



HAL
open science

A follow-up on quantitative and qualitative olfactory dysfunction and other symptoms in patients recovering from COVID-19 smell loss

Kathrin Ohla, M.G. Veldhuizen, Tomer Green, M.E. Hannum, A.J. Bakke, S.T. Moein, Arnaud Tognetti, E.M. Postma, Robert Pellegrino, D.L.D. Hwang, et al.

► To cite this version:

Kathrin Ohla, M.G. Veldhuizen, Tomer Green, M.E. Hannum, A.J. Bakke, et al.. A follow-up on quantitative and qualitative olfactory dysfunction and other symptoms in patients recovering from COVID-19 smell loss. *Rhinology*, 2022, 60 (3), pp.207-2017. <10.4193/rhin21.415>. <halshs-03923537>

HAL Id: halshs-03923537

<https://shs.hal.science/halshs-03923537v1>

Submitted on 4 Jan 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.



HAL Authorization

A follow-up on quantitative and qualitative olfactory dysfunction and other symptoms in patients recovering from COVID-19 smell loss*

Kathrin Ohla^{1,2,3,†}, Maria G. Veldhuizen^{4,†}, Tomer Green⁵, Mackenzie E. Hannum⁶, Alyssa J. Bakke³, Shima T. Moein⁷, Arnaud Tognetti⁸, Elbrich M. Postma⁹, Robert Pellegrino⁶, Daniel Liang-Dar Hwang¹⁰, Javier Albayay¹¹, Sachiko Koyama¹², Alissa A. Nolden¹³, Thierry Thomas-Danguin¹⁴, Carla Mucignat-Caretta¹⁵, Nick S. Menger¹⁶, Ilja Croijmans¹⁷, Lina Öztürk⁴, Hüseyin Yanık⁴, Denis Pierron¹⁸, Veronica Pereda-Loth¹⁹, Alexia Nunez-Parra²⁰, Aldair M. Martinez Pineda¹⁹, David Gillespie²¹, Michael C. Farruggia²², Cinzia Cecchetto¹⁵, Marco A. Fornazieri²³, Carl Philpott²⁴, Vera Voznessenskaya²⁵, Keiland W. Cooper²⁶, Paloma Rohlfs Dominguez²⁷, Orietta Calcinoni²⁸, Jasper de Groot²⁹, Sanne Boesveldt⁹, Surabhi Bhutani³⁰, Elisabeth M. Weir³, Cara Exten³, Paule V. Joseph³¹, Valentina Parma⁶, John E. Hayes^{3#}, Masha Y. Niv^{5#}

Rhinology, Vol 60, 6: 207 - 217, 2022

<https://doi.org/10.4193/Rhin21.415>

***Received for publication:**

November 12, 2021

Accepted: March 6, 2022

† co-first authors

co-corresponding authors

other authors listed by relative contributions

¹ Helmut-Schmidt-University/University of the Armed Forces Hamburg, Germany

² Firmenich SA, Satigny, Switzerland

³ The Pennsylvania State University, USA

⁴ Mersin University, Turkey

⁵ The Hebrew University of Jerusalem, Israel

⁶ Monell Chemical Senses Center, Philadelphia, USA

⁷ Institute for Research in Fundamental Sciences (IPM), Iran

⁸ Karolinska Institutet, Stockholm, Sweden

⁹ Wageningen University & Research, the Netherlands

¹⁰ The University of Queensland, Australia

¹¹ University of Trento, Italy

¹² Indiana University, USA

¹³ University of Massachusetts, Amherst, USA

¹⁴ INRAE, CSGA, France

¹⁵ University of Padova, Italy

¹⁶ University of Tübingen, Germany

¹⁷ Utrecht University, the Netherlands

¹⁸ CNRS, France

¹⁹ Université Toulouse III, France

²⁰ University of Chile, Chile

²¹ University College London, UK

²² Yale University, USA

²³ Universidade Estadual de Londrina, Brazil

²⁴ University of East Anglia, UK

²⁵ Severtsov Institute of Ecology & Evolution, Moscow, Russia

²⁶ University of California, Irvine, USA

²⁷ Universidad del País Vasco/Euskal Herriko Unibertsitatea, Spain

²⁸ private practice - VMPCT, Italy

²⁹ Radboud University, the Netherlands

³⁰ San Diego State University, USA

³¹ National Institutes of Health/ NINR/NIAAA, USA

Abstract

Background: Sudden smell loss is a specific early symptom of COVID-19, which, prior to the emergence of Omicron, had estimated prevalence of ~40% to 75%. Chemosensory impairments affect physical and mental health, and dietary behavior. Thus, it is critical to understand the rate and time course of smell recovery. The aim of this cohort study was to characterize smell function and recovery up to 11 months post COVID-19 infection.

Methods: This longitudinal survey of individuals suffering COVID-19-related smell loss assessed disease symptoms and gustatory and olfactory function. Participants (n=12,313) who completed an initial survey (S1) about respiratory symptoms, chemosensory function and COVID-19 diagnosis between April and September 2020, were invited to complete a follow-up survey (S2). Between September 2020 and February 2021, 27.5% participants responded (n=3,386), with 1,468 being diagnosed with COVID-19 and suffering co-occurring smell and taste loss at the beginning of their illness.

Results: At follow-up (median time since COVID-19 onset ~200 days), ~60% of women and ~48% of men reported less than 80% of their pre-illness smell ability. Taste typically recovered faster than smell, and taste loss rarely persisted if smell recovered. Prevalence of parosmia and phantosmia was ~10% of participants in S1 and increased substantially in S2: ~47% for parosmia and ~25% for phantosmia. Persistent smell impairment was associated with more symptoms overall, suggesting it may be a key marker of long-COVID illness. The ability to smell during COVID-19 was rated slightly lower by those who did not eventually recover their pre-illness ability to smell at S2.

Conclusions: While smell ability improves for many individuals who lost it during acute COVID-19, the prevalence of parosmia and phantosmia increases substantially over time. Olfactory dysfunction is associated with broader persistent symptoms of COVID-19, and may last for many months following acute COVID-19. Taste loss in the absence of smell loss is rare. Persistent qualitative smell symptoms are emerging as common long-term sequelae; more research into treatment options is strongly warranted given that even conservative estimates suggest millions of individuals may experience parosmia following COVID-19. Healthcare providers worldwide need to be prepared to treat post COVID-19 secondary effects on physical and mental health.

Trial registration: This project was pre-registered at OSF 1.

Key words: parosmia, phantosmia, olfaction disorders, long COVID, post-COVID, public health, smell

Introduction

In March 2020, the World Health Organization (WHO) declared that Coronavirus Disease 19 (COVID-19), caused by SARS-CoV-2 infection, had reached pandemic levels⁽¹⁾. Although the symptoms of COVID-19 are highly variable across infected individuals⁽²⁾, sudden loss of taste and smell was quickly identified as a hallmark symptom⁽³⁻⁵⁾. Self-reported smell loss was shown to be useful for both diagnosis⁽⁶⁻⁸⁾ and population surveillance⁽⁹⁾, at least for SARS-CoV-2 variants common in 2020.

Classically, patient complaints of smell loss with the common cold arise from a blocked or stuffy nose that prevents volatile odorants from reaching olfactory receptors near the top of the nasal cavity, while gustation is not affected⁽¹⁰⁾. However, with COVID-19, sudden smell loss was commonly observed without nasal blockage⁽¹¹⁻¹³⁾, and prototypical tastes were also impaired^(6,7) as supported by direct assessment with odor-free tastants (e.g., sugar)⁽¹⁴⁾.

Most individuals (>75-80%) reporting taste and smell impair-

ments due to COVID-19 tend to recover these senses within a few months, but smell impairment is still reported by 25-40% of patients after one or two months^(6,15) and by 15%-28% patients at 6 months^(15,16). Given the widespread confusion between taste, smell and flavor⁽¹⁷⁾, data on taste recovery are less clear, although taste qualities may recover more rapidly than smell⁽¹⁶⁾. Some individuals recover from acute smell loss, only to subsequently report other olfactory dysfunction, such as parosmia (smell distortions) and phantosmia (phantom smells or olfactory hallucinations)^(18,19).

Factors associated with persistent smell and taste dysfunction following acute COVID-19 illness remain unknown. Some early reports suggested COVID-19 smell loss might be associated with a milder disease course^(20,21), although smell and taste impairments were also seen in severely ill patients^(22,23). Pre-COVID, firm data on the incidence of parosmia were generally lacking, but some estimates place it near 4% in the general public and ~12-24% of ENT patients⁽²⁴⁾. Data from a clinical sample presenting for specialist assessment suggest parosmia may occur ~4 to 8

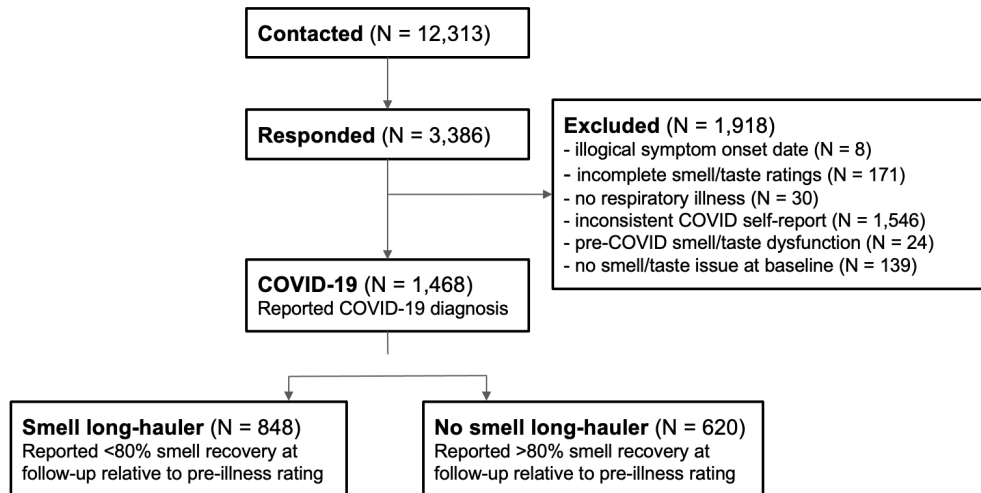


Figure 1. Summary of participants described in the current study. As shown in the exclusion box, the majority of S2 respondents were excluded from present analyses due to inconsistent reports of their COVID-19 diagnosis between S1 and S2. Participants were also excluded for missing or inconsistent data, chemosensory dysfunction prior to COVID-19.

weeks after the onset of anosmia or hyposmia, often following an upper respiratory infection⁽²⁵⁾. Accordingly, we reasoned a follow-up survey may capture additional dysfunctions not seen on our initial survey^(4,6).

