

Original Article

Recent Smell Loss Is the Best Predictor of COVID-19 Among Individuals With Recent Respiratory Symptoms

Richard C. Gerkin^{1,*}, Kathrin Ohla^{2,*}, Maria G. Veldhuizen³,
 Paule V. Joseph^{4,5,6}, Christine E. Kelly⁷, Alyssa J. Bakke⁸,
 Kimberley E. Steele^{6,9}, Michael C. Farruggia¹⁰, Robert Pellegrino¹¹,
 Marta Y. Pepino¹², Cédric Bouysset¹³, Graciela M. Soler^{14,15},
 Veronica Pereda-Loth¹⁶, Michele Dibattista¹⁷, Keiland W. Cooper¹⁸,
 Ilja Croijmans¹⁹, Antonella Di Pizio²⁰, Mehmet Hakan Ozdener²¹,
 Alexander W. Fjaeldstad²², Cailu Lin²¹, Mari A. Sandell²³, Preet B. Singh²⁴,
 V. Evelyn Brindha²⁵, Shannon B. Olsson²⁶, Luis R. Saraiva²⁷,
 Gaurav Ahuja²⁸, Mohammed K. Alwashahi²⁹, Surabhi Bhutani³⁰,
 Anna D'Errico³¹, Marco A. Fornazieri³², Jérôme Golebiowski¹³,
 Liang Dar Hwang³³, Lina Öztürk³, Eugeni Roura³⁴, Sara Spinelli³⁵,
 Katherine L. Whitcroft³⁶, Farhoud Faraji³⁷, Florian Ph.S. Fischmeister³⁸,
 Thomas Heinbockel³⁹, Julien W. Hsieh⁴⁰, Caroline Huart⁴¹,
 Iordanis Konstantinidis⁴², Anna Menini⁴³, Gabriella Morini⁴⁴,
 Jonas K. Olofsson⁴⁵, Carl M. Philpott⁴⁶, Denis Pierron¹⁶,
 Vonnie D. C. Shields⁴⁷, Vera V. Voznessenskaya⁴⁸, Javier Albayay⁴⁹,
 Aytug Altundag⁵⁰, Moustafa Bensafi⁵¹, María Adelaida Bock⁵²,
 Orietta Calcinoni⁵³, William Fredborg⁴⁵, Christophe Laudamiel⁵⁴,
 Juyun Lim⁵⁵, Johan N. Lundström⁵⁶, Alberto Macchi^{57,58}, Pablo Meyer⁵⁹,
 Shima T. Moein⁶⁰, Enrique Santamaría⁶¹, Debarka Sengupta²⁸,
 Paloma Rohlf's Dominguez⁶², Hüseyin Yanik⁶³, GCCR Group Author,
 Thomas Hummel⁹⁰, John E. Hayes⁸, Danielle R. Reed²¹, Masha Y. Niv¹⁰⁷,
 Steven D. Munger^{85,108,†} and Valentina Parma^{109,†}

¹School of Life Sciences, Arizona State University, Tempe, AZ, USA, ²Institute of Neuroscience and Medicine (INM3), Forschungszentrum Jülich, Jülich, Germany, ³Department of Anatomy, Mersin University, Yenisehir/Mersin, Turkey, ⁴National Institute of Nursing Research, Bethesda, MD, USA, ⁵National Institute of Alcohol Abuse and Alcoholism, Bethesda, MD, USA, ⁶National Institutes of Health, Bethesda, MD, USA, ⁷AbScent, Andover, Hampshire, UK, ⁸Department of Food Science, The Pennsylvania State University, University Park, PA, USA, ⁹National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, USA, ¹⁰Interdepartmental Neuroscience Program, Yale University, New Haven, CT, USA, ¹¹Department of Food Science, University of Tennessee, Knoxville, TN, USA, ¹²Department of Food Science and Human Nutrition, University of Illinois at Urbana Champaign, Urbana, IL, USA, ¹³Institut de Chimie de Nice, UMR CNRS 7272, Université Côte d'Azur, Nice, France ¹⁴Grupo de Estudio de Olfato y Gusto (GEOG), Buenos Aires, Argentina, ¹⁵Department of Otorhinolaryngology, University of Buenos Aires, Buenos Aires, Argentina, ¹⁶Medecine Evolutive UMR5288, University of Toulouse, Toulouse, France, ¹⁷Department of Basic

Medical Science, Neuroscience and Sense Organs, Università degli Studi di Bari A. Moro, Bari, Italy, ¹⁸Department of Neurobiology and Behavior, University of California, Irvine, Irvine, CA, USA, ¹⁹Department of Psychology, Utrecht University, Utrecht, the Netherlands, ²⁰Leibniz-Institute for Food Systems Biology at the Technical University of Munich, Freising, Germany, ²¹Monell Chemical Senses Center, Philadelphia, PA, USA, ²²Flavour Clinic, Department of Otorhinolaryngology, Regional Hospital West Jutland, Holstebro, Denmark, ²³Department of Food and Nutrition, University of Helsinki, Helsinki, Finland, ²⁴Department of Oral Surgery and Oral Medicine, Faculty of Dentistry, University of Oslo, Oslo, Norway, ²⁵Department of Electrical and Electronics Engineering, Karunya Institute of Technology and Sciences, Karunya Nagar, Coimbatore, Tamil Nadu, India, ²⁶National Centre for Biological Sciences, Tata Institute of Fundamental Research, GKVK Campus, Bengaluru, Karnataka, India, ²⁷Research Branch, Sidra Medicine, Doha, Qatar, ²⁸Computational Biology, Indraprastha Institute of Information Technology, New Delhi, India, ²⁹ENT Division, Surgery Department, Sultan Qaboos University, Muscat, Oman, ³⁰School of Exercise and Nutritional Sciences, San Diego State University, San Diego, CA, USA, ³¹Cellular and Molecular Neurobiology, Goethe University Frankfurt, Frankfurt, Germany, ³²Clinical Surgery, Universidade Estadual de Londrina, Londrina, Brazil, ³³The University of Queensland Diamantina Institute, The University of Queensland, Woolloongabba, QLD, Australia, ³⁴Centre for Nutrition and Food Sciences, Queensland Alliance for Agriculture and Food Innovation, The University of Queensland, St. Lucia, QLD, Australia, ³⁵Department of Agriculture, Food, Environment and Forestry (DAGRI), University of Florence, Florence, Italy, ³⁶Ear Institute, University College London, London, UK, ³⁷Department of Surgery, Division of Otolaryngology-Head and Neck Surgery, University of California San Diego Health, La Jolla, CA, USA, ³⁸Department of Psychology, University of Graz, Graz, Austria, ³⁹Department of Anatomy, College of Medicine, Howard University, Washington, DC, USA, ⁴⁰Department of Otorhinolaryngology, Rhinology-Olfactology Unit, Geneva University Hospitals, Geneva, Switzerland, ⁴¹ENT Department, Cliniques Universitaires Saint-Luc, Brussels, Belgium, ⁴²ORL Department, Papageorgiou Hospital, Aristotle University, Thessaloniki, Greece, ⁴³Neuroscience Area, SISSA, International School for Advanced Studies, Trieste, Italy, ⁴⁴University of Gastronomic Sciences, Pollenzo, Italy, ⁴⁵Department of Psychology, Stockholm University, Stockholm, Sweden, ⁴⁶Norwich Medical School, The Norfolk Smell & Taste Clinic, University of East Anglia, Norwich, UK, ⁴⁷Biological Sciences Department, Fisher College of Science and Mathematics, Towson University, Towson, MD, USA, ⁴⁸Severtsov Institute of Ecology and Evolution RAS, Moscow, Russia, ⁴⁹Department of General Psychology, University of Padova, Padova, Italy, ⁵⁰Otorhinolaryngology Department, Biruni University, Zeytinburnu/İstanbul, Turkey, ⁵¹Lyon Neuroscience Research Center, CNRS, Bron, France, ⁵²Departamento de Salud Pública ORL, Hospital General Barrio Obrero, Asunción, Paraguay, ⁵³Private Practice, Milan, Italy, ⁵⁴Department of Scent Engineering, DreamAir LLC, New York, NY, USA, ⁵⁵Department of Food Science and Technology, Oregon State University, Corvallis, OR, USA, ⁵⁶Department of Clinical Neuroscience, Karolinska Institutet, Stockholm, Sweden, ⁵⁷ENT Department, University of Insubria Varese, ASST-Sette Laghi, Varese, Italy, ⁵⁸Italian Academy of Rhinology, Varese, Italy, ⁵⁹Health Care and Life Sciences, IBM T.J. Watson Research Center, Yorktown Heights, NY, USA, ⁶⁰School of Biological Sciences, Institute for Research in Fundamental Sciences, Tehran, Iran, ⁶¹Clinical Neuroproteomics Unit, Navarrabiomed-IdiSNA, Pamplona, Spain, ⁶²Department of Psychology and Anthropology, University of Extremadura, Cáceres, Spain, ⁶³Department of Electrical and Electronics Engineering, Mersin University, Yenişehir/Mersin, Turkey, ⁶⁴Center for Smell and Taste, University of Florida, Gainesville, FL, USA, ⁶⁵Department of Otorhinolaryngology, Smell & Taste Clinic, TU Dresden, Dresden, Germany, ¹⁰⁷The Faculty of Agriculture, Food and Environment, The Hebrew University of Jerusalem, Rehovot, Israel, ¹⁰⁸Department of Pharmacology and Therapeutics, University of Florida, Gainesville, FL, USA and ¹⁰⁹Department of Psychology, Temple University, Philadelphia, PA, USA

