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Recovery from COVID-19-related olfactory disorders and quality of life: insights from an observational online study

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19 ABSTRACT

20 Although olfactory disorders (OD) are among the most significant symptoms of COVID-19,
21 recovery time from COVID-19 related OD as well as their consequences on the quality of life
22 remain poorly documented. We investigated the characteristics and behavioral consequences
23 of COVID-19 related OD using a large-scale study involving 3111 French respondents (78%
24 women) to an online questionnaire over a period of 9 months covering different epidemic
25 waves (from April 8th 2020 to January 13th 2021). In the patients who subjectively recovered
26 from COVID-19 related OD (N = 609), recovery occurred on average after 16 days and most
27 of the time within one month (“normal” recovery range); 49 subjectively recovered in 1 to 2.5
28 months, and several cases took up to 6.5 months. Among the patients with ongoing OD (N =
29 2502), 974 were outside the “normal” recovery range (persistent OD) and reported OD for 1
30 to 10 months. Developing a persistent OD was more likely with increasing age and in
31 women, and was more often associated with parosmia and phantosmia. The deleterious
32 impact of COVID-19 related OD on the quality of life was significantly aggravated by OD
33 duration, and was more pronounced in women. Because persistent OD is not infrequent after
34 COVID-19, has deleterious consequences on the quality of life, and receives few solutions
35 from the health practitioners, it would be beneficial to implement screening and treatment
36 programs to minimize the long-term behavioral consequences of COVID-19 related OD.

37

38 KEY WORDS

39 COVID-19, smell loss, quality of life, mental health, self-report.

40 INTRODUCTION

41

42 Disturbances of smell and taste perception are among the most significant symptoms of
43 the recently emerged COVID-19 disease. Several studies based on self-reports recorded a
44 relatively high prevalence in many countries: 46-47% of COVID-19 patients were found to
45 have olfactory disorders (OD) in France (Bénézit et al., 2020; Klopfenstein et al., 2020), 32%
46 in Spain (Beltrán- Corbellini et al., 2020), 19-24% in Italy (Giacomelli et al., 2020; Vaira et
47 al., 2020), 49-65% in Germany (Haehner et al., 2020; Hornuss et al., 2020), 59% in the UK
48 (Menni et al., 2020), 59% in the US (Yan et al., 2020), 28% in Iran (Moein et al., 2020) and
49 36% in Israël (Levinson et al., 2020). This prevalence was significantly higher in patients
50 than in COVID-19 negative controls (Beltrán- Corbellini et al., 2020; Bénézit et al., 2020;
51 Hornuss et al., 2020; Menni et al., 2020; Moein et al., 2020). The actual prevalence may even
52 be higher because studies relying on subjective assessments of OD typically produce lower
53 estimates of prevalence than studies relying on objective assessments (Desiato et al., 2021).

54 So far, the characteristics of COVID-19-related OD have been described as follows.
55 They appear suddenly rather than gradually (Bagheri et al., 2020), total loss of olfactory
56 perceptions (anosmia) is more frequent than hyposmia (decreased olfactory
57 perceptions) (Beltrán- Corbellini et al., 2020; Lechien et al., 2020; Moein et al., 2020; but see
58 Giacomelli et al., 2020; Hornuss et al., 2020), and OD are often concomitant with taste
59 disorders (Bénézit et al., 2020; Giacomelli et al., 2020; Levinson et al., 2020; Moein et al.,
60 2020; Parma et al., 2020). Investigation of gender and age differences yielded heterogeneous
61 conclusions, with female patients being more affected by OD in some studies (Giacomelli et
62 al., 2020; Haehner et al., 2020; Lechien et al., 2020) but not in others (Beltrán- Corbellini et
63 al., 2020; Moein et al., 2020), and patients with OD being younger than those without
64 (Beltrán- Corbellini et al., 2020; Giacomelli et al., 2020), which is however not confirmed in

65 other studies involving younger samples (Haehner et al., 2020; Hornuss et al., 2020). Finally,
66 although first reports indicated that COVID-19-related OD last about 7 to 9 days on average
67 (Beltrán- Corbellini et al., 2020; Klopfenstein et al., 2020; Lechien et al., 2020; Levinson et
68 al., 2020), more recent evidence shows that 37% of the patients report persistent OD at 1.5
69 month after the first consultation, and 14% report a partial (not total) recovery
70 (Chiesa- Estomba et al., 2020). At 6 months follow-up, 5 to 11% of patients were found to
71 still suffer from OD (Huang et al., 2021; Lechien et al., 2021a).

72 Past studies performed before the COVID-19 pandemics shown that OD can have
73 serious consequences on quality of life (Vennemann et al., 2008; Keller and Malaspina, 2013;
74 Croy et al., 2014; Philpott and Boak, 2014; Manesse et al., 2017; Drareni et al., 2019).
75 Patients with impaired sense of smell are more likely to experience domestic accidents, report
76 feelings of insecurity in their social relationships as well as alterations of eating behavior,
77 which can lead to a tendency to isolation and depression (Croy et al., 2014; Philpott and
78 Boak, 2014). Furthermore, women (Philpott and Boak, 2014) and current smokers
79 (Vennemann et al., 2008) seem to have more severe impacts of OD on their quality of life.

