyright 2023, with permission from Elsevier.

TABLE 2 Analysis of failure to recover by age and gender.

Groups	Percentage (count) Complete recovery	Partial or no recovery	*p* Value
Age group (*n* = 920)			
<40 years old (*n* = 410)	45.6% (187)	54.4% (223)	0.001
>40 years old (*n* = 510)	32.9% (168)	67.1% (342)	
Sex group (*n* = 930)			
Female (*n* = 752)	36.7% (276)	63.3% (476)	0.021
Male (*n* = 178)	46.1% (82)	53.9% (96)	

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approximately 3 weeks, with only a 70% recovery rate for those with anosmia for ≥3 weeks.[12] Likewise, in a prospective observational study in Brazil, 77 of 143 (68.3%) patients reported complete subjective recovery after a median of 76 days from the beginning of COVID-19 symptoms.[13] Furthermore, other studies with a follow-up period ranging from 1 year to 18 months demonstrated a range of complete subjective recovery rates, ranging from 54% to 86.9%.[14–18] The lower rate of complete recovery (38.2%) observed in our study was likely due to its being a self-selected cohort rather than a cross-section of participants with COVID-19-related smell loss recruited at the onset of their illness. Respondents self-selected, potentially creating a selection bias, such that those with longstanding or ongoing losses may have been motivated to participate, while those with brief losses with full recovery may not have chosen to participate. Further, the subjective and self-reported nature of the survey data allows for recall bias. Finally, insufficient data exists to determine if differences in virology or population susceptibility between the studies undertaken in different countries may have impacted reported rates of recovery.

Our data revealed that 8.8% of people who recovered took longer than 1 year after infection, while with few reported recovery occurring beyond 18 months. This suggests that meaningful, albeit subjective, smell recovery may occur well beyond the 1-year mark. A similar length of smell recovery is seen in posttraumatic olfactory dysfunction, with most patients reporting olfactory recovery within 6 months of trauma and, although possible, very few reporting recovery 1 or 2 years postinjury.[19,20] However, in our study, not all participants reported olfactory recovery, with 7.5% reporting no smell recovery at the 2-year mark.[21] Other studies following cohorts up to 12 months post-COVID-19 infection have demonstrated similar results, with between 5% and 8.5% of participants showing no olfactory recovery at their latest timepoint.[14,15,22,23]

Predictors of recovery

We also sought to determine if there were factors that might predict the likelihood of recovery of chemosensory function. Table 2 details the impact of age and sex on recovery rates in those diagnosed with COVID-19 over 3 months since the time of study enrollment (diagnosed January 2020–February 2022). Subjects under the age of 40 reported complete recovery at a higher rate (45.6%) than those over the age of 40 (32.9%; $p = 0.001$). Further analysis showed that those over 40 were more likely to have no recovery compared to those under 40 (14.1% vs. 5.1%; $p = 0.001$). Males were significantly more likely to completely recover than females (46.1% vs. 36.7%, $p = 0.021$), although both sexes were equally likely to demonstrate no improvement at all (9.4% vs. 14.0%, $p = 0.069$).[21] Upon longer follow-up, analysis of the 798 participants who had completed 6-month follow-up surveys demonstrated that age <40 was positively associated with smell recovery (83.2% vs. 74.5%, $p < 0.003$), whereas race, sex, smoking history, body mass index, and blood type were not.[10]

Initially, few other studies investigated factors impacting olfactory recovery. Saussez et al.[8] examined olfactory recovery of 288 participants within 60 days of onset of olfactory dysfunction and found no significant markers of recovery in COVID-19 participants among viral load, symptom severity, age, or sex. Makaronidis et al.[24] however, found that among their 480 subjects, men were more likely to fully recover their sense of smell compared to women (72.8% vs. 51.4%), while age, race, and smoking status had no bearing on recovery. Both studies, however, are limited by short patient follow-up and smaller patient populations. Petrocelli et al.,[23] studying olfactory recovery in 300 participants at 6 months follow-up, found that age <50, but no other demographic or symptomatic variables, was significantly associated with improved chemosensory recovery. They postulated this may be due to the decreased ability of older individuals to withstand the impact of the COVID-19 infection on their sense of smell. This study also demonstrated men reporting