Non-byline authors: Sanne Boesveldt⁶⁴, Jasper H. B. de Groot⁶⁵, Caterina Dinnella³⁵, Jessica Freiherr⁶⁶, Tatiana Laktionova⁴⁸, Sajidxa Marino⁶⁷, Erminio Monteleone³⁵, Alexia Nunez-Parra⁶⁸, Olagunju Abdulrahman⁶⁹, Marina Ritchie¹⁸, Thierry Thomas-Danguin⁷⁰, Julie Walsh-Messinger⁷¹, Rashid Al Abri²⁹, Rafieh Alizadeh⁷², Emmanuelle Bignon¹³, Elena Cantone⁷³, Maria Paola Cecchini⁷⁴, Jingguo Chen⁷⁵, Maria Dolors Guàrdia⁷⁶, Kara C. Hoover⁷⁷, Noam Kami⁷⁸, Marta Navarro³⁴, Alissa A. Nolden⁷⁹, Patricia Portillo Mazal⁸⁰, Nicholas R. Rowan⁸¹, Atiye Sarabi-Jamab⁸², Nicholas S. Archer⁸³, Ben Chen⁸⁴, Elizabeth A. Di Valerio⁸⁵, Emma L. Feeney⁸⁶, Johannes Frasnelli⁸⁷, Mackenzie E. Hannum²¹, Claire Hopkins⁸⁸, Hadar Klein⁸⁹, Coralie Mignot⁹⁰, Carla Mucignat⁹¹, Yuping Ning⁹², Elif E. Ozturk⁹³, Mei Peng⁹⁴, Ozlem Saatci⁹⁵, Elizabeth A. Sell⁹⁶, Carol H. Yan³⁷,

**Raul Alfaro¹², Cinzia Cecchetto⁴⁹, Gérard Coureaud⁹⁷, Riley D. Herriman²¹,
Jeb M. Justice^{85,98}, Pavan Kumar Kaushik²⁶, Sachiko Koyama⁹⁹,
Jonathan B. Overdevest¹⁰⁰, Nicola Pirastu¹⁰¹, Vicente A. Ramirez¹⁰²,
S. Craig Roberts¹⁰³, Barry C. Smith¹⁰⁴, Hongyuan Cao¹⁰⁵, Hong Wang²¹,
Patrick Balungwe Birindwa¹⁰⁶ and Marius Baguma¹⁰⁶**

⁶⁴Division of Human Nutrition and Health, Wageningen University, Wageningen, the Netherlands, ⁶⁵Behavioral Science Institute, Radboud University, Nijmegen, the Netherlands, ⁶⁶Department of Psychiatry and Psychotherapy, Friedrich-Alexander-Universität Erlangen-Nürnberg, Erlangen, Germany, ⁶⁷Centro de Otorrinolaringología Respira Libre, Caracas, Venezuela, ⁶⁸Department of Biology, University of Chile, Santiago, Chile, ⁶⁹Department of Physiology, The Federal University of Technology, Akure, Nigeria, ⁷⁰CSGA-Centre for Taste and Feeding Behavior, INRAE, CNRS, AgroSup Dijon, University Bourgogne Franche-Comté, Besançon, France, ⁷¹Department of Psychology, University of Dayton, Dayton, OH, USA, ⁷²ENT and Head and Neck Research Center and Department, The Five Senses Institute, Iran University of Medical Sciences, Tehran, Iran, ⁷³Neuroscience Department, University of Naples "Federico II", Napoli, Italy, ⁷⁴Department of Neuroscience, Biomedicine and Movement Sciences, Anatomy and Histology Section, University of Verona, Verona, Italy, ⁷⁵Department of Otolaryngology-Head and Neck Surgery, Second Affiliated Hospital of Xi'an Jiaotong University, Xi'an, China, ⁷⁶Food Technology Programme, IRTA, Girona, Spain, ⁷⁷Department of Anthropology, University of Alaska Fairbanks, Fairbanks, AK, USA, ⁷⁸Department of Medicine, Hadassah - Hebrew University Medical Center, Jerusalem, Israel, ⁷⁹Department of Food Science, University of Massachusetts, Amherst, MA, USA, ⁸⁰Servicio de Otorrinolaringología, Hospital Italiano de Buenos Aires, Buenos Aires, Argentina, ⁸¹Department of Otolaryngology-Head and Neck Surgery, Johns Hopkins University School of Medicine, Baltimore, MD, USA, ⁸²School of Cognitive Sciences, Institute for Research in Fundamental Sciences (IPM), Tehran, Iran, ⁸³Agriculture and Food, Commonwealth Scientific and Industrial Research Organisation (CSIRO), Canberra, ACT, Australia, ⁸⁴Department of Psychiatry, The Affiliated Brain Hospital of Guangzhou Medical University, Guangzhou, China, ⁸⁶Institute of Food and Health, University College Dublin, Dublin, Ireland, ⁸⁷Department of Anatomy, Université du Québec à Trois-Rivières, Trois-Rivières, QC, Canada, ⁸⁸ENT Department, Guy's and St. Thomas' Hospitals, London, UK, ⁸⁹Department of Biochemistry, Food Science and Nutrition, The Hebrew University of Jerusalem, Rehovot, Israel, ⁹¹Department of Molecular Medicine, University of Padova, Padova, Italy, ⁹²Department of Neurology, The Affiliated Brain Hospital of Guangzhou Medical University, Guangzhou, China, ⁹³Department of Nutrition and Dietetics, Kilis and Aralik University, Kilis, Turkey, ⁹⁴Sensory Neuroscience Laboratory, University of Otago, Dunedin, New Zealand, ⁹⁵Department of Otorhinolaryngology, Sancaktepe Education and Research Hospital, Sancaktepe/Istanbul, Turkey, ⁹⁶Perelman School of Medicine, University of Pennsylvania, University Park, PA, USA, ⁹⁷CMOENES Groups, Centre de Recherche en Neurosciences de Lyon, Bron, France, ⁹⁸Department of Otolaryngology, University of Florida, Gainesville, FL, USA, ⁹⁹Department of Chemistry, Indiana University, Bloomington, IN, USA, ¹⁰⁰Department of Otolaryngology - Head & Neck Surgery, Columbia University Medical Center, New York, NY, USA, ¹⁰¹Centre for Global Health, Usher Institute, University of Edinburgh, Edinburgh, UK, ¹⁰²Department of Public Health, University of California Merced, Merced, CA, USA, ¹⁰³Division of Psychology, University of Stirling, Stirling, UK, ¹⁰⁴Centre for the Study of the Senses, University of London, London, UK, ¹⁰⁵Department of Statistics, Florida State University, Tallahassee, FL, USA, ¹⁰⁶First Department of Specialties, Hôpital Provincial Général de Bukavu, Faculty of Medicine, Université Catholique de Bukavu, Bukavu, Democratic Republic of the Congo

* Co-first authors.

† Co-last authors.

