# Transient loss and recovery of oral chemesthesis, taste and smell with COVID-19: a small case-control series

by

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28    **Abstract**

29         Anosmia is common with respiratory virus infections, but loss of taste or

30    chemesthesis is rare. Reports of true taste loss with COVID-19 were viewed skeptically

31    until confirmed by multiple studies. Nasal menthol thresholds are elevated in some with

32    prior COVID-19 infections, but data on oral chemesthesis are lacking. Many patients

33    recover quickly, but precise timing and synchrony of recovery are unclear. Here, we

34    collected broad sensory measures over 28 days, recruiting adults (18-45 years) who were

35    COVID-19 positive or recently exposed (close contacts per U.S. CDC criteria at the time

36    of the study) in the first half of 2021. Participants received nose clips, red commercial

37    jellybeans (Sour Cherry and Cinnamon), and scratch-n-sniff cards (ScentCheckPro).

38    Among COVID-19 cases who entered the study on or before Day 10 of infection,

39    Gaussian Process Regression showed odor identification and odor intensity (two distinct

40    measures of function) each declined relative to controls (close contacts who never

41    developed COVID-19), but effects were larger for intensity than identification. To assess

42    changes during early onset, we identified four COVID-19 cases who enrolled on or prior

43    to Day 1 of their illness – this allowed for visualization of baseline ratings, loss, and

44    recovery of function over time. Four controls were matched for age, gender, and race.

45    Variables included sourness and sweetness (Sour Cherry jellybeans), oral burn

46    (Cinnamon jellybeans), mean orthonasal intensity of four odors (ScentCheckPro), and

47    perceived nasal blockage. Data were plotted over 28 days, creating panel plots for the

48    eight cases and controls. Controls exhibited stable ratings over time. By contrast,

49    COVID-19 cases showed sharp deviations over time. No single pattern of taste loss or

50    recovery was apparent, implying different taste qualities might recover at different rates.

51    Oral burn was transiently reduced for some before recovering quickly, suggesting acute

52    loss may be missed in data collected after acute illness ends. Changes in odor intensity

53    or odor identification were not explained by nasal blockage. Collectively, intensive daily

54    testing shows orthonasal smell, oral chemesthesis and taste were each altered by acute

55    COVID-19 infection, and this disruption was dyssynchronous for different modalities,

56    with variable loss and recovery rates across modalities and individuals.

57

**1. Introduction**

The COVID-19 pandemic caused by the SARS-CoV-2 virus is one of the most devastating infectious disease outbreaks since the H1N1 avian flu of 1918 [1, 2]. By the end of 2021, roughly two years after the start of the pandemic, there were over 281 million cases of COVID-19 globally, resulting in over 5.4 million deaths [3]. Early in the pandemic, SARS-CoV-2 infection was associated with myriad symptoms, one of the most common being anosmia [4-7]. Meta-analyses of dozens of early studies suggested half to three-quarters of COVID-19 patients lost their sense of smell [8]. Further, smell loss was the most predictive symptom of COVID-19 [9] in the first several waves.

In contrast to other respiratory illnesses that cause acute anosmia – including those caused by rhinoviruses, influenza viruses, and common coronaviruses – both taste and chemesthesis function were reportedly lost in some people with COVID-19 [10-12]. Taste loss in the absence of smell loss is rare [13], and many individuals may mistakenly conflate the impaired flavor perception associated with anosmia with a true loss of taste function. However, one large crowd-sourced study reported ~60% of COVID-19-positive individuals had impaired perception of specific taste qualities (i.e., sweet, salty, sour or bitter tastes), suggesting taste loss in these individuals is distinct from impaired flavor perception accompanying smell loss [10, 14]. The findings of that study and others based on self-reports (e.g., [15-17]), were confirmed by psychophysical tests of taste function, suggesting ~47 to 64% of COVID-19 positive individuals experience taste loss [18, 19]. As a result, taste dysfunction (distinct from impaired flavor perception due to smell loss) is now also recognized as a common symptom of COVID-19 [20, 21].

Data on disruption of chemesthesis associated with COVID-19 remains quite limited. Consistent with many patient anecdotes that chili and ethanol burn were transiently depressed (e.g., [22]), studies relying on self-report suggested roughly half of individuals with COVID-19 experienced disruptions of chemesthesis [10]. In a small study of Italians with COVID-19-associated smell loss, 57% of patients had reported a severe impairment of nasal chemesthesis at initial diagnosis, but over 90% reported full recovery of chemesthesis six months later [23]. A Swedish study that used "olfactory" stimuli known to concomitantly activate the trigeminal system (e.g., vinegar, chopped garlic, vodka) provided evidence for impairment of nasal chemesthesis [24]. Thus, while self-report and clinical assessment both suggest COVID-19 may associate with acute

90   impairment of chemesthesis in many individuals, the time course of loss and recovery is

91   lacking, as is any assessment of the impact on oral chemesthesis. We attempt to fill

92   these knowledge gaps here.

93      In approximately 85% of COVID-19 cases where chemosensation (smell, taste

94   and/or chemesthesis) has been affected, recovery of chemosensory function is typically

95   seen within ~6 weeks [6, 25, 26]. Unfortunately, some patients do not report

96   appreciable recovery after many months [13, 26-30]. However, without daily

97   chemosensory testing, the precise timing of recovery remains unknown [6, 25, 31].

98   Because patient anecdotes suggest the timing of recovery of different chemical senses

99   may be dyssynchronous [26], we assessed smell, taste, and chemesthesis function

100  acutely and transiently over 28 days by collecting longitudinal data using commercially

101  available chemosensory stimuli in a cohort of patients diagnosed with COVID-19 and

102  control participants without COVID-19 in early 2021. Here, we present a small case-

103  control series using temporally intensive data collection from remote daily testing. We

104  focus on a handful of COVID-19 cases that allow for visualization of  loss and recovery of

105  chemosensory function as well as baseline ratings obtained prior to the onset of illness.

106  **2. Methods**

107  **2.1 Study design and recruitment**

108     This prospective study investigated COVID-19-related chemosensory dysfunction

109  in a community-derived sample of 18- to 45-year-old adults recruited on and around the

110  campus of a large public university in rural central Pennsylvania (i.e., the area

111  surrounding State College, PA). Enrollment began in February, 2021, on a rolling basis

112  using geotargeted ads on social media, and ended in May, 2021. Potentially interested

113  individuals were asked to contact a study team member (author EMW) via email if they

114  believed they were qualified for the study, who then emailed them a link to a brief

115  screening questionnaire. The screening questionnaire asked questions about

116  demographics, prior diagnosis of COVID-19, contact with a COVID-19-positive (COVID-

117  19+) individual, and any recent symptoms of COVID-19. Contact with a COVID-19+

118  individual was defined by the Centers for Disease Control (CDC) screening criteria in

119  use at the time of enrollment (specifically, 15 or more minutes within 6 feet of a

120  confirmed case of COVID-19). Due to the fluidity of the COVID-19 pandemic in early

121   2021, however, a strict timeline was not rigidly enforced and enrollment occurred on a

122   case-by-case basis. As vaccines were not available to non-health care workers at study

123   initiation in February, 2021, but became more widely available during the enrollment

124   window, we added a short retroactive questionnaire to the end of the study to gather

125   self-reported information on vaccination status and date. No attempt was made to

126   confirm these reports against medical records.

127         Participants with the following conditions were excluded: not diagnosed with

128   COVID-19 or not a close contact of a COVID-19+ individual, pregnant, food allergies (or

129   another reason they could not consume commercial jelly beans), prior history of a

130   disease of the central nervous system (including Alzheimer's disease, multiple sclerosis,

131   Parkinson's disease, Huntington's disease, brain tumor), nasal obstruction

132   (tumor/polyps), a history of nasal surgery, history of a severe head injury/concussion,

133   history of chronic sinus infections, history of radiation therapy to the head or neck

134   (ever), recent chemotherapy (within the last year), a prior diagnosis of smell or taste

135   loss, diabetes, history of lung/pulmonary disease or neurological disease, were unwilling

136   to create a PayPal account for compensation if they did not already have one, or were

137   below 18 years or above 45 years of age.

138         Data were collected using REDCap, a secure data capture platform for clinical

139   research [32, 33] on a server hosted and maintained by the Penn State College of

140   Medicine in Hershey, PA. The study was performed in compliance with the principles of

141   the Declaration of Helsinki, informed consent was obtained electronically, and the

142   specific protocol was approved by the Institutional Review Board at Penn State

143   (STUDY00016377). The subject identification numbers referenced below were known

144   only to our research staff and were not known to the participants or other individuals.

145   **2.2 Chemosensory stimuli and assessment**

146         The longitudinal design consisted of brief daily assessment every day for 28 days,

147   followed by four additional follow-up sessions every 2 weeks, for a total of 32 sessions

148   over a 12-week period. This report focuses on data from the first 28 days of testing. In

149   each daily session, participants were asked to complete questions on COVID-19 status or

150   symptoms that had changed since the last session, as well as self-administered

151   psychophysical smell and taste tests. They were instructed to minimize any distracting

152    smells or odors before any sensory testing and were also asked not to eat or drink

153    (anything other than water) or smoke for at least 30 minutes prior to testing.

154         Upon enrollment, the first author arranged contactless delivery of all research

155    materials in a large plastic zip-top bag. Specifically, participants were given 32

156    ScentCheckPro cards (Item #098515, Lot #0821) from Taylor Corp (North Mankato,

157    MN). Each ScentCheckPro card consisted of 4 microencapsulated scents in a scratch-n-

158    sniff format, with one scent located near each corner of the postcard sized card. The four

159    scents on a given card were some combination of the following: coconut, grape, coffee,

160    lemon, bubble gum, popcorn, pine, cinnamon, flowers, banana, or none of these.

161         Participants were also given 36 lidded plastic 2 oz souffle cups (Solo P200N; Lake

162    Forest IL) labeled with blinding codes. Individual cups contained one of two kinds of red

163    colored jellybeans (Jelly Belly, Fairfield, CA): either Sour Cherry (Lot #20200601) or

164    Cinnamon (Lot #200731). Each cup contained three jellybeans of a single flavor.

165    Jellybeans are a highly familiar confection in the United States that are made with

166    sweeteners (sugar, and/or corn syrup), corn starch, confectioners glaze, added color and

167    natural or artificial flavors. They have a shiny candy shell and a soft gel center, and come

168    in many different colors and flavors including fruit or spice flavors. With the nose

169    pinched closed, the Sour Cherry jellybean used here evoke both sweetness and sourness,

170    while the Cinnamon jellybean elicits sweetness and a mild warming/burning sensation.

171    Because of the glazed outer shell, jellybeans have little to no orthonasal smell, and both

172    jellybeans had a similar red color, so there were no obvious cues of the specific flavor in

173    each cup. Across days, jellybean presentation order was counterbalanced with pairwise

174    randomization, so that a participant who was presented with Sour Cherry on Day 1

175    would get Cinnamon on Day 2, while the next participant would start with Cinnamon on

176    Day 1 before receiving Sour Cherry on Day 2. This procedure was used to maximize the

177    range of chemosensory stimuli used in the study (i.e., taste, smell, and chemesthesis)

178    while minimizing participant burden on any given day of the study (i.e., a very brief test

179    time to enhance compliance). Individual lidded cups were labeled with random 3-digit

180    blinding codes, and these codes were programmed into REDCap prompts for each

181    session to help ensure participants sampled the correct jellybean on the correct day. We

182    also provided a disposable foam padded nose clip (A-M Systems; Sequim WA; Model

183   #166500, Lot #189615) to allow ratings of oral sensation to be collected with occluded

184   nostrils to minimize olfactory input.