80 How COVID-19 patients with OD recover their perceptual abilities on the longer-term,
81 and how this relates to individual characteristics, is currently poorly documented. The first
82 aim of this observational study was to describe the various forms of OD reported by the
83 participants, using online self-reports of patients who declared having been diagnosed with
84 COVID-19 and having lost their sense of smell between February 2020 and January 2021.
85 The second aim was to investigate the temporal dynamics of subjective recovery from OD
86 due to COVID-19, and the factors involved in the cases of slower recovery. Persistent OD
87 have been examined more thoroughly, given their anticipated deleterious consequences for
88 the patients. The third aim was to investigate the consequences of COVID-19-related OD on
89 patients' behavior, by linking the characteristics of a participant and of his/her OD to the

90 quality of life assessed with a 16-item questionnaire. Finally, the fourth aim of this study was
91 to describe how ODs were managed by the medical staff in the context of the COVID-19
92 pandemic. The impact of COVID-19-related OD on quality of life as a function of recovery
93 dynamics is an important societal concern, which has clinical implications regarding whether
94 and how these sensory disorders require medical care.

95

96 MATERIALS and METHODS

97 Participants

98 The online questionnaire was advertised at the national level in France and intended for
99 people with OD, be it caused by COVID-19 or not. In this article, we included participants
100 who i) reported OD and ii) were diagnosed COVID-19 positive by a health practitioner from
101 February 1st 2020 onwards and based on a laboratory test (74%: PCR-test after nasal swab
102 62%, chest radio 0.2%, other e.g. blood test 11.4%, unknown 0.4%) or based on their
103 symptoms (26%). Although the diagnosis based only on the symptoms has a higher rate of
104 uncertainty, we used it as an inclusion criterion because at the beginning of the pandemic
105 many patients were diagnosed this way due to very limited access to PCR tests. Note that the
106 conclusions of this article remain the same if only participants reporting a PCR test are
107 included. Other inclusion criteria were: iii) responding to the full questionnaire (i.e., no drop
108 out before the end of the questionnaire), iv) completing the questionnaire for the first time, v)
109 aged over 18 years old, vi) answering between April 8th 2020 (questionnaire release) and
110 January 13th 2021, and vii) providing usable data on OD duration and declaring OD onset
111 maximum 1 week prior to COVID-19 onset. In total, responses of 3111 individuals were
112 used. Participants were mostly women (78.1%), and were aged 40.5 ± 12.5 years (range 18-

113 85). Men and women did not differ on age (Mean±SD: 40.2±13.1 and 40.6±12.4 years
114 respectively; $t_{3109}=0.751$, $p=0.453$). The study was approved by the ethics committee of the
115 Institute of Biological Sciences of the CNRS on the 3rd of April 2020. All individuals
116 provided informed consent when participating in the survey.

117

118 Questionnaire

119 The online questionnaire was accessible from a French information website dedicated
120 to the sense of smell (<https://project.crn1.fr/odorat-info/>). It was advertised at the national
121 level in France through different channels (numerous audio-visual media communications,
122 authors' professional and personal networks, advertisements posted in local health centers and
123 pharmacies). The call was directed to people who noticed a change in their sense of smell, be
124 it caused by COVID-19 or not, and be it still present or not. The stated purpose of the study
125 was to help us better understand how OD manifest themselves and what impact they have on
126 quality of life, especially in the context of the COVID-19 crisis. The questionnaire comprised
127 4 sections (see details in **Appendix** and in Data Analysis section for the relevant variables we
128 used in this paper): *i*) chemosensory disorders (smell, taste, trigeminal): characteristics and
129 management by health practitioners, *ii*) incapacitating character of chemosensory disorders
130 and impact on quality of life (QoL) on 16 items related to food, social interactions, danger
131 detection and enjoyment of the environment, *iii*) sociodemographic information, and *iv*)
132 information related with COVID-19. The questionnaire was completed only once by the
133 participants (not meant for a follow-up), providing information at a single time-point.
134 Participants responded at varied times after the onset of the disease (and after the onset of
135 their COVID-19 related OD), as illustrated in **Fig. S1**.

136

137 Data Analysis

138 *Variables.* For data analysis, we calculated the duration of a participant's OD, based on
139 the reported date of OD onset and the reported date of OD disappearance, for individuals who
140 subjectively recovered. Age, gender, height and weight from which we computed Body Mass
141 Index, smoking status (yes or no), type of OD (total, i.e. anosmia, or partial, i.e. hyposmia),
142 speed of OD onset (sudden or progressive) and constancy of OD (fluctuating or constant)
143 were also included. For the quality of life, three variables were used. First, the response to the
144 question whether OD was incapacitating for a participant's personal life (yes/no). Second, the
145 16 QoL item scores (-1, 0, 1 corresponding to the answers "less than usual", "neither more
146 nor less than usual", "more than usual"). Third, a variable called TotalImpact (ranging from 0
147 to 16) summarizing the 16 QoL items and which is equal to the number of times a respondent
148 answered either "less than usual" or "more than usual" (i.e., deviated from "neither more nor
149 less than usual").

150

151 *Analyses.* Analyses were performed in R 4.0.3 (R core team, 2021) and the level of
152 significance was set at $\alpha = 0.05$. To facilitate the interpretation of the regression coefficients,
153 all numerical variables were centered and scaled prior to inclusion in all models (Schielezeth,
154 2010).

155 First, we aimed at identifying the factors associated with OD duration for participants
156 who subjectively recovered from OD. We used a generalised linear model with the positive
157 negative binomial family (vglm function from the R package VGAM, Yee, 2021) and
158 participant's (i) age, (ii) gender, (iii) BMI, (iv) smoking status, (v) OD type, (vi) OD onset
159 speed, (vii) OD constancy and (viii) age by gender interaction as explanatory variables. Age
160 by gender interaction was included because such interactions may occur in olfaction (e.g.,
161 Manesse et al., 2021). A backward model selection, based on Likelihood Ratio Tests (LRT)

162 and using the `ltest` function from the R package `lmtest` (Zeileis and Hothorn, 2002), allowed
163 us to obtain a minimal model containing only variables having a significant effect.