Correspondence to be sent to: Valentina Parma, Department of Psychology, Temple University, 1701 N 13th St, Philadelphia, PA 19122, USA. e-mail: valentina.parma@temple.edu

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Abstract

In a preregistered, cross-sectional study, we investigated whether olfactory loss is a reliable predictor of COVID-19 using a crowdsourced questionnaire in 23 languages to assess symptoms in individuals self-reporting recent respiratory illness. We quantified changes in chemosensory abilities during the course of the respiratory illness using 0–100 visual analog scales (VAS) for participants reporting a positive (C19+; $n = 4148$) or negative (C19–; $n = 546$) COVID-19 laboratory test outcome. Logistic regression models identified univariate and multivariate predictors of COVID-19

status and post-COVID-19 olfactory recovery. Both C19+ and C19– groups exhibited smell loss, but it was significantly larger in C19+ participants (mean \pm SD, C19+: -82.5 ± 27.2 points; C19–: -59.8 ± 37.7). Smell loss during illness was the best predictor of COVID-19 in both univariate and multivariate models (ROC AUC = 0.72). Additional variables provide negligible model improvement. VAS ratings of smell loss were more predictive than binary chemosensory yes/no-questions or other cardinal symptoms (e.g., fever). Olfactory recovery within 40 days of respiratory symptom onset was reported for ~50% of participants and was best predicted by time since respiratory symptom onset. We find that quantified smell loss is the best predictor of COVID-19 amongst those with symptoms of respiratory illness. To aid clinicians and contact tracers in identifying individuals with a high likelihood of having COVID-19, we propose a novel 0–10 scale to screen for recent olfactory loss, the ODoR-19. We find that numeric ratings ≤ 2 indicate high odds of symptomatic COVID-19 ($4 < \text{OR} < 10$). Once independently validated, this tool could be deployed when viral lab tests are impractical or unavailable.

Key words: anosmia, chemosensory, coronavirus, hyposmia, olfactory, prediction

Introduction

The novel coronavirus SARS-CoV-2 responsible for the global COVID-19 pandemic has left a staggering level of morbidity, mortality, and societal and economic disruption in its wake (CDC 2020). Initial publications indicated that sudden smell and taste loss are cardinal, early, and potentially specific symptoms of COVID-19, including in otherwise asymptomatic individuals (Giacomelli et al. 2020; Hornuss et al. 2020; Kim et al. 2020; Lechien et al. 2020; Menni, Sudre, et al. 2020; Menni, Valdes, et al. 2020; Mizrahi et al. 2020; Moein et al. 2020; Paderno et al. 2020; Parma, Ohla, et al. 2020; Walsh-Messinger et al. 2020; Weiss et al. 2020; Yan, Faraji, Prajapati, Boone, et al. 2020). While fever and cough are common symptoms of diverse viral infections, the potential specificity of chemosensory loss to COVID-19 could make it valuable in screening and diagnosis.

Anosmia and other chemosensory disorders have serious health and quality-of-life consequences for patients. However, the general lack of awareness of anosmia and other chemosensory disorders by clinicians and the public, including their association with upper respiratory infections (Soler et al. 2020), contributed to an underappreciated role of chemosensory symptoms in the diagnosis of COVID-19. Additionally, the impact of smell loss as a clinical consequence of COVID-19 has not been adequately addressed. Thus, there is an urgent need to better define the chemosensory dysfunctions associated with COVID-19 and to determine their relevance as predictors of this disease. Additionally, it is critical to develop rapid clinical tools to efficiently and effectively integrate chemosensory assessments into COVID-19 screening and treatment protocols. Information on the duration and reversibility of post-COVID-19 chemosensory impairment is also lacking.

We used binary, categorical, and continuous self-report measures to determine the chemosensory phenotype, along with other symptoms and characteristics, of COVID-19-positive (C19+) and COVID-19-negative (C19–) individuals who had reported recent symptoms of respiratory illness. Using those results in logistic regression models, we identified predictors of COVID-19 and recovery from smell loss. Finally, we propose the Olfactory Determination Rating scale for COVID-19 (ODoR-19) as a quick, simple-to-use, telemedicine-friendly tool to improve the utility of current COVID-19 screening protocols, particularly when access to rapid testing for SARS-CoV-2 is limited.

Materials and methods

Study design

This preregistered (Parma, Veldhuizen, et al. 2020), cross-sectional online study was approved by the Office of Research Protections of The Pennsylvania State University (STUDY00014904); it is in accordance with the revised Declaration of Helsinki, and compliant with privacy laws in the United States and European Union. Data reported here were collected from the Global Consortium for Chemosensory Research (GCCR) core questionnaire (Appendix 1 and <https://gcchemosens.org>; Parma, Ohla, et al. 2020). This online crowdsourced survey is currently deployed in 35 languages among community-dwelling individuals via social and traditional media as well as the GCCR website. It was also presented to clinicians to relay to their patients. The goal of the survey was to determine if changes in chemosensory function distinguish individuals with COVID-19 from those with other respiratory illnesses. The survey included binary response and categorical questions (e.g., Appendix 1, Questions 6, 9) and visual analog scales (VAS) (e.g., Appendix 1, Question 13) to measure self-reported chemosensory ability and other symptoms in adults with current or recent respiratory illness. Data reported here include responses in Arabic, Bengali, Chinese (Simplified and Traditional), Danish, Dutch, English, Farsi, Finnish, French, German, Greek, Hebrew, Hindi, Italian, Japanese, Korean, Norwegian, Portuguese, Russian, Spanish, Swedish, Turkish, and Urdu.

The GCCR survey has been online since 7 April 2020. Data collected between 7 April and 18 April 2020 were previously analyzed with respect to chemosensory function of participants with a positive COVID-19 diagnosis (Parma, Ohla, et al. 2020).

Sample description

After applying preregistered exclusion criteria (Parma, Veldhuizen, et al. 2020), 15 747 participants were included in reported analyses. Their demographic information is summarized in Figure 1. The inclusion criteria for the present analyses were: recent or current respiratory illness (resolution of symptoms no more than 2 weeks prior to survey completion, if no, excluded), a specific date of onset for respiratory illness symptoms (any date since 1 January 2020), and a reported COVID-19 diagnosis via laboratory test (e.g., viral PCR or antigen test, based on Question 6; see below). The entry criterion for participation in the survey was a recent (symptoms present in the past 2 weeks) or current respiratory illness. Accordingly,

only participants who responded “yes” to Question 6—“Within the past 2 weeks, have you been diagnosed with or suspect that you have a respiratory illness?”—were allowed to complete the survey (see Appendix 1 for all survey questions). To investigate the recovery of chemosensory functions, we only included participants who provided the date of onset of respiratory illness symptoms (Question 7: “What date did you first notice symptoms of your recent respiratory illness?”). Based on responses to Question 8—“Have you been diagnosed with COVID-19?”—participants were assigned to either of four groups (Figure 1). The C19+ Lab-tested group (C19+) included those that responded with either option 2 (“Yes—diagnosed with viral swab”) or option 3 (“Yes—diagnosed with another lab test”). The C19– Lab-tested group (C19–) responded with option 5 (“No, I had a negative test, but I have symptoms”). The C19+ Clinical group responded with option 1 (“Yes—diagnosed with symptoms only”). The C19 Unknown group responded with option 4 (“No, I was not diagnosed, but I have symptoms”). Participants who responded with option 6 (“No—I do not have any symptoms”), option 7 (“Don’t know”), or option 8 (“Other”) were deemed undefinable and excluded from these analyses. Symptom characteristics in C19+ and C19– groups are reported in Supplementary Table S1.