The aim of this preregistered study was to characterize smell impairment and recovery in connection with taste loss and other symptoms, by recontacting respondents of our initial survey^(4,6) to collect longitudinal data in a large cohort of participants diagnosed with COVID-19.

Material and Methods

Study design

This longitudinal, observational online cohort study entails a follow-up survey (S2) of respondents between 2 and 10 months after completion of the initial core survey (S1) by the Global Consortium for Chemosensory Research (GCCR)^(4,6,26). Participants self-selected to participate in S1. They were invited via email to participate in S2 if they previously agreed to be re-contacted, provided an email address, completed S1 in English, Spanish, Italian, Dutch, French, and reported a change in smell, taste and/or flavor (via symptom checkbox) in S1. The protocol complies with the revised Declaration of Helsinki and was approved as an exempt study by the Office of Research Protections at The Pennsylvania State University in the U.S.A. (STUDY00014904). The full questionnaire is provided in the Supplementary Materials.

Participants

Participants (n=12,313) who completed the initial GCCR survey (S1) between April and September 2020 and agreed to be recontacted via email were invited to complete a follow-up survey

(S2). Email invitations were sent in five languages (French: n=4,306, English: n=3,422, Dutch: n=1,840, Spanish: n=1,575, Italian: n=1,165) between September and November 2020 to those who consented to be re-contacted. Data were exported in February 2021. We received 3,386 responses (2,448 women, 927 men, 1 non-binary; age range 20 to 85 years) for S2, corresponding to a response rate of ~28%. Of these, 1,918 participants were excluded from further analysis (Figure 1 for details). Thus, the final dataset reported here consisted of 1,468 individuals who reported smell or taste loss at baseline (S1) and consistent positive COVID-19 diagnoses at S1 and S2. The demographics, and overall symptoms of these individuals are reported in Table 1.

To be included in the present analysis, participants had to report a consistent COVID-19 diagnosis on both S1 and S2: i.e., positive COVID-19 diagnosis via clinical presentation (i.e., via symptoms and history), or via viral swab, or another laboratory test. Duplicate entries were removed, and exclusion criteria are summarized in Figure 1. At the request of a reviewer, we reran all analyses after removing all individuals (n=422) who were diagnosed by a clinician via symptoms (i.e., diagnosed via clinical presentation without a confirmatory test); the major findings did not change, thus we present the results for the larger cohort here. Readers interested in results for the lab-test only group (n=1046) are referred to the Supplemental Materials.

There was no predetermination of the sample size. A pilot inquiry in English (n=100) was used to estimate feasible response rate among S1 completers⁽⁴⁾, and invitations were sent out in the 5 languages with the greatest number of responses.

Table 1. Descriptive data of all participants and the smell long-hauler (LH) and no smell long-hauler (nLH) groups.

Categorical variables	All		LH		nLH		statistics				
	%	n	%	n	%	n	Chi2	p	OR	CI low	CI high
Prior conditions											
High blood pressure	8.24	121	7.67	65	9.03	56	0.71	0.398	0.84	-0.14	0.05
Heart disease	0.41	6	0.59	5	0.16	1	0.73	0.392	3.67	-0.13	0.64
Diabetes	2.04	30	1.89	16	2.26	14	0.10	0.757	0.83	-0.24	0.15
Obesity	8.99	132	9.79	83	7.90	49	1.33	0.248	1.26	-0.03	0.15
Lung disease (asthma / copd)	5.11	75	5.31	45	4.84	30	0.08	0.778	1.10	-0.10	0.14
Head trauma	0.14	2	0.24	2	0.00	0	0.24	0.621	Inf	0.15	0.70
Neurological disease	0.68	10	0.94	8	0.32	2	1.23	0.268	2.94	-0.08	0.52
Cancer (chemo-therapy)	0.14	2	0.12	1	0.16	1	0.00	1.000	0.73	-0.85	0.69
Cancer (no chemo-therapy)	0.14	2	0.24	2	0.00	0	0.24	0.621	Inf	0.15	0.70
Chronic sinus problems	4.02	59	3.42	29	4.84	30	1.52	0.218	0.70	-0.23	0.05
Seasonal allergies/hay fever	16.42	241	16.27	138	16.61	103	0.01	0.919	0.98	-0.08	0.06
No conditions	60.15	883	59.79	507	60.65	376	0.08	0.781	0.96	-0.06	0.04
Gender							18.87	7.98E-05			
Women	75.68	1111	60.85	676	39.15	435					
Men	24.25	356	48.03	171	51.97	185					
Non-binary	0.07	1	100.00	1	0.00	0					
Language							30.30	4.26E-06			
Dutch	9.13	134	64.93	87	35.07	47					
English	37.74	554	62.27	345	37.73	209					
French	33.65	494	47.98	237	52.02	257					
Italian	6.81	100	66.00	66	34.00	34					
Spanish	12.67	186	60.75	113	39.25	73					
	mean	SD	mean	SD	mean	SD	t-test	p		CI lo	CI hi
Age in years	43.89	12.17	44.37	12.16	43.23	12.18	-1.76	0.078		-2.40	0.13

Variables, data sources, and measurement

Details of the baseline variables have been described previously⁽⁴⁾. The follow-up survey collected ratings of smell and taste function on horizontal 101-point visual analog scales, and self-reporting of parosmia and phantosmia. Other COVID-19 symptoms were collected via checklist and free text comments. Exact presentation and wording of questions are available in the Supplemental Materials.

Bias minimization

The survey was conducted in multiple languages to increase generalizability. Also, because participants self-selected to respond, analysis and conclusions were restricted to individuals

with COVID-19 who had chemosensory loss at disease onset. Given the potential bias that may arise from differential response rates (i.e., a possibility that those who had recovered fully might be less likely to participate in S2), we attempted to mitigate this by being highly conservative in the estimation calculations presented in our final conclusions.

Quantitative and binary variables

Here, S2 respondents were grouped according to whether their smell loss persisted or recovered. Participants who returned to less than 80% of their pre-COVID smell ability (as reported in S1) were categorized as smell long-haulers; the rest were classified as non-long-haulers. The cutoff of 80% was specified in the pre-

Table 2. Cumulative percentage of participants who recovered their pre-illness ability to smell or taste by months from the onset of disease.

Time in months	2	3	4	5	6	7	8	9	10	11
Smell										
Women	0.18	1.26	2.43	4.05	6.66	12.69	27.27	29.43	35.37	39.15
Men	0.28	1.68	3.93	6.17	9.26	14.88	35.95	37.92	45.22	51.96
Taste										
Women	0.27	1.89	3.87	5.94	10.08	18.72	39.33	43.20	51.93	56.07
Men	0.56	2.24	4.77	7.30	11.23	18.53	45.78	48.31	58.70	64.88

registration (see <https://osf.io/3e6zc>). It was chosen to account for normal variation of chemosensory ability. This choice reflects the common range between 10th percentile⁽²⁷⁾ to 30th percentile⁽²⁸⁾ for separating normosmics from those with quantitative dysfunction. We also report the prevalence of parosmia and phantosmia for the total sample.

Smell (taste) impairment for the two surveys were calculated for each participant using the following equations:

$$S1: \frac{\text{taste or smell ability during illness}}{\text{taste or smell ability pre COVID19}} \times 100$$

$$S2: \frac{\text{current ability to taste or smell}}{\text{taste or smell ability pre COVID19}} \times 100$$

To further assess the type of olfactory dysfunction experienced, we relied on self report using a check-all-that-apply question with four distinct prompts. Positive endorsement of 'I cannot smell at all / Smells smell less strong' was considered to be indicative of anosmia or hyposmia, positive endorsement of 'Smells smell different than they did before (the quality of smell has changed)' was taken as being indicative of parosmia, and positive endorsement of 'I can smell things that aren't there (e.g. I smell burning when nothing is on fire)' was considered indicative of phantosmia. See Supplement Materials for complete wording and formatting.

Statistical analysis

Demographics

To report demographics across the whole sample and to assess potential confounding variables, we calculated proportions of the presence of each of the following comorbidities: high blood pressure, heart disease, diabetes, obesity, lung disease (asthma/COPD), head trauma, neurological disease, cancer (treated with chemotherapy), cancer (no chemotherapy), chronic sinus problems, seasonal allergies/hay fever, and no condition. We also calculated the probability in each of the smell long-hauler groups. We tested distributional differences with Pearson's chi-square tests with the R base function "prop.test". We used

an alpha of 0.0042 to determine significance (i.e., a Bonferroni corrected alpha of 0.05 for 12 conditions). We repeated this for language and gender distributions. For age we calculated the average and performed an independent sample t-test with an alpha of 0.05.

Differences in probability of smell distortions and other COVID-19 symptoms between participants with persistent versus recovered smell loss

To test differences in smell distortions at the time of S2 between smell long-haulers and non long-haulers, we calculated probability tables of presence and absence of parosmia and phantosmia in each of the smell long-hauler groups. We tested distributional differences with Pearson's chi-square tests with the R base function "prop.test". We used an alpha of 0.025 to determine significance (i.e., a Bonferroni corrected alpha of 0.05 for two types of distortion). We repeated this analysis for the symptoms at the time of S1 to check for any pre-existing differences prior to developing persistent smell long-hauler status.

Differences in symptom counts

To assess effects of smell long-hauler-status on illness severity, we summed the presence of each of commonly listed COVID-19 symptoms (fever, dry cough, cough with mucus, difficulty breathing / shortness of breath, chest tightness, runny nose, sore throat, loss of appetite, headache, muscle aches, fatigue, diarrhea, abdominal pain, nausea, excluding smell and taste symptoms under "changes in food flavor" and "changes in smell"), leading to scores ranging from 0-14. Since this "count" variable was not continuous or categorical (i.e., the total number of symptoms), we used logistic regression with a Poisson distribution for the dependent variable. This was implemented via the "glm" function in R, using the "poisson" option. The assumption of equality between variance and mean of each category of the independent variable was checked⁽²⁹⁾ and a "quasi-Poisson" family variant was applied if overdispersion was observed. To estimate relative risk, a Poisson regression with a robust error variance was calculated with the package Sandwich⁽³⁰⁻³²⁾.