164 Second, we aimed at identifying the factors influencing the probability to report a
165 persistent OD or to have subjectively recovered. We started by focusing on defining the
166 “normal” duration range of recovery from OD in our sample. To do so, rules using the
167 InterQuartile Range (IQR) of the distribution are routinely used (Rousseeuw & Hubert,
168 2011). With this technique, points outside the range [first quartile - 1.5 * IQR, third quartile +
169 1.5 * IQR] are considered as outliers. In our case, the “normal” range is thus [7 - 1.5 * 10, 17
170 + 1.5 * 10] or [-8, 32] and OD durations longer than 32 days are considered as outliers. Then,
171 we filtered out respondents with ongoing OD but who were still within the “normal” range
172 (1-32 days), because our approach does not allow us to know whether in the future these
173 participants will be recovering within the “normal” range, or whether they will develop
174 longer-lasting OD. We defined a new independent binary variable - persistence of OD -
175 which is equal to 1 when respondents had persistent OD (> 32 days, not recovered yet, N =
176 974) and 0 when respondents had subjectively recovered from their OD (N = 609). This
177 variable was modelled by a logistic regression with the same 8 explanatory variables
178 described above. Again, model selection allowed us to only retain the significant explanatory
179 variables (stepwise model selection based on Akaike Information Criteria (AIC) with the step
180 function from the R package `stats`).

181

182 Third, we aimed at identifying the variables that predicted the impacts of OD on the
183 quality of life of all participants (N = 3111). We ran a linear regression on the composite
184 variable `TotalImpact` with 9 explanatory variables which are the same 8 already described to
185 which we added (ix) the duration of OD, and a stepwise model selection based on AIC was
186 conducted. Then, we analyzed the 16 QoL item scores. To determine whether the impact was

187 significant, we compared the distribution of the answers “neither more nor less than usual”
188 versus “less than usual” and “more than usual” grouped together, using raw numbers
189 converted in percentage rounded to the nearest whole number, with the theoretical
190 distribution if OD induced no change (i.e., 100/0), using χ^2 tests. To describe the direction of
191 the impact (reduction or increase), we compared with χ^2 tests the number of respondents who
192 answered “More than usual” to the number of “Less than usual” responses (irrespective of
193 how many respondents answered “Same as usual”). P-values were Bonferroni corrected for
194 repeated testing (significant at $\alpha = 0.05 / 16$ items = 0.003125). To determine the variables
195 explaining the variations in responses to each quality of life item, we performed Multivariate
196 Ordinal Regressions (MOR) using the mvord function in the R package mvord (Hirk et al.,
197 2020), including the same 9 explanatory variables described just before. Due to computation
198 time constraints, it was not possible to run a single MOR for the 16 QoL items: 4 MORs were
199 therefore run on 4 sub-groups of items that were identified with a factor analysis (see details
200 in **Supplementary Method** and **Fig. S2**). Again, model selection using LRT was performed
201 to only retain the significant explanatory variables. As 4 MORs were conducted instead of 1,
202 a Bonferroni correction was applied to the p-values, reported as significant at $\alpha = 0.05 / 4 =$
203 0.0125.

204

205 RESULTS

206 Self-reported characteristics of COVID-19-related ODs

207 COVID-19-related ODs were often associated with taste disorders (71.0% of the 3111
208 included respondents) and in 25.5% of the cases with a dysfunction of the trigeminal
209 sensitivity. Only 15.0% of the COVID-19 patients with OD reported having a blocked nose
210 when they underwent the dysfunction. All included participant had decreased olfactory

211 perceptions (quantitative OD), but qualitative disorders were also described: parosmia (odors
212 smelling different from what they usually do) in 55.8% of the respondents, and phantosmia
213 (olfactory hallucinations, see detailed descriptions in **Supplementary Results**) in 34.6%.
214 Note that 26.6% reported having both parosmia and phantosmia. The quantitative alterations
215 were characterized by: 1) type of OD: a clear predominance of anosmia (86.4% vs. 13.6%
216 hyposmia), 2) onset speed of OD: a sudden onset (86.8% vs. 13.2% progressive onset), and 3)
217 constancy of OD: a constant alteration (67.4% vs. 32.6% fluctuating). How the frequency of
218 these characteristics were affected by age and gender was analyzed using logistic regressions:
219 Women had a higher probability than men to report a fluctuating rather than constant OD ($\beta =$
220 0.22 ± 0.10 , $z = 2.36$, $p = 0.02$; no gender differences for type or speed of OD: $\beta = 0.02 \pm$
221 0.13 , $z = 0.15$, $p = 0.881$ and $\beta = 0.24 \pm 0.14$, $z = 1.76$, $p = 0.08$, respectively). Moreover,
222 increasing age was associated with an increased probability to report a sudden rather than
223 progressive onset ($\beta = 0.29 \pm 0.06$, $z = 5.12$, $p < 0.001$) and a fluctuating rather than constant
224 OD ($\beta = 0.14 \pm 0.04$, $z = 3.66$, $p < 0.001$) (no effect on OD type: $\beta = 0.003 \pm 0.052$, $z = 0.06$,
225 $p = 0.955$).

