



## Recovery From COVID-19-Related Olfactory Disorders and Quality of Life: Insights From an Observational Online Study

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## ABSTRACT

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

## KEY WORDS

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

## INTRODUCTION

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

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

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

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

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

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

## MATERIALS and METHODS

### Participants

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

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

## Questionnaire

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

## Data Analysis

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

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

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



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

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

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

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

## RESULTS

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

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

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

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

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

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

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*Figures 1 & 2 about here*

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

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

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*Figures 3 & 4 about here*

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

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

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

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*Figure 5 about here*

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

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*Figure 6 about here*

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

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

## Self-reported management of COVID-19 related OD

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

## DISCUSSION

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

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

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



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

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

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

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

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

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

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

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

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

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## Appendix - Online questionnaire

### Section 1. Chemosensory disorders

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

#### *A. Your sense of smell*

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

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

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

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

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

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

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

*(8) How did you recover? With surgery/With medication (specify)/With training/With 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

## Figure legends

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

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

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

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

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

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