The specific collider bias characterizing this sample due to the high fraction of C19+ participants and high prevalence of chemosensory disorders in both groups underestimates the positive correlation between smell loss and COVID-19 (Supplementary Figure S1). Thus, it represents a conservative scenario to test the hypothesis that smell loss reliably predicts COVID-19 status. We also conducted propensity matching to produce equally sized populations of C19+ and C19– subjects ($n = 546$ each) with matched age and gender distributions, obtaining results similar to those reported in the main text (Supplementary Figure S1). We benchmarked the GCCR data set to the representative samples collected with the Imperial College London YouGov Covid 19 Behaviour Tracker (henceforth, YouGov; countries shared across data sets: Brazil, Canada, Denmark, Finland, France, Germany, Italy, Mexico, the Netherlands, Norway, Spain, Sweden, the United Kingdom, the United States; YouGov: $N = 8674$, GCCR: $N = 3962$; data publicly available at <https://github.com/YouGov-Data/covid-19-tracker>). Benchmarking shows the GCCR sample underestimates the positive association between smell loss and C19+ (Supplementary Figure S1, Supplementary Table S2). The country-wise fraction of C19+ participants is correlated ($r \sim 0.45$) when responses from the same calendar

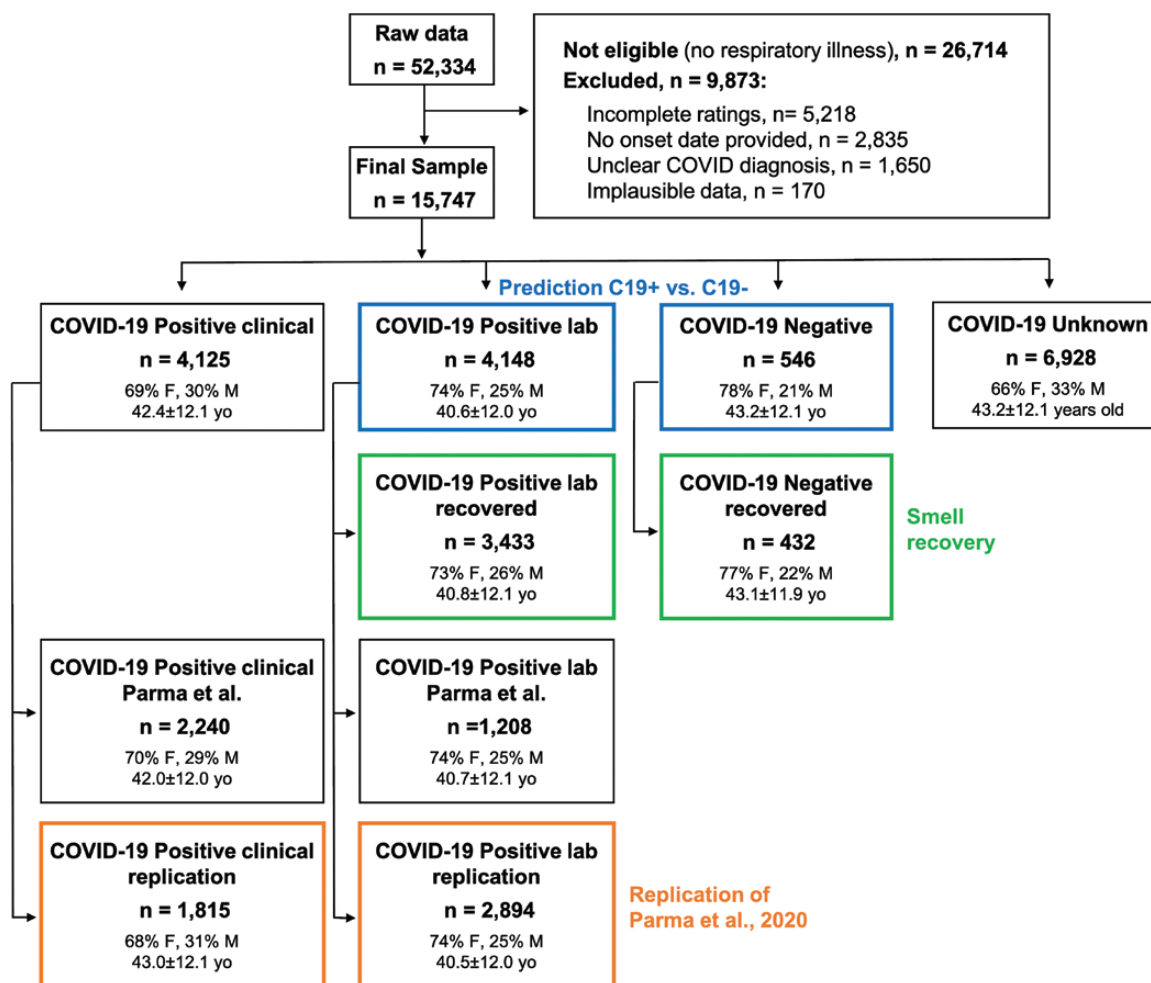


Figure 1. Flow diagram showing participant demographics. Participants included in the prediction of COVID-19 status are framed in blue. Participants included in the smell recovery models are framed in green. Participants included in the replication of a previous study (Parma, Ohla, et al. 2020; Parma, Veldhuizen, et al. 2020) are framed in orange. Gender percentages omit <1% of participants who answered “other” or “preferred not to say.” Participants described in the green boxes are a subset of those described in the blue boxes. n = number of participants; yo = age in years; W = women; M = men; unclear COVID diagnosis = responses “No—I do not have any symptoms,” “Don’t know” or “Other” to survey Question 8 (“Have you been diagnosed with COVID-19?”).

week are aligned (Supplementary Figure S2). These findings are in line with other comparisons between crowdsourced versus representative health data (Kraemer et al. 2017), confirming that trends identified in crowdsourced data reasonably approximate population data. Because the GCCR cohort is not demographically balanced, it should not be used to estimate prevalence. However, the representative YouGov cohort indicates globally one-third of C19+ individuals report smell loss (Supplementary Table S1).

Statistical analyses

Statistical analyses were performed in Python 3.7.6 using the pandas (Reback et al. 2020), scikit-learn (Pedregosa et al. 2011), and statsmodels (Seabold and Perktold 2010) packages. The data and annotated code are included as Supplementary material and will be publicly available on GitHub (<http://github.com/GCCR/GCCR002>) upon publication. The data matrix derived from survey responses had strictly nonnegative values and was normalized (column-wise $\min = 0$, $\max = 1$) to apply regularization in an equitable fashion across variables and give regression coefficients the same interpretation for each feature. Missing values were handled as follows: we only included participants in the recovery group who responded to questions pertinent to recovery (Appendix 1, questions 28–32). Other missing data were limited to: (1) a detailed breakdown of smoking frequency (questions 35 and 37) for self-reported nonsmokers, imputed as zero frequency; (2) an absence of any listed prior conditions in question 38 (including “None”) for 6% of respondents, imputed as no prior conditions; (3) 1.9% of respondents did not indicate whether they had recovered from illness or not, and who were dropped from analysis of recovery; and (4) <0.02% of questions about specific taste qualities, imputed with median values. Prediction targets themselves were never imputed. Responses incompatible with model generalization (e.g., open-ended questions) were excluded. A one-hot encoding was applied to all categorical variables to produce binary indicators of category membership.

L1-regularized logistic regression models using a range of penalty values (α) were assessed using cross-validation. Each model attempted to predict, using the value of the response to a single question (and an additive constant), whether a subject reported a C19+ or C19– status. Coefficients in a logistic regression model can be interpreted as changes in odds or as odds ratios when two values are compared. Each such model included an intercept term and one or more normalized variables. We obtained very similar results for all values of α (results not shown), as expected, because the sample size is much larger than the number of variables. Models with similar AUC values (but with nonzero coefficients for additional, likely spurious variables) were obtained for smaller values of α , and inferior results for larger ones (which contained fewer or no nonzero coefficients). We reported results for $\alpha = 1$ here, as it consistently produced sparse models with the highest cross-validation accuracy. Quantitatively similar AUC values were obtained for other models predicting COVID-19 status using multiple variables including ridge regression and random forest, but L1-regularized logistic regression consistently produced sparser models with comparable cross-validation accuracy.

Model quality was measured using receiver operating characteristic (ROC) area under the curve (AUC). Each ROC curve—constructed using predictions on holdout test sets and concatenated over these test sets—summarizes the tradeoff between sensitivity (fraction of C19+ cases correctly identified) and specificity (fraction of C19– cases correctly identified) as the threshold value for the predictor is varied. Cross-validation was performed in 100 random splits of

80% training set and 20% test set, and ROC curves were concatenated over each test set. ROC curves were computed on predicted probabilities from each model, circumventing the high-cardinality bias of AUC. For univariate models, ROC curves are invariant to all monotonic transformations of the data, and thus AUC is independent of most modeling details. To correctly compute P values for model coefficients, the normalized data were standardized (mean 0, variance 1) and then coefficients back-transformed to normalized form after fitting. Uncertainty is given as \pm standard deviation for descriptive analyses, and \pm standard error for model-derived quantities (e.g., AUC). For the replication of Parma, Ohla, et al. (2020), we included Bayes factors (BF) and we used data newly collected from 19 April to 3 July 2020 (see Supplementary Material, Supplementary Figure S3, Supplementary Table S2).