226

227 Self-reported timing of recovery from COVID-19-related OD

228 *Participants who subjectively recovered from OD.* Among the 3111 COVID-19 patients
229 with OD who completed the online questionnaire, $N = 609$ (19.6%) reported that they had
230 recovered their smell. In these patients, subjective recovery took 16.3 ± 19.3 days on average
231 [median: 11 days], ranging from 1 (appears and disappears the same day) to 196 days (**Fig.**
232 **1A**). This recovery duration was significantly predicted by constancy and type of OD (but not
233 gender, age, BMI, smoking status, or onset speed of OD). Patients with fluctuating (vs.
234 constant) OD (**Fig. 2A**) and with a total (vs. partial) OD (**Fig. 2B**) took longer to subjectively

235 recover from their OD (zero-truncated negative binomial minimal model: $\beta = 0.26 \pm 0.07$, $z =$
236 3.65 , $p < 0.001$ and $\beta = 0.33 \pm 0.14$, $z = 2.30$, $p < 0.05$, respectively).

237 *Figures 1 & 2 about here*

239 *Persistent OD.* Among the COVID-19 patients with OD who had not subjectively
240 recovered their smell at the time they completed the questionnaire (N = 2502), 1528 were
241 within what could be called the “normal” range of recovery time, i.e., from 1 to 32 days (see
242 Methods). 974 were outside this range and thus considered as displaying persistent COVID-
243 19-related OD (**Fig. 1B**). These patients represent almost one third (31.3 %) of the 3111
244 participants spontaneously responding to our online questionnaire. They reported OD
245 durations of up to 312 days (i.e., ~10 months). Four factors significantly differentiated this
246 sub-group (persistent OD) from the group who subjectively recovered (**Fig. 3A**). The
247 participants with persistent OD were much more likely to have partial compared to total
248 olfactory loss (logistic regression minimal model: $\beta = 1.63 \pm 0.18$, $z = 8.82$, $p < 2e-16$, OR =
249 5.01 [3.59-7.41], **Fig. 3B**). Women were more likely to report persistent OD compared to
250 men (logistic regression minimal model: $\beta = 0.65 \pm 0.13$, $z = 5.10$, $p < 0.001$, OR = 1.92
251 [1.50-2.48], **Fig. 3C**). Furthermore, persistent OD were more likely to have a sudden onset
252 rather than a progressive one (logistic regression minimal model: $\beta = 0.61 \pm 0.17$, $z = 3.50$, p
253 < 0.001 , OR = 1.84 [1.31-2.60], **Fig. 3D**). Finally, older respondents reported persistent OD
254 more frequently (logistic regression minimal model: $\beta = 0.32 \pm 0.05$, $z = 5.75$, $p < 0.001$, OR
255 of each additional year = 1.38 [1.24-1.54], **Fig. 3E**). The constancy of OD, smoking status,
256 BMI and the interaction between gender and age were not retained in the minimal model.
257 Finally, participants with persistent OD were much more likely to declare a parosmia or a
258 phantosmia ($\chi^2 = 68.1$, $df = 1$, $p < 0.001$ and $\chi^2 = 67.6$, $df = 1$, $p < 0.001$, respectively, χ^2 test

259 comparing patients with persistent OD vs. patients who subjectively recovered; **Fig. 4A** and
260 **4B**).

261 *Figures 3 & 4 about here*

262

263 COVID-19-related OD and self-reported quality of life

264 *Disabling character.* When asked whether losing their smell was incapacitating for
265 their personal life, 73.1% (N = 2275 out of 3111) of the COVID-19 patients with OD
266 considered that it was.

267 *QoL questionnaire: Total impact and factors of variation.* The total impact was
268 significantly greater than 0 (intercept in the minimal model: $\beta = 4.35 \pm 0.18$, $t = 23.85$, $p <$
269 $2e-16$). Six factors were found to significantly influence the TotalImpact of OD on a
270 respondent's quality of life (i.e., number of situations where the respondents reported
271 behaving differently than usual). OD disturbed more facets of quality of life when it lasted
272 longer (minimal model: $\beta = 0.67 \pm 0.06$, $t = 12.14$, $p < 2e-16$, **Fig. 5A**). Younger respondents
273 reported higher total impact than older respondents did (minimal model: $\beta = -0.45 \pm 0.05$, $t =$
274 -8.58 , $p < 2e-16$, **Fig. 5B**). Women reported a broader impact of OD on their quality of life
275 than men (minimal model: $\beta = 1.48 \pm 0.12$, $t = 11.96$, $p < 2e-16$, **Fig. 5C**). Total OD had
276 stronger effects on quality of life than partial OD (minimal model: $\beta = 1.27 \pm 0.15$, $t = 8.22$, p
277 $= 3e-16$, **Fig. 5D**). Similarly, constant OD had stronger effects on quality of life than
278 fluctuating OD (minimal model: $\beta = 0.50 \pm 0.12$, $t = 4.28$, $p = 2e-05$, **Fig. 5E**). Finally,
279 smokers reported a stronger impact of OD on their quality of life than non-smokers (minimal
280 model: $\beta = 0.44 \pm 0.13$, $t = 3.40$, $p = 0.0007$, **Fig. 5F**). Onset speed of OD, BMI and the
281 interaction between gender and age were not retained in the minimal model.