higher rates of complete recovery versus women (46.1% vs. 36.7%, $p = 0.021$). In a pre-COVID-19 meta-analysis performed by Sorokowski et al.,[25] women outperformed men in almost all aspects of olfaction. As such, it may be plausible that women may have heightened awareness of olfaction, along with greater awareness of its dysfunction, and thus be more likely to place themselves in the partial recovery group compared to their male counterparts. While men reported higher rates of complete recovery in our study, we found no significant difference in rates of reporting "no recovery at all" between men and women. This finding was corroborated by Saussez et al.[8]

While younger age appears likely associated with smell recovery, other factors revealed in this study warrant further discussion. In our cohort of 798 participants, analysis of symptomology (Table 3) demonstrated that the presence of nasal congestion was positively associated with smell recovery (with 81.6% vs. without: 74.9%, $p < 0.03$), whereas the presence of difficulty breathing was negatively associated with smell recovery (82.3% vs. 73.3%, $p < 0.004$). The number of symptoms exhibited by each participant did not correlate with recovery status. Of the "pre-existing" self-reported medical comorbidities (Table 4), only a history of head injury (80.2% vs. 61.3%, $p < 0.017$) was negatively associated with smell recovery. Neither the total number of comorbidities nor the number of medications used nor the use of any individual medications taken during active COVID-19 infection queried in our survey (tylenol, nonsteroidal anti-inflammatory drugs, zithromax, remdesivir, hydroxychloroquine, or chloroquine) were correlated with recovery status.[10] Similarly, Fornazieri et al.[26] also found that the number of comorbidities, number of medications, or types of medications did not play a significant role in predicting smell recovery in 73 COVID-19-positive participants.

Although rates of nasal congestion in COVID-19 are relatively low, participants with nasal congestion were more likely to recover than those without.[27] When it occurs, mucosal inflammation may reflect the presence of a "conductive" olfactory insult, and thus would be more likely to recover once acute infection subsides. Moreover, nasal congestion may theoretically decrease nasal and retronasal airflow, decreasing additional viral presentation to the nasal mucosa, thereby protecting the olfactory nerves from "sensorineural" olfactory insult.

Finally, our finding of prior head injury as a negative predictive factor for smell recovery may further support the "second hit" theory, which proposes that neural damage may be exacerbated by a previous injury.[28,29] However to our knowledge, there are no studies that examine prior head injury as a risk factor for COVID-19-related olfactory dysfunction.

TABLE 3 Sense of smell recovery and co-existing COVID-19 symptoms ($n = 798$).

Symptoms		Percentage (count) Overall ($n = 798$)	Recovered ($n = 634$)	Abnormal smell ($n = 164$)	p Value
Number of symptoms	1	6.1% (49)	81.6% (40)	18.4% (9)	0.9689
	2	8.5% (68)	80.9% (55)	19.1% (13)	
	3	13.5% (108)	79.6% (86)	20.4% (22)	
	4	13.3% (106)	78.3% (83)	21.7% (23)	
	5	15.7% (125)	82.4% (103)	17.6% (22)	
	6	17.4% (139)	79.1% (110)	20.9% (29)	
	7	12.7% (101)	77.2% (78)	22.8% (23)	
	8	9.3% (74)	79.7% (59)	20.3% (15)	
	9	3.5% (28)	71.4% (20)	28.6% (8)	
Difficulty breathing	No	68.0% (543)	82.3% (447)	17.7% (96)	0.0039
	Yes	32.0% (255)	73.3% (187)	26.7% (68)	
Cough	No	41.0% (327)	78.3% (257)	21.4% (70)	0.6188
	Yes	59.0% (471)	80.0% (377)	20.0% (94)	
Fever	No	54.0% (431)	78.7% (339)	21.3% (92)	0.5469
	Yes	46.0% (367)	80.4% (295)	19.6% (72)	
Weakness or fatigue	No	21.7% (173)	83.2% (144)	16.8% (29)	0.1559
	Yes	78.3% (625)	78.4% (490)	21.6% (135)	
Muscles aches	No	39.6% (316)	82.6% (261)	17.4% (55)	0.0727
	Yes	60.4% (482)	77.4% (373)	22.6% (109)	
Diarrhea	No	61.5% (491)	79.6% (391)	20.4% (100)	0.8703
	Yes	38.5% (307)	79.2% (243)	20.8% (64)	
Nasal congestion/ stuffy nose	No	32.5% (259)	74.9% (194)	25.1% (65)	0.0295
	Yes	67.5% (539)	81.6% (440)	18.4% (99)	
Runny nose	No	63.2% (504)	79.4% (400)	20.6% (104)	0.9390
	Yes	36.8% (294)	79.6% (234)	20.4% (60)	
Headache	No	24.4% (195)	82.1% (160)	17.9% (35)	0.2953
	Yes	75.6% (603)	78.6% (474)	21.4% (129)	