Results

Chemosensory loss associates with COVID-19

In a previous publication using an earlier tranche of data obtained from this survey, we reported that smell, taste, and chemesthesis abilities drop significantly in both lab-tested C19+ participants and those diagnosed by clinical assessment (Parma, Ohla, et al. 2020). In a preregistered replication of that analysis, we confirm those findings using the current data tranche (Supplementary Figure S3, Supplementary Table S3).

Next, we compared chemosensory abilities and nasal blockage in lab-tested C19+ and C19– participants. Ratings for each of these before the onset of respiratory illness (baseline ratings) show small (2–3 points on a 100-point scale) but significant (smell, $P = 3.2 \times 10^{-5}$; taste, $P = 1.8 \times 10^{-6}$; chemesthesis, $P = 0.016$; nasal blockage, $P = 0.004$) differences between C19+ and C19– individuals, as expected with very large sample sizes (Figure 2). However, these differences are much smaller than the chemosensory differences seen between C19+ and C19– individuals during their illness: C19+ participants reported a greater loss of smell (C19+: -82.5 ± 27.2 points; C19–: -59.8 ± 37.7 points; $P = 1.1 \times 10^{-59}$, extreme evidence of difference: $BF_{10} = 8.97 \times 10^{+61}$; Figure 2A,B, Supplementary Table S4), taste (C19+: -71.6 ± 31.8 points; C19–: -55.2 ± 37.5 points; $P = 7 \times 10^{-24}$, extreme evidence of difference: $BF_{10} = 6.67 \times 10^{+24}$; Figure 2C,D, Supplementary Table S4) and chemesthesis ability (C19+: -36.8 ± 37.1 points; C19–: -28.7 ± 37.1 points; $P = 4.6 \times 10^{-5}$, extreme evidence of difference: $BF_{10} = 3182$; Figure 2E,F, Supplementary Table S4). However, both groups reported a similar degree of nasal obstruction (Figure 2G,H, Supplementary Table S4). Self-reported changes in smell, taste, and chemesthesis were highly correlated within both groups (C19+: $0.71 < r < 0.83$; C19–: $0.76 < r < 0.87$) and orthogonal to nasal obstruction changes (C19+: $r = -0.20$; C19–: $r = -0.13$).

Prediction of COVID-19 status from survey responses

When only binary (yes/no) and categorical responses are analyzed, we found that chemosensory symptoms are more strongly associated with COVID-19 than are fever, cough, or other common non-chemosensory symptoms (Figure 3A). Using AUC to assess prediction quality (Figure 3B), we found that self-reported smell ability during illness, reported on a continuous scale, was the most predictive survey question for COVID-19 status (AUC = 0.71). Changes in smell as a result of illness (i.e., the difference between smell ability during and before illness) were similarly predictive (AUC = 0.69). Changes in taste ability (assessed via rating) were the next most predictive

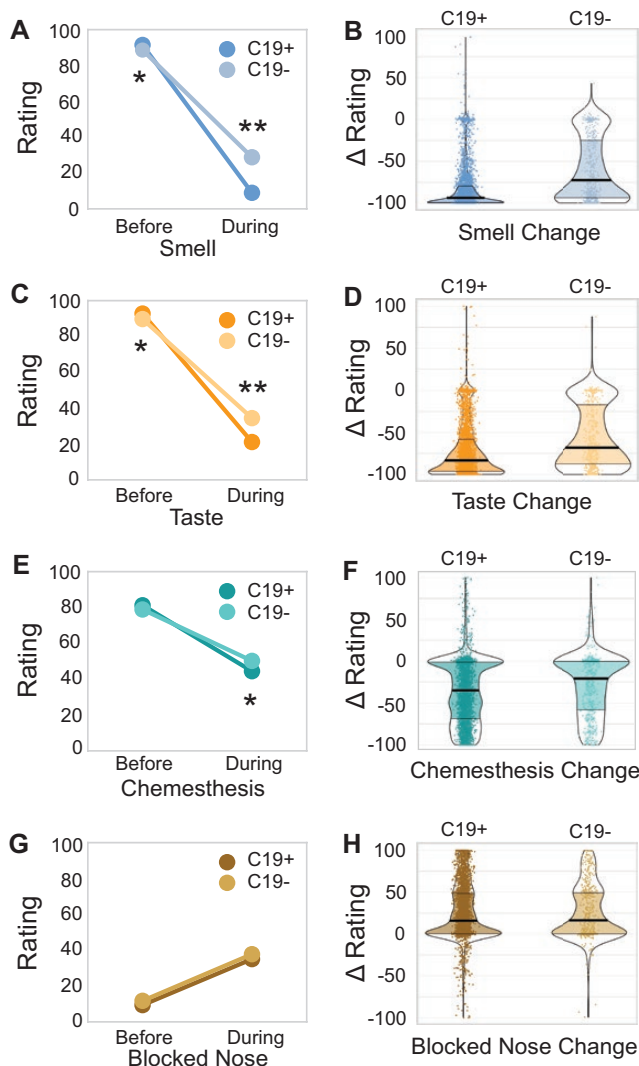


Figure 2. Chemosensory ability and nasal obstruction in C19+ and C19- participants. Self-reported smell (A, B), taste (C, D), chemesthesis (E, F), and nasal obstruction (G, H: formulated as “How blocked was your nose?”) before and during respiratory illness in C19+ (darker shades) and C19- (lighter shades) participants. Ratings were given on 0–100 visual analog scales. Left panels (A, C, E, G) show mean values. Right panels (B, D, F, H) show distributions of the change scores (during minus before). Thicker sections indicate relatively more subjects (higher density of responses). The thick black horizontal bar indicates the median, the shaded area within each violin indicates the interquartile range. Each dot represents the rating of a single participant. * indicates $P < 10^{-4}$, ** indicates $P < 10^{-23}$.

variables (AUC = 0.64–0.65) (Figure 3B). Models fit to the same data but with shuffled COVID-19 status consistently produced AUC ~0.5 for all variables. The most predictive non-chemosensory symptom, sore throat (which was negatively associated with COVID-19) was substantially less predictive (AUC = 0.58) than the top chemosensory symptoms. Nasal obstruction was not predictive (AUC = 0.52). Responses given on a continuous scale were more predictive (AUC = 0.71) than binary responses to parallel questions (e.g., Appendix 1, Question 10 and 15 vs. 14, Supplementary Figure S5) (AUC = 0.60–0.62), likely because a continuous scale contains a greater amount of diagnostic information (Supplementary Figure S4).

Next, we examined which simple multivariate model would best predict COVID-19 status. As some questions have highly correlated

responses, the question most complementary to “Smell during illness” is unlikely to be one that carries redundant information. Adding “Days since Onset of Respiratory Symptoms” (DOS), which was measured relative to the survey completion date, to “Smell during illness” (Smell Only) produced the largest incremental gain in predictive performance (AUC = 0.72, +0.01 vs. the Smell Only model) (Figure 3C).

We directly compared the Smell Only + DOS model to other candidate models. The Smell Only + DOS model (Figure 3D) yielded an equal or higher AUC than the model including the three cardinal symptoms (fever, cough, difficulty breathing) identified by the US Centers for Disease Control and Prevention (CDC) (AUC = 0.55) or the full model using 70 variables (AUC = 0.72). Because the Smell Only + DOS model exhibits the same AUC as the full model it strikes a good balance between model parsimony and predictive accuracy for C19+. However, the Smell Only model also offers reasonable sensitivity of 0.85 (at specificity = 0.51, cutoff = 13 on the 100-point VAS) and/or specificity of 0.75 (at sensitivity = 0.51, cutoff = 1) as desired. By sharp contrast, fever has a sensitivity of only 0.54 with specificity of 0.49, and dry cough has sensitivity of 0.52 and specificity of 0.46. Since some subjects had already fully ($N = 1867$) or partially ($N = 1998$) recovered from their respiratory symptoms by the date of completion of the survey, we asked how effectively Smell loss and DOS predict COVID-19 status in the most clinically actionable population: those whose core respiratory symptoms had not resolved. If we exclude those participants who had fully recovered from their respiratory symptoms at the time of survey completion, the ability to predict C19+ status based on Smell Only and Smell Only + DOS increases (Smell Only AUC = 0.73, Smell Only + DOS AUC = 0.76; $N = 2827$). Further excluding those who had partially recovered from respiratory symptoms produced even larger gains (Smell Only AUC = 0.750 Smell During + DOS AUC = 0.788; $N = 829$).