282 *Figure 5 about here*

283

284 *QoL questionnaire: Impact per item and factors of variation.* Considering the 16
285 quality of life items separately, the distribution of the answers (“neither more nor less than
286 usual” versus “less than usual” + “more than usual”) significantly differed from theoretical
287 distribution (no change: 100/0) for all items (all ps < 0.001) except Burn clothes (p = 0.1552),
288 indicating significant impact of OD for 15 out of 16 items. To describe the main direction of
289 these changes, we compared the frequency of displaying each behavior “more” versus “less”
290 than before losing the sense of smell (see **Fig. S3**). Participants more frequently reported an
291 increase than a decrease for 11 items (Seek close ones’ odor, Control own body odor, Add
292 salt, Burn meals, Add spices, Prefer to eat alone, Eat rotten food, Take showers, Have
293 domestic accidents, Add sugar and Add fat; χ^2 -tests, all ps < 0.001, items in green in **Fig. 6**).
294 For the remaining 5 items, participants more frequently reported a decrease than an increase
295 (Wear perfume, Detect smokes/gas, Enjoy smelling flowers, Enjoy eating; χ^2 -tests, all ps <
296 0.001, items in blue in **Fig. 6**) or no difference (Burn clothes, p = 0.018 which is higher than
297 the Bonferroni corrected alpha, item in black in **Fig. 6**).

298 *Figure 6 about here*

299
300 Among the most salient results obtained when considering each item of the quality of
301 life questionnaire separately (**Fig. S4-S7**), we found that OD duration as well as gender and
302 age had significant effects on many items (see summary of the effects in **Fig. 6**). Specifically,
303 a long-lasting OD increased the probability to report 1) adding salt, sugar, spices and fat to
304 dishes, 2) experiencing domestic accidents, burning meals and eating rotten food, and 3)
305 controlling one’s body odor, taking showers and seeking the smell of loved ones, more than
306 usual. In addition, women, compared to men, reported 1) adding salt, 2) having domestic
307 accidents and burning meals, 3) controlling body odor of self and the loved ones, and taking
308 showers, more than usual, but also 4) having less pleasure smelling flowers and wearing
309 perfume less often. Finally, younger participants reported eating rotten food more often than

310 older ones, and displayed more variation (i.e., answering either “more” or “less”) in salting
311 habits and eating pleasure. Results involving the other explanatory variables (age by gender
312 interaction, BMI, smoking status and OD characteristics) can be found in **Supplementary**
313 **Results**.

314 Self-reported management of COVID-19 related OD

315 When questioned about the management of their OD in the context of COVID-19, less than
316 half of the COVID-19 patients with OD (41.5%, N = 1292) reported that they consulted
317 specifically for their sensory loss. Most of them (87.5%) were examined by a general
318 practitioner (GP). Some patients (19.0%) consulted a specialist (ENT physician in 88.6% of
319 the cases). In most cases, OD only served to orient the health practitioner towards a diagnosis
320 of COVID-19 without considering them as a symptom to treat, despite the concern many
321 patients had regarding their sensory loss. Treatment of olfactory loss was rarely evoked, but
322 when it was, the practitioner’s most frequent answers were either to just wait for a
323 spontaneous recovery (18.3% of the consultations) or to try olfactory training (among other
324 even more anecdotal options such as nasal sprays, nasal wash or vitamins). Olfactory training
325 has been recommended by only 3.6% of the GP consultations and 18.4% of the ENT
326 consultations, and took very heterogeneous forms (no standard protocol).

327

328 DISCUSSION

329 Using self-reports of more than 3100 respondents collected over a period of 9 months
330 covering different epidemic waves in France (from April 8th 2020 to January 13th 2021), this
331 study showed that COVID-19 related OD i) last longer than initially thought (several months)
332 in many patients, ii) have significant impacts on the quality of life and that this impact is

333 increasingly deleterious with OD duration, and iii) receive very few treatment options from
334 the health practitioners despite their behavioral consequences.

335 From a methodological point of view, it must be kept in mind that this approach
336 inevitably has limits compared with an experimental setting controlled by an experimenter. In
337 particular, there might be some imprecision i) in how participants self-evaluated their sense
338 of smell (it is well known that we are poorly able to do so: Landis et al., 2003; Manesse et al.,
339 2021), although we tried to minimize this imprecision by asking very specific and detailed
340 questions (see Appendix A), and ii) in how participants reported dates, especially for those
341 who answered several months after the onset of their OD (see **Fig. S1**). For long-lasting OD,
342 this questionnaire was not designed to allow for a systematic description of the variations of
343 OD that could have occurred over time. Another source of imprecision is that we had to trust
344 participants with the positivity of their Covid test, or with their diagnosis when it was based
345 on symptoms alone. There might be a selection bias such that the respondents are people
346 willing to participate in scientific research and probably the most affected by their olfactory
347 loss (as suggested also by the greater proportion of female participants, who are known to be
348 more affected by smells and smell disorders; Martin et al., 2001; Nordin et al., 2004). Finally,
349 this is not a follow-up study since the information is collected once at a single time-point over
350 the course of the disease, and no prevalence data can be extracted from this study. Bearing
351 this in mind, we can however rely on the validity of our results, which are fully in line with
352 previous studies: we found that COVID-19 related OD is characterized by a more frequent
353 anosmia than hyposmia, with a sudden onset mostly, association with taste and trigeminal
354 disorders, and with infrequent blocked nose as reported elsewhere (Lechien et al., 2020;
355 Parma et al., 2020; Speth et al., 2020) and descriptions of the phantom smells are very similar
356 to what has been found in other studies (burned, foul, rotten; Leopold, 2002). Moreover, the
357 way we conducted our analyses allow us to draw valid conclusions in the sample we

358 considered, especially by investigating the factors of variation of OD characteristics and OD
359 consequences on the quality of life within the respondents.