To further characterize rare symptoms not provided in the COVID-19 symptoms checklist, additional symptoms, such as

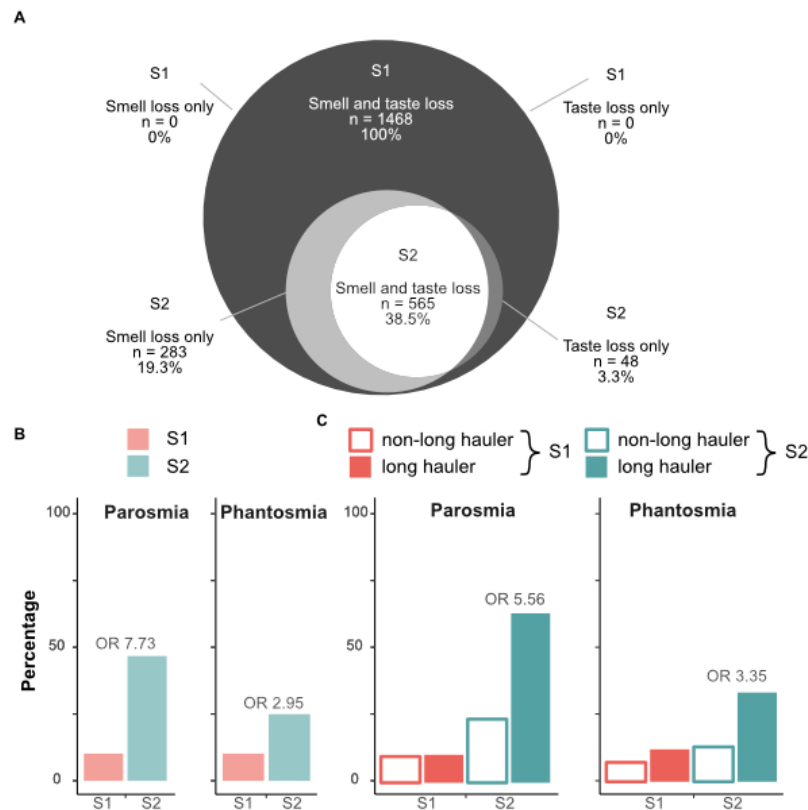


Figure 2. A: Proportions of participants with smell, taste, and combined smell and taste impairments during baseline (S1, dark gray) and follow-up (S2, lighter grays and white). B: Proportions of qualitative smell changes at S1 (pink) and S2 (green), across all participants. C: Same analysis as B but stratified by individuals who later regained smell ability (white fill) or exhibited smell long-hauling (solid fill).

“brain fog”, “memory loss”, were extracted from free text comments. Comments in Spanish, Italian, Dutch, and French were translated into English by scientists who were native speakers of each language, and pooled. In total, 559 comments containing symptoms were analyzed [214 French (74 men, 140 women), 195 English (54 men, 141 women), 65 Spanish (22 men, 43 women), 54 Dutch (14 men, 40 women), and 31 Italian (13 men, 18 women)].

To test for differences in overall symptoms between smell long-haulers and non long-haulers at S2, we calculated probabilities for each of the 16 symptoms (headache, fatigue, difficulty breathing/shortness of breath, diarrhea, nausea, fever, abdominal pain, changes in food flavour, changes in smell, chest tightness, cough with mucus, dry cough, loss of appetite, muscle aches, runny nose, sore throat) in each group. As above, we tested for distribution differences, with a Bonferroni corrected alpha of 0.003125 (0.05/16 tests, one for each symptom). We repeated this analysis for S1 symptoms to check for preexisting differences prior to developing smell long-hauler status.

Smell ability during COVID-19 infection (measured at S1) was compared between smell long-haulers and non long-haulers (defined from S2) using a Welch’s test.

Results

Descriptive data for all 1,468 participants are summarized in Table 1. The mean age was ~44 years, fewer men than women took part, and more responses were collected in English and French, as expected from the relative distribution of email invitations sent. The time elapsed between S1 and S2 ranged from 23 to 291 days (median: 200 days), corresponding to 36 to 326 days (median: 225 days) since disease onset (Supplementary Figure S1). This timing enabled the calculation of cumulative rate of recovery (Table 2).

During the first months after onset of COVID-19 symptoms, less than 10% of participants reported full smell recovery, gradually increasing to 39% in women and 52% in men by up to 11 months (Table 2). Comparatively, the reports for taste recovery were greater (~56 to ~65% by 11 months). 58% of those in the final S2 dataset were classified as smell long-haulers (see methods), with ~39% also reporting persistent taste impairment and ~20% reporting recovered taste (Figure 2A). Only ~3% reported impaired taste with recovered smell. This suggests smell and taste recover separately, and these different sensory modalities can be distinguished by the respondents.

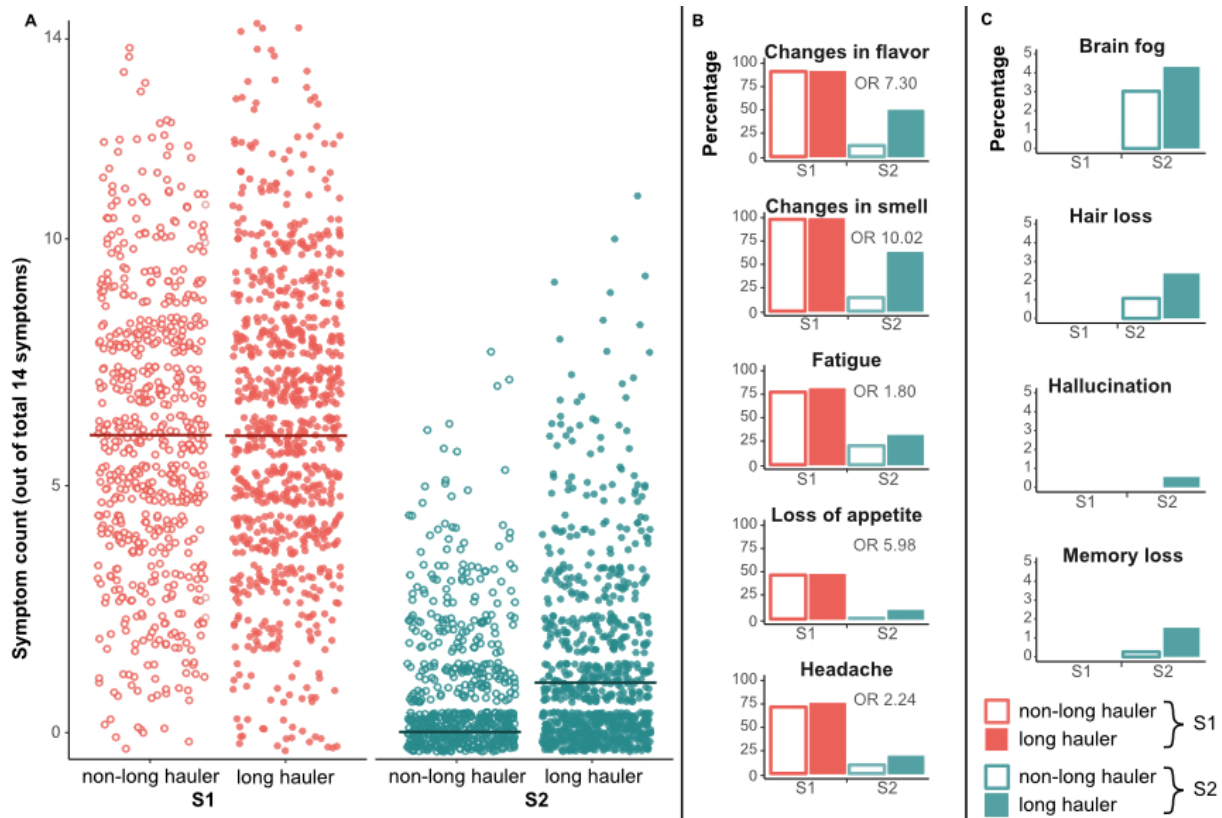


Figure 3. A: Comparison of overall number of non-chemosensory symptoms at baseline (S1, pink) and follow-up (S2, green), stratified by smell long-hauler (LH) status at S2 with white fill indicating non-long haulers and solid fill indicating long-haulers. B: Comparison of selected symptoms at S1 and S2 stratified by smell long-haulers status at S2. C: Percentage of rare symptoms spontaneously mentioned in free text responses in English, Spanish, Dutch, Italian, and French.

Qualitative disorders of smell, specifically parosmia and phantosmia, were more frequently observed at S2 (46.8% and 24.7%, respectively) than S1 (10.2% and 10.1%, respectively; Figure 2B). Parosmia was significantly more common at S2 than S1 ($\chi^2 = 480.12$, 95% CI = 0.41-0.48, $p < 0.001$, OR = 7.73). Phantosmia also was significantly more common at S2 than S1 ($\chi^2 = 110.2$, 95% CI = 0.21-0.30, $p < 0.001$, OR = 2.95). Further, such dysfunction was significantly more common in smell long-haulers compared to non-long-haulers, as 63.6% of smell long-haulers reported parosmia versus 23.9% of non-long-haulers ($\chi^2 = 225.0$, 95% CI = 0.34-0.44, $p < 0.001$, OR = 5.56) and 33.5% of smell long-haulers reported phantosmia versus 13.1% of non-long-haulers ($\chi^2 = 78.9$, 95% CI = 0.21-0.32, $p < 0.001$, OR = 3.35). Among smell long-haulers, the incidence of parosmia was not significantly different between women and men (64% versus 58%). Qualitative terms from open-ended text responses were also captured. Typical participant reports for parosmia were “Some things now smell different and unpleasant” or “like chemicals”; reports for phantosmia include responses like “Sometimes I can smell burning but no one else around me can.”

The total number of symptoms decreased at S2 (Figure 3). However, smell long-haulers reported more overall symptoms

(median = 1) at S2 compared to non-long-haulers (median = 0). This was confirmed via quasi-Poisson regression ($\beta_1 = 0.48$, 95% CI = 0.32-0.64, $T = 5.66$, $p < 0.0001$). Notably, these groups were not different at S1 (both medians = 6).

