Prevalence and recovery rate of persistent olfactory dysfunction in COVID-19: the COVORTS study

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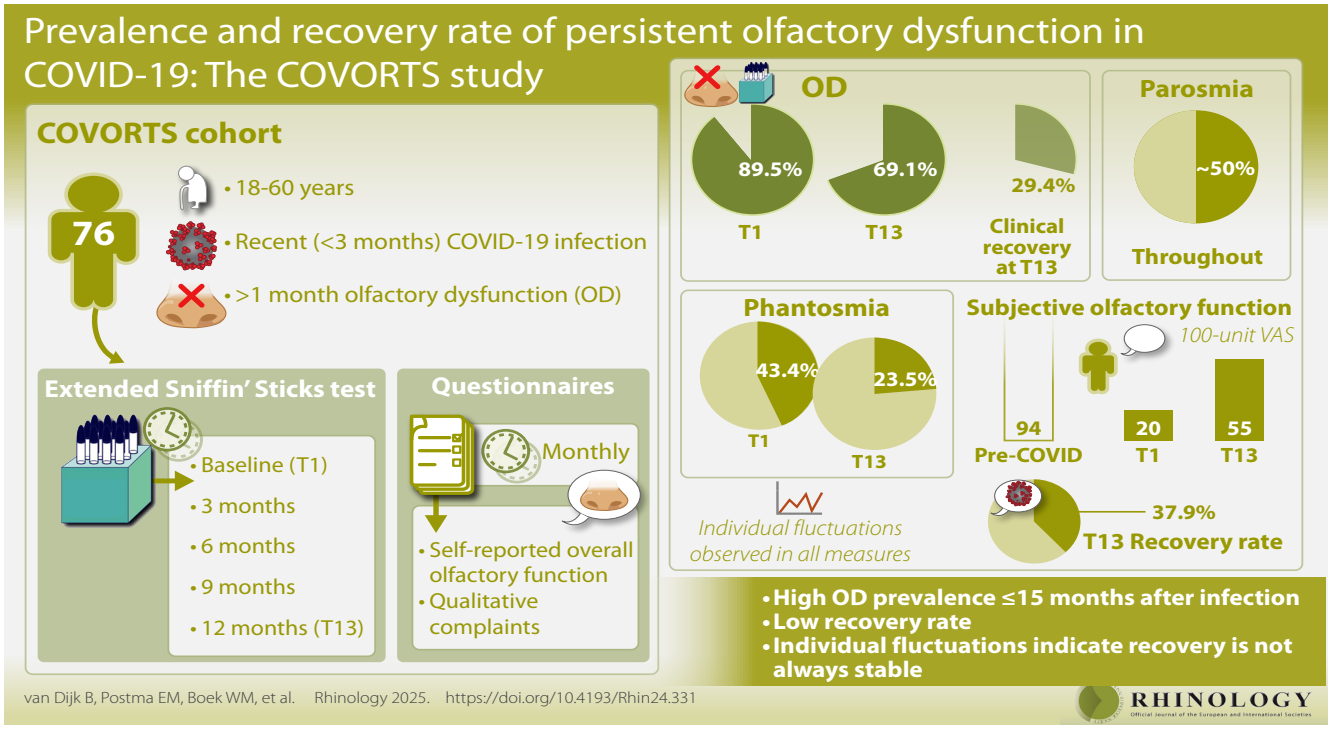
Rhinology 63: 3, 0 - 0, 2025
https://doi.org/10.4193/Rhin24.331



Abstract

Background: Olfactory dysfunction is a well-recognized symptom of COVID-19 infection. However, prevalence and recovery rate of these persistent symptoms differ across reports. Here, we report prevalence and recovery rate of psychophysically measured quantitative olfactory dysfunction, qualitative complaints, and subjective olfactory functioning up to 15 months after infection. **Methodology**: The COVORTS cohort included 76 patients between 18-60 years with recent (<3 months) COVID-19 infection and persistent (>1 month) olfactory dysfunction. The (extended) Sniffin' Sticks test was performed at baseline (T1), and 3 months, 6 months, 9 months, and 12 months later (T13). Monthly online questionnaires were completed on self-reported overall olfactory functioning and qualitative complaints. **Results**: Prevalence of quantitative olfactory dysfunction was 89.5% at baseline, and 69.1% at T13. Clinically relevant recovery was achieved by 29.4% of patients at T13. Prevalence of parosmia remained around 50%, while phantosmia slowly decreased from 43.4% to 23.5%. Subjective olfactory functioning slowly improved over time before levelling out at around half of pre-illness ability. At T13, 37.9% of patients reported an improvement of at least 80% of pre-COVID function. Fluctuations were observed within individuals for all three measurements. **Conclusions**: Irrespective of measurement method, prevalence of olfactory dysfunction remains high up to 15 months after infection, and recovery rate is low. Individual fluctuations were observed between timepoints, indicating that recovery is not stable. Acknowledgement of symptoms, knowledge of fluctuations, and longer follow-up to evaluate further recovery are crucial to improve patient management.