185          Once a day, participants were asked to rate how blocked their nose was using a

186   horizontal 0-100 visual analog scale (VAS) scale anchored with 'Not blocked at all' to

187   'Completely blocked'. Participants were then asked to scratch the spot containing the

188   encapsulated odorant on each postcard sized smell card with a coin or fingernail for 5-10

189   seconds before sniffing; they were then asked to bring the card one inch from their nose

190   and sniff the odor. For each odor spot, participants were asked to first identify the odor

191   they smelled from four multiple choice options presented in REDCap before rating the

192   perceived intensity of the odor on a 0-100 VAS anchored with labels of 'None' to 'Very

193   intense'. This process was repeated for the four different odorants on a given card.

194          Next, participants were asked to pinch their nose closed using the provided nose

195   clip and put all three jellybeans from the cup into their mouth. With their nose *pinched*

196   *closed*, they were asked to chew the jellybeans slowly, and rate the perceived intensity of

197   various qualities on five different horizontal 0-100 VAS scales labeled 'None' to 'Very

198   intense'. These qualities included: *sourness*, *sweetness*, *warming/burning*, *cherry*

199   *flavor*, and *cinnamon flavor*. Participants were then asked to *unpinch* their nose and

200   exhale (while still chewing the jellybeans) and rate the same five intensity scales with

201   their nose *unpinched* (data not shown). All five scales were presented in both conditions

202   (nose closed / nose open) to minimize any "dumping" artifacts [34]. To decrease daily

203   test time and participant burden on days 1 through 28, participants assessed only one

204   jellybean flavor per day (either Sour Cherry or Cinnamon, counterbalanced as described

205   above). In four follow up sessions at weeks 6, 8, 10 and 12, a longer assessment was

206   deemed reasonable, so participants were presented with two cups of jellybeans, one with

207   each flavor. These data are not reported here.

208   **2.3 Categorization of participants as COVID-19 cases versus controls**

209          For the purposes of this study, a *COVID-19 contact* was defined as a participant

210   who had been exposed to a COVID-19+ individual (e.g., 15 or more minutes within 6 feet

211   of a confirmed case of COVID-19, per US CDC guidelines at the time), but never

212   developed any symptoms or received a positive diagnosis in subsequent testing.

213   Conversely, a *COVID-19 case* was defined as a participant who was either formally

214   diagnosed with COVID-19 *or* began having symptoms while enrolled in the study

215     following their recent exposure. By studying close contacts who later became cases while

216     enrolled in our study, we were able to observe acute changes in chemosensation using

217     controlled stimuli from the earliest days of their infection. When COVID-19 symptoms

218     started prior to the participant receiving a positive COVID-19 diagnosis via clinical

219     testing (typically a positive PCR test), an *estimated day of infection (Day 0)* was defined

220     as the first day of symptoms. When a positive test preceded COVID-19 symptoms, the

221     date of the positive test was used as *Day 0 of infection*. Data from controls were not

222     centered on the day of infection, as these participants enrolled at their discretion. For

223     these individuals, the *day of rating (Day 0)* is defined as the first day of their

224     participation in the study.

225     **2.4 Data analysis**

226     Between February and May of 2021 (i.e., in the months prior to the Delta and Omicron

227     waves in North America), a total of 55 participants were enrolled in the study. For this

228     analysis, 39 participants with confirmed COVID-19 infection were identified as *COVID-*

229     *19 cases* (Figure 1). Of these 39, 15 participants were identified as having an active

230     COVID-19 infection and enrolled in the study prior to or during the first 10 days of

231     infection. Of these 15 participants, four COVID-19 cases entered the study on or before

232     day 1 of their infection, allowing us to capture acute changes in their symptoms

233     throughout their entire infectious period, including early onset of symptoms. As shown

234     in Figure 1, three more cases enrolled on days 2-4 of infection, and nine enrolled on day

235     5-10 of their infection. An additional 24 participants who had enrolled were identified as

236     COVID-19 cases, but only after their initial 10-days of infection had passed. Because we

237     were not able to enroll these subjects early enough to capture potential changes in

238     chemosensory function during acute illness, data from these subjects were not included

239     in the present analyses. We plan to analyze and publish these data elsewhere to better

240     understand recovery over time, but the focus of the current report is initial loss during

241     early illness. Finally, in this analyses, 15 participants were identified as *controls* (i.e.,

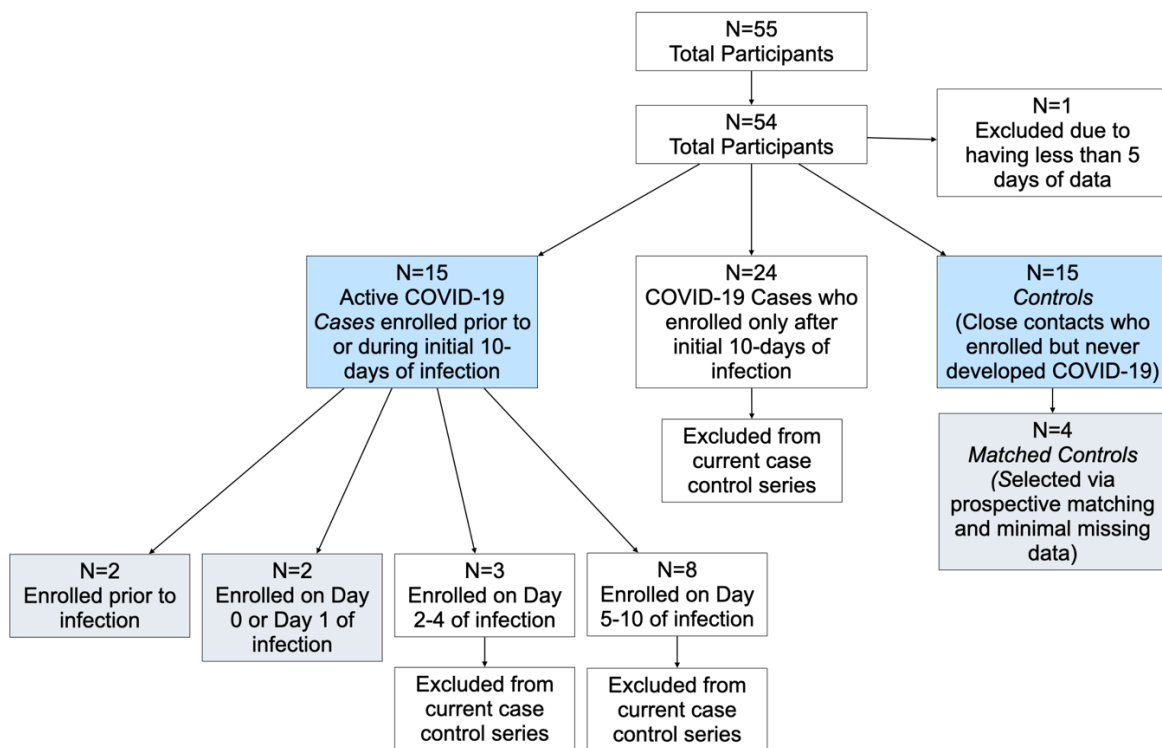242     they did not develop COVID-19 during the duration of the study).

243

244



Figure 1: Flow diagram summarizing selection of cases and controls for this case series. Blue boxes indicate the 30 participants included in the Gaussian Process model regression, and gray boxes indicate the 8 individuals shown in the in-depth panel plots.

245 Here, we wanted to assess whether deviation of smell intensity in the cases differed from
246 controls, so we identified the fifteen COVID-19 cases in our study who had enrolled on
247 or before day 10 of either infection and tested if their average deviation in smell
248 intensity over time differed from the 15 participants who were controls. To do this, a
249 grand mean of smell intensity was calculated for the controls across all days and
250 individuals. Deviation scores (deltas) for the 15 COVID-19 cases were then calculated by
251 subtracting that individual's ratings from the grand mean of the 15 controls, resulting in
252 a deviation score for smell intensity. Similarly, for the controls, we subtracted each
253 control's *individual* rating from the *grand mean* of all controls, to get a deviation score
254 for that rating relative to performance of the group. We used a Gaussian Process

255  Regression model to analyze the deviation (delta) scores for *cases* and *controls* over

256  time (both individually and as a group). A Gaussian Process model is a probabilistic

257  unsupervised machine learning concept used for regressions in which the model makes

258  predictions by utilizing prior knowledge about the smoothness of plausible time series

259  and provides uncertainty measures for such predictions [35]. COVID-19 cases were

260  normalized on Day 0 of infection and missing values were extrapolated via the Gaussian

261  Process Regression model. Controls were normalized on Day 0 of rating. To be

262  conservative and avoid overfitting sparse data, ratings of the two jellybean flavors were

263  not modeled via Gaussian Process Regressions, as the counterbalancing of flavors across

264  days meant only half as many data points were available for analysis. Analyses and data

265  visualization were conducted using SAS software (Version 9.4), R using RStudio

266  software (Version 2021.09.0), Python software (Version 3.9.10), or DataGraph version

267  4.7.1 (Visual Data Tools, Inc; Arlington TX).

268      Elsewhere, it has been suggested smell and taste changes occur within the first

269  four days of disease onset [36], and the median incubation period for symptom onset is

270  approximately five days [37]. We observed the same overall pattern within our data; as

271  reported below, it became clear the confidence interval of cases did not include zero in

272  the first week of infection. Given the unique opportunity to explore acute and early

273  changes in chemosensation in a small number of participants who had been enrolled

274  prior to acute illness, we also performed an in-depth analysis of these individuals, in

275  hopes of better understanding the initial trajectory of changes in chemosensation.

276  **2.4 Selection of participants for in-depth case control series**

277      Here, we describe a very small case series restricted to four specific cases who

278  enrolled in the study prior to or on Day 1 of infection (Figure 1). Studying these four

279  participants in detail allowed us to capture changes in symptoms throughout their entire

280  infectious period, including early onset of symptoms. More specifically, this prospective

281  approach maximizes the potential to capture baseline ratings, loss, and recovery of

282  chemosensory function that would not be possible with patients recruited only after they

283  were ill. This is a distinct and unique feature of this case series, as most other studies

284  have assessed chemosensory function multiple days into a participant's isolation period,

285  which does not allow for visualization of initial loss [30, 38-43]. For the other 12

286  participants who entered on or before Day 10 of infection (see Figure 1), we did not

287  capture their initial loss, so they are not included in this analysis.

288  From the 15 *controls*, four were selected as *matched controls* for the four COVID-

289  19 *cases*, based on age, gender, and race (Figure 1). To be considered for matching with

290  a specific COVID-19 case, potential candidates were required to (a) provide data on a

291  minimum of 80% of days, and (b) remain active for the full 28-day data collection

292  period (to avoid bias from dropout over time). If more than one potential candidate met

293  the age, gender, and race criteria to be included in a matched pair, the control used here

294  was randomly selected. Matching was performed manually by an experienced

295  epidemiologist (author CE). This process resulted in a final analysis of four *cases* and

296  four *matched controls* (Figure 1; Table 1).