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Abbreviation: COVID-19, coronavirus disease 2019.

Quality of life and safety

Smell and taste losses resulting from a variety of causes have previously been reported to impact the quality of life and patient safety.[30–35] Included within our 6-month follow-up surveys were questions assessing the quality of life ("Reduced enjoyment of life," "My enjoyment of food was reduced," "My appetite was reduced," "I lost weight," "I missed the enjoyment of fragrances," "I was depressed," "I worried about body odors," or "None of these") and safety concerns ("I was unable to smell smoke that others noticed," "I burned food on the stove or in the oven," "I ingested

TABLE 4 Sense of smell recovery and comorbidities at the 6-month survey ($n = 798$).

Comorbidities		Percentage (count) Overall ($n = 798$)	Recovered ($n = 634$)	Abnormal smell ($n = 164$)	p Value
Number of comorbidities	0	51.3% (409)	79.7% (326)	20.3% (83)	0.9287
	1	33.7% (269)	78.8% (212)	21.2% (57)	
	2	11.5% (92)	81.5% (75)	18.5% (17)	
	3	2.8% (22)	72.7% (16)	27.3% (6)	
	4	0.6% (5)	80.0% (4)	20.0% (1)	
	5	0.1% (1)	100.0% (1)	0 (0)	
Diabetes	No	97.5% (778)	79.2% (616)	20.8% (162)	0.1999
	Yes	2.5% (20)	90.0% (18)	10.0% (2)	
Cardiovascular disease	No	89.1% (711)	80.5% (572)	19.5% (139)	0.0537
	Yes	10.9% (87)	71.3% (62)	28.7% (25)	
Seasonal allergies	No	63.7% (508)	78.0% (396)	22.0% (112)	0.1631
	Yes	36.3% (290)	82.1% (238)	17.9% (52)	
Chronic sinus infection	No	96.0% (766)	79.2% (607)	20.8% (159)	0.4675
	Yes	4.0% (32)	84.4% (27)	15.6% (5)	
Nasal polyps	No	99.4% (793)	79.3% (629)	20.7% (164)	0.1286
	Yes	0.6% (5)	100.0% (5)	0 (0)	
Chronic respiratory disease	No	90.4% (721)	79.6% (574)	20.4% (147)	0.7293
	Yes	9.6% (77)	77.9% (60)	22.1% (17)	
Neurological disease	No	99.7% (796)	79.4% (632)	20.6% (164)	0.3371
	Yes	0.3% (2)	100.0% (2)	0 (0)	
Previous head injury	No	96.1% (767)	80.2% (615)	19.8% (152)	0.0181
	Yes	3.9% (31)	61.3% (19)	38.7% (12)	

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Abbreviation: COVID-19, coronavirus disease 2019.