360 Analysis of the COVID-19 related OD duration, limited to the patients who said that
361 they recovered their sense of smell, indicated that subjective recovery occurred most of the
362 time within a month (1-32 days for 90% of the healed patients) with an average of 16 days
363 and a median of 11 days. The remaining 10% took more time to subjectively recover, mostly
364 between 1 and 2.5 months, but sometimes more (up to 6 months). These numbers are slightly
365 higher than those published earlier during the pandemic (7-9 days on average;
366 Beltrán- Corbellini et al., 2020; Klopfenstein et al., 2020; Levinson et al., 2020), probably
367 because these earlier studies did not have sufficient hindsight to examine longer healings.
368 Indeed, more recent reports provide duration ranges that are consistent with our findings
369 (most of the patients recovered by 30 days in D’Ascanio et al., 2021) and there is increasing
370 evidence that part of the patients who lost their sense of smell following SARS-CoV-2
371 infection are slower to recover (Chiesa- Estomba et al., 2020; Huang et al., 2021). Our data
372 sheds an additional light on those persistent ODs and reveals that many patients (one third of
373 the respondents in our study) have not recovered within the first month, and report subjective
374 OD durations up to 312 days (10 months). Although our study does not allow us to establish
375 the prevalence of these persistent ODs, this proportion is consistent with other reports on
376 long-term sequelae (33–36% of incomplete recovery of olfactory and gustatory function,
377 Willi et al., 2021). We noticed that several hundreds of respondents (N = 329) still suffered
378 from OD since they contracted the virus during the first wave (spring 2020). Here, we must
379 acknowledge that it is difficult to state with certainty that all patients who reported to be
380 cured are really cured: Indeed, recurring testimony in open-ended questions of the survey
381 revealed that patients can recover from total anosmia, spend several weeks with a seemingly
382 normal sense of smell before experiencing qualitative disorders (parosmia, phantosmia).

383 Mechanistically, the discrepancies of recovery times (from a few days to several
384 months) between individuals could be partly explained by how severely the SARS-CoV-2
385 virus has damaged the olfactory system (Cooper et al., 2020), even though the mechanisms
386 are still discussed (Lechien 2021b). In the most benign cases, SARS-CoV-2 induces
387 inflammatory processes in the nasal cavity that prevent odorants from reaching the olfactory
388 epithelium (Eliezer et al., 2020). Concomitantly, olfactory neurons may be dysfunctional due
389 to the local inflammation (Bryche et al., 2020). In such cases, recovery time should be less
390 than 1 month (Eliezer et al., 2020; Bryche et al., 2020). In the most severe scenarios, cells of
391 the olfactory epithelium are infected by the virus because they possess ACE2 receptors which
392 are gateways to the cells. When sustentacular (supporting) cells are infected, structure
393 damage and ionic imbalance cause the inactivation and eventually the death of the olfactory
394 neurons (Cooper et al., 2020). When basal cells are infected, the consequences are likely to
395 be even more severe because neural regeneration is heavily compromised. In the current state
396 of knowledge, it seems that olfactory neurons themselves cannot be infected (Brann et al.,
397 2020, but see Satarker and Nampoothiri, 2020; Meinhardt et al., 2021) although a very recent
398 study contradicts this hypothesis (de Melo, 2021).

399 When investigating the parameters of the disease and the individual characteristics of
400 the patients, we were able to identify which factors were the best predictors of the speed of
401 subjective recovery. First, in the subjectively recovered group, total loss is associated with
402 longer recovery, which could be due to a more severe damage/inflammation in the olfactory
403 cleft and olfactory epithelium area. Longer subjective recovery times were also associated
404 with more fluctuating OD. Second, the probability to develop a persistent OD (>32 days;
405 compared with successful subjective recovery) was increased by increasing age and by
406 gender, namely by being a woman. One can hypothesize that peripheral damage of the
407 olfactory epithelium takes longer to spontaneously be repaired in the elderly, due to slower

408 neural regeneration processes (Watabe-Rudolph et al., 2011), although this would need
409 further testing. Regarding the gender differences, it cannot be excluded that the well-known
410 higher awareness of women regarding smells in general make them better able to detect
411 alterations of their perceptions, and to report them in such a study. Also, we found that partial
412 OD and sudden onset were associated more with a persistent OD than with subjective
413 recovery. Although sudden onset is difficult to interpret, partial OD is corroborated by the
414 higher frequency of parosmia and phantosmia in persistent OD. Indeed, it seems that OD
415 characteristics vary during the recovery process (which could unfortunately not be
416 apprehended here since we did not repeat the measures for each respondent). Namely, after a
417 period of severe loss of smell (quantitative loss), patients regain olfactory perceptions but in
418 some of them these sensations are still not fully normal (qualitative alterations). Parosmia can
419 be due to the fact that only some olfactory receptors are functional but not all, thereby
420 distorting the usual pattern of activation (Parker et al., 2021); Phantosmia is associated with
421 disordered growth of olfactory axons (Leopold, 2002). Both mechanisms are likely to occur
422 during recovery and neural regeneration.

423 The fact that 1) COVID-19 related OD can be particularly long-lasting, 2) it does not
424 concern only several isolated cases but hundreds of people, and 3) we still do not have
425 enough hindsight to formulate a prognosis for recovery / recovery time (which may therefore
426 be underestimated in our study), should draw attention to the consequences for the patients'
427 quality of life. Altogether, participants in our study very frequently reported that COVID-19
428 related OD are incapacitating (73%), and we found that their quality of life was significantly
429 impacted in almost all tackled domains (food, social, alarm). Although we cannot fully
430 exclude that it could have been worsened by the impact of the pandemic/lockdowns
431 themselves since we did not compare with a control group, this is in accordance with
432 previous studies on smell loss (Keller and Malaspina, 2013; Croy et al., 2014; Philpott and