When we examined each of the symptoms, including smell and taste symptoms, we observed changes in flavor ($\chi^2 = 224.9$, 95% CI = 0.37-0.46, $p < 0.001$, OR = 7.30) and in smell ($\chi^2 = 340.17$, 95% CI = 0.44-0.53, $p < 0.001$, OR = 10.02) as expected, in addition to other symptoms like fatigue ($\chi^2 = 22.09$, 95% CI = 0.08-0.20, $p < 0.001$, OR = 1.80), headache ($\chi^2 = 23.99$, 95% CI = 0.11-0.25, $p < 0.001$, OR = 2.24), and loss of appetite ($\chi^2 = 33.58$, 95% CI = 0.25-0.40, $p < 0.001$, OR = 5.98), all of which were more frequent in smell long-haulers than in non-long-haulers (Figure 3B). This suggests smell long-haulers had greater overall morbidity. Analysis of spontaneous mentions of rare symptoms in free text responses also supports the notion that smell long-haulers experience more symptoms: spontaneous comments included brain fog, hair loss, hallucination, and memory loss. Formal statistics were not applied due to low incidence of these reports (Figure 3C).

To identify variables with potential prognostic value in predicting who would eventually become a smell long-hauler, we

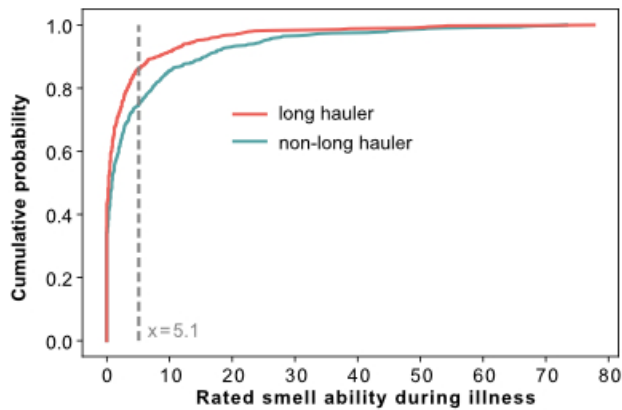


Figure 4. Distribution of ratings for smell ability at baseline (S1), stratified by whether a participant was classified as a smell long-hauler (pink) or non long-hauler (green) at follow-up (S2). In the original survey (i.e., baseline), the majority of both groups (i.e., more than 50%) reported complete smell loss (a score of zero on a VAS, shown on the x-axis); however, a greater proportion of those who would later become long haulers reported almost complete loss at S1, and fewer of the non long haulers reported near total loss at S1. The dashed vertical line indicates the smell ability rating (on a VAS from 0-100) where the two groups differ maximally.

looked for differences in multiple S1 measures across the smell long-hauler and non-long-hauler groups from S2. None of these were significant, save one: the self-rated ability to smell during COVID-19 illness was slightly lower (Welch's t-test, statistic = -4.33, $p < 0.0001$) in smell long-haulers ($n=848$) than in non-long-haulers ($n=620$), with means of $2.96 (\pm 7.64, 95\% \text{ CI} = 2.45-3.48)$ and $5.11 (\pm 10.49, 95\% \text{ CI} = 4.28-5.94)$, respectively. This was confirmed when the distributions of smell ability at S1 were compared by status at S2 (Kolmogorov-Smirnov test statistic = 0.12; $p < 0.0001$). As shown in Figure 4, a greater number of smell long-haulers rated their smell ability during illness below 5 (on a 101-point scale), relative to non-long-haulers, although the prognostic value of this small difference still needs to be confirmed.

Given other work on long-COVID^(15,33), we performed an exploratory analysis (see supplement) to compare fully recovered individuals ($N=153$) with those still experiencing 1 or more long-term symptoms ($N=202$). The number of overall symptoms experienced during acute COVID-19 was predictive of long-term symptoms. Consistent with Sudre et al.⁽³³⁾, the greater the number of symptoms experienced by the participants during the first 2 weeks of the disease, the more likely they were to have long-term symptoms more than 2 months later. This is also in line with more severe outcomes of hospitalized vs non-hospitalized COVID-19 patients⁽³⁴⁾.

Discussion

Our follow-up of 1,462 participants suggests that ~60% of women and ~48% of men recover less than 80% of their pre-illness olfactory ability multiple months (200 days median) since COVID-19 onset. Using a much more conservative cutoff (i.e., recovery to just 50% of pre-illness ability, rather than 80%) results in a lower incidence, but ~30% of participants are still classified as smell long-haulers. Such percentages are similar to those recently reported elsewhere for long-term follow-up of COVID-19 patients⁽³⁵⁾. Here, taste recovered more quickly and rarely persisted if smell recovered. Prevalence of parosmia and phantosmia rose from 10% during the baseline survey to ~47% and ~25% at the follow-up. These olfactory dysfunctions were more common for smell long-haulers than non long-haulers. Persistent smell loss also coincided with more COVID-19 symptoms at follow-up and a higher incidence of follow-up symptoms, such as headache.

Qualitative olfactory disorders are common, comprising up to half of smell impairment complaints, at least prior to COVID-19; critically, these qualitative disorders show distinct patterns of demographics, medical history, and perceptual experiences⁽³⁶⁻³⁸⁾. Parosmia often occurs during recovery from prior viral olfactory loss⁽³⁸⁻⁴¹⁾. Mechanistically, this may arise from a mismatch in rewiring in the olfactory bulb during neurogenesis⁽⁴²⁾, differences across olfactory sensory neurons (OSNs) in time to recover⁽⁴³⁾, or changes in receptor expression⁽⁴⁴⁾. Specific to COVID-19, patients experiencing parosmia tend to be younger and report a lower quality of life than those with simple loss⁽⁴⁵⁾. Phantosmia is also common following viral smell loss; however, its co-occurrence with recovery is less clear^(38,46).

Previously, some speculated smell loss might indicate milder COVID-19 morbidity⁽²¹⁾. Our data fail to support this; instead, we found smell long-haulers had more symptoms than recovered participants. This suggests under-reporting of smell dysfunction among severely ill patients elsewhere may reflect a sampling bias; it seems highly likely (and understandable) that clinicians treating critically ill patients were less focused on anosmia or parosmia as symptoms, and such patients were presumably unavailable for acute chemosensory testing.

There is important practical value in being able to predict which patients may develop long term smell loss. We found a greater reduction in ability to smell during COVID-19 among those who later became smell long-haulers compared to those who recovered smell ability, although this difference was numerically small. Despite the small relative effect size seen here, such a difference may still be prognostically useful, as pre-COVID data suggest residual olfactory function at initial assessment was predictive of future recovery⁽⁴⁷⁾. Tentatively, this suggests early

assessment with a validated smell test during acute COVID-19 may be prognostically useful in predicting recovery, although additional data would be needed to confirm this.

While some studies suggest self-reports may underestimate smell loss prevalence relative to direct assessment^(19,48,49), others found correlations between self-reporting and direct assessments^(50,51). Furthermore, although direct assessments have been proposed very recently⁽⁵²⁾, self-report remains the current standard of care for assessment of parosmia and phantosmia⁽⁵³⁾, at least until newly proposed methods can be further validated. The presence of parosmia in nearly half of the smell long-haulers in our sample is not surprising for post-viral olfactory dysfunction⁽⁵⁴⁾, and in other recent datasets (i.e., healthcare workers in the UK⁽⁵⁵⁾ and Sweden⁽⁵⁶⁾, and social media scraping^(18,57), parosmia is also emerging as a common sequela of COVID-19.

Limitations of this web-based study include recruitment of participants for S1 via social media (with additional coverage in traditional media), which may explain why participants under 60 years of age and women are overrepresented in our sample. The ~28% response rate for S2 may reflect that many S1 participants had spontaneously recovered olfactory and/or gustatory function and were therefore no longer interested in responding. The time lapse between disease onset and follow-up survey varies between participants.

Here, we included 422 COVID-19 positive participants based on clinical diagnosis via symptoms and history, because early in the pandemic, PCR or antigen-based testing was often unavailable. Previously, we found very similar chemosensory profiles in individuals with COVID-19 diagnosis based on lab tests such as PCR versus clinical examination⁽⁴⁾. After excluding those diagnosed via clinical assessment and retaining only those diagnosed via testing (see Supplemental Materials), we observed no meaningful changes in the proportions of smell long-haulers and non-smell long-haulers compared to the data from the full sample reported here (n=1,046 versus n=1,468). Age and gender were also similarly distributed in both samples.

Furthermore, launch dates and pandemic situations varied between different countries, and time between surveys S1 and S2 differed by individuals. Last, we should caution that our participants were not formally tested with a validated smell test – rather, they self-reported perceived smell ability using a visual analog scale, which may lack sufficient precision for diagnosis and follow up of individual patients; still, it is notable that the crowdsourced approach used here reveals similar proportions of parosmic and phantosmic individuals as other longterm studies that did use clinical assessment⁽⁵⁶⁾. Collectively, despite these limitations, our findings characterize profiles of smell and

taste loss recovery, with important downstream implications for public health.

As of November 2021, there are over 245 million people worldwide recovering from COVID-19⁽⁵⁸⁾. According to meta-analysis⁽⁴⁸⁾, 77% of those with COVID-19 have acute smell loss when smell function is measured directly or 44% if based on self-reports. If we conservatively assume half of those with COVID-19 experience acute smell loss, this suggests ~18 million Americans may have experienced acute anosmia. If we are highly conservative and assume all of the individuals who did not respond to our follow-up survey recovered, we calculate 50% (smell long haulers) of 30% (response rate), resulting in ~2.7 million Americans and ~15 millions worldwide may be smell long-haulers. Present data suggest ~47% of smell long-haulers report parosmia, which would translate to over a million Americans (and over 7 million worldwide) with parosmia as a result of COVID-19. While olfactory symptoms may be formally classified as mild outcomes by some health authorities, the possibility that millions of individuals may experience long term anosmia and parosmia as a consequence of prior COVID-19 infection is highly concerning, given the downstream impacts this will likely have on dietary habits⁽⁵⁹⁾, quality of life⁽³⁸⁾, and mental health⁽⁶⁰⁾. We also find that smell long-haulers report other post-acute sequelae of COVID-19.