spoiled foods," "I was exposed to a gas leak and did not know it," "I did not recognize the smell of soiled diapers," or "None of these") associated with smell loss. Of the respondents, 96% reported at least one defined quality of life deficit (Figure 2) and over 75% reported three or more deficits. Furthermore, 56% reported an overall decreased enjoyment of life, while the most common deficit reported was "reduced enjoyment of food" (87%).[36] Similarly, Elkholi et al.[31] showed that 76% of COVID-19-positive participants reported a decreased quality of life, most commonly "less awareness of personal hygiene" and "less interested in food and drink." In addition to various methodological differences from the current study, Elkholi et al.[31] specifically focused on participants reporting anosmia, excluding those reporting distorted smell perception (parosmia and/or phantosmia), as well as individuals without any nonolfactory symptoms associated with COVID-19 infection. Although prior studies have highlighted notable safety concerns and adverse quality of life effects of olfactory dysfunction, regardless of cause the high prevalence of this dysfunction in those affected by COVID-19 raises concern of a substantial population burden.[30,31,37,38]

In our study, a large proportion of participants reported a decreased enjoyment of life in general (56%), along with other concerns such as depression (43%), loss of appetite (55%), and weight loss (37%).[36] Prior studies have demonstrated lower rates of generalized enjoyment in life (25%),[30] with similar rates of "mood changes" (68%)[39] and decreased appetite (56%).[39] Notably, these other studies observed participants for greater than 1 year and may therefore make comparison difficult. Perhaps, persistent olfactory dysfunction for longer time periods may lead to adoption of compensatory strategies with reduced subjective impact, but this is difficult to quantify and some participants may be unaware of their own compensatory strategies.[33,39] Further, selection bias inherent in our study may have led those most impacted by their deficits to

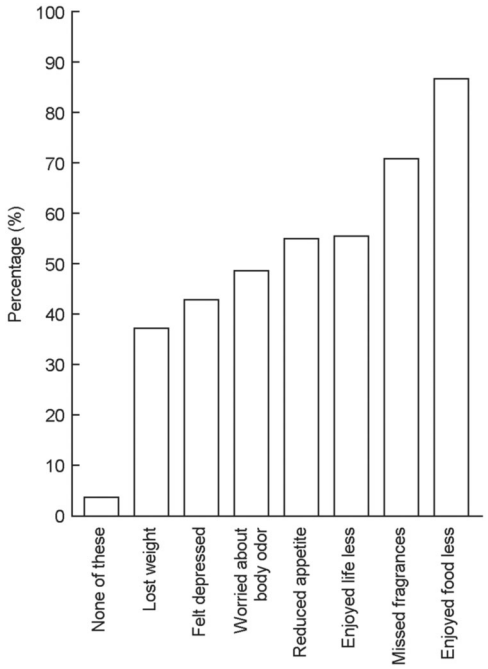

FIGURE 2 Prevalence of quality-of-life issues in coronavirus disease 2019 (COVID-19) positive participants with loss of smell/taste (n = 322). Reprinted from Coelho DH, Reiter ER, Budd SG, Shin Y, Kons ZA, Costanzo RM, Quality of life and safety impact of COVID-19-associated smell and taste disturbances, 42, 103001, Copyright 2023, with permission from Elsevier.

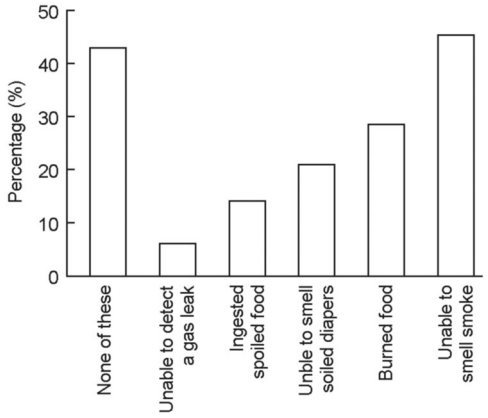

FIGURE 3 Prevalence of safety issues in coronavirus disease 2019 (COVID-19)-positive participants with loss of smell/taste (n = 319). Reprinted from Quality of life and safety impact of COVID-19-associated smell and taste disturbances, 42, Coelho DH, Reiter ER, Budd SG, Shin Y, Kons ZA, Costanzo RM, Quality of life and safety impact of COVID-19-associated smell and taste disturbances, 103001, Copyright 2023, with permission from Elsevier.