433 Boak, 2014; Manesse et al., 2017; Drareni et al., 2019). Most importantly, the impact on the
434 quality of life is all the more so deleterious that duration of OD is long. More specifically,
435 when OD is prolonged, food compensation by adding ingredients possibly harmful for
436 nutritional balance (sugar, fat, salt) is increasing, therefore posing a threat to health. Longer
437 ODs were also associated with a higher likelihood of domestic accidents (in general, but also
438 ingesting spoiled food or letting a dish burn), which constitute a significant source of danger.
439 Finally, behaviors related to own body odor and the odor of the loved ones were also
440 increasingly disturbed with increasing OD duration. This likely reflects the decreasing ability
441 to cope with the OD as it develops over time. Besides this significant modulation of the
442 quality of life by OD duration, we found that age and gender were also significantly
443 influential. Namely, women were more affected than men in several domestic and social
444 contexts, in accordance with their higher attention to smells in such situations (Martin et al.,
445 2001; Frasnelli and Hummel, 2005). Younger individuals' quality of life was more impacted
446 than in the older ones: Although again we cannot fully exclude an effect of the
447 pandemic/lockdowns, which could be more pronounced on the youngest, the decrease in
448 olfactory capacities with age (Doty et al., 1984; Hummel et al., 1997) could also make the
449 oldest less sensitive to the deleterious effects of olfactory alterations. Total and constant OD
450 were found to be more deleterious on quality of life as well, which is understandable given
451 the lack of respite associated with these forms of OD. Finally, smokers were more impacted
452 as well, which is difficult to explain since they are known to have diminished olfactory
453 functioning (Vennemann et al., 2008), but could be an indirect effect of more severe forms of
454 the disease (as smoking leads to more severe forms of COVID-19: Li et al., 2021; Engin et
455 al., 2020) rather than a direct effect of OD per se.

456 These deleterious consequences of OD for the COVID-19 patients' quality of life are
457 important findings for the management of COVID-19 related smell disorders. This may affect

458 the mental health of the patients by leading to mood disorders and depression (Kohli et al.,
459 2016). In the current context, marked by the fear of the virus and of its new variants and by
460 the feeling that this health crisis is unending, the management of mental health is crucial for
461 public health (Fiorillo and Gorwood, 2020; Pfefferbaum and North, 2020). However, the
462 management of olfactory disorders by health practitioners remains clearly insufficient.
463 Knowledge about smell disorders is poor in the general population (although it probably
464 recently increased due to media coverage during the COVID-19 pandemic). In addition, smell
465 loss is generally believed – also by medical staff – to be less disabling than other sensory
466 losses, and medical advice consequently is often insufficient (Landis et al., 2009). Our study
467 confirmed this. When patients consulted about their olfactory loss, this symptom helped
468 health practitioners to make the diagnosis of COVID-19 without being considered as a
469 symptom to treat most of the time. A lack of knowledge about the treatment options was also
470 noticed, since only 4% of general practitioners (18% of ENT specialists) recommended
471 olfactory training, an interesting and easy-to-implement option to help recover olfaction
472 (Hummel et al., 2009; Manesse et al., 2018).

473 To conclude, despite some limitations (possible aggravation of OD impact on quality of
474 life by the pandemic/lockdowns themselves, women disproportionately represented in the
475 studied samples, some degree of imprecision in the participants responses due to long delays
476 between questionnaire completion and OD onset), our study provides pieces of evidence for
477 the following. COVID-19 related smell disorders appear to be quite severe, can be reported as
478 long-lasting, and seem to significantly degrade the patients' quality of life thereby
479 constituting a potential threat to their mental and physical health. These disorders should thus
480 be considered seriously by health practitioners and public health decision-makers in a context
481 which is currently highly stressing and socially isolating. Careful screening of COVID-19

482 related smell disorders and the development of treatment programs are highly encouraged to
483 minimize the long-term cognitive and behavioral consequences of COVID-19.

484

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649

650 Appendix - Online questionnaire

651 Section 1. Chemosensory disorders

652 Participants were asked about their perceptions of smells, tastes and trigeminal sensations
653 using the following questions. We also asked the participants whether they consulted a health
654 practitioner specifically for their chemosensory disorders; Which category of practitioner
655 (GP, specialist; which specialist); What were they told and what exam/test were they given;
656 Were they explicitly diagnosed as having dysosmia or dysgeusia (= smell or taste disorders).

657

658 A. *Your sense of smell*

659 (1) *In the last days/weeks, have you had any difficulties perceiving odors (e.g., food,*
660 *coffee, perfumes, or soap)? No/Yes*

661 (2) *Is this loss of smell: Mild, Partial / Total?*

662 (3) *Was the onset: Sudden/Progressive?*

663 (4) *When did this change occur? [date]*

664 (5) *Is this condition permanent or do you occasionally experience normal odor*
665 *perception (fluctuating)? Permanent/Fluctuating*

666 (6) *Do you know the cause of this change? Yes/No. If yes, specify the origin: Sino-nasal*
667 *origin (nasal obstruction due to rhinitis, sinusitis, nasal polyp)/Traumatic origin*
668 *(following a shock, an accident)/Infectious origin (following a viral/bacterial/fungal*
669 *infection)/Congenital origin (since birth)*

670 (7) *Has this change disappeared since? Yes/No. If yes, when did it disappear? [date]*

671 (8) *How did you recover? With surgery/With medication (specify)/With training/With*
672 *other treatments (specify)/Without treatment*

673

674 (9) *In the past few days/weeks, have smells seemed different from what they usually are*
675 *(i.e., they don't smell the same)? No/Yes*

676 (10) *In the past few days/weeks, have you had any olfactory hallucinations (phantom*
677 *smells)? No/Yes (describe)*