Conclusion

Our study provides insights into the symptoms of many individuals diagnosed with COVID-19, who experienced persistent smell and taste loss, up to 11 months (6-7 months median) since disease onset. Prevalence of parosmia before the pandemic was estimated as 4% in adults. We find that parosmia increases from ~10% at baseline of COVID-19 patients suffering smell loss to almost 50% at follow-up, suggesting parosmia as a common symptom post-COVID-19, consistent with other recent reports^(56,61,62); whether parosmia might associate with less anosmia over the long run⁽⁴⁷⁾ is unknown. Here, we find a small but significant difference in the amount of smell loss in smell long-haulers versus those who do not become long-haulers. Further studies are needed to determine if objective smell tests have prognostic value in predicting persistent smell loss. It is important that health providers, patients, and their families are aware of the potential for quantitative and qualitative smell dysfunction following viral infection, and that they are educated about the course of disease and management⁽⁵⁴⁾. Millions of people worldwide are likely affected and additional research as well as development of new treatment options are needed.

Data availability

The data will be made available in an Open Science Framework (OSF) registry upon publication.

Acknowledgments

We thank all members of the Global Consortium for Chemosensory Research (GCCR) for the core survey and for help with translations. We thank Danielle R. Reed and Thomas Hummel for their valuable contributions in the initial stages of this work.

Authorship contribution

KO and MVG co-first authors; other authors listed by relative contributions; JEH and MYN co-corresponding authors:

Funding

This work was supported by the following grants: NIH T32 (DC000014) and F32 (DC020100) to M.E. Hannum; NSF DGE1839285 to K.W. Cooper; EXTREM-O (CNRS, CNES) to D. Pierron, A.M. Martinez Peneda, and V. Pereda-Loth; NIH NI-

AAA Z01AA000135, NIH Distinguished Scholar program, and Rockefeller University Heilbrunn Nurse Scholar Award to P.V. Joseph; NIH T32 DC000014-40 and F32 (DC020380) to R. Pellegrino; Edmond de Rothschild Foundation grant to M.Y. Niv; 2232 International Fellowship for Outstanding Researchers Program of TÜBİTAK 118C299 to M.G. Veldhuizen; Deployment of both surveys by the Penn State Sensory Evaluation Center was supported by discretionary funds controlled by Prof. Hayes, including an unrestricted gift from James and Helen Zallie in support of Sensory Science.

Conflict of interest

Prof. Hayes is a co-founder of Redolynt LLC. Prof. Philpott is a trustee of the charity Fifth Sense. None of the other authors have any conflicts to disclose.

References

- https://www.who.int/director-general/speeches/detail/who-director-general-opening-remarks-at-the-media-briefing-on-covid-19---11-march-2020
- Koyama S, Ueha R, Kondo K. Loss of Smell and Taste in Patients With Suspected COVID-19: Analyses of Patients' Reports on Social Media. *J Med Internet Res*. 2021;23(4):e26459.
- Moein S T, Hashemian S M, Mansourafshar B, Khorram-Tousi A, Tabarsi P, Doty R L. Smell dysfunction: a biomarker for COVID-19. *Int Forum Allergy Rhinol*. 2020;10(8):944-950.
- Parma V, Ohla K, Veldhuizen MG, et al. More Than Smell-COVID-19 Is Associated With Severe Impairment of Smell, Taste, and Chemesthesis. *Chem Senses*. 2020;45(7):609-622.
- CDC. Coronavirus Disease 2019 (COVID-19) in the U.S. Centers for Disease Control and Prevention. Published July 25, 2020. Accessed July 30, 2020. <https://www.cdc.gov/coronavirus/2019-ncov/cases-updates/cases-in-us.html>
- Gerkin RC, Ohla K, Veldhuizen MG, et al. Recent Smell Loss Is the Best Predictor of COVID-19 Among Individuals With Recent Respiratory Symptoms. *Chem Senses*. 2021;46(bjaa081).
- Karni N, Klein H, Asseo K, et al. Self-rated smell ability enables highly specific predictors of COVID-19 status: a case control study in Israel. *Open Forum Infect Dis*. 2020;Dec 28:ofaa589.
- Menni C, Valdes AM, Freidin MB, et al. Real-time tracking of self-reported symptoms to predict potential COVID-19. *Nat Med*. 2020;26(7):1037-1040.
- Pierron D, Pereda-Loth V, Mantel M, et al. Smell and taste changes are early indicators of the COVID-19 pandemic and political decision effectiveness. *Nat Commun*. 2020;11(1):5152.
- Dalton P. Olfaction and anosmia in rhinosinusitis. *Curr Allergy Asthma Rep*. 2004;4(3):230-236.
- Brann DH, Tsukahara T, Weinreb C, et al. Non-neuronal expression of SARS-CoV-2 entry genes in the olfactory system suggests mechanisms underlying COVID-19-associated anosmia. *Sci Adv*. 2020;6(31):eabc5801.
- Cooper K W, Brann D H, Farruggia M C, et al. COVID-19 and the chemical senses: supporting players take center stage. *Neuron*. 2020;107(2):219-233.
- Hagemann J, Onorato GL, Jutel M, et al. Differentiation of COVID-19 signs and symptoms from allergic rhinitis and common cold: An ARIA-EAACI-GA2 LEN consensus. *Allergy*. 2021;76(8):2354-2366.
- Huart C, Philpott C, Konstantinidis I, et al. Comparison of COVID-19 and common cold chemosensory dysfunction. *Rhinology*. 2020;58(6):623-625.
- Blomberg B, Mohn KGI, Brokstad KA, et al. Long COVID in a prospective cohort of home-isolated patients. *Nat Med*. 2021;27(9):1607-1613.
- Klein H, Asseo K, Karni N, et al. Onset, duration and unresolved symptoms, including smell and taste changes, in mild COVID-19 infection: a cohort study in Israeli patients. *Clin Microbiol Infect*. 2021 Feb 16;27(5):769-774.
- Boltong A, Keast RSJ, Aranda SK. A matter of taste: making the distinction between taste and flavor is essential for improving management of dysgeusia. *Support Care Cancer Off J Multinat Assoc Support Care Cancer*. 2011;19(4):441-442.
- Burges Watson DL, Campbell M, Hopkins C, Smith B, Kelly C, Deary V. Altered smell and taste: Anosmia, parosmia and the impact of long Covid-19. *PLoS One*. 2021;16(9):e0256998.
- Vaira LA, Lechien JR, Khalife M, et al. Psychophysical Evaluation of the Olfactory Function: European Multicenter Study on 774 COVID-19 Patients. *Pathogens*. 2021;10(1):62.
- Iravani B, Arshamian A, Ravia A, et al. Relationship between odor intensity estimates and COVID-19 population prediction in a Swedish sample. *Chem Senses*. 2020;45(6):449-456.
- Yan CH, Faraji F, Prajapati DP, Ostrander BT, DeConde AS. Self-reported olfactory loss associates with outpatient clinical course in COVID-19. *Int Forum Allergy Rhinol*. 2020;10(7):821-831.
- Amadu AM, Vaira LA, Lechien JR, et al. Analysis of the correlations between the severity of lung involvement and olfactory psychophysical scores in coronavirus disease 2019 (COVID-19) patients. *Int Forum Allergy Rhinol*. 2022 Jan;12(1):103-107.
- Cocco A, Amami P, Desai A, Voza A, Ferrel F, Albanese A. Neurological features in SARS-CoV-2-infected patients with smell and taste disorder. *J Neurol*. 2021;268(5):1570-1572.
- Nordin S, Brämerson A, Millqvist E, Bende M. Prevalence of parosmia: the Skövde population-based studies. *Rhinology*. 2007;45(1):50-53.
- Bonfils P, Avan P, Falcon P, Malinvaud D. Distorted Odorant Perception: Analysis of a Series of 56 Patients With Parosmia. *Arch Otolaryngol Neck Surg*. 2005;131(2):107-112.
- COVID-19 BSSR Research Tool. Published online 2020. https://www.nlm.nih.gov/dr2/COVID-19_BSSR_Research_Tools.pdf
- Hummel T, Kobal G, Gudziol H, Mackay-Sim A. Normative data for the "Sniffin' Sticks" including tests of odor identification, odor discrimination, and olfactory thresholds: an upgrade based on a group of more than 3,000 subjects. *Eur Arch Otorhinolaryngol*. 2007 Mar;264(3):237-43.
- Hoffman HJ, Rawal S, Li CM, Duffy VB. New chemosensory component in the U.S. National Health and Nutrition Examination