Table 1:  Participant demographics from COVID-19 case-control series identifying cases and matched controls.

| ID | Status | Race (Self-Identified) | Gender (Self-Identified) | Age Range | Estimated Day of Infection relative to Day 0 of the Study |
|----|--------|------------------------|--------------------------|-----------|----------------------------------------------------------|
| 35 | Case | White/Caucasian | Female | 18-23 | -4 |
| 3 | Control | White/Caucasian | Female | 18-23 | n/a |
| | | | | | |
| 45 | Case | White/Caucasian | Female | 18-23 | 0 |
| 10 | Control | White/Caucasian | Female | 18-23 | n/a |
| | | | | | |
| 62 | Case | White/Caucasian | Male | 18-23 | 1 |
| 10 | Control | White/Caucasian | Male | 18-23 | n/a |
| | | | | | |
| 63 | Case | White/Caucasian | Female | 38-43 | -14* |
| 22 | Control | White/Caucasian | Female | 38-43 | n/a |

* Follow up via email revealed this participant was exposed twice. Based on symptoms, the first exposure resulted in enrollment as a close contact, but not infection. The participant only became ill following the second exposure.

297  For these four *cases* and their *matched controls*, we plotted six key variables

298  related to smell, taste, and chemesthesis. Specific outcomes were selected *a priori* by

299  two authors (EMW and JEH) as being the most salient and theoretically interesting

300  variables. These were: perceived *nasal blockage,* mean orthonasal *smell intensity* of the

301  four odorants on a given ScentCheckPro card, *sourness* and *sweetness* (from the Sour

302    Cherry jellybeans), and oral *burn* (from the Cinnamon jellybeans). Also, we included

303    *daily number correct* on the odor identification task. These seven variables were then

304    plotted across all 28 days to create a series of panel plots for all eight individuals.

305         In summary, ratings were collected on 101 point VAS, and variables summarized

306    here were: daily ratings of *nasal blockage*; a daily measure of orthonasal *smell intensity*

307    derived from the mean of four scratch-n-sniff spots on a ScentCheckPro card for a given

308    day; oral *burn* ratings collected every other day from a Cinnamon jellybean; and

309    *sweetness* and *sourness* ratings collected every other day from a Sour Cherry jellybean.

310    **3. Results and Discussion**

311    **3.1 Odor identification scores and ratings of orthonasal intensity from a**

312    **commercial scratch-n-sniff card**

313         For controls, the grand mean correct on the daily odor identification (OdorID)

314    across the entire study period was 3.32 out of 4 possible (Figure 2, Supplemental

315    Figures 1, 2). There was some evidence of a learning effect, as controls got slightly better

316    at the task over time (see upward slope, Figure 2A and 2B). For OdorID, the delta score

317    for cases deviates from zero, with a maximal dip occurring around days 5 to 8 (Figure

318    2A and 2B). Conversely, this dip was not observed in the controls, indicating that the

319    drop in OdorID performance was limited to COVID-19 cases.

320         After performing the OdorID task for 4 days, the median number correct for

321    controls increased by ~0.5, and after 14 days (two weeks), the median number correct

322    for controls increased by ~0.7-0.8 above the grand mean; that is, there was nearly

323    perfect performance on a 4 item OdorID task. Based on odor intensity ratings (discussed

324    below), smell loss for cases appears to be maximal near Day 5 (see Figure 2C and 2D).

325    Accordingly, we would also expect OdorID performance to be lowest on Day 5. However,

326    this is just when the first increase due to the learning effect appears to occur (Figure 2A

327    and 2B). If we assume cases (at least those who are not totally anosmic) show similar

328    ability to learn as the controls, this offsetting bump upward would minimize the

329    apparent dip in OdorID performance seen around Day 5. Thus, the COVID-19-

330    associated drop in identification performance may appear smaller than it actually is due

331    to a simultaneous offsetting increase in performance due to learning (or practice).

332    Evidence of such learning is also seen in Supplemental Figures 1 and 2.

333    Regarding suprathreshold odor intensity, the grand mean of perceived intensity ratings

334    for controls across time was 59.47 on 0 to 100 VAS. The mean on Day 0 was used to

335    calculate daily deviation scores for cases and controls (Figure 2C and 2D). Data were

336    centered using Day 0 means so the delta could be more easily compared across the data

337    set. For the cases (Figure 2C and 2D), the delta score of smell intensity clearly deviates

338    from zero, and this difference was maximal in the first week of infection, as noted above.

339    In sharp contrast, this pattern is not seen in the controls, with a score of zero falling

340    inside the interquartile range across the entire study period (Figure 2D). This indicates

341    there was a significant drop in smell intensity for cases but not controls for ratings of the

342    scratch-n-sniff spots on commercial ScentCheckPro cards. In contrast with the learning

343    seen for the OdorID data, we failed to observe any evidence of a learning effect for smell

344    intensity ratings. Collectively, these data suggest OdorID tasks may be less sensitive to

345    acute changes in smell with COVID-19, relative to odor intensity ratings, at least in

346    repeated testing situations that encourage learning or practice effects.

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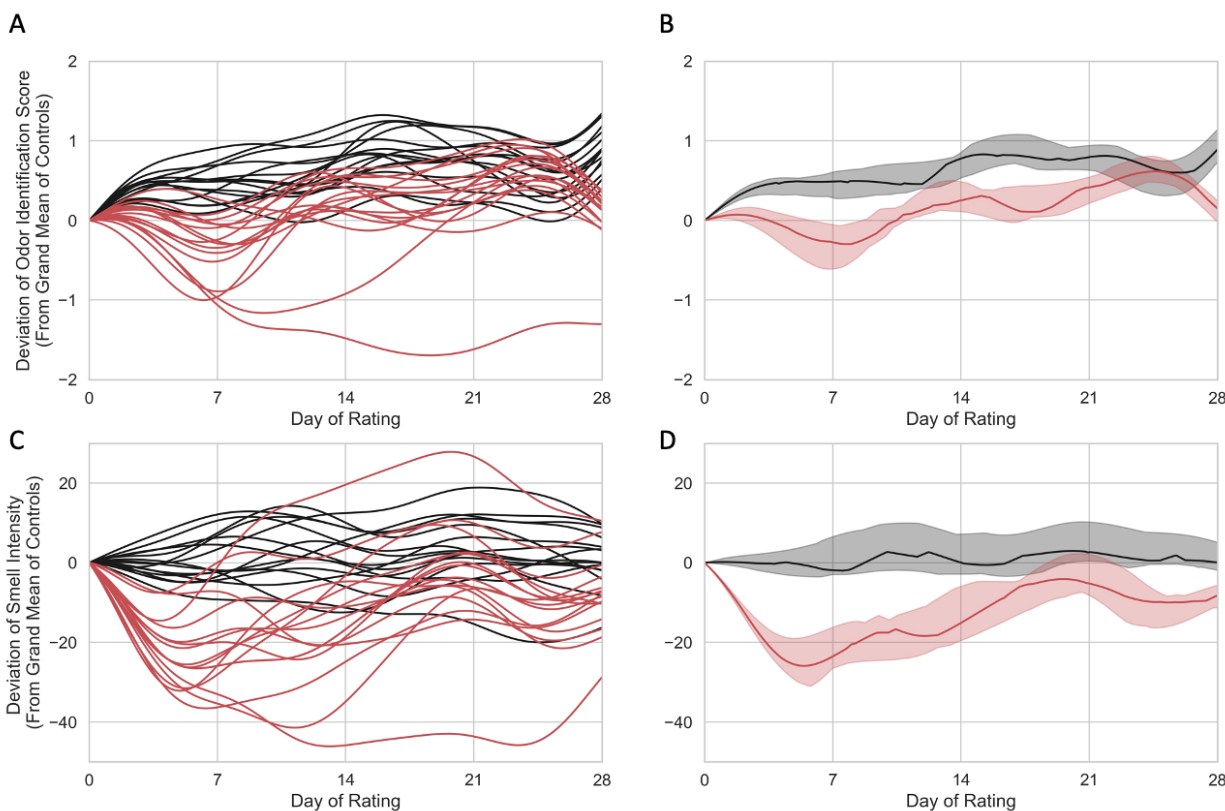


Figure 2. Individual (left) and group level (right) Gaussian Process Regression models for 15 controls (red) and 15 COVID-19 cases (black) who entered the study on or before day 10 of their infection. For cases, Day of Rating is centered on estimated day of infection. Odor identification scores (top) and odor intensity ratings (bottom) are shown as deviation scores calculated from a grand mean of controls across time. **(A)** Individual odor identification data in a Gaussian Process Regression model of deviation scores from 15 COVID-19 cases (red) and 15 controls (black). **(B)** Group level odor identification data in a Gaussian Process Regression model for COVID-19 cases (red) and controls (black). **(C)** Individual deviation scores for smell intensity ratings for 15 COVID-19 cases (red) and 15 controls. **(D)** Group level smell intensity data in a Gaussian Process Regression model for 15 COVID-19 cases (red) and 15 controls (black). In panels B and D, the solid line represents the group median, and the shaded region shows the interquartile range. Panels A and C show maximal loss roughly around day. Panel B shows some evidence of a learning effect for the OdorID task in the controls; no evidence of learning is seen for controls in the intensity task shown in panel D.

349     **3.2 Demographics of participants in case control series**

350     Given the maximal deviation in smell early in acute illness, we chose to explore the

351     specific changes in multiple chemosensory modalities in the handful of cases who

352     enrolled *prior* to onset of acute illness in greater detail. Demographics of four COVID-19

353     cases and four matched controls are summarized in Table 1. The mean age of

354     participants with COVID-19 was 26 years of age (range 21-43) and the mean age of

355     matched controls was 25.5 years of age (range 22-38).

356

357     **3.3 Controls**

358     Throughout the course of the study, controls exhibited normal function for smell,

359     taste, and chemesthesis (Figure 3). Specifically, mean scores on odor identification,

360     orthonasal smell intensity ratings, and ratings of perceived nasal blockage were

361     relatively constant across days, although some participants were more variable than

362     others. A few patterns deserve comment. For example, with Subject 1 we see a clear

363     learning effect for odor identification where they became better at the task over time

364     (Figure 3). Separately, controls may vary in perceived nasal blockage from day to day.

365     For example, with Subject 3, we see a slight decrease in orthonasal smell intensity and a

366     slight increase in nasal blockage in the last four days of testing (Figure 3). Such mild

367     transient hyposmia would be wholly consistent with conductive smell loss due to nasal

368     blockage typically seen with allergies or the common cold. Similarly, for taste, ratings of

369     sweetness and sourness remained relatively constant throughout the course of the study

370     for controls, although ratings were noisier for some participants than others. One rating

371     for Subject 22 deserves comment: in the third week of testing, we observed a sharp drop

372     in sour taste intensity and sharp increase in burn intensity, but only for a single day

373     (Figure 3). While we cannot be sure, we suspect they simply picked the wrong cup from

374     the bag of samples, as Sour Cherry jellybeans should not burn and should be sour.

375     Subject 22 may have misread the 3-digit blinding code, or our research team may have

376     mislabeled the cup. Either way, this single datum does not alter their overall pattern.

377     Also, we note Subject 22 tends to give Cinnamon jellybeans a relatively high amount of

378     oral burn relative to the other participants; we might speculate they eat spicy food

379     infrequently, as large variation in burn ratings due to dietary exposure is very common

380     (e.g., [44-47]).