Recovery from smell loss

Recovery from smell loss was modest (approximately half the initial average loss) in C19+ participants with full or partial resolution of respiratory symptoms. Overall, self-reported, post-illness olfactory ability was still lower for C19+ (39.9 ± 34.7) than C19- (52.2 ± 35.2 , $P = 2.8 \times 10^{-11}$, Supplementary Figure S6A). However, the mean recovery of smell (after illness relative to during illness) was greater for C19+ (30.5 ± 35.7) than C19- (24.6 ± 31.9 , $P = 0.0002$, Supplementary Figure S6B). A similar but smaller effect of COVID-19 status on recovery was observed for taste (Supplementary Figure S6C,D), whereas little to no association with COVID-19 was observed for recovery of chemesthesis (Supplementary Figure S6E,F) or nasal obstruction (Supplementary Figure S6G,H). When illness-induced change in olfactory function (during minus before illness) and recovery of olfactory function (after minus during illness) were evaluated, we identified three respondent clusters: those self-reporting no loss of smell (Intact Smell), those reporting recovery from smell loss (Recovered Smell), and those reporting smell loss without recovery by up to 40 days (Persistent Smell Loss, Figure 4, Supplementary Table S4). Intact smell was reported by only 8.5% of the participants in the C19+ group but by 27.5% in the C19- group ($P = 3.8 \times 10^{-31}$). A greater proportion of C19+ participants were included in both the Recovered Smell group (C19+: 40.9%, C19-: 33.3%; $P = 4.9 \times 10^{-10}$) and the Persistent Smell Loss group (C19+: 50.7%, C19-: 39.2%; $P = 5 \times 10^{-5}$; Figure 4A,B). Using logistic regression, the only variable that could predict the probability of recovery from smell loss was DOS (AUC = 0.62); all other

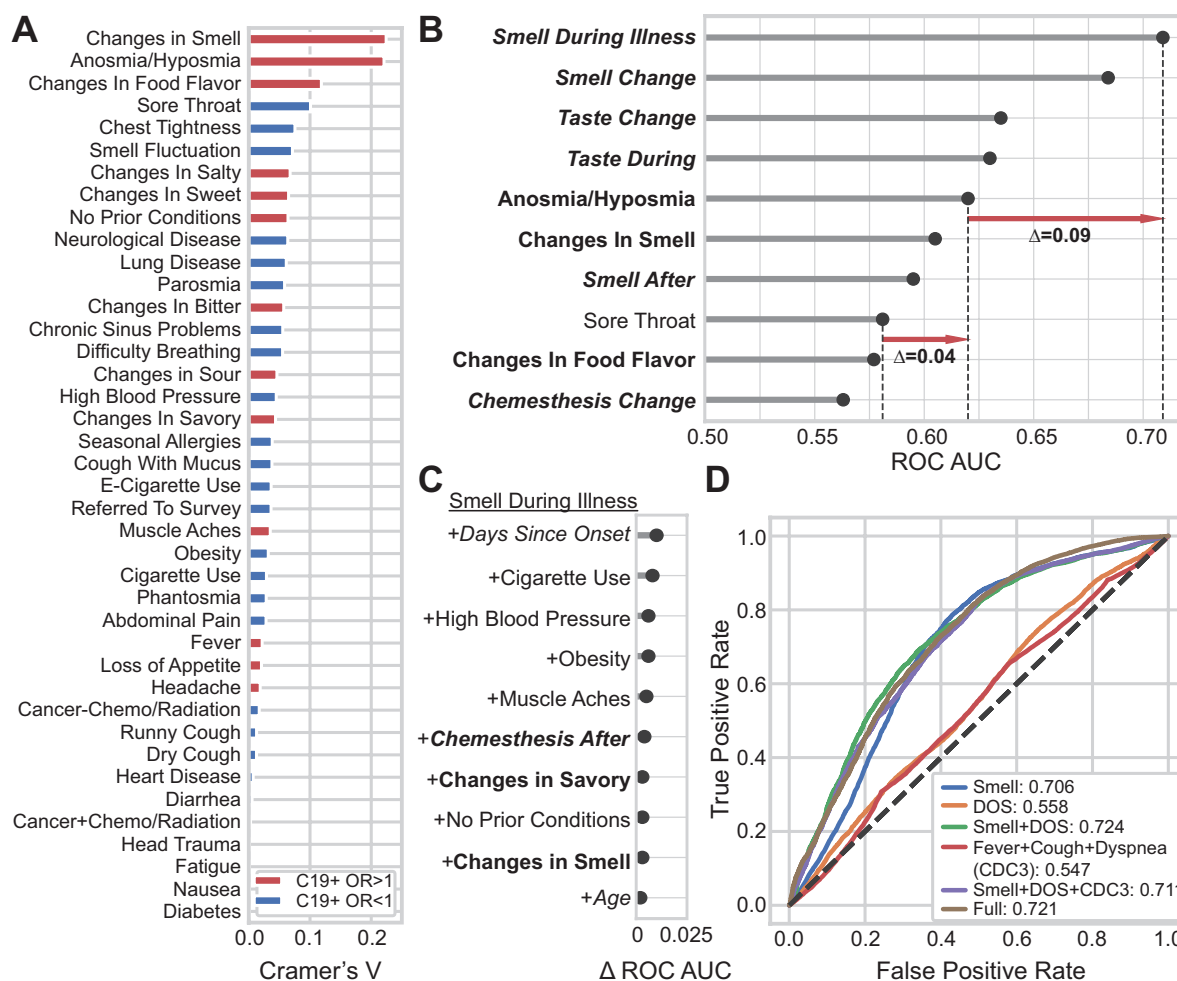


Figure 3. Smell loss is the strongest predictor of COVID-19 status. (A) A normalized measure of association (Cramer's V) between binary or categorical responses on COVID-19 status. $V = 0$ reflects no association between the response and COVID-19 status; $V = 1$ reflects a perfect association; $V > 0.1$ is considered a meaningful association. Variables in red are positively associated with C19+ (odds ratio > 1); variables in blue are negatively associated with C19+ (odds ratio < 1). (B) Logistic regression is used to predict COVID-19 status from individual variables. Top-10 single variables are ranked by performance (cross-validated area under the ROC curve, AUC). Chemosensory-related variables (bold) show greater predictive accuracy than non-chemosensory variables (non-bold). Responses provided on the numeric scale (italic) were more informative than binary responses (non-italic). Red arrows indicate differences in prediction quality (in AUC) between variables. (C) Adding variables to "Smell During Illness" results in little improvement to the model; only Days Since Onset of Respiratory Symptoms (DOS) relative to survey completion date yields meaningful improvement. (D) ROC curves for several models. A model using "Smell during illness" (Smell Only, abbreviated "Smell" in the figure) is compared against models containing this feature along with DOS, as well as models including the three cardinal CDC variables (fever, dry cough, difficulty breathing). "Full" indicates a regularized model fit using 70 survey variables, which achieves prediction accuracy similar to the parsimonious model "Smell Only + DOS."

single variables were extremely poor predictors ($AUC \leq 0.54$). DOS is not acting as a proxy for initial smell loss: C19+ participants in both the Recovered Smell and Persistent Smell Loss clusters reported a similar *magnitude* of olfactory loss, irrespective of time since respiratory symptom onset. By contrast, the degree of self-reported smell recovery increased over time, with a plateau at 30 days (Figure 4C).

Simple screening for COVID-19: the ODoR-19

Our results indicate that a continuous rating of current olfactory function is the single best predictor of COVID-19 in the presence of respiratory symptoms and it improves the discrimination between C19+ and C19- compared with a binary question on smell loss. For example, the Smell Only model reached a specificity of 0.83 at the low end of the VAS (sensitivity = 0.36, cutoff = 0). When considering

the odds of a COVID-19 diagnosis as a function of current olfactory ability, our data indicate that this probability is greater than 0.8 when current smell ability is rated at 20 or below on a 0–100 scale (Figure 5A). This rating translates into an odds ratio > 4 (Figure 5B). The inflection point at which the odds ratio plateaus at 1 is 30/100 (Figure 5C).

