Recent smell loss is the best predictor of COVID-19 among individuals with recent respiratory symptoms

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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±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<OR<10). Once independently validated, this tool could be deployed when viral lab tests are impractical or unavailable.

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 et al., 2020a; Menni et al., 2020b; Mizrahi et al., 2020; Moein et al., 2020; Paderno et al., 2020; Parma et al., 2020a; Walsh-Messinger et al., 2020; Weiss et al., 2020; Yan et al., 2020a). 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 **O**lfactory **D**eterminati**o**n **R**ating 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.

Methods

Study design

This preregistered (Parma et al., 2020b), 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 U.S.A. and European Union. Data reported here were collected from the Global Consortium for Chemosensory Research (GCCR) core questionnaire (**Appendix 1** and https://gcchemosensr.org; Parma et al., 2020a). 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 (RIs). The survey included binary response and categorical questions (e.g. **Appendix 1**, Questions 6, 9) and visual analog scales (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 April 7, 2020. Data collected between April 7 and April 18, 2020, were previously analyzed with respect to chemosensory function of participants with a positive COVID-19 diagnosis (Parma et al., 2020a).

Sample description

After applying pre-registered exclusion criteria (Parma et al., 2020b), 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 two weeks prior to survey completion, if no, excluded), a specific date of onset for respiratory illness symptoms (any date since January 1, 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 two weeks) or current respiratory illness. Accordingly, only participants who responded "yes" to Question 6 – "Within the past two 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 **Table S1**.

INSERT FIGURE 1 HERE

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 (**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 (**Figure S1**)**.** We benchmarked the GCCR dataset to the representative samples collected with the Imperial College London YouGov Covid 19 Behaviour Tracker (henceforth, YouGov; countries shared across datasets: Brazil, Canada, Denmark, Finland, France, Germany, Italy, Mexico, Netherlands, Norway, Spain, Sweden, UK, USA; YouGov: N=8,674, GCCR: N=3,962; 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+ (**Figure S1, Table S2**). The country-wise fraction of C19+ participants is correlated (r~0.45) when responses from the same calendar week are aligned (**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 (**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 is included as supplemental material and will be publicly available on GitHub (http://github.com/GCCR/GCCR002) upon publication. The data matrix derived from survey responses had strictly non-negative 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 I**, questions 28-32). Other missing data were limited to: (1) a detailed breakdown of smoking frequency (questions 35 and 37) for self-reported non-smokers, 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, since the sample size is much larger than the number of variables. Models with similar AUC values (but with non-zero coefficients for additional, likely spurious variables) were obtained for smaller values of α, and inferior results for larger ones (which contained fewer or no non-zero coefficients). We reported results for α=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 ± standard deviation for descriptive analyses, and ±standard error for model-derived quantities (e.g. AUC). For the replication of Parma et al. (2020a), we included Bayes Factors (BF) and we used data newly collected from April 19 to July 3, 2020 (see Supplementary Material, **Figure S3, 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 et al., 2020a). In a preregistered replication of that analysis we confirm those findings using the current data tranche (**Figure S3, 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, $p=3.2\times10^{-5}$; taste, $p=1.8\times10^{-6}$; 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; $p=1.1\times10^{-59}$, extreme evidence of difference: $BF_{10}=8.97e+61$; **Figure 2A,B; Table S4**), taste (C19+: -71.6±31.8 points; C19-: -55.2±37.5 points; $p=7\times10^{-24}$, extreme evidence of difference: $BF_{10}=6.67e+24$; **Figure 2C,D; Table S4**) and chemesthesis ability (C19+: -36.8±37.1 points; C19-: -28.7±37.1 points;

$p=4.6x10^{-5}$, extreme evidence of difference: $BF_{10}=3182$; **Figure 2E,F; Table S4**). However, both groups reported a similar degree of nasal obstruction (**Figure 2G,H; 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).

INSERT FIGURE 2 HERE

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) was similarly predictive (AUC=0.69). Changes in taste ability (assessed via rating) were the next most predictive 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 versus 14, **Figure S5**) (AUC=0.60-0.62), likely because a continuous scale contains a greater amount of diagnostic information (**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 "**D**ays since **O**nset of Respiratory **S**ymptoms" (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 versus 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 Days

Since Onset 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 only partially recovered from respiratory symptoms produced even larger gains (Smell Only AUC=0.750 Smell During + DOS AUC=0.788; N=829).