678 (11) *During these odor changes, did you have a blocked nose? No/Yes*

679

680 *B. Your sense of taste*

681 (12) *In the last few days/weeks, have you experienced any changes in taste perception*
682 *(sweet, salty, sour, bitter)? No/Yes (specify: Difficulty perceiving tastes/Tastes seem*
683 *different than usual/I have phantom tastes (describe)).*

684

685 *C. Your trigeminal perceptions*

686 (13) *In the last few days/weeks, have you had any changes in the perception of*
687 *pungency/irritation/cold/hot (in the nose and mouth)? No/Yes (specify: Difficulty in*
688 *perceiving spiciness-irritancy-cold-hotness/The spiciness-irritancy-cold-hotness*
689 *seems different from usual/I have phantom sensations of prickly/irritating/cold/hot*
690 *(describe)).*

691

692 *D. About your sensory changes*

693 (14) *Have you consulted a physician about your sensory changes? No/Yes. If yes:*

694 (a) *Who did you consult? (several responses allowed) A general practitioner/A*
695 *specialist (specify which specialty)*

696 (b) *What were you told, and what exam/test were you given?*

697 (c) Have you been explicitly diagnosed as dysosmic or dysgeusic (= with smell or
698 taste disorders)? No/Yes

699 Section 2. Quality of life

700 Participants were first asked whether chemosensory disorders were incapacitating. Then, they
701 were questioned about 16 feelings or habits related to food, social interactions, danger
702 detection and enjoyment of the environment (items adapted from Manesse et al., 2018).
703 Participants answered “more than usual”, “less than usual” or “neither more nor less than
704 usual” to the following questions:

705 *“During your sensory modifications,*

706 *(1) Did you enjoy eating*

707 *(2) Did you let your meals burn in the oven or on the stove*

708 *(3) Did you wear perfume*

709 *(4) Did you add sugar to your meals to make them match up to your taste*

710 *(5) Did you prefer eating alone*

711 *(6) Did you have domestic accidents*

712 *(7) Did you add salt to your meals to make them match up to your taste*

713 *(8) Did you seek to control your body odors (in order to not bother others, for example)*

714 *(9) Did you detect the odor of smoke and gas*

715 *(10) Did you add spicy condiments (chili pepper, mustard) to your meals to make them match*
716 *up to your taste*

717 *(11) Did you enjoy smelling flowers’ perfume*

718 *(12) Did you accidentally eat rotten food*

719 *(13) Did you add fatty condiments (mayonnaise, oil) to your meals to make them match up to*
720 *your taste*

721 *(14) Did you take showers*

722 *(15) Did you burn your clothes while ironing them*

723 *(16) Did you seek to smell the odors of your close ones (children, partner)''*

724

725 Figure legends

726 **Fig. 1.** **A)** Distribution of the self-reported OD duration by participants who recovered their
727 sense of smell (N = 609, 90.5% recovered within 32 days or less). **B)** Distribution of the self-
728 reported OD duration by the participants who still suffer from OD (N = 2502; 974
729 participants have persistent OD, i.e. they have not recovered after 32 days). The insets display
730 the distributions of OD durations longer than 32 days. On the inset of panel B, the
731 distribution between 200 and 300 days corresponds to respondents who contracted COVID-
732 19 during the first wave of the disease in spring 2020 (N = 329). Note the different scales on
733 the x and y axes between the main panels and the insets.
734

735 **Fig. 2.** Effects of **A)** constancy of OD on OD duration (longer duration for participants
736 reporting fluctuating OD) and **B)** type of OD on OD duration (longer duration for participants
737 reporting total OD) (N = 609). The size and the color darkness of the squares is proportional
738 to the number of participants reporting fluctuating, constant, partial or total OD; the
739 horizontal red lines represent the median OD duration (in days). For illustration purposes, the
740 days have been grouped by 5 (however, the median and the analysis take the whole
741 distribution of durations into account).
742

743 **Fig. 3.** Four factors linked to the development of persistent OD (versus recovered). **A)** Odds
744 ratios of the four factors (out of eight) that were retained in the minimal model of the logistic
745 regression explaining persistent OD (versus recovered); logarithmic scale. Percentage of
746 cases of persistent OD versus recovered as a function of **B)** OD type (partial, total), **C)**
747 Gender (men, women), **D)** OD onset speed (progressive, sudden), and **E)** Age. The color and
748 size of squares are proportional to the reported proportions. The blue line and grey shaded
749 area correspond to the predicted values and their 95% confidence interval.
750

751 **Fig. 4.** Frequency of **A)** parosmia and **B)** phantosmia in patients with persistent COVID-
752 related OD (ongoing OD for more than 32 days, N = 974) and in patients who recovered from
753 their COVID-related OD (N = 609). The colour and size of squares are proportional to the
754 reported proportions.
755

756 **Fig. 5.** Six factors influencing significantly the impact of COVID-related OD on the patients'
757 quality of life: **A)** OD duration, **B)** Age, **C)** Gender, **D)** OD type, **E)** OD frequency, and **F)**
758 Smoking status (N = 3111). The blue line and grey shaded area correspond to the predicted
759 values and their 95% confidence interval. The colour and size of squares are proportional to
760 the number of participants reporting a specific number of impacts on quality of life.
761

762 **Fig. 6.** Effects of OD duration, gender and age on each of the 16 items of the quality of life
763 questionnaire (N = 3111). Items in green received more "more than usual" than "less than
764 usual" answers, and items in blue had the reverse pattern (significant χ^2 -tests; no difference
765 for the item in black; see frequencies in **Fig. S2**).
766