381    In summary, daily data from these four *controls* suggest individuals without

382    COVID-19 are able to correctly identify the odors from the ScentCheckPro cards, and to

383    consistently rate the various attributes from the cards (orthonasal intensity) and the

384    jellybeans (taste, burn). While some minor variation is observed over time and across

385    participants, the ratings are generally stable over the study period, in sharp contrast to
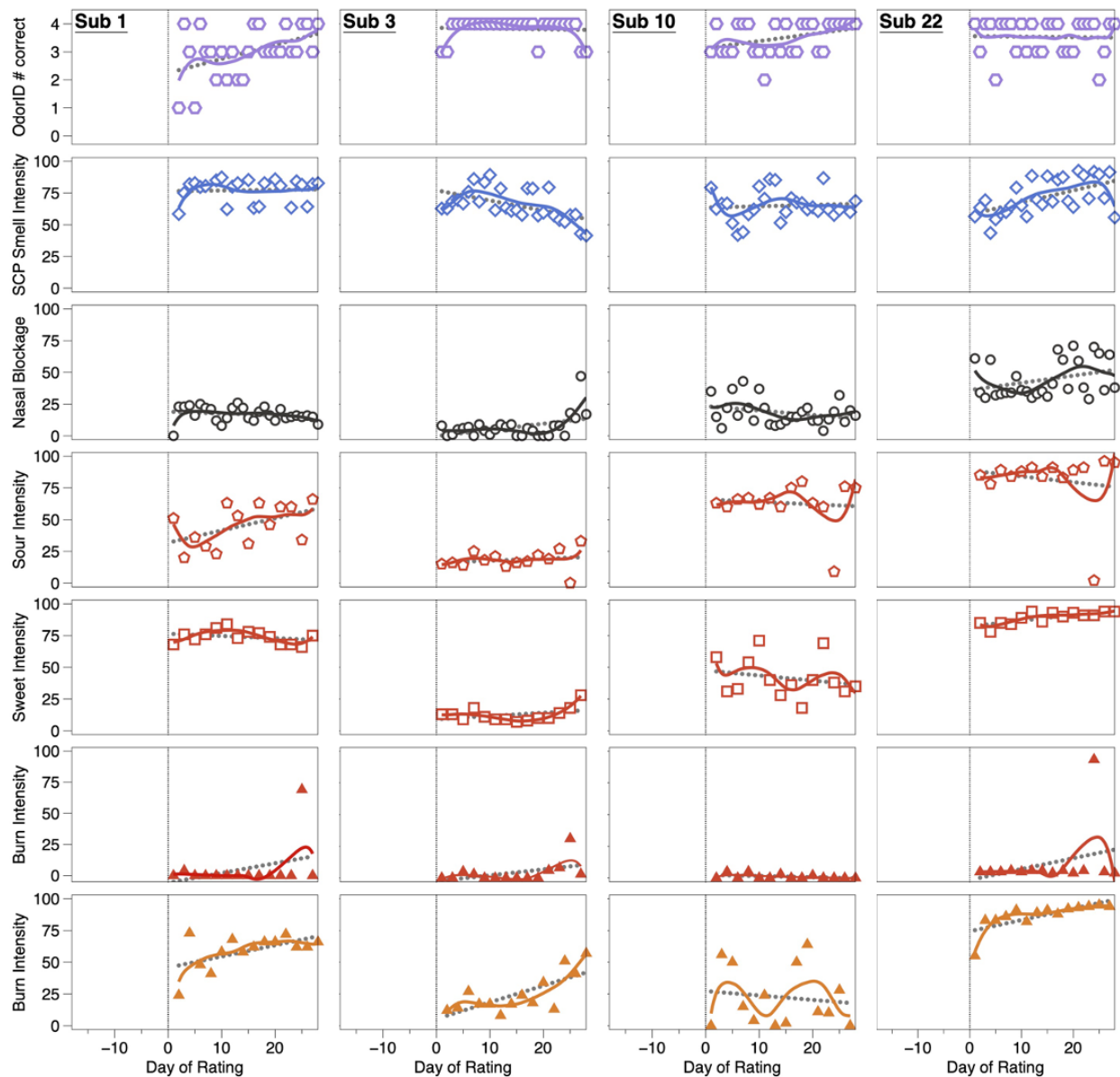
386    the COVID-19+ cases (Figure 4).

387

Figure 3: OdorID scores, and intensity ratings from matched controls over time. These participants (Subjects 1, 3, 10, and 22) show generally consistent ratings across the study. To help illustrate uniformity across the observation period, solid (colored) lines were fit via LOESS regression and dotted lines (gray) were fit via linear regression. A vertical line on Day 0 highlights the start of the 28-day study. Open hexagons (1st row) are the number correct on a ScentCheckPro card, while open diamonds (2nd row) are the mean daily smell intensity ratings from the same card. Open circles (3rd row) reflect ratings of perceived nasal blockage. Red symbols (rows 4, 5, and 6) reflect specific quality ratings from Sour Cherry jellybeans collected with a pinched nose. Orange triangles (row 7) indicate burn ratings from Cinnamon jellybeans collected with a pinched nose.

### 3.4 Cases

388

389      All four cases converted from being close contacts to being COVID-19+ while
390 enrolled in the study, enabling visualization of changes in their responses over time
391 (Figure 4). For brevity, we only highlight a few notable points here and a more detailed
392 account is provided in the supplemental materials. When smell loss was observed, it was
393 largely unrelated to nasal blockage, consistent with prior reports [4-7, 10] and the idea
394 that COVID-19-associated smell loss arises from ACE2 receptor-mediated disruption of
395 the olfactory epithelium, rather than the conductive losses typically seen with the
396 common cold. Regarding chemesthesis, the lack of burn from the Sour Cherry jellybeans
397 served as a negative control, suggesting participants were successful in discriminating
398 between burn from a Cinnamon jellybean and a lack of burn from a Sour Cherry
399 jellybean. From this, we can assume changes in burn observed here for the Cinnamon
400 jellybeans was not merely a failure to understand the task.

### 3.4.1 Subject 35

401

402      Symptoms for Subject 35 included cough, runny nose/congestion, sore throat,
403 and headache. Odor intensity ratings dropped through day 15 before recovering; her
404 OdorID scores showed a similar pattern, but her data were noisier given the learning
405 effect noted previously. Her nasal blockage resolved around Day 8, but she still showed
406 impaired smell. Sourness ratings declined until ~Day 15 while sweetness declined until
407 ~Day 6, before each began to recover. This was not merely a taste/flavor semantic
408 confusion, as ratings were obtained while wearing nose clips. Her data also suggest
409 sweet and sour taste are each transiently affected with an active COVID-19 infection,
410 and loss and recovery may be dyssynchronous (i.e., sweetness did not recover as swiftly
411 as sourness). Separately, she showed large changes in burn from Cinnamon jellybeans,
412 suggesting oral chemesthesis is affected by COVID-19 infection, and this may be
413 dyssynchronous from altered taste or smell function.

### 3.4.2 Subject 45

414

415      Subject 45 reported no symptoms despite becoming an active COVID-19 case
416 while enrolled. Notably, despite being nominally asymptomatic, she clearly showed
417 altered smell function that was reflected in both in OdorID performance and orthonasal
418 intensity ratings, with maximal loss around Day 5. This highlights that some COVID-
419 19+ individuals may be unaware of altered smell function, consistent with meta-analysis

420     by Hannum and colleagues [8, 48]. As above, this transient disruption could not be

421     attributed to nasal blockage. Regarding taste ratings, she also exhibited temporal

422     dyssynchrony for different qualities. For the Cinnamon jellybeans, she showed a

423     monotonic increase in burn over ~3 weeks, before showing a small drop at the end of

424     the study. Elsewhere, some patients reported an increase in the ability to feel sensations

425     in the mouth (including burning) during recovery from COVID-19 [49], so her temporal

426     pattern may potentially reflect acute hypoalgesia, followed by hyperalgesia, before

427     eventually returning to normal. In any case, her data support the idea that oral

428     chemesthesis can be affected acutely by SARS-CoV-2 infection.

429     **3.4.3 Subject 62**

430     Like Subject 45, Subject 62 failed to report any symptoms, but unlike the prior

431     cases, his orthonasal intensity ratings and OdorID performance remained relatively

432     constant over time, and nasal blockage was generally low. This highlights that while

433     many individuals with COVID-19 experience smell loss, some do not (e.g., [8, 48]).

434     Regarding taste, noisy data preclude any strong conclusions, but tentatively, it seems he

435     may have experienced large changes in both sweetness and sourness. That said, there is

436     a sharp drop in sour taste intensity and sharp increase in burn intensity on two separate

437     days (Figure 4). We suspect Subject 62 may have simply tasted the wrong sample on

438     these days, as Sour Cherry jellybeans should be sour without any burn. Still, despite

439     these caveats, his panel plots also suggest he experienced acute changes in oral

440     chemesthesis without concomitant smell loss. If true, this would highlight that

441     mechanisms of loss across all three chemosensory modalities are likely to be distinct.

442     **3.4.3 Subject 63**

443     Subject 63 enrolled 2 weeks before becoming a case. This greatly exceeds the

444     expected incubation period (5 to 7 days) [37, 50], so we contacted her via email and she

445     reported a second exposure to a COVID-19+ individual. Thus, we assume she became ill

446     upon her second exposure rather than the initial exposure that caused her to enroll. Her

447     data reveal changes in smell, taste, and chemesthesis. However, the 28-day observation

448     period only captures initial illness without recovery, as she initially enrolled after an

449     exposure that did not cause infection. Consistent with this interpretation, she did not

450     report any symptoms for the first 2 weeks, before reporting many symptoms (sore

451     throat, fever or chills, dry cough, body aches, fatigue, diarrhea, nausea or vomiting,

452    headache, and dry cough). Notably, her mean orthonasal ratings began to decline

453    somewhat a few days before the estimated day of infection, in the absence of nasal

454    blockage. Further, her intensity data suggest she experienced hyposmia, rather than full

455    anosmia, so it is not surprising that her OdorID performance remained relatively

456    constant across the study period. This suggests rated smell intensity might provide more

457    nuanced assessment of smell function versus odor identification (as discussed above).

458    Her taste data were somewhat noisy, but it seems sourness may have been more affected

459    than sweetness.  Tentatively, her plots suggest she lost taste function in a quality specific

460    manner, along with partial smell loss and loss of oral chemesthesis, with staggered

461    timing of each.