Key words: COVID-19, Olfaction disorders, smell, prevalence

Introduction

Chemosensory dysfunctions, especially olfactory dysfunction, are a common symptom of COVID-19 infection. Global prevalence estimates of COVID-19-related chemosensory dysfunction range from 47.4% [1] in times when the Alpha and Delta variants were most prominent, to 3.7% [2] during the Omicron variants. For the majority of these patients, chemosensory symptoms resolve relatively quickly (within two weeks to two months), but around 5% of patients report persistent complaints [3–5]. However, the long-term prevalence and recovery rates of especially those patients with persistent olfactory dysfunction remains unclear.

First of all, olfactory dysfunction can be classified as quantitative (hyposmia, anosmia) or qualitative (parosmia and phantosmia) [6]. Both types have been linked to persistent COVID-19-related olfactory dysfunction [7]. Specifically, it has been reported that patients can experience a period of anosmia in the acute phase of the infection, followed by hyposmia (sometimes) paired with qualitative complaints [7,8]. Despite this, many reports – especially in the first years of the pandemic - only focus on quantitative olfactory dysfunction, resulting in an underestimation of persistent complaints.

Furthermore, the method of measuring these symptoms differs between studies. At the start of the pandemic, most reports were (understandably) based on self-evaluation. It has been well-established that self-reported and psychophysical measurements of olfactory dysfunction are poorly correlated [9,10]. A meta-analysis focussing on COVID-19-related anosmia and hyposmia revealed that subjective measures showed a lower prevalence compared to psychophysically measured olfactory loss [11]. On the other hand, typical psychophysical measurements only include information on quantitative olfactory functioning, whereas subjective measures can include information on both quantitative and qualitative complaints. Therefore, the accuracy of psychophysical testing to evaluate the presence of olfactory dysfunction in patients with persistent complaints may change depending on whether patients also start to experience qualitative complaints.

Lastly, most studies on prevalence and recovery rate include all patients with COVID-19-related olfactory dysfunction in the acute phase, or even any patient with a confirmed SARS-CoV-2 infection without chemosensory complaints. Although there are some reports focussing specifically on patients with persistent complaints [12,13], there is still a lack of knowledge on the course of symptoms for these patients due to the abovementioned issues.

Persistent olfactory dysfunction, especially qualitative symptoms, can result in significant disruption of quality of life and eating behaviour [14–16]. With more than 776 million reported cases of COVID-19 worldwide [17], information on the prevalence and recovery rate of persistent olfactory symptoms is important to patients and medical professionals alike. Therefore, the COVORTS study was set up as a cohort study to investigate the course of persistent chemosensory dysfunction after COVID-19 infection, as well as its effects on eating behaviour and quality of life. In this paper we aimed to evaluate the prevalence and recovery rate of persistent COVID-19-related olfactory dysfunction up to 15 months after infection within this cohort, measured as 1) psychophysical quantitative olfactory dysfunction, 2) presence of qualitative complaints, and 3) subjective overall olfactory functioning.

Materials and methods

Study population

Patients in this study were part of the COVORTS cohort (COVid cohORT on Smell loss), previously introduced in Boesveldt et al. [18]. This cohort included patients between 18-60 years with persistent (>1 month) self-reported olfactory dysfunction after COVID-19 infection. Patients were recruited within 3 months after COVID-19 infection, confirmed with a positive PCR-test, or a positive SARS-CoV-2-antigen self-test. Patients were excluded from the cohort if they had a pre-existing smell and/or taste disorder, were pregnant/intended to become pregnant within the duration of study participation, or were normosmic according to the psychophysical olfaction test performed during the first test session (score≥30.75 on the Sniffin' Sticks test [19]) in combination with no self-reported parosmia complaints. Patients were included between November 2021 and March 2023. This study was approved by a regional medical research ethics committee (28-09-2021, file NL77954.091.21) and carried out in compliance with relevant laws and institutional guidelines and in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans. Patients were recruited via traditional and social media, the Dutch association for patients with smell and taste loss (Reuksmaakstoornis.nl), the patient organization PostCovidNL, and the National Institute for Public Health and the Environment. Interested patients were contacted and verbal informed consent was obtained. After this, patients filled out a screening questionnaire. When patients were deemed eligible for inclusion in the study, the first test session was scheduled. At the start of this first test session, written consent was provided by the patients. Patients received financial compensation for their contribution.