- Survey (NHANES): first-year results for measured olfactory dysfunction. *Rev Endocr Metab Disord.* 2016;17(2):221-240.
29. Dean C, Lawless JF. Tests for Detecting Overdispersion in Poisson Regression Models. *J Am Stat Assoc.* 1989;84(406):467-472.
 30. Zeileis A. Object-oriented Computation of Sandwich Estimators. *J Stat Softw.* 2006;16(1):1-16.
 31. Zeileis A, Köll S, Graham N. Various Versatile Variances: An Object-Oriented Implementation of Clustered Covariances in R. *J Stat Softw.* 2020;95(1):1-36.
 32. Zou G. A modified poisson regression approach to prospective studies with binary data. *Am J Epidemiol.* 2004;159(7):702-706.
 33. Sudre CH, Murray B, Varsavsky T, et al. Attributes and predictors of long COVID. *Nat Med.* 2021;27(4):626-631.
 34. Lund LC, Hallas J, Nielsen H, et al. Post-acute effects of SARS-CoV-2 infection in individuals not requiring hospital admission: a Danish population-based cohort study. *Lancet Infect Dis.* 2021 Oct;21(10):1373-1382.
 35. Boscolo-Rizzo P, Hummel T, Hopkins C, et al. High prevalence of long-term olfactory, gustatory, and chemesthesis dysfunction in post-COVID-19 patients: a matched case-control study with one-year follow-up using a comprehensive psychophysical evaluation. *Rhinology.* 2021;59(6):517-527.
 36. Hong SC, Holbrook EH, Leopold DA, Hummel T. Distorted olfactory perception: a systematic review. *Acta Otolaryngol (Stockh).* 2012;132 Suppl 1:S27-31.
 37. Leopold D. Distortion of Olfactory Perception: Diagnosis and Treatment. *Chem Senses.* 2002;27:611-615.
 38. Pellegrino R, Mainland JD, Kelly CE, Parker JK, Hummel T. Prevalence and Correlates of Parosmia and Phantosmia among Smell Disorders. *Chem Senses.* 2021 Jan 1;46:bjab046.
 39. Liu DT, Sabha M, Damm M, et al. Parosmia is Associated with Relevant Olfactory Recovery After Olfactory Training. *Laryngoscope.* 2021;131(3):618-623.
 40. Nordin S, Murphy C, Davidson TM, Quiñonez C, Jalowayski AA, Ellison DW. Prevalence and assessment of qualitative olfactory dysfunction in different age groups. *Laryngoscope.* 1996;106(6):739-744.
 41. Reden J, Maroldt H, Fritz A, Zahnert T, Hummel T. A study on the prognostic significance of qualitative olfactory dysfunction. *Eur Arch Otorhinolaryngol.* 2007 Feb;264(2):139-44.
 42. Holbrook EH, Leopold DA, Schwob JE. Abnormalities of axon growth in human olfactory mucosa. *Laryngoscope.* 2005;115(12):2144-2154.
 43. Parker JK, Kelly CE, Gane SB. Molecular Mechanism of Parosmia. medRxiv preprint doi: <https://doi.org/10.1101/2021.02.05.21251085>;
 44. Rodriguez S, Cao L, Rickenbacher GT, et al. Innate immune signaling in the olfactory epithelium reduces odorant receptor levels: modeling transient smell loss in COVID-19 patients. medRxiv. 2020 Jun 16;2020.06.14.20131128.
 45. Lerner DK, Garvey KL, Arrighi-Allisan AE, et al. Clinical Features of Parosmia Associated With COVID-19 Infection. *Laryngoscope.* 2022 Mar;132(3):633-639.
 46. Bainbridge KE, Byrd-Clark D, Leopold D. Factors Associated With Phantom Odor Perception Among US Adults: Findings From the National Health and Nutrition Examination Survey. *JAMA Otolaryngol-Head Neck Surg.* 2018;144(9):807-814.
 47. Hummel T, Lötsch J. Prognostic Factors of Olfactory Dysfunction. *Arch Otolaryngol-Head Neck Surg.* 2010;136(4):347-351.
 48. Hannum M E, Ramirez V A, Lipson S J, et al. Objective Sensory Testing Methods Reveal a Higher Prevalence of Olfactory Loss in COVID-19-Positive Patients Compared to Subjective Methods: A Systematic Review and Meta-Analysis. *Chem Senses.* 2020;45(9):856-874.
 49. Kumar AA, Lee SWY, Lock C, Keong NC. Geographical Variations in Host Predisposition to COVID-19 Related Anosmia, Ageusia, and Neurological Syndromes. *Front Med (Lausanne).* 2021 Apr 29;8:661359.
 50. Landis BN, Hummel T, Hugentobler M, Giger R, Lacroix JS. Ratings of overall olfactory function. *Chem Senses.* 2003;28(8):691-694.
 51. Nørgaard HJ, Fjaeldstad AW. Differences in Correlation between Subjective and Measured Olfactory and Gustatory Dysfunctions after Initial Ear, Nose and Throat Evaluation. *Int Arch Otorhinolaryngol.* 2021;25(4):e563-e569.
 52. Liu DT, Welge-Lüssen A, Besser G, Mueller CA, Renner B. Assessment of odor hedonic perception: the Sniffin' sticks parosmia test (SSParoT). *Sci Rep.* 2020;10(1):18019.
 53. Addison AB, Wong B, Ahmed T, et al. Clinical Olfactory Working Group consensus statement on the treatment of postinfectious olfactory dysfunction. *J Allergy Clin Immunol.* 2021;147(5):1704-1719.
 54. Philpott C, Dixon J, Boak D. Qualitative Olfactory Disorders: Patient Experiences and Self-Management. *Allergy Rhinol.* 2021;12:21526567211004252.
 55. Lechner M, Liu J, Counsell N, et al. Course of symptoms for loss of sense of smell and taste over time in one thousand forty-one healthcare workers during the Covid-19 pandemic: Our experience. *Clin Otolaryngol.* 2021;46(2):451-457.
 56. Tognetti A, Thunell E, Olsson MJ, et al. High prevalence of olfactory disorders 18 months after contracting COVID-19. medRxiv 2022.01.20.22269490;
 57. Parker JK, Kelly CE, Smith BC, Kirkwood AF, Hopkins C, Gane S. Patients' Perspectives on Qualitative Olfactory Dysfunction: Thematic Analysis of Social Media Posts. *JMIR Form Res.* 2021;5(12):e29086.
 58. WHO. WHO Coronavirus Disease (COVID-19) Dashboard With Vaccination Data - United States of America. Accessed August 26, 2021. <https://covid19.who.int>
 59. Postma EM, De Graaf C, Boesveldt S. Food preferences and intake in a population of Dutch individuals with self-reported smell loss: An online survey. *Food Qual Prefer.* 2020;79:103771.
 60. Yom-Tov E, Lekkas D, Jacobson NC. Association of COVID19-induced anosmia and ageusia with depression and suicidal ideation. *J Affect Disord Rep.* 2021;5:100156.
 61. Lerner DK, Garvey KL, Arrighi-Allisan AE, et al. Clinical Features of Parosmia Associated With COVID-19 Infection. *Laryngoscope.* 2022 Mar;132(3):633-9.
 62. Rashid RA, Alaqeedy AA, Al-Ani RM. Parosmia due to COVID-19 disease: a 268 case series. *Ind J Otolaryngol Head Neck Surg.* 2021:1-8.

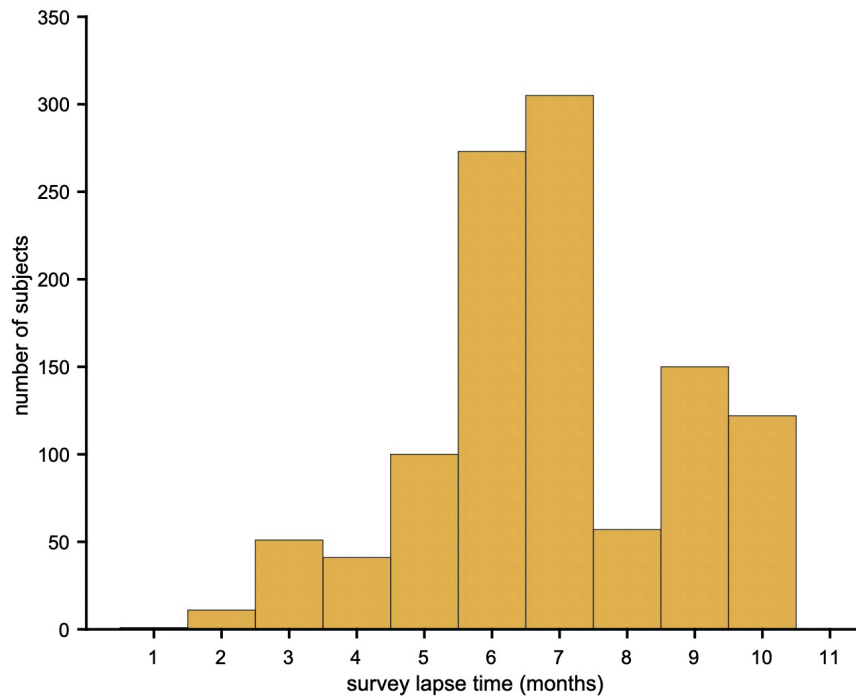
John E. Hayes, PhD
Sensory Evaluation Center
The Pennsylvania State University
University Park PA 16803
College of Agricultural Sciences
The Pennsylvania State University
University Park PA 16803
220 Erickson Food Science Building
University Park PA 16803
USA

Tel: +1-814-441-4393
E-mail: jeh40@psu.edu

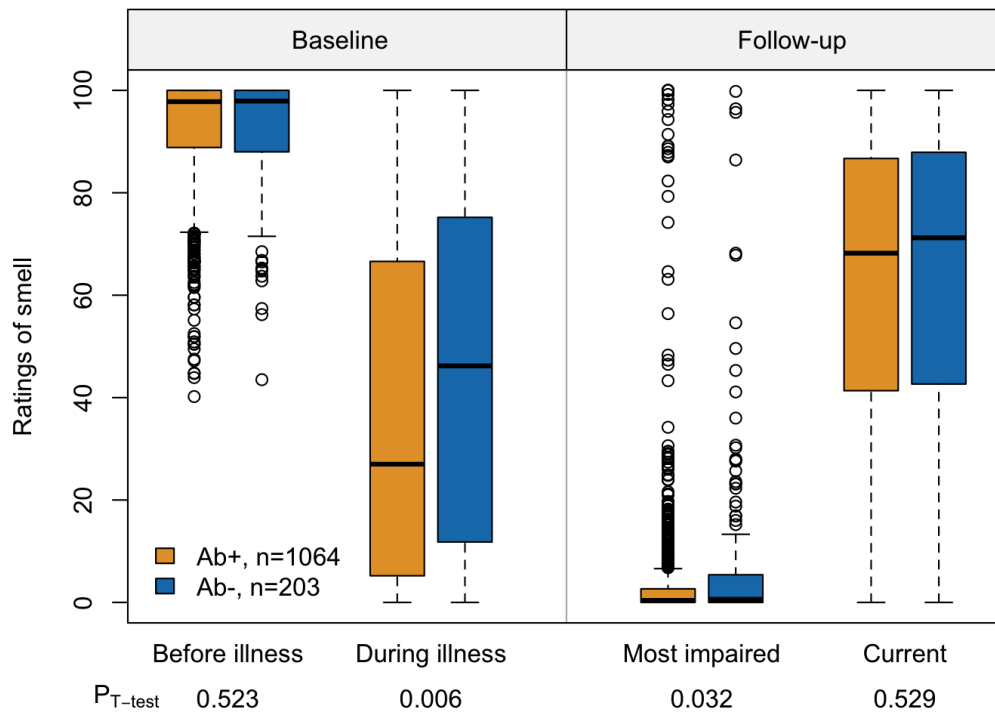
Masha Niv, PhD
The Robert H. Smith Faculty of Agriculture
Food and Environment
The Hebrew University of Jerusalem
Herzl street
Rehovot 76100
Israel

Tel: +972-8-9489664
E-mail: masha.niv@mail.huji.ac.il

SUPPLEMENTARY MATERIAL



Supplementary Figure 1. Distribution of time lapse between S1 and S2.