A 0–10 rating scale, such as the pain scale, is widely used in clinical environments. With the goal of enabling clinicians and other health professionals to quickly and simply assess self-reported smell loss in the context of COVID-19, we transformed the 0–100 rating scale used in this survey to a 0–10 numeric rating scale, the ODoR-19. In our samples, responses to the ODoR-19 scale ≤ 2 indicate high odds of COVID-19 positivity ($4 < OR < 10$, Figure 5D). An ODoR-19 response of 3 indicates a borderline risk ($OR = 1.2$). Upon independent validation, the ODoR-19 could be administered in person

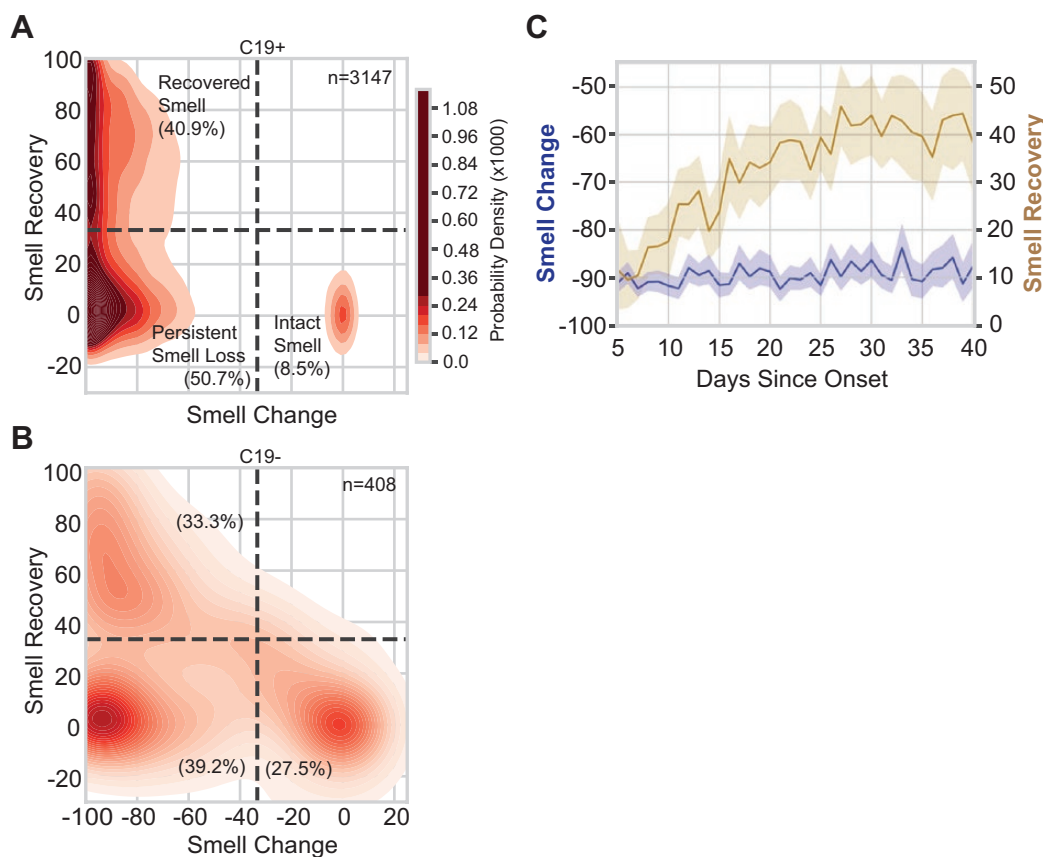


Figure 4. Smell loss, recovery, and time course. (A, B) Joint distribution of smell loss (during illness ratings) and smell recovery (after illness ratings) for C19+ (A) and C19- (B) participants. Darker color indicates a higher probability density; the color map is shared between (A) and (B); dashed lines are placed at a third of the way across the rating scale to aid visualization of the clusters. Severe smell loss that is either persistent (lower left) or recovered (upper left) was more common in C19+ than C19-. *n* indicates the number of participants in each panel. % indicates the percentage of participants of the given COVID status in each quadrant. (C) In C19+ participants who lost their sense of smell (Recovered Smell + Persistent Smell Loss), the degree of smell recovery (right y axis) increased over ~30 days since onset of respiratory symptoms before plateauing; the degree of reported smell change (left y axis) did not vary in that window of observation. Solid lines indicate the mean of the measure, the shaded region indicates the 95% confidence interval.

or via telemedicine to improve early COVID-19 screening for individuals without preexisting smell and/or taste disorders.

Discussion

Self-reported smell loss was much greater in C19+ than C19- participants, but present in both groups. The use of a VAS to assess olfactory loss better predicted COVID-19 status than using a binary question. We found that the best predictor of COVID-19-associated smell recovery, within the time frame captured by the survey (~40 days), was DOS.

The SARS-CoV-2 pandemic requires healthcare providers and contact tracers to quickly and reliably assess an individual's COVID-19 risk, often remotely. Thus, reliable screening tools are critical to assess a person's likelihood of having COVID-19 and to justify self-quarantine and/or testing recommendations. Indeed, some reports suggest that COVID-19-associated smell loss might be an indicator of disease severity (Paderno et al. 2020; Yan, Faraji, Prajapati, Ostrander, et al. 2020). Current symptom criteria (e.g., fever, dry cough) are less specific than severe olfactory loss in distinguishing between COVID-19 and other respiratory illnesses. Indeed, the value of our ODoR-19 tool would lie in the high specificity of values ≤ 2 for indicating COVID-19 positivity, as seen with our sample, therefore representing a valuable addition to the current repertoire of

COVID-19 screening tools. Those who receive a negative outcome from a COVID-19 viral test, yet report significant idiopathic smell loss, should be considered as high-priority candidates for COVID-19 re-testing and self-isolation.

Our online survey and sampling methodology likely selected participants with a heightened interest in smell and taste and/or their disturbances. This self-selection bias could be viewed as a limitation because the C19- group also showed chemosensory loss. However, finding a difference between groups in a sample with a high barrier for discriminating between C19+ and C19- supports the robustness of our findings. A simple model of collider bias suggests that our findings are likely conservative estimates of the association between COVID-19 and smell loss (Supplementary Figure S1). Additionally, this observation is supported by the correlation between the GCCR survey data and that of the representative YouGov data reported here (Supplementary Figure S2, Supplementary Table S2).

Our results suggest that chemosensory impairment has strong COVID-19 predictive value, and is useful when access to viral testing is limited or absent. As with any self-report measure, veracity of self-reports cannot be guaranteed. However, the ability to screen individuals in real-time should outweigh this potential confound (Mermelstein et al. 2007). While objective smell tests are the gold standard for assessing olfactory function (Doty et al. 1984; Hummel

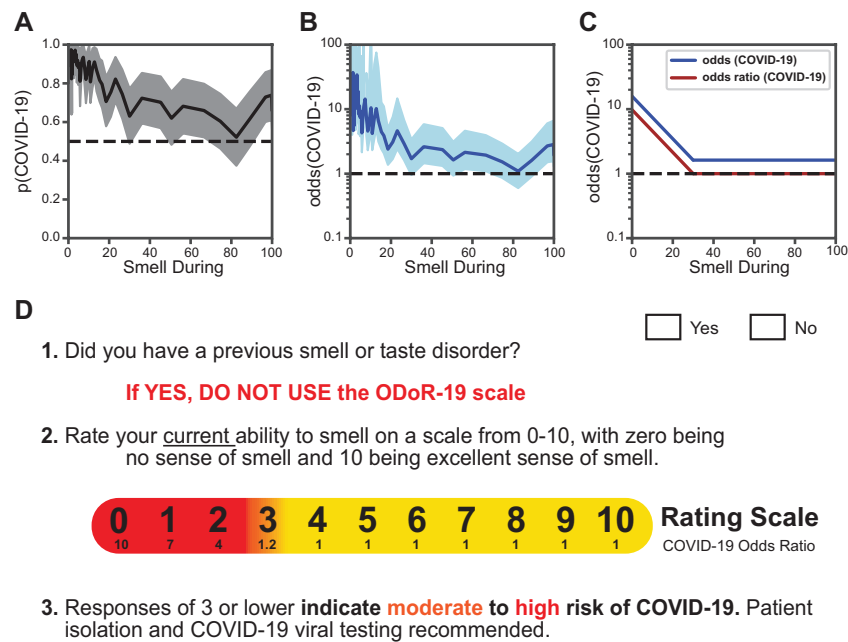


Figure 5. The odds of a COVID-19 diagnosis as a function of olfactory ability in individuals with respiratory symptoms. (A) The solid line indicates the probability of a COVID-19 diagnosis as a function of “Smell during illness” ratings in our sample. The shaded region indicates the 95% confidence interval. (B) The solid line expresses the probability of a COVID-19+ diagnosis as a function of “Smell during illness” in odds ($p/[1-p]$); it is shown on a logarithmic scale. The shaded region indicates the 95% confidence interval. (C) Stylized depiction of change in the odds of a COVID-19 diagnosis and of the odds ratio. (D) The ODoR-19 tool. After healthcare providers or contact tracers have excluded previous smell and/or taste disorders (such as those resulting from head trauma, chronic rhinosinusitis, or previous viral illness) in patients with respiratory symptoms, the patient can be asked to rate their *current* ability to smell on a scale from 0 to 10, with 0 being no sense of smell and 10 being excellent sense of smell. If the patient reports a value below or equal to 3, there is a high (red) or moderate (orange) probability that the patient has COVID-19. Values in yellow (ratings above 3) cannot rule out COVID-19.