INSERT FIGURE 3 HERE

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=2.8e-11, **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, **Figure S6B**). A similar but smaller effect of COVID-19 status on recovery was observed for taste (**Figure S6C, D**), while little to no association with COVID-19 was observed for recovery of chemesthesis (**Figure S6E, F**) or nasal obstruction (**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, 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=3.8e-31). A greater proportion of C19+ participants were included in both the Recovered Smell group (C19+: 40.9%, C19-: 33.3%; p=4.9e-10) and the Persistent Smell Loss group (C19+: 50.7%, C19-: 39.2%; p=5e-5; **Figure 4A, B**). Using logistic regression, the only variable that could predict the *probability* of recovery from smell loss was Days Since Onset of respiratory symptoms (AUC=0.62); all other single variables were extremely poor predictors (AUC <=0.54). Days Since Onset of respiratory symptoms 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**).

INSERT FIGURE 4 HERE

Simple screening for COVID-19: the **O**lfactory **D**etermination **R**ating scale in COVID-**19** (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 to 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 indicates 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 or via telemedicine to improve early COVID-19 screening for individuals without preexisting smell and/or taste disorders.

INSERT FIGURE 5 HERE

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 days since onset of respiratory symptoms.

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 et al., 2020b). 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 since 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 (**Figure S1**). Additionally, this observation is supported by the correlation between the GCCR survey data and that of the representative YouGov data reported here (**Figure S2**, **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 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 two 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.). 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 et al., 2014a), dietary behavior (Kershaw and Mattes, 2018), cardiovascular health (Gallo et al., 2020), and mental health (Malaty and Malaty, 2013; Croy et al., 2014b). 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 pre-existing 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.

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Conflict of interest

Richard C. Gerkin is an advisor for Climax Foods, Equity Compensation (RCG); Kathrin Ohla consults for for-profit corporations and non-profit organizations on topics related to food/consumer product perception; John E. Hayes 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 Thomas Hummel collaborates with and received funding from Sony, Stuttgart, Germany; Smell and Taste Lab, Geneva, Switzerland; Takasago, Paris, France; aspuraclip, Berlin, Germany. Christine E. Kelly is the founder of AbScent, a charity registered in England and Wales, No. 1183468. Christophe Laudamiel has received funding from scent related institutions and corporations, however for work totally unrelated to the field of the present study. Steven D. Munger is Editor-in-Chief of *Chemical Senses*. He played no role in the editorial assessment of this paper.

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Figure captions

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 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?").

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 $p < 10^{-23}$.

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 **D**ays Since **O**nset of Respiratory **S**ymptoms relative to survey completion date (DOS) yields meaningful improvement. (**D**) ROC curves for several models. A model using "Smell during illness" (Smell Only, abbreviated "Smell" in 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".