462

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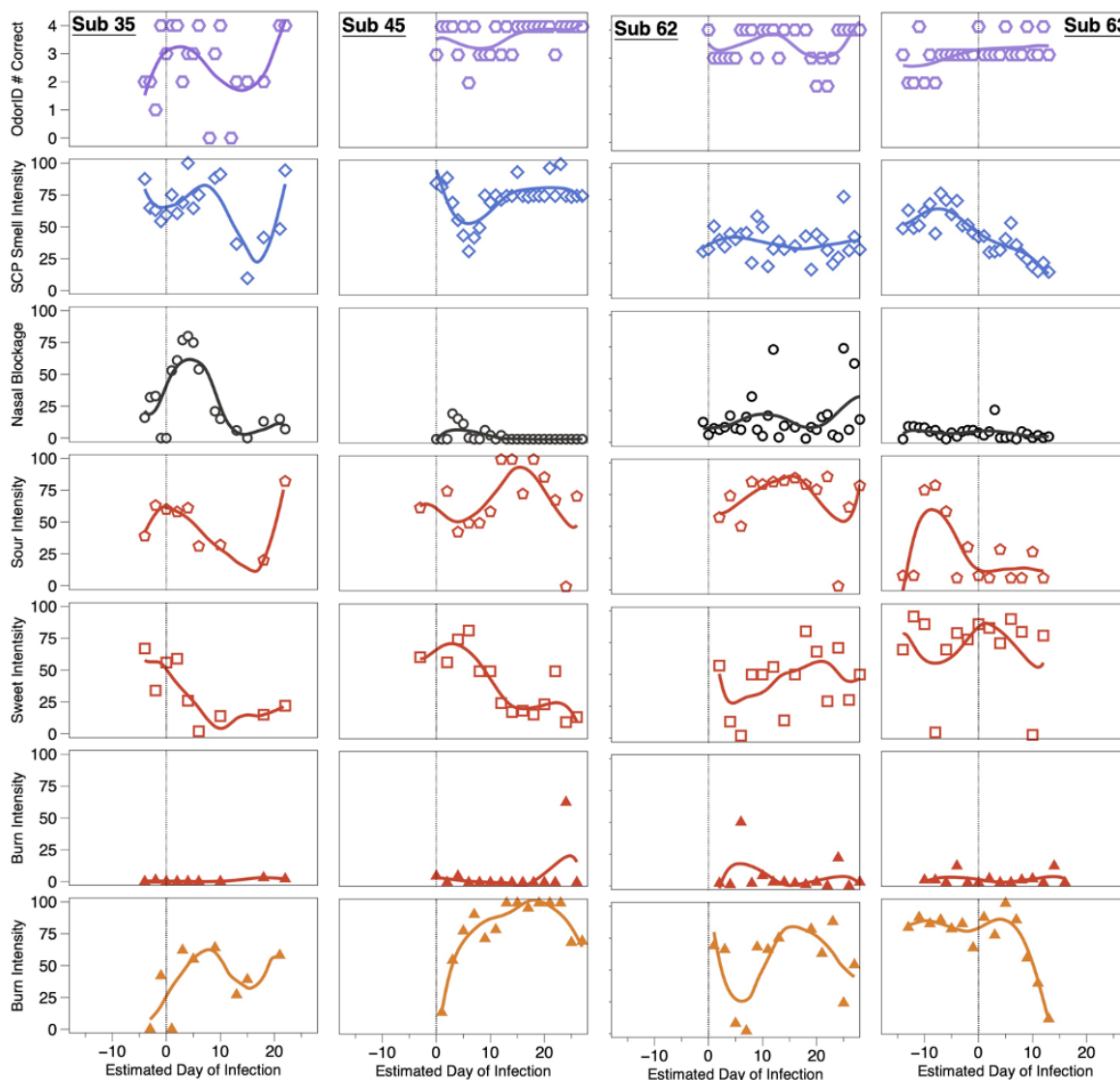


Figure 4: OdorID scores and VAS ratings from four COVID-19 positive individuals. COVID-19 cases (subjects 35, 45, 62, and 63) tended to show transient alterations of smell, taste, and/or chemesthesis during the observation period. To help illustrate uniformity across the study days, solid lines were fit via LOESS regression. A vertical line at Day 0 was added to highlight the estimated day of infection. Symbols and rows match those used in Figure 3: row 1 is daily number correct, and row 2 is orthonasal intensity of four scratch-n-sniff patches from a ScentCheckPro card, row 3 is ratings of perceived nasal blockage, rows 4-6 are sour, sweet, and burn ratings for Sour Cherry jellybeans with the nose pinched, and row 7 is burn for Cinnamon jellybeans with the nose pinched.

464 **3.4 General Discussion**

465        By using intensive longitudinal data collected daily for 28 days, we were able to

466 assess COVID-19-associated changes over time. Further, by leveraging enrollment of

467 individuals upon exposure rather than waiting until they were already ill, we were able

468 to create a small case control series that captured both initial loss and recovery. We can

469 draw several conclusions from the results described here. First, number correct on a

470 short odor identification task may potentially miss dysfunction in hyposmic individuals

471 who have clearly depressed perceived intensity, but who still retain enough function to

472 successfully complete an identification task. Longer tests, such as the 40-question

473 University of Pennsylvania Smell Identification Test (Sensonics), may be better at

474 differentiating these levels of smell loss, though their greater cost and time-to-complete

475 make them impractical for this type of intensive longitudinal study. Second, we find

476 smell loss appears maximal around Day 5, but this varies somewhat across participants.

477 Third, COVID-19 related chemosensory dysfunction can manifest as reduced oral

478 chemesthesis, reduced taste, and/or reduced orthonasal smell with little to no nasal

479 blockage, with temporally staggered onset and time course. Collectively, these results,

480 although limited in scope, extend prior work by providing direct assessment of multiple

481 sensory modalities repeatedly over time using stable, commercially-available products

482 as stimuli.

483        A strength of this study involved the use of commercial stimuli like jellybeans to

484 collect ratings while the nose was blocked with nose clips. First, because of their glazed

485 candy shell, jellybeans have little to no orthonasal scent and the odorant is only released

486 from the food matrix upon chewing. For our purpose, this gave us a convenience way to

487 deliver consistent shelf stable stimuli safely during a pandemic. All jellybeans of the

488 same flavor came from the same lot; given routine quality control measures in

489 commercial manufacturing, we are confident participants received consistent stimuli

490 even if we do not know the exact formulation of the jellybeans. Second, our use of

491 similarly colored jellybeans with different flavors minimizes potential biases

492 participants may have from prior experience or knowledge with other foods (e.g., this is

493 a lemon, and I know lemons tend to be sour [51]). When this lack of expectation is

494 coupled with the use of nose clips, we believe the data shown here reflect true

495 differences in taste and chemesthesis and not merely they result of a flavor taste

496     confusion. Other studies have also reported loss in function when using taste stimuli

497     that do not have an olfactory component [52].

498        Currently, there is disagreement regarding whether different types of taste cells

499     are differentially affected by SARS-CoV-2 infection. Indeed, several studies have showed

500     quality-specific differences (i.e., [27, 43, 53-56]), while others have not (i.e., [18, 40-42,

501     57-61]). Here, sourness and sweetness from consistent stimuli were lost and recovered

502     at similar rates for some participants, but this was not uniformly true. This implies

503     specific taste qualities may recover at different rates, although additional work is needed

504     to confirm this. Also, our data indicate taste qualities may be differentially affected,

505     consistent with other reports [19, 62]. While the specific mechanisms underlying taste

506     dysfunction with SARS-CoV-2 infection remain unclear, several mechanisms have be

507     proposed. For example, ACE2 could allow for the infection of Type 2 (sweet, bitter and

508     umami) taste receptor cells by SARS-CoV-2. Saliva could affect gustation as salivary

509     glands express high levels of ACE2 and TMPRSS2. SARS-CoV-2 may even affect the

510     central nervous system, as the virus has been detected in the cerebrospinal fluid [63-67].

511        Anecdotal reports and preliminary psychophysics suggest loss of chemesthesis

512     with SARS-CoV-2 infection is real [10, 23, 30, 68]. We extend prior reports here by

513     showing oral chemesthesis, not just nasal chemesthesis, may be altered by COVID-19.

514     This effect appears to be highly transitory, which could cause underreporting, especially

515     when assessment occurs multiple days after illness has started. Definitionally,

516     chemesthesis includes both thermal and tactile percepts like warming, cooling, and

517     buzzing, and these sensations occur via distinct and specialized receptors. Even if

518     focusing solely on burn, multiple receptors like TRPV1 and TRPA1 are involved. Despite

519     multiple advantages of commercial stimuli (high consistency, low cost, shelf stability,

520     etc.), use of commercial jellybeans here limits interpretation somewhat. That is,

521     cinnamon flavored candies presumably contain cinnamaldehyde, a well-known TRPA1

522     agonist [69, 70].However, we cannot rule out whether they contain capsaicin (or

523     another TRPV1 agonist), as food labeling laws in the United States allow manufacturers

524     to declare such ingredients as natural or artificial flavors on the package without being

525     more specific, so we cannot make strong inferences about which specific chemesthetic

526     mechanisms might be affected by SARS-CoV-2 infection. Nonetheless, present data

527     extend prior work by clearly showing oral burn can be transiently affected by COVID-19.

### 4. Limitations and Conclusions

Our data suggest intensive cohort study designs are imperative for understanding and tracking symptoms of COVID-19 patients. Through intensive daily ratings we were able to examine and follow participants from initial exposure to catch symptoms as the emerged, allowing for the visualization of symptom onset, not just recovery. Thus, a strength of this study is the nature of the cohort examined, and it exemplifies a need for more cohort studies to catch patients before and during the most infectious period of their illness. A few limitations should be briefly noted. First, all sensory testing in this study was performed remotely at home, due to pandemic related safety restrictions meant to protect both participants and our research team. Because participants made daily ratings at their leisure without direct supervision, we cannot obtain the same level of stimulus control we would have with an in-person lab-based study. Also, while all study materials were clearly labeled, we cannot preclude whether participants may have occasionally chosen the incorrect blinding codes on some days or that our staff might have mislabeled these samples. Further, we should note the commercial ScentCheckPro scratch-n-sniff cards used here were not validated as a clinical smell test; also, they were originally designed as an odor identification task, rather than a smell intensity task, so we cannot assume all stimulus concentrations were precisely matched for intensity. This concern is partially offset however by the randomization of odorants on any given card, and the use of daily means. Finally, we fully acknowledge this study had a very small number of participants (albeit with many data points per participant), so present findings should be taken as tentative until confirmed. Attempts to generalize the incidence or prevalence of distinct types of loss or dysfunction should not be made from this small case-control series. Despite these limitations, this dataset is highly unique in that it captures changes very early in COVID-19 illness with intensive daily sampling.

Here, we extend current knowledge by showing oral chemesthesis, taste, and/or orthonasal smell function can each be acutely affected by COVID-19. Further, we find such disruption may be dyssynchronous for the different chemical senses, with differing rates of loss and recovery across modalities and individuals. Also, odor intensity ratings revealed potentially hyposmic individuals who might be missed if smell function is only assessed via odor identification scores. Finally, disrupted chemosensation, especially for

559   chemesthesis, appears to be highly transient, suggesting studies that collect a single

560   snapshot in time, often retrospectively, may underestimate the true prevalence of loss.

561

562   ### *5. Acknowledgements*

563   The authors wish to thank our participants for their time and critical contribution to this

564   work.