Supplementary Figure 2. Comparison of self-report ability to smell between individuals who tested positive (Ab+) and negative (Ab-) for the COVID-19 antibody. Ratings before illness and during illness were collected at the baseline and most impaired and current ratings were collected at the follow-up.

Supplementary Table 1. Comparison of symptoms between long haulers and non-longhaulers.

Survey	Symptom	longhauler		non long hauler		Chi-square	P-value	P-value Bonferroni corrected	Odds ratio	95% CI	
		%	n	%	n					lower bound	higher bound
S1	fever	56.37%	478	58.23%	361	0.432	0.511		0.93	-0.07	0.03
S1	dry cough	54.48%	462	56.45%	350	0.486	0.486		0.92	-0.07	0.03
S1	cough with mucus	17.92%	152	18.87%	117	0.156	0.693		0.94	-0.08	0.05
S1	difficulty breathing / shortness of breath	37.85%	321	36.94%	229	0.093	0.761		1.04	-0.04	0.06
S1	chest tightness	36.79%	312	32.42%	201	2.824	0.093		1.21	-0.01	0.10
S1	runny nose	37.62%	319	38.39%	238	0.060	0.806		0.97	-0.06	0.05
S1	sore throat	38.09%	323	33.71%	209	2.787	0.095		1.21	-0.01	0.10
S1	changes in food flavor	91.04%	772	91.13%	565	0.000	1.000		0.99	-0.09	0.09
S1	changes in smell	98.70%	837	98.23%	609	0.276	0.599		1.37	-0.15	0.31
S1	loss of appetite	47.29%	401	47.10%	292	0.000	0.984		1.01	-0.05	0.05
S1	headache	75.00%	636	71.29%	442	2.340	0.126		1.21	-0.01	0.11
S1	muscle aches	63.56%	539	60.81%	377	1.044	0.307		1.12	-0.03	0.08
S1	fatigue	81.37%	690	77.74%	482	2.704	0.100		1.25	-0.01	0.12
S1	diarrhea	35.02%	297	36.61%	227	0.328	0.567		0.93	-0.07	0.04
S1	abdominal pain	18.40%	156	14.68%	91	3.278	0.070		1.31	0.00	0.13
S1	nausea	26.42%	224	22.26%	138	3.111	0.078		1.25	-0.01	0.11
S2	fever	0.71%	6	0.49%	3	0.039	0.843		1.46	-0.28	0.45
S2	dry cough	6.49%	55	4.38%	27	2.640	0.104		1.52	-0.01	0.21
S2	cough with mucus	4.72%	40	3.08%	19	2.085	0.149		1.56	-0.03	0.23
S2	difficulty breathing / shortness of breath	10.39%	88	6.81%	42	5.228	0.022	0.356	1.59	0.02	0.20
S2	chest tightness	6.26%	53	6.32%	39	0.000	1.000		0.99	-0.11	0.10
S2	runny nose	7.91%	67	4.54%	28	6.145	0.013	0.211	1.81	0.03	0.24
S2	sore throat	4.25%	36	3.08%	19	1.049	0.306		1.40	-0.06	0.22
S2	changes in food flavor	49.47%	419	11.83%	73	224.940	0.000	0.000	7.30	0.37	0.46
S2	changes in smell	62.81%	532	14.42%	89	340.170	0.000	0.000	10.02	0.44	0.53
S2	loss of appetite	8.97%	76	1.62%	10	33.580	0.000	0.000	5.98	0.25	0.40
S2	headache	18.54%	157	9.24%	57	23.990	0.000	0.000	2.24	0.11	0.25
S2	muscle aches	11.69%	99	8.27%	51	4.180	0.041	0.654	1.47	0.01	0.17
S2	fatigue	31.40%	266	20.26%	125	22.090	0.000	0.000	1.80	0.08	0.20
S2	diarrhea	4.84%	41	2.76%	17	3.550	0.060		1.80	0.00	0.26
S2	abdominal pain	4.96%	42	4.38%	27	0.156	0.693		1.14	-0.09	0.16
S2	nausea	5.43%	46	3.24%	20	3.483	0.062		1.71	0.00	0.25

Differences in smell changes between COVID-19 antibody test results. Participants were asked whether they have been tested for the COVID-19 antibody at the follow-up. Among participants who had consistent COVID-19 diagnosis (1,468 positive and 913 negative), 1,064 and 203 reported having positive (Ab+) and negative (Ab-) antibody test results, respectively, with the remaining reporting no antibody test (n=1100) or unknown (n=17). We conducted a t-test to assess the difference in the self-report ability to smell between Ab+ and Ab- at four time points, which were before illness, during illness, most impaired and current. We showed that participants with Ab+ had lower ratings of smell during illness and at the most impaired period (Supplementary Figure 2). There were no differences before illness and at the current time. These results were consistent with our previous study comparing the ratings of smell between participants who were diagnosed with COVID-19 + and COVID-19 -, providing additional support for the reduced olfactory function in COVID-19.

Is the number of symptoms experienced during the first two weeks of illness predictive of long-COVID?

Participants

To examine whether the number of symptoms experienced during the first two weeks of illness is predictive of long-COVID, we performed analyses on a separate sub-group of recontacted participants, namely COVID-19 positive participants who responded both to S1 during the first 14 days of illness and to S2 more than 2 months (≥61 days) after disease onset. From this sub-group (N=355), we categorized participants according to their disease status at S2: those who reported to still experiencing at least 1 symptom more than 61 days after the disease onset were defined as ‘Long-COVID’ (N=202, 161 women, 41

men) while those who reported 0 symptom were defined as ‘Recovered’ (N=153, 104 women, 49 men).

Statistical analyses

We used a logistic regression (glm function with a binomial error structure of the stats package in R) to assess whether the two categories of participants (Long-COVID vs Recovered) differed in terms of overall number of symptoms they respectively experienced during the first two weeks of disease. Our dependent variable was the “Participants’ category” (Long-COVID vs Recovered). Our explanatory variable was the “Number of symptoms” reported during the first two weeks. We also included “Age” and “Gender” as control variables. Finally, we added the variable ‘Time-lapse’ corresponding to the number of days between disease

onset and the date of S2 completion as a control variable. In other words, the model was: Participants' category ~ Number of symptoms + Age + Gender + Time-lapse. We centred Age and Time-lapse in order to make the effects more easily biologically interpretable. The significance of each variable was tested with likelihood ratio tests comparing the full model to those without the term of interest and the α -level was set to 0.05.

Results

The logistic regression revealed a significant effect of the number of symptoms during the first 14 days of disease ($\beta=0.10$, $SE = 0.04$, 95% CI = 1.032-1.196, $\chi^2 = 7.98$, $p = 0.005$, OR = 1.11): participants who developed long-COVID (i.e., they are still experiencing at least one symptom after 61 days) experienced a significantly higher number of symptoms (Mean \pm SD = 8.3 \pm 3.07 symptoms) during the first 14 days of disease compared to the participants who had fully recovered after two months (Mean \pm SD = 7.3 \pm 2.87 symptoms). Importantly, the number of days between disease onset and S2 completion does not significantly differ between the two categories of participants ($\beta=-0.001$, $SE = 0.002$, 95% CI = 0.995-1.003, $\chi^2 = 0.24$, $p = 0.62$, OR = 1.00). No significant effect of age ($\beta=0.02$, $SE = 0.009$, 95% CI = 0.997-1.036, $\chi^2 = 2.84$, $p = 0.09$, OR = 1.02) or gender ($\beta=0.46$, $SE = 0.25$,

95% CI = 0.961-2.612, $\chi^2 = 3.25$, $p = 0.07$, OR = 1.58) was found.

In summary, these findings indicate that the greater the number of symptoms COVID-19 patients experienced during the first 2 weeks of illness, the more likely they are to have long-term symptoms, which is in line with previous findings 18. This is also in line with more severe outcomes of hospitalized versus non-hospitalized COVID-19 patients 34.

Rerunning analysis without clinically diagnosed participants

Since we cannot exclude the possibility that some of the clinically diagnosed individuals may have been misdiagnosed, and were suffering from a respiratory illness other than COVID-19, we reanalyzed our data using only those who reported a lab based diagnosis ; when doing so, we observed no changes in the proportions of smell long-haulers and non smell long-haulers compared to the data from the full sample reported here. Parosmia and phantosmia reports were slightly overestimated in the full sample at baseline, but similar for parosmia and underestimated for phantosmia at follow-up. Age and gender were also similarly distributed in both samples, as summarized in Supplementary Table 2.

Supplementary Table 2. Demographics and smell dysfunction of individuals with COVID-19 diagnosis based on lab test and clinical diagnosis and those with lab test only.

Variable	Time	Lab tested & clinical diagnosis (N=1,468)	Lab tested (N=1,046)
Smell long haulers		57.8%	58.79%
Non smell long haulers		42.2%	41.21%
Parosmia	S1	10.2%	8.6%
Parosmia	S2	46.79%	47.94%
Phantosmia	S1	10.08%	8.99%
Phantosmia	S2	24.86%	23.82%
Age mean in years		43.88	43.59
Male / Female		24.23% / 75.77%	23.81% / 76.19%
Survey timelapse min		23	23
Survey timelapse max		291	291

1) Welcome and Consent

I consent to participate.

- [1]Yes
 [0]No

Question Type: Choose only 1
 Branching logic: if [0]=checked, then go to Section 4) End of test

2) About your illness

In which year (YYYY) were you born?

Question Type: Numeric
 Branching logic: if year of birth greater than 2001 then go to Section 4) End of test

What is your current country of residence?

Question Type: Comment

Optional: What city, town, or region do you currently live in?

Question Type: Comment

Which gender do you most identify with?

- [0]Female
 [1]Male
 [2]Another not listed here
 [3]Prefer not to say

Question Type: Choose only 1

Within the past two weeks, have you been diagnosed with or suspect that you have a respiratory illness?

- [1]Yes
 [0]No

Question Type: Choose only 1
 Branching: if [0]=checked, then go to Section 4) Re-contact

What **date** did you **first notice symptoms** of your recent respiratory illness? Provide your best guess or leave blank if you do not remember. Click the box below to display a calendar.

Question Type: Numeric

Have you been diagnosed with **COVID-19**?