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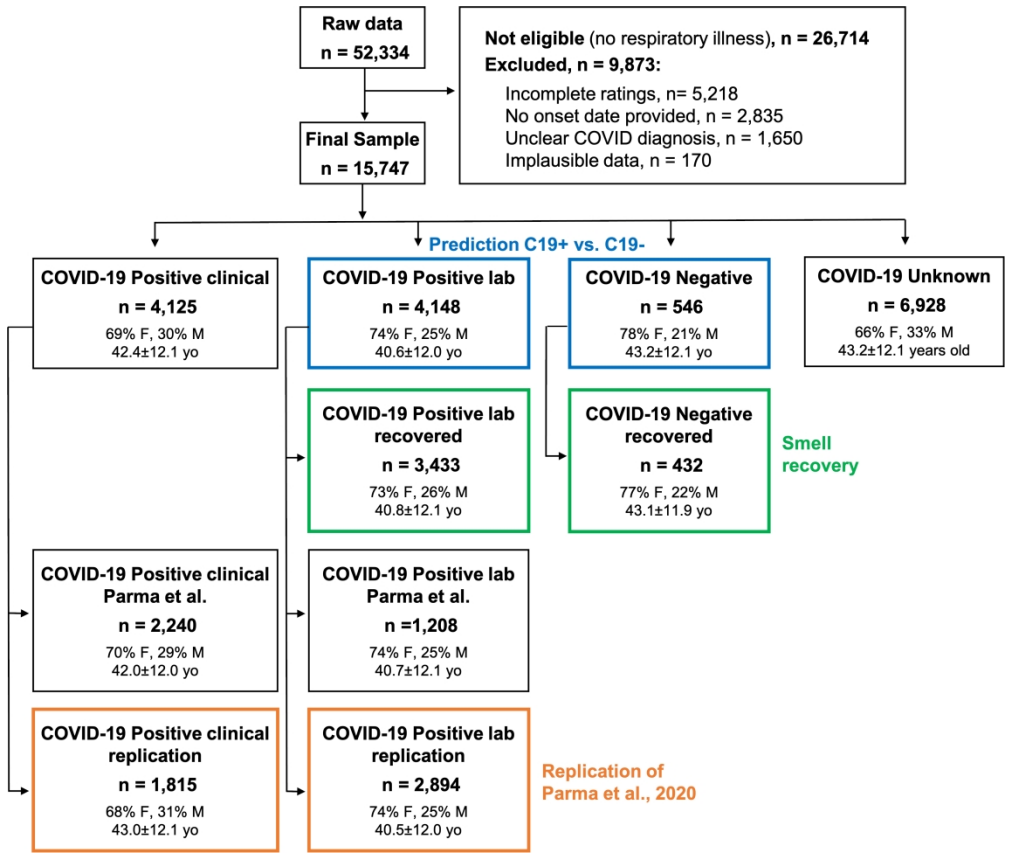
Figure 5. The odds of a COVID-19 diagnosis as a function of olfactory ability in individuals with respiratory symptoms. (**A**) The solid line indicates the probability of a COVID-19 diagnosis as a function of "Smell during illness" ratings in our sample. The shaded region indicates the 95% confidence 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 0-10, 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.



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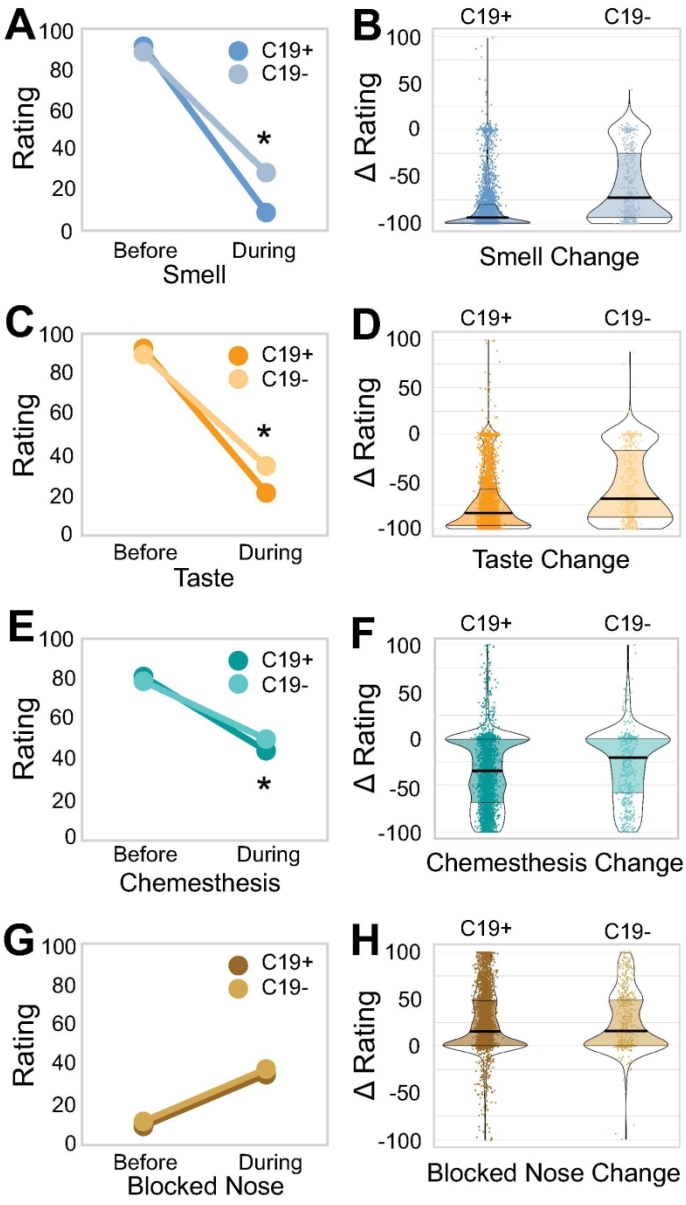