enroll, leading to higher reported rates of quality of life concerns. Speth et al.[32] used validated surveys for depression and anxiety to assess changes associated with COVID-19, finding a significant association between depression with age and chemosensory loss as well as anxiety with age and chemosensory loss. They also hypothesized that the coronavirus may have a direct effect on the central nervous system causing emotional disturbances, thereby increasing the risk for depression and anxiety in COVID-19-affected individuals. While Elkholi et al.[31] documented a lower prevalence of depression (15.8%), their study employed open-ended questions regarding the "main effect" on well-being rather than targeted questions assessing depression. Olfactory loss may promote depression through an inability to enjoy odors and fragrances and may promote anxiety through concerns including an inability to smell one's own body odor, smell if a diaper needs to be changed, or the ability to smell smoke. Likewise, the impact of social isolation seen from "quarantine" as a means to reduce COVID-19 transmission likely promoted depression and anxiety as well. The relationship between COVID-19 and both anxiety and depression is similarly supported in other studies as well.[33,39,40] Ultimately, none of these studies nor the current study assessed for psychiatric conditions existing before COVID-19 infection, nor does there exist a control population of COVID-19 participants without chemosensory change to allow for comparison, making interpretation of these outcomes unclear.

Over 57% of subjects reported at least one, and 36% two or more safety-related issues associated with COVID-19 smell loss (Figure 3). Of the queried safety concerns, the most commonly reported was "I was unable to smell smoke that others noticed."[36] The presence of potential safety hazards, such as the inability to detect smoke, gas leaks, or spoiled foods, has been studied in non-COVID-19 populations. Generally, the incidence of these "safety hazards" increases with worsening olfactory deficits.[34,35,41] Pence et al.[41] demonstrated a 40% risk of potential safety hazards in their study—lower than the 57% identified in our COVID-19 cohort. This is surprising as Pence et al.'s patients had longer time period of loss over which a higher incidence of adverse safety events would be expected to occur.[41] Whether this is truly due to higher level of olfactory deficits in our COVID-19 population, inherent peripheral central processing differences unique to COVID-19, different study methodology, or other factors remains unclear. Further, they reported a significantly lower inability to smell smoke (7%) versus the 45% seen in this study, which may have affected the risk of potential safety hazards.[41] Lastly, our study's participants were predominantly young (mean age of 42 years) female subjects (80%), a substantially different demographic profile than those studied by Pence et al.[41] with potentially different exposures to and thus risk of specific safety hazards.[34]

CONCLUSION

These are the findings of a large, national, prospective database of subjective chemosensory change following COVID-19 infection. Most participants who report olfactory loss from COVID-19 infection tend to recover quickly. In some, recovery can occur beyond 12 months, while a small proportion report persistent smell loss even 2 years after their initial COVID-19 infection and thus likely permanently. Factors that seem associated with the likelihood of recovery include younger age, presence of nasal congestion, and no

prior history of head trauma. Both during and after active infection, many participants reported significant impacts on quality of life and personal safety. These findings have largely been corroborated by subsequent studies. Nonetheless, the information gleaned from a prospective, large database in clarifying chemosensory loss early in the pandemic has been invaluable.

AUTHOR CONTRIBUTIONS

Mihai A. Bentan: Design; analysis; interpretation; drafting; final approval. **Evan R. Reiter**: Design; analysis; interpretation; drafting; final approval. **Richard M. Costanzo**: Design; analysis; interpretation; drafting; final approval. **Daniel H. Coelho**: Conception; design; analysis; interpretation; drafting; final approval.

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CONFLICT OF INTEREST STATEMENT

The authors declare no conflict of interest.

DATA AVAILABILITY STATEMENT

Because this manuscript is a composition of previous works, no data is available. To request data, please contact the authors of the referenced articles.

ETHICS STATEMENT

The study was approved by the Virginia Commonwealth University Institutional Review Board (HM20019186).

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