565

566   ### *6. Funding / COI disclosure*

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577

578     **Supplemental Materials**

579

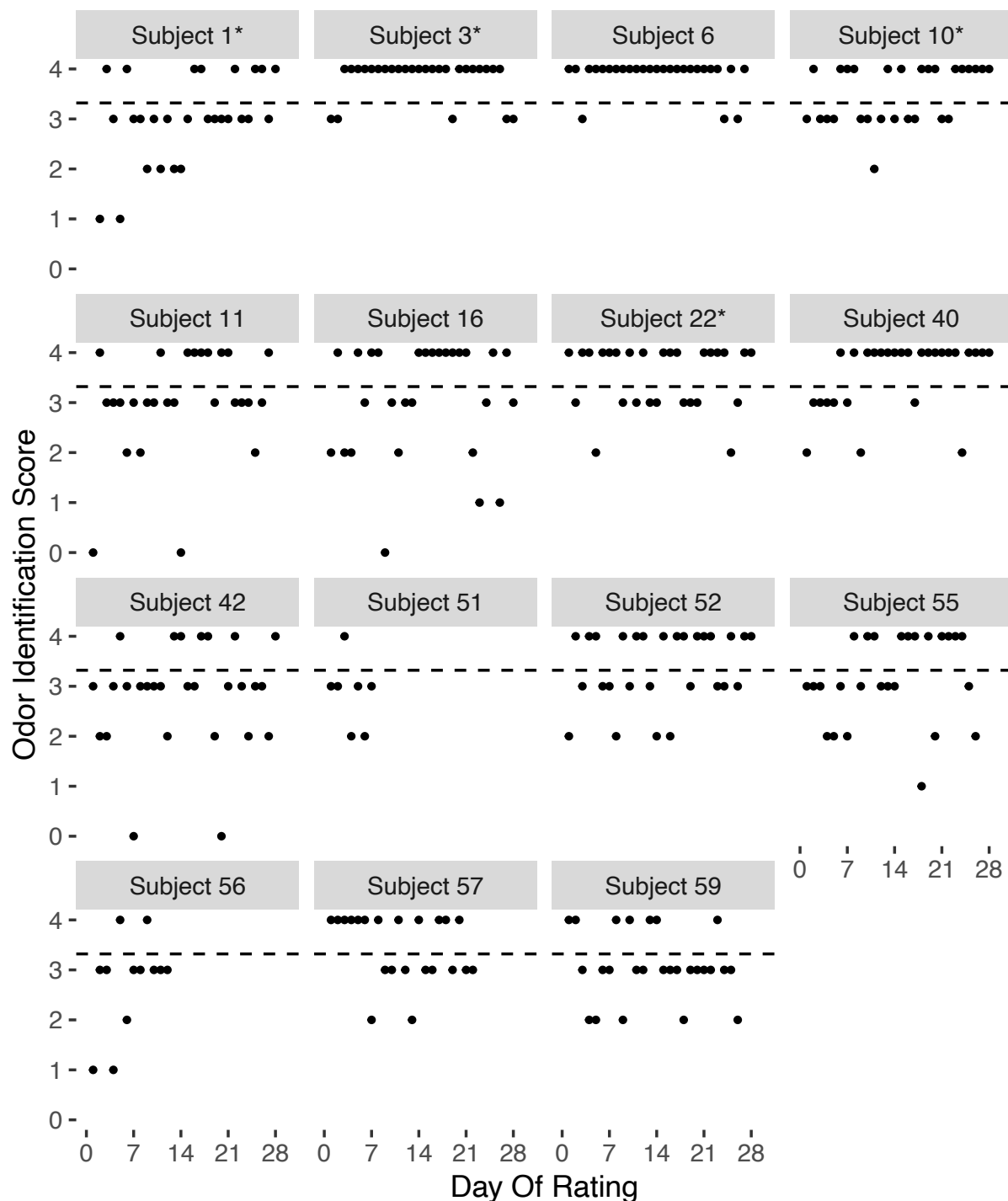580     *Supplemental Figure 1*

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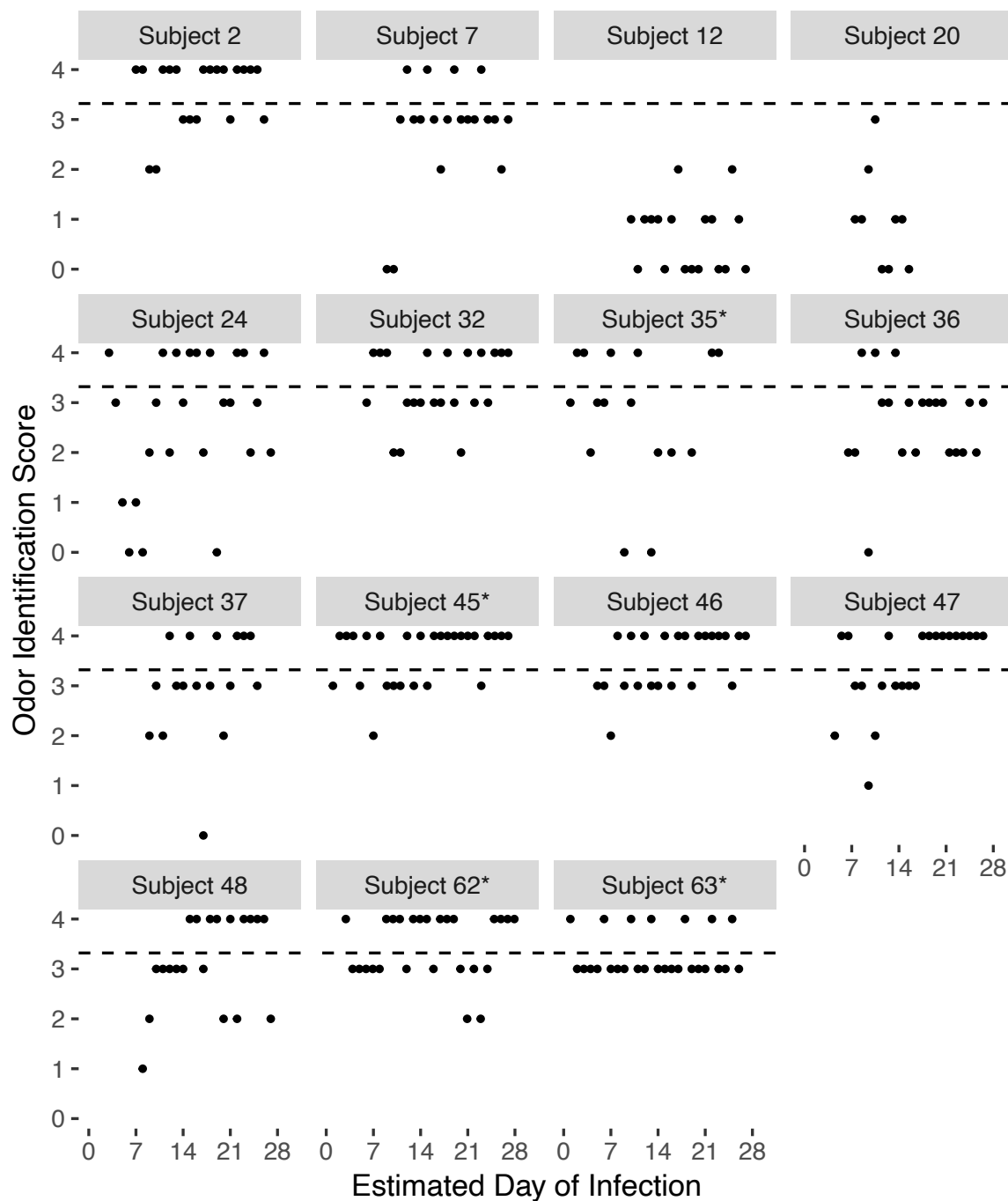


582

583     Raw daily odor identification scores from the ScentCheckPro cards over time for the

584     COVID-19 cases (n=15) who entered the study on or before day 10 of their infection.

*Supplemental Figure 2*



Raw daily odor identification scores from the ScentCheckPro cards over time for the 15 controls.

**Supplemental narrative and discussion of symptoms for the 4 cases**

*Subject 35*

591

592

593 Subject 35 became a case during the study, enabling visualization of the falling

594 and rising phases of her responses (see Figure 4). Her symptoms included cough, runny

595 nose/congestion, sore throat, and headache. Regarding orthonasal scratch-n-sniff

596 intensity ratings, daily means decreased through day 15 before recovering. OdorID

597 scores showed a similar pattern, but data were noisier given the learning effect

598 described above. Together, this suggests her orthonasal olfaction was transiently

599 affected during active COVID-19 infection, as expected (e.g., [19, 71, 72]). Notably, she

600 showed impaired smell even after nasal blockage resolved around Day 8, and her

601 maximal smell loss and maximal nasal blockage were dyssynchronous. This is consistent

602 with other reports showing COVID-19 smell loss is not associated with nasal blockage

603 [4-7, 10], presumably because COVID-19-associated loss arises from ACE2 receptor-

604 mediated disruption of the olfactory epithelium, and not the conductive losses seen with

605 the common cold.

606 Her sourness ratings from the Sour Cherry jellybean declined until ~Day 15,

607 when ratings began to increase, while sweetness declined until ~Day 6, before beginning

608 to recover. The decline and subsequent rise of sweet and sour taste likely signifies

609 normal recovery, although Figure 4 also shows dyssynchronous recovery of these tastes

610 (i.e., sweetness did not recover as swiftly as sourness). These data indicate sweet and

611 sour taste are each transiently affected with an active COVID-19 infection, and this was

612 *not* merely a taste/flavor semantic confusion, as ratings were obtained while wearing

613 nose clips. Subject 35 also showed large changes in burn from the Cinnamon jellybeans,

614 suggesting oral chemesthesis is affected by COVID-19. The lack of burn from the Sour

615 Cherry jellybeans serves as a negative control, indicating she was successful in

616 discriminating between burn from a Cinnamon jellybean and a lack of burn from a Sour

617 Cherry jellybean (a pattern also seen in the three other cases shown in Figure 4). These

618 data indicate perception of oral burn can be affected by an active COVID-19 infection

619 dyssynchronously from taste or smell. While patient anecdotes (including social media

620 posts) have previously suggested nasal and/or oral chemesthesis may be affected by

621 SARS-CoV-2 infection [39, 49, 73], the daily assessment and prospective design used

622 here provide quantitative evidence of altered oral chemesthesis with COVID-19.

### Subject 45

Subject 45 converted from being a close contact to an active COVID-19 case during the study, but unlike Subject 35, Subject 45 never reported any symptoms during her infection. Yet. despite being nominally asymptomatic, she still showed a clear drop in both OdorID performance and ratings of orthonasal intensity around Day 5 (with a bigger effect size for intensity). This highlights that some individuals infected with SARS-CoV-2 may be unaware of the impact on their sensory abilities, consistent with recent meta-analysis by Hannum and colleagues [8, 48]. Nor was this transient disruption in smell due to nasal blockage (as reported elsewhere [4-7, 10]). As her infection progressed, sourness from the Sour Cherry jellybean was variable, and sweetness from this jellybean steadily declined over the course of infection, again indicative of temporal dyssynchrony for different taste qualities. In contrast to burn rating from the Sour Cherry jellybean (which stayed near 0 across the study period, as expected), burn from the Cinnamon jellybean steadily increased in a monotonic fashion until a small drop was observed at the end of the study. Taken together with data from Subject 35, this indicates suggests oral chemesthesis is altered by active SARS-CoV-2 infection. Another study noted that during recovery from COVID-19, some patients report an increase in the ability to feel sensations in the mouth, including burning [49].

### Subject 62

Subject 62's infection began 1 day before enrollment. Like Subject 45, he failed to self-report any symptoms, but unlike Subjects 35 and 45, his orthonasal intensity ratings and OdorID performance remained relatively constant throughout the study period, and his nasal blockage was generally low – while many individuals experience smell loss with COVID-19, some do not (e.g., [8, 48]). Regarding taste, noisy data make it hard to draw any strong conclusions, but it still seems he may have experienced substantial changes in sour and sweet taste. Regarding burn, he rated the burn from Sour Cherry jellybeans near zero for the entire study, suggesting he successfully distinguished burn from the Cinnamon jellybean from the lack of burn from the Sour Cherry jellybean (like the other cases). Two other values merit comment: in the 1st and 3rd week of testing, a sharp drop in sour taste intensity and sharp increase in burn intensity can be seen on two separate days; we suspect he may have misread the blinding codes, tasting the wrong sample on these days, as Sour Cherry jellybeans

655   should be sour without any burn. Still, despite noise in his ratings, his panel plots for

656   burn suggest he experienced transient changes in oral chemesthesis. If this case did in

657   fact experience altered burn and altered taste without concomitant smell loss, this

658   would emphasize that mechanisms of loss across all three modalities are distinct, with

659   the caveat that the noise in these data should temper any strong inferences.