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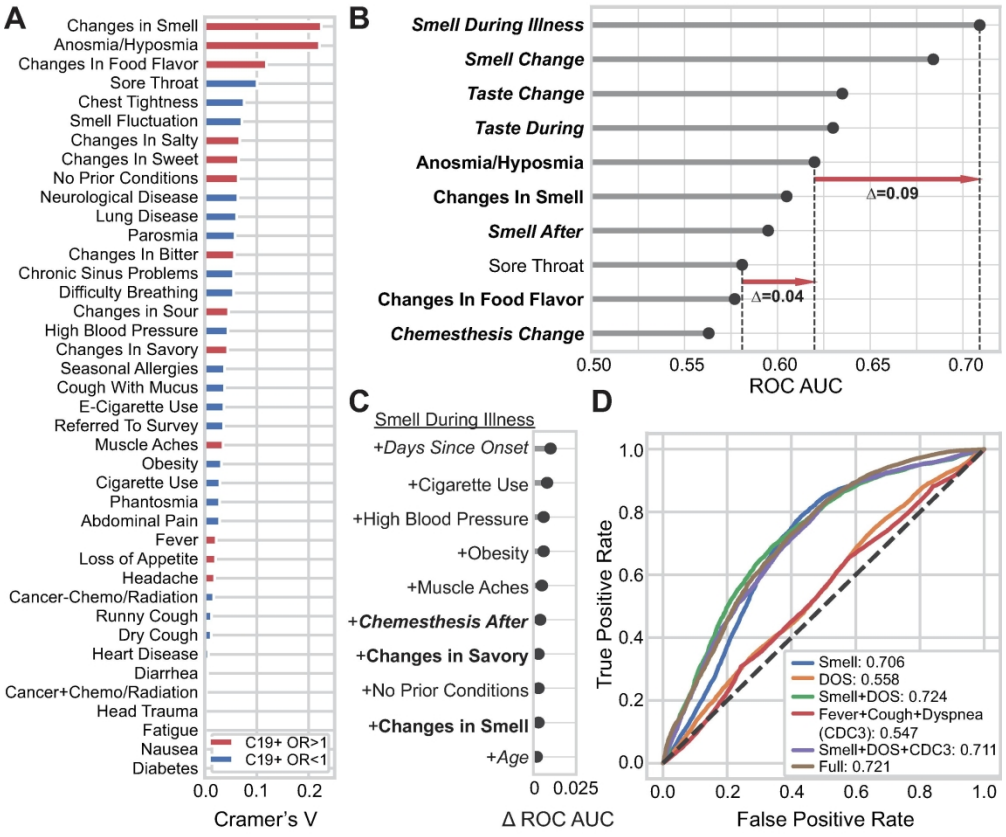

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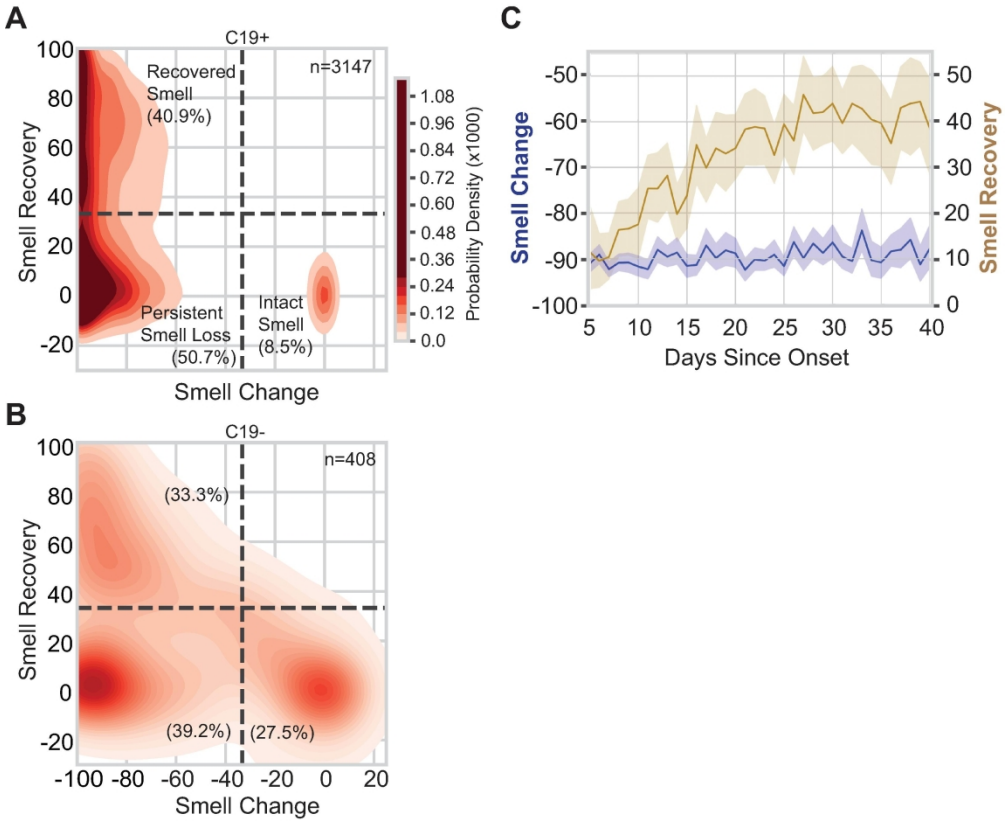