- [1]Yes-diagnosed based on symptoms only
 [2]Yes-diagnosed with viral swab
 [3]Yes-diagnosed with another lab test
 [4]No-I was not diagnosed, but I have symptoms
 [5]No-I had a negative test, but I have symptoms
 [6]No-I do not have any symptoms
 [7]Don't Know
 [8]Other

Question Type: Choose only 1

Were you diagnosed with any **other respiratory illnesses (not COVID-19)** in the **last two weeks**? (Select all that apply)

- [1]Strep throat (Streptococcal bacteria)
 [2]Another bacterial illness
 [3]Flu (influenza)
 [4]Another viral illness
 [5]Other
 [6]None

Question Type: Choose n

Have you had any of the following symptoms with **your recent respiratory illness or diagnosis**? (Select all that apply)

- [1]Fever
- [2]Dry cough
- [3]Cough with mucus
- [4]Difficulty breathing/shortness of breath
- [5]Chest tightness
- [6]Runny nose
- [7]Sore throat
- [8]Changes in food flavor
- [9]Changes in smell
- [10]Loss of appetite
- [11]Headache
- [12]Muscle aches
- [13]Fatigue
- [14]Diarrhea
- [15]Abdominal pain
- [16]Nausea
- [17]No symptoms

Question Type: Choose n

Optional: Please describe the progression or order you noticed your symptoms

Question Type: Comment

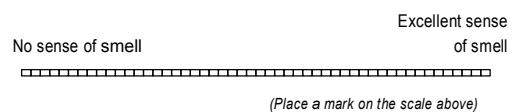
Optional: What treatment(s) or medication(s) have you received for your recent **respiratory illness or diagnosis**?

Question Type: Comment

The next section of this survey is focused on your experience of smell, taste, and food flavor during your recent respiratory illness or diagnosis.

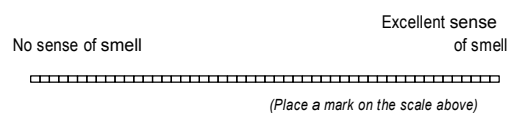
These questions relate to your sense of smell (for example, sniffing flowers or soap, or smelling garbage) but not the flavor of food in your mouth.

Rate your ability to **smell** BEFORE your **recent respiratory illness or diagnosis**



Question Type: Line Scale

Rate your ability to **smell** DURING your **recent respiratory illness or diagnosis**



Question Type: Line Scale

Have you experienced any of the following changes in **smell** with your **recent respiratory illness or diagnosis**? (Select all that apply)

- [1]I cannot smell at all / Smells smell less strong than they did before
- [2]Smells smell different than they did before (the quality of smell has changed)
- [3]I can smell things that aren't there (e.g. I smell burning when nothing is on fire)
- [4]Sense of smell fluctuates (e.g. comes and goes)

Question Type: Choose n

Optional: Please describe any changes in smell

Optional: Describe any changes in these other sensations during your **recent respiratory illness or diagnosis**.

Question Type: Comment

Optional: Think about a food or beverage you consume regularly - for example, your morning coffee or tea or a piece of fruit you have each day. Has the taste, smell, or flavor changed with your recent respiratory illness or diagnosis? If so, **please describe how and be sure to indicate which food or beverage you are describing**.

Question Type: Comment

Optional: Is there anything else you would like to tell us about how your recent respiratory illness or diagnosis has affected your sense of smell, taste, and flavor?

Question Type: Comment

Have you recovered from your **recent respiratory illness or diagnosis**? (For example you no longer have a cough, fever, or shortness of breath.)

- No
- Yes - partly
- Yes - fully
- Don't know

Question Type: Choose only 1

Branching: if [0]=checked, then go to Section 3) General Health Information

The next section of this survey is focused on your experiences of smell, taste, and food flavor after your recovery from your recent respiratory illness or diagnosis.

Rate your ability to **smell** AFTER your recovery



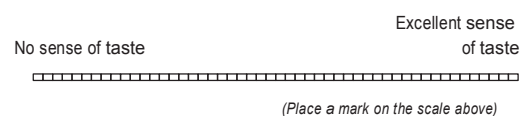
Question Type: Line Scale

How **blocked** was your nose AFTER your recovery



Question Type: Line Scale

Rate your ability to **taste** AFTER your recovery



Question Type: Line Scale

Optional: Describe any changes in these other sensations during your **recent respiratory illness or diagnosis**.

Question Type: Comment

Optional: Think about a food or beverage you consume regularly - for example, your morning coffee or tea or a piece of fruit you have each day. Has the taste, smell, or flavor changed with your recent respiratory illness or diagnosis? If so, **please describe how and be sure to indicate which food or beverage you are describing**.

Question Type: Comment

Optional: Is there anything else you would like to tell us about how your recent respiratory illness or diagnosis has affected your sense of smell, taste, and flavor?

Question Type: Comment

Have you recovered from your **recent respiratory illness or diagnosis**? (For example you no longer have a cough, fever, or shortness of breath.)

- No
- Yes - partly
- Yes - fully
- Don't know

Question Type: Choose only 1

Branching: if [0]=checked, then go to Section 3) General Health Information

The next section of this survey is focused on your experiences of smell, taste, and food flavor after your recovery from your recent respiratory illness or diagnosis.

Rate your ability to **smell** AFTER your recovery

No sense of smell Excellent sense of smell

(Place a mark on the scale above)

Question Type: Line Scale

How **blocked** was your nose AFTER your recovery

Not at all blocked Completely blocked

(Place a mark on the scale above)

Question Type: Line Scale

Rate your ability to **taste** AFTER your recovery

No sense of taste Excellent sense of taste

(Place a mark on the scale above)

Question Type: Line Scale

Rate your **ability to feel these other sensations like burning, cooling, and tingling** AFTER your recovery

Not sensitive at all Very sensitive

(Place a mark on the scale above)

Question Type: Line Scale

How were you directed to this survey?

- [1]Clinician or healthcare professional
- [2]Media (social media, print, radio, tv, etc)
- [3]Word of mouth
- [4]Other

Question Type: Choose only 1

The next section of this survey will ask some optional questions about your habits and general health.

3. General Health Information

Optional: Have you smoked at least 100 combustible cigarettes or cigars in your entire life?

- [0]No
- [1]Yes
- [2]Prefer not to say
- [3]Don't know

Question Type: Choose only 1

Optional: During the past 30 days, on how many days did you smoke combustible cigarettes or cigars?

Question Type: Numeric

Optional: Have you ever used an e-cigarette ('vaped'/'Juuled') even one time? (E-cigarettes are battery-powered devices that usually contain liquid nicotine, and do not produce smoke.)

- [0]No
- [1]Yes
- [2]Prefer not to say
- [3]Don't know

Question Type: Choose only 1

Optional: During the past 30 days, on how many days did you use an e-cigarette?

Question Type: Numeric (range 0-30; integer)

Did you have any of the following **in the 6 months prior** to your recent respiratory illness or diagnosis? (Select all that apply)

- [1]High blood pressure
- [2]Heart disease (heart attack or stroke)
- [3]Diabetes (high blood sugar)
- [4]Obesity
- [5]Lung disease (asthma/COPD)
- [6]Head trauma
- [7]Neurological disease
- [8]Cancer that required chemotherapy or radiation
- [9]Cancer that did NOT require chemotherapy or radiation
- [10]Chronic sinus problems
- [11]Seasonal allergies/hay fever
- [12]None

Question Type: Choose n

Optional: Any other medical conditions that you would like to mention?

Question Type: Comment

Optional: Which medication(s) do you take regularly? For example, medications for pain, blood pressure, thyroid function, anti-viral, etc.

Question Type: Comment

Optional: Is there anything we didn't ask about that you would like to share with us?

Question Type: Comment

4. Re-contact

We may want to re-contact you for follow up research on this topic. **Is it okay if our team or other researchers re-contact you to participate in future research?** By saying yes, you agree that we can share your email address with other researchers for this purpose.

- [1]Yes
 [0]No

Question Type: Choose only 1

Branching logic: if [0]=checked, then go to: Section 5)End of test

Please provide your full email address, so you can be contacted for future studies by our team or other researchers.

Question Type: Comment

5. End of Test

You have now completed the survey and may close your browser

Thank you for your time!

Notes

- "In which year (YYYY) were you born?
-- value must be 1900 or greater
- "What **date** did you **first notice symptoms** of your recent respiratory illness? Provide your best guess or leave blank if you do not remember.
Click the box below to display a calendar"
-- format (mm/dd/yyyy)
- "Have you been diagnosed with COVID-19"
-- if [8] Other was selected, a comment is required
- "Were you diagnosed with any other respiratory illnesses (not COVID-19) in the last two weeks? (Select all that apply)"
-- if [6] None was selected, no other options can be selected.
- "Have you had any of the following symptoms with your **recent respiratory illness or diagnosis**? (Select all that apply)"
-- if [17] No symptoms was selected, no other options can be selected.
- "Rate your ability to smell BEFORE your **recent respiratory illness or diagnosis**"
-- Line Scale Range 0-100, intervals of 1. All following line scales formatted similarly
- "**OPTIONAL:** During the past 30 days, on how many days did you smoke combustible cigarettes or cigars?" and "**OPTIONAL:** During the past 30 days, on how many days did you use an e-cigarette?"
-- value must be between 0-30
- Did you have any of the following in the 6 months prior to your **recent respiratory illness or diagnosis**? (Select all that apply)
-- if [12] None was selected, no other options can be selected.

Think about a food or beverage you consume regularly – for example, your morning coffee or tea or a piece of fruit you have each day.

Thinking about your experience **TODAY**, how has the taste, smell, or flavor changed compared to before you experienced smell and/or taste impairment?

_[text] _____

Please be sure to indicate which food or beverage you are describing.

Type 'none' if this is not applicable.

Question Type: Comment

Thinking back to the time period when you were diagnosed or tested positive for COVID-19, please describe your entire experience from onset to recovery. In particular, please make note of the timing or progression of any symptoms.

_[text] _____

Type 'none' if this is not applicable.

Question Type: Comment

Is there anything we didn't ask about that you would like to share with us?

Type 'none' if this is not applicable.

_[text] _____

Question Type: Comment

**You have now completed the survey and may close your browser.
Thank you for your time!
Your participation in our previous survey helped researchers understand
more about smell and taste impairment.**