660   ***Subject 63***

661         Subject 63 enrolled 2 weeks days before becoming a case. Because this greatly

662   exceeds the expected incubation period of 5 to 7 days [37, 50], our study team contacted

663   her via email. At that point, she reported a second exposure to an individual with

664   COVID-19 – we assume this second exposure was the source of the infection

665   documented here. Her data reveals changes in smell, taste, and chemesthesis as she

666   transitioned from being a close contact to being a case, but the observation period only

667   captures her initial illness without any recovery as she had enrolled after her first

668   exposure that did not cause an infection. Consistent with this interpretation, she did not

669   report any symptoms for the first 2 weeks, but then began reporting many symptoms

670   (sore throat, fever or chills, dry cough, body aches, fatigue, diarrhea, nausea or

671   vomiting, headache, and dry cough). Notably, her mean orthonasal ratings began to

672   decline somewhat a few days before the estimated day of infection, but she indicated

673   little to no nasal blockage, as expected [4-7, 10]. Also, her intensity ratings suggest she

674   experienced hyposmia, rather than full anosmia, so it is unsurprising that her OdorID

675   performance remained relatively constant across the study period, with some evidence

676   of a slight learning effect near the beginning of the study. As discussed previously, this

677   suggests rated smell intensity might provide more nuanced assessment of smell function

678   versus odor identification. We have no obvious explanation for her unexpectedly low

679   sourness ratings on the first two days of the study. Still, if her peak ratings during this

680   initial (uninfected) period are tentatively treated as a baseline, we see a subsequent

681   decline in sourness around the time her other symptoms appeared. For the rest of the

682   study, her sour ratings remained relatively depressed, at least relative to the maximal

683   values she reported pre-infection. In contrast, sweetness, while noisy, appeared more

684   constant across the entire study. Tentatively, these plots suggest Subject 63 lost some

685   taste function in a quality specific manner, as well as partial smell loss and loss of oral

686   chemesthesis, with staggered timing of each, during her infection.

## References

1. Morens, D.M., J.K. Taubenberger, and A.S. Fauci, *A centenary tale of two pandemics: the 1918 influenza pandemic and COVID-19, part I.* American journal of public health, 2021. **111**(6): p. 1086-1094.

2. da Costa, V.G., M.V. Saivish, D.E.R. Santos, R.F. de Lima Silva, and M.L. Moreli, *Comparative epidemiology between the 2009 H1N1 influenza and COVID-19 pandemics.* Journal of infection and public health, 2020. **13**(12): p. 1797-1804.

3. WHO. *World Health Organization (COVID-19) Dashboard. .* 2022; Available from: https://covid19.who.int.

4. Passarelli, P.C., M.A. Lopez, G.M. Bonaviri, F. Garcia-Godoy, and A. D'Addona, *Taste and smell as chemosensory dysfunctions in COVID-19 infection.* Am J Dent, 2020. **33**(3): p. 135-137.

5. Pellegrino, R., K.W. Cooper, A. Di Pizio, P.V. Joseph, S. Bhutani, and V. Parma, *Coronaviruses and the chemical senses: past, present, and future.* Chemical senses, 2020. **45**(6): p. 415-422.

6. Printza, A., M. Katotomichelakis, K. Valsamidis, S. Metallidis, P. Panagopoulos, M. Panopoulou, et al., *Smell and Taste Loss Recovery Time in COVID-19 Patients and Disease Severity.* Journal of Clinical Medicine, 2021. **10**(5): p. 966.

7. Menni, C., A.M. Valdes, M.B. Freidin, C.H. Sudre, L.H. Nguyen, D.A. Drew, et al., *Real-time tracking of self-reported symptoms to predict potential COVID-19.* Nature medicine, 2020: p. 1-4.

8. Hannum, M.E., V.A. Ramirez, S.J. Lipson, R.D. Herriman, A.K. Toskala, C. Lin, 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.* medRxiv, 2020.

9. Gerkin, R.C., K. Ohla, M.G. Veldhuizen, P.V. Joseph, C.E. Kelly, A.J. Bakke, et al., *Recent smell loss is the best predictor of COVID-19 among individuals with recent respiratory symptoms.* Chemical senses, 2021. **46**.

10. Parma, V., K. Ohla, M.G. Veldhuizen, M.Y. Niv, C.E. Kelly, A.J. Bakke, et al., *More than smell—COVID-19 is associated with severe impairment of smell, taste, and chemesthesis.* Chemical Senses, 2020. **45**(7): p. 609-622.

11. Karni, N., H. Klein, K. Asseo, Y. Benjamini, S. Israel, M. Nimri, et al., *Self-rated smell ability enables highly specific predictors of COVID-19 status: a case control study in Israel.* medRxiv, 2020: p. 2020.07.30.20164327.

12. Huart, C., C. Philpott, I. Konstantinidis, A. Altundag, E.M.C. Trecca, M. Cassano, et al., *Comparison of COVID-19 and common cold chemosensory dysfunction.* Rhinology, 2020.

13. Ohla, K., M.G. Veldhuizen, T. Green, M.E. Hannum, A.J. Bakke, S. Moein, et al., *Increasing incidence of parosmia and phantosmia in patients recovering from COVID-19 smell loss.* medRxiv, 2021.

14. Green, B.G., *Introduction: what is chemesthesis?* Chemesthesis: Chemical touch in food and eating, 2016: p. 1-7.

730    15.    Borsetto, D., C. Hopkins, V. Philips, R. Obholzer, G. Tirelli, J. Polesel, et al., *Self-reported*
731           *alteration of sense of smell or taste in patients with COVID-19: a systematic review and*
732           *meta-analysis on 3563 patients.* Rhinology, 2020. **58**(5): p. 430-436.
733    16.    Dawson, P., E.M. Rabold, R.L. Laws, E.E. Conners, R. Gharpure, S. Yin, et al., *Loss of taste*
734           *and smell as distinguishing symptoms of COVID-19.* Clinical Infectious Diseases, 2020.
735    17.    Printza, A. and J. Constantinidis, *The role of self-reported smell and taste disorders in*
736           *suspected COVID-19.* European Archives of Oto-Rhino-Laryngology, 2020. **277**: p. 2625-
737           2630.
738    18.    Mazzatenta, A., G. Neri, D. D'Ardes, C. De Luca, S. Marinari, E. Porreca, et al., *Smell and*
739           *taste in severe CoViD-19: self-reported vs. testing.* Frontiers in Medicine, 2020. **7**.
740    19.    Konstantinidis, I., A. Delides, E. Tsakiropoulou, P. Maragoudakis, S. Sapounas, and S.
741           Tsiodras, *Short-Term Follow-Up of Self-Isolated COVID-19 Patients with Smell and Taste*
742           *Dysfunction in Greece: Two Phenotypes of Recovery.* ORL, 2020. **82**(6): p. 295-303.
743    20.    Callejon-Leblic, M.A., R. Moreno-Luna, A. Del Cuvillo, I.M. Reyes-Tejero, M.A. Garcia-
744           Villaran, M. Santos-Peña, et al., *Loss of Smell and Taste Can Accurately Predict COVID-19*
745           *Infection: A Machine-Learning Approach.* Journal of clinical medicine, 2021. **10**(4): p.
746           570.
747    21.    Liou, J.-M., M.-J. Chen, T.-C. Hong, and M.-S. Wu, *Alteration of taste or smell as a*
748           *predictor of COVID-19.* Gut, 2021. **70**(4): p. 806-807.
749    22.    Hayes, J.E.P., Valentina. *COVID-19, smell and taste – how is COVID-19 different from*
750           *other respiratory diseases?* 2020; Available from: https://theconversation.com/covid-
751           19-smell-and-taste-how-is-covid-19-different-from-other-respiratory-diseases-139543.
752    23.    Ferreli, F., M. Di Bari, F. Gaino, A. Albanese, L.S. Politi, G. Spriano, et al. *Trigeminal*
753           *features in COVID-19 patients with smell impairment*. in *International Forum of Allergy &*
754           *Rhinology*. 2021: Wiley-Blackwell.
755    24.    Iravani, B., A. Arshamian, A. Ravia, E. Mishor, K. Snitz, S. Shushan, et al., *Relationship*
756           *between odor intensity estimates and COVID-19 prevalence prediction in a Swedish*
757           *population.* Chemical senses, 2020. **45**(6): p. 449-456.
758    25.    Paderno, A., D. Mattavelli, V. Rampinelli, A. Grammatica, E. Raffetti, M. Tomasoni, et al.,
759           *Olfactory and gustatory outcomes in COVID-19: A prospective evaluation in*
760           *nonhospitalized subjects.* Otolaryngology–Head and Neck Surgery, 2020. **163**(6): p.
761           1144-1149.
762    26.    Gerkin, R.C., K. Ohla, M.G. Veldhuizen, P.V. Joseph, C.E. Kelly, A.J. Bakke, et al., *The best*
763           *COVID-19 predictor is recent smell loss: a cross-sectional study.* medRxiv, 2020.
764    27.    Niklassen, A.S., J. Draf, C. Huart, C. Hintschich, S. Bocksberger, E.M.C. Trecca, et al.,
765           *COVID-19: Recovery from chemosensory dysfunction. A multicentre study on smell and*
766           *taste.* The Laryngoscope, 2021. **131**(5): p. 1095-1100.
767    28.    Blomberg, B., K.G.-I. Mohn, K.A. Brokstad, F. Zhou, D.W. Linchausen, B.-A. Hansen, et al.,
768           *Long COVID in a prospective cohort of home-isolated patients.* Nature Medicine, 2021: p.
769           1-7.
770    29.    Klein, H., K. Asseo, N. Karni, Y. Benjamini, R. Nir-Paz, M. Muszkat, et al., *Onset, duration*
771           *and unresolved symptoms, including smell and taste changes, in mild COVID-19*
772           *infection: a cohort study in Israeli patients.* Clinical Microbiology and Infection, 2021.

30.  Otte, M.S., M.-L. Bork, P.H. Zimmermann, J.P. Klußmann, and J.-C. Lüers, *Patients with COVID-19-associated olfactory impairment also show impaired trigeminal function.* Auris Nasus Larynx, 2021.

31.  Boscolo-Rizzo, P., F. Guida, J. Polesel, A.V. Marcuzzo, P. Antonucci, V. Capriotti, et al., *Self-reported smell and taste recovery in coronavirus disease 2019 patients: a one-year prospective study.* European Archives of Oto-Rhino-Laryngology, 2022. **279**(1): p. 515-520.

32.  Harris, P.A., R. Taylor, R. Thielke, J. Payne, N. Gonzalez, and J.G. Conde, *Research electronic data capture (REDCap)—a metadata-driven methodology and workflow process for providing translational research informatics support.* Journal of biomedical informatics, 2009. **42**(2): p. 377-381.

33.  Harris, P.A., R. Taylor, B.L. Minor, V. Elliott, M. Fernandez, L. O'Neal, et al., *The REDCap consortium: Building an international community of software platform partners.* Journal of biomedical informatics, 2019. **95**: p. 103208.