Figure 4: Smell loss, recovery, and time course. (A, B) Joint distribution of smell loss (during minus before illness ratings) and smell recovery (after minus during illness ratings) for C19+ (A) and C19- (B) participants. Darker color indicates a higher probability density; the color map is shared between (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.

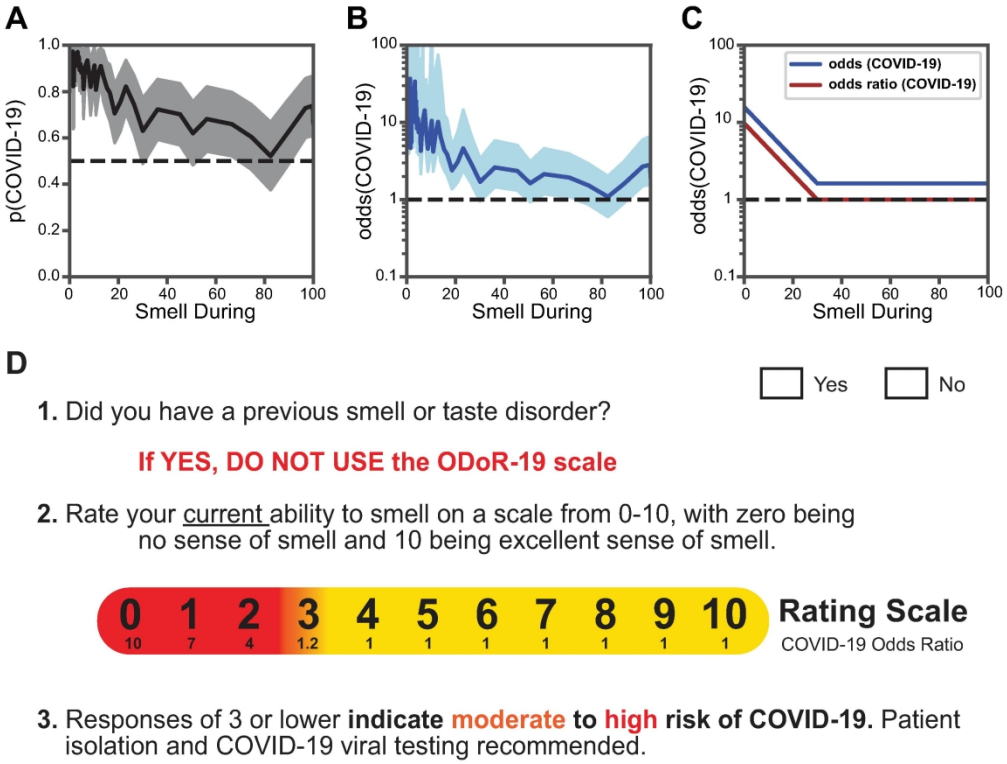

Figure 5. The odds of a COVID-19 diagnosis as a function of olfactory ability in individuals with respiratory symptoms. (A) The solid line indicates the probability of a COVID-19 diagnosis as a function of "Smell during illness" ratings in our sample. The shaded region indicates the 95% confidence interval. (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 0-10, 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.