et al. 1997), they are costly, time-consuming to administer, and can require in-person interactions with potentially infectious patients (Doty et al. 1984; Oleszkiewicz et al. 2019). By contrast, self-report measures are free, quick, and can be administered in person or remotely. We cannot exclude that our C19- sample contains COVID-19 false negatives (Kucirka et al. 2020). However, self-reported smell during illness distinguishes between C19+ and C19-, but not between randomly shuffled cases, suggesting that the difference between C19+ and C19-, even in a sample with over-represented chemosensory dysfunction, is substantial and can be captured via self-report.

Approximately half of the participants in the C19+ group had recovered their sense of smell by the date that they completed the survey (Figure 4A). The mean recovery from smell loss increased with duration from respiratory symptom onset for ~30 days before reaching a steady-state for at least an additional 10 days, suggesting the presence of at least two subgroups of participants: one group (40.9%) that recovers more quickly (within 30 days of respiratory symptom onset) and another (50.7%) that may take more time to recover. Our survey may overestimate the size of the latter group because some individuals who recover from respiratory symptoms within 2 weeks of their onset may have been missed in our sample due to the recruitment criteria. While we cannot offer a complete picture of recovery from olfactory loss in COVID-19-positive individuals, they do align with other early reports (Chiesa-Estomba et al. 2020). The COVID-19 pandemic will greatly increase the number of patients suffering from anosmia and other chemosensory disorders (Rawal et al. 2016), conditions that significantly affect quality of life (Smeets et al. 2009; Croy, Nordin, et al. 2014), dietary behavior (Kershaw and Mattes 2018), cardiovascular health (Gallo et al. 2020), and mental health (Malaty and

Malaty 2013; Croy, Symmank, et al. 2014). Thus, it is necessary to prepare healthcare providers to address the long-term needs of these patients.

Based on our results, we propose the use of the ODoR-19 tool, a quick, free, and effective smell-based screening method for COVID-19. ODoR-19 combines the utility of a continuous scale with the ease and speed needed for a screening tool for individuals without preexisting smell and taste disorders (e.g., from head trauma, chronic rhinosinusitis; Malaty and Malaty 2013). ODoR-19 is safe for remote administration during an illness with high viral spread and can precede and complement viral testing. This tool has the potential to improve screening for patients with limited or no access to medical care around the globe.

Supplementary material

Supplementary data are available at *Chemical Senses* online.

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Conflict of interest

R.C.G. is an advisor for Climax Foods, Equity Compensation (RCG); K.O. consults for for-profit corporations and nonprofit organizations on topics related to food/consumer product perception; J.E.H. has consulted for for-profit food/consumer product corporations in the last 3 years on projects wholly unrelated to this study; also, he is Director of the Sensory Evaluation Center at Penn State, which routinely conducts product tests for industrial clients to facilitate experiential learning for students. Since 2018, T.H. collaborates with and received funding from Sony, Stuttgart, Germany; Smell and Taste Lab, Geneva, Switzerland; Takasago, Paris, France; aspUraclip, Berlin, Germany. C.E.K. is the founder of AbScent, a charity registered in England and Wales, No. 1183468. C.L. has received funding from scent related institutions and corporations, however, for work totally unrelated to the field of the present study. S.D.M. is Editor-in-Chief of *Chemical Senses*. He played no role in the editorial assessment of this paper.

Author contributions

Author contributions are described according to the following single letter codes and follow the CRediT Contributor Roles taxonomy.

Conceptualization—"C," Methodology—"M," Data Curation—"D," Formal Analysis—"A," Funding Acquisition—"F," Investigation—"I," Project Administration—"A," Resources—"R," Software—"S," Supervision—"U," Validation—"L," Visualization—"V," Writing Original Draft—"W," Writing Review Editing—"E."

Author contributions are as follows: V.P.—CMDAIRULVWE; R.C.G.—CMDAIRSLVWE; S.D.M.—CMDAIAULVWE; K.O.—CMIAIRULVWE; A.J.B.—CMDIARSUE; A.D.P.—CMIAIRULVWE; J.E.H.—CMDFIARUE; M.Y.N.—CMDIARUWE; M.Y.P.—DAIRULVWE; M.G.V.—CMIAIRUWE; K.W.C.—DIARSLWE; M.D.—AIARULWE; P.B.S.—CMFIRUWE; V.E.B.—CMDIARLE; D.R.R.—CMIAUWE; I.C.—CMDIRWE; M.K.A.—CMDIARE; M.A.F.—FIARULE; M.A.S.—MIARUWE; P.V.J.—CMARUWE; A.A.—IARUWE; A.W.F.—DIRUWE; A.M.—CMIRWE; C.H.—MIARWE; C.E.K.—CMARUE; D.P.—IRULWE; G.A.—CMIARE; G.M.—CMIRWE; G.M.S.—MILWE; I.K.—IARUWE; J.G.—IARUWE; J.W.H.—CMIUWE; K.L.W.—CMIUWE; L.D.H.—MIARWE; L.Ö.—IARUWE; M.H.O.—CMIRWE; O.C.—CMIRWE; S.B.O.—MIARUE; T.H.—CMAUWE; V.P.L.—MILWE; A.D.E.—CIRWE; A.M.—MIRUL; C.L.—DIARS; E.R.—CIRUE; F.P.S.F.—MIRLE; H.Y.—MIRWE; J.L.—MIRWE; J.N.L.—MFIRE; J.K.O.—MFIRE; L.R.S.—IARUE; M.B.—MIUWE; M.A.B.—DIRUE; C.M.P.—CIUWE; R.P.—MILWE; S.B.—CMIWE; S.S.—MIRWE; V.V.V.—IRUWE; A.A.N.—MIWE; A.N.P.—IRWE; C.D.—IRWE; C.L.—MIRE; D.S.—MDRE; E.C.—CIWE; E.M.—IRWE; E.S.—IWE; F.F.—MRUE; J.A.—DIRE; J.C.—DIRE; J.F.—IRWE; J.W.M.—CMIE; J.d.G.—CIWE; K.E.S.—CMWE; M.D.G.—IRWE; M.N.—CMIR; O.A.—RLWE; P.M.—MIWE; P.P.M.—IRWE; P.R.D.—IRWE; R.A.A.—CIUE; S.B.—MIRE; S.T.M.—IRWE; T.H.—IUWE; T.L.—IRWE; T.T.D.—ILWE; V.D.C.S.—IUWE; W.F.—IRUE; B.C.—IRE; C.B.—SLE; C.H.—IWE; C.M.—IWE; E.L.F.—IWE; E.E.O.—IRE; J.F.—IRE; M.P.C.—IWE; M.C.F.—IWE; M.E.H.—MIE; M.P.—IUE; N.S.A.—IWE; N.K.—CMD; N.R.R.—IWE; O.S.—IWE; S.M.—RSU; M.R.—IRE; A.S.J.—LE; B.C.S.—ME; C.C.—WE; C.M.—AU; C.H.Y.—IE; E.B.—RE; E.A.D.V.—VE; E.A.S.—IE; G.C.—WE; H.K.—DR; J.M.J.—CE; J.B.O.—CE; K.C.H.—WE; N.P.—DV; P.K.K.—RE; R.A.—WE; R.A.—IR; R.D.H.—IE; S.K.—WE; S.C.R.—IE; V.A.R.—LE; Y.N.—IE; H.C.—IE; H.W.—IE; M.B.—IE; M.v.d.B.—IR; P.B.B.—IE.

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