34.  Clark, C.C. and H.T. Lawless, *Limiting response alternatives in time-intensity scaling: an examination of the halo-dumping effect.* Chemical senses, 1994. **19**(6): p. 583-594.

35.  Wang, J., *An intuitive tutorial to Gaussian processes regression.* arXiv preprint arXiv:2009.10862, 2020.

36.  Klein, H., K. Asseo, N. Karni, Y. Benjamini, R. Nir-Paz, M. Muszkat, et al., *Onset, duration and unresolved symptoms, including smell and taste changes, in mild COVID-19 infection: a cohort study in Israeli patients.* Clinical Microbiology and Infection, 2021. **27**(5): p. 769-774.

37.  Lauer, S.A., K.H. Grantz, Q. Bi, F.K. Jones, Q. Zheng, H.R. Meredith, et al., *The Incubation Period of Coronavirus Disease 2019 (COVID-19) From Publicly Reported Confirmed Cases: Estimation and Application.* Annals of Internal Medicine, 2020. **172**(9): p. 577-582.

38.  Printza, A. and J. Constantinidis, *The role of self-reported smell and taste disorders in suspected COVID-19.* European Archives of Oto-Rhino-Laryngology, 2020. **277**(9): p. 2625-2630.

39.  Cecchetto, C., A. Di Pizio, F. Genovese, O. Calcinoni, A. Macchi, A. Dunkel, et al., *Assessing the extent and timing of chemosensory impairments during COVID-19 pandemic.* Scientific Reports, 2021. **11**(1): p. 1-12.

40.  Vaira, L.A., J.R. Lechien, G. Salzano, F.A. Salzano, F. Maglitto, S. Saussez, et al., *Gustatory Dysfunction: A Highly Specific and Smell-Independent Symptom of COVID-19.* Indian Journal of Otolaryngology and Head & Neck Surgery, 2020: p. 1-3.

41.  Vaira, L.A., C. Hopkins, G. Salzano, M. Petrocelli, A. Melis, M. Cucurullo, et al., *Olfactory and gustatory function impairment in COVID-19 patients: Italian objective multicenter-study.* Head & neck, 2020. **42**(7): p. 1560-1569.

42.  Hintschich, C.A., J.J. Wenzel, T. Hummel, M.K. Hankir, T. Kühnel, V. Vielsmeier, et al. *Psychophysical tests reveal impaired olfaction but preserved gustation in COVID-19 patients*. in *International forum of allergy & rhinology*. 2020: Wiley-Blackwell.

43.  Singer-Cornelius, T., J. Cornelius, M. Oberle, F.U. Metternich, and S.J. Brockmeier, *Objective gustatory and olfactory dysfunction in COVID-19 patients: a prospective cross-sectional study.* European Archives of Oto-Rhino-Laryngology, 2021: p. 1-8.

816    44.    Lyu, C., D. Schijvens, J.E. Hayes, and M. Stieger, *Capsaicin burn increases thickness*
817           *discrimination thresholds independently of chronic chili intake.* Food Research
818           International, 2021. **149**: p. 110702.
819    45.    Nolden, A.A. and J.E. Hayes, *Perceptual and affective responses to sampled capsaicin*
820           *differ by reported intake.* Food quality and preference, 2017. **55**: p. 26-34.
821    46.    Lawless, H., *Oral chemical irritation: Psychophysical properties.* Chemical Senses, 1984.
822           **9**(2): p. 143-155.
823    47.    Lawless, H., P. Rozin, and J. Shenker, *Effects of oral capsaicin on gustatory, olfactory and*
824           *irritant sensations and flavor identification in humans who regularly or rarely consume*
825           *chili pepper.* Chemical senses, 1985. **10**(4): p. 579-589.
826    48.    Hannum, M.E., R.J. Koch, V.A. Ramirez, S.S. Marks, A.K. Toskala, R.D. Herriman, et al.,
827           *Taste loss as a distinct symptom of COVID-19: A systematic review and meta-analysis.*
828           medRxiv, 2021: p. 2021.10.09.21264771.
829    49.    Al-Rawi, N.H., A.R. Sammouda, E.A. AlRahin, F.A. Al Ali, G.S. Al Arayedh, H.A.
830           Daryanavard, et al., *Prevalence of Anosmia or Ageusia in COVID-19 Patients Among UAE*
831           *Population.* International Dental Journal, 2021.
832    50.    Cimolai, N., *In pursuit of the right tail for the COVID-19 incubation period.* Public Health,
833           2021. **194**: p. 149-155.
834    51.    Hintschich, C.A., M.Y. Niv, and T. Hummel. *The taste of the pandemic—contemporary*
835           *review on the current state of research on gustation in coronavirus disease 2019 (COVID-*
836           *19).* in *International Forum of Allergy & Rhinology*: Wiley Online Library.
837    52.    Nguyen, H., J. Albayay, R. Höchenberger, S. Bhutani, S. Boesveldt, N.A. Busch, et al.,
838           *Covid-19 affects taste independently of smell: results from a combined chemosensory*
839           *home test and online survey from a global cohort (N=10,953).* medRxiv, 2023: p.
840           2023.01.16.23284630.
841    53.    Salcan, İ., F. Karakeçili, S. Salcan, E. Ünver, S. Akyüz, E. Seçkin, et al., *Is taste and smell*
842           *impairment irreversible in COVID-19 patients?* European Archives of Oto-Rhino-
843           Laryngology, 2021. **278**(2): p. 411-415.
844    54.    Altin, F., C. Cingi, T. Uzun, and C. Bal, *Olfactory and gustatory abnormalities in COVID-19*
845           *cases.* European Archives of Oto-Rhino-Laryngology, 2020. **277**(10): p. 2775-2781.
846    55.    Bidkar, V., M. Mishra, K. Selvaraj, P. Joshi, B. Shrikrishna, S. Dabhekar, et al., *Testing*
847           *Olfactory and Gustatory Dysfunctions among Quarantine COVID-19 Suspects.* Indian
848           Journal of Otolaryngology and Head & Neck Surgery, 2020: p. 1-6.
849    56.    Adamczyk, K., M. Herman, J. Fraczek, R. Piec, B. Szykula-Piec, A. Zaczynski, et al.,
850           *Sensitivity and specifity of prediction models based on gustatory disorders in diagnosing*
851           *COVID-19 patients: a case-control study.* medRxiv, 2020.
852    57.    Vaira, L.A., G. Deiana, A.G. Fois, P. Pirina, G. Madeddu, A. De Vito, et al., *Objective*
853           *evaluation of anosmia and ageusia in COVID-19 patients: single-center experience on 72*
854           *cases.* Head & neck, 2020. **42**(6): p. 1252-1258.
855    58.    Vaira, L.A., C. Hopkins, M. Petrocelli, J. Lechien, C. Chiesa-Estomba, G. Salzano, et al.,
856           *Smell and taste recovery in coronavirus disease 2019 patients: a 60-day objective and*
857           *prospective study.* The Journal of Laryngology & Otology, 2020. **134**(8): p. 703-709.
858    59.    Vaira, L.A., C. Hopkins, M. Petrocelli, J.R. Lechien, D. Soma, F. Giovanditto, et al., *Do*
859           *olfactory and gustatory psychophysical scores have prognostic value in COVID-19*

860        *patients? A prospective study of 106 patients.* Journal of Otolaryngology-Head & Neck
861        Surgery, 2020. **49**(1): p. 1-10.

862   60.   Vaira, L.A., G. Salzano, M. Petrocelli, G. Deiana, F.A. Salzano, and G. De Riu, *Validation of*
863        *a self-administered olfactory and gustatory test for the remotely evaluation of COVID-19*
864        *patients in home quarantine.* Head & neck, 2020. **42**(7): p. 1570-1576.

865   61.   Petrocelli, M., S. Cutrupi, G. Salzano, F. Maglitto, F. Salzano, J. Lechien, et al., *Six-month*
866        *smell and taste recovery rates in coronavirus disease 2019 patients: a prospective*
867        *psychophysical study.* The Journal of Laryngology & Otology, 2021: p. 1-6.

868   62.   Burges Watson, D.L., M. Campbell, C. Hopkins, B. Smith, C. Kelly, and V. Deary, *Altered*
869        *smell and taste: Anosmia, parosmia and the impact of long Covid-19.* PloS one, 2021.
870        **16**(9): p. e0256998.

871   63.   Doyle, M.E., A. Appleton, Q.-R. Liu, Q. Yao, C.H. Mazucanti, and J.M. Egan, *Human Taste*
872        *Cells Express ACE2: a Portal for SARS-CoV-2 Infection.* bioRxiv, 2021.

873   64.   Hoffmann, M., H. Kleine-Weber, S. Schroeder, N. Krüger, T. Herrler, S. Erichsen, et al.,
874        *SARS-CoV-2 cell entry depends on ACE2 and TMPRSS2 and is blocked by a clinically*
875        *proven protease inhibitor.* cell, 2020. **181**(2): p. 271-280. e8.

876   65.   Xu, H., L. Zhong, J. Deng, J. Peng, H. Dan, X. Zeng, et al., *High expression of ACE2 receptor*
877        *of 2019-nCoV on the epithelial cells of oral mucosa.* International journal of oral science,
878        2020. **12**(1): p. 1-5.

879   66.   Lewis, A., J. Frontera, D.G. Placantonakis, J. Lighter, S. Galetta, L. Balcer, et al.,
880        *Cerebrospinal fluid in COVID-19: A systematic review of the literature.* Journal of the
881        neurological sciences, 2021: p. 117316.

882   67.   Matschke, J., M. Lütgehetmann, C. Hagel, J.P. Sperhake, A.S. Schröder, C. Edler, et al.,
883        *Neuropathology of patients with COVID-19 in Germany: a post-mortem case series.* The
884        Lancet Neurology, 2020. **19**(11): p. 919-929.

885   68.   Hayes, J.E., & Parma, V. *COVID-19, smell and taste – how is COVID-19 different from*
886        *other respiratory diseases?* . 2020.

887   69.   Alpizar, Y.A., T. Voets, and K. Talavera, *Molecular mechanisms underlying the role of TRP*
888        *channels in chemesthesis.* Chemesthesis: Chemical Touch in Food and Eating, 2016: p.
889        48.

890   70.   Bandell, M., G.M. Story, S.W. Hwang, V. Viswanath, S.R. Eid, M.J. Petrus, et al., *Noxious*
891        *cold ion channel TRPA1 is activated by pungent compounds and bradykinin.* Neuron,
892        2004. **41**(6): p. 849-857.

893   71.   Chiesa-Estomba, C.M., J.R. Lechien, T. Radulesco, J. Michel, L.J. Sowerby, C. Hopkins, et
894        al., *Patterns of smell recovery in 751 patients affected by the COVID-19 outbreak.*
895        European journal of neurology, 2020. **27**(11): p. 2318-2321.

896   72.   Reiter, E.R., D.H. Coelho, Z.A. Kons, and R.M. Costanzo, *Subjective smell and taste*
897        *changes during the COVID-19 pandemic: Short term recovery.* American Journal of
898        Otolaryngology, 2020. **41**(6): p. 102639.

899   73.   Chaaban, N., A.T.Z.B. Høier, and B.V. Andersen, *A Detailed Characterisation of Appetite,*
900        *Sensory Perceptional, and Eating-Behavioural Effects of COVID-19: Self-Reports from the*
901        *Acute and Post-Acute Phase of Disease.* Foods, 2021. **10**(4): p. 892.

902