Study design

In the COVORTS study, patients were followed longitudinally for a period of 12 months (Figure 1). Every month, patients filled out an online questionnaire. On top of that, patients were visited at home by the researchers every 3 months for extensive psychophysical testing of olfactory functioning. Timepoints for these measurements were T1 (performed as soon as possible after inclusion, 'baseline'), T4 (3 months after baseline), T7 (6

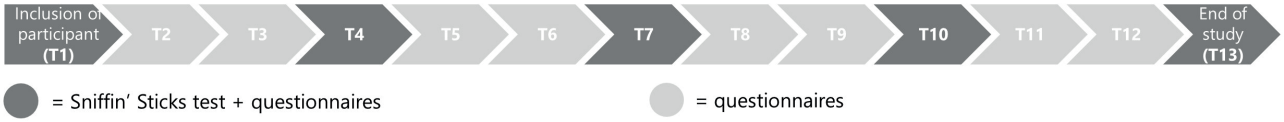


Figure 1. Timeline of all measurements for patients in the COVORTS cohort. Questionnaires included demographics, self-reported olfactory function and type of olfactory symptoms.

months after baseline), T10 (9 months after baseline), and T13 (12 months after baseline).

Measurements

Patients were instructed not to eat or drink anything (except water or tea) at least one hour before a test session (30 minutes in the case of the online questionnaire), and to not wear perfume on testing days. The monthly questionnaire consisted of a demographic questionnaire followed by a questionnaire on self-reported smell function and type of olfactory symptoms. The home-visits consisted of the Sniffin' Sticks test battery. More questionnaires and (psychophysical) tests were performed during the monthly questionnaire and home-visits but are outside the scope of this paper (see Boesveldt et al. [18] for several of these other measurements).

Psychophysical quantitative olfactory functioning

Quantitative olfactory functioning was evaluated with the Sniffin' Sticks test battery (Burghart, Wedel, Germany)[20]. The test consist of three parts: odour threshold, odour discrimination, and odour identification. For this study, the extended version of the Sniffin' Sticks was used, which contains 32 odours instead of 16 for the identification test [21], and combinations of pens were randomized across patients and test sessions to limit learning effects. Likewise, for the discrimination test, the order of triplets was randomized across patients and test sessions.
Results of the three subtests are presented as a composite "Sniffin' Sticks score" (range 1-48) which is the sum of the results obtained for threshold, discrimination and identification measures, with higher scores indicating better olfactory function. A Sniffin' Sticks score of 16.25 and below is defined as anosmia; a score between 16.25 and 30.75 as hyposmia; and a score of 30.75 and above as normosmia [19].

Demographics questionnaire

At the baseline measurement, patients were asked to report their date of birth, gender (male, female, other, rather not say), pregnancy status, intention to become pregnant in the coming year, weight (kg), height (cm), and severity of COVID-19 symptoms during the acute phase (no complaints or mild complaints, moderate complaints, severe complaints, critical complaints), COVID-19 vaccination status (yes/no, and if yes, further details about which vaccines and how many doses), whether they performed any smell training or received any treatment for their chemosensory loss (yes/no, and if yes, what and how long/often). At the follow-up questionnaires, patients were again asked about the use of smell training or any other types of treatment, their weight (only during months with a home-visit), whether they were reinfected with COVID-19, and whether they received any new vaccination against the SARS-CoV-2 virus in the past month.

Presence of qualitative symptoms and subjective overall olfactory functioning

In the monthly questionnaire, patients were asked whether they experienced any of the following symptoms in a check-all-that-apply question: 1) "I cannot smell at all"; 2) "Odours smell less strong than they did before"; 3) "Odours smell different than they did before (the quality of the odour has changed)"; 4) "I can smell things that are not there (for example, I smell fire when nothing is on fire)"; 5) "Sense of smell fluctuates (comes and goes)"; and 6) "None of the above". Options 3 and 4 were used to diagnose patients with parosmia and phantosmia, respectively. In addition, patients were asked to quantify their former (i.e., pre-COVID-19 infection) and current olfactory ability on a 100-unit visual analogue scale (VAS), anchored "no sense of smell at all", to "excellent sense of smell", similarly to Parma et al. [22].

Table 1. Patient characteristics (n=76) at T1 (baseline).

Parameter	Value
Age (years, mean ± SD, range)	46.6 ± 10.5 (18 – 60)
Gender (female / male, n)	63 (82.9%) / 13 (17.1%)
BMI (kg/m^2, mean ± SD, range)	25.6 ± 4.4 (19.3 – 37.9)
Vaccination status (yes / no, n)	65 (85.5%)/ 11 (14.5%)
Severity of Covid-19 symptoms (n) • No symptoms to mild symptoms • Moderate symptoms • Severe symptoms • Critical symptoms	 11 (14.5%) 53 (69.7%) 12 (15.8%) 0
Days since infection to T1 (mean ± SD, range)	82.9 ± 22.0 (37 – 128)
Use of smell training (yes / no, n)	9 (11.8%) / 67 (88.2%)
Other treatments (yes / no, n)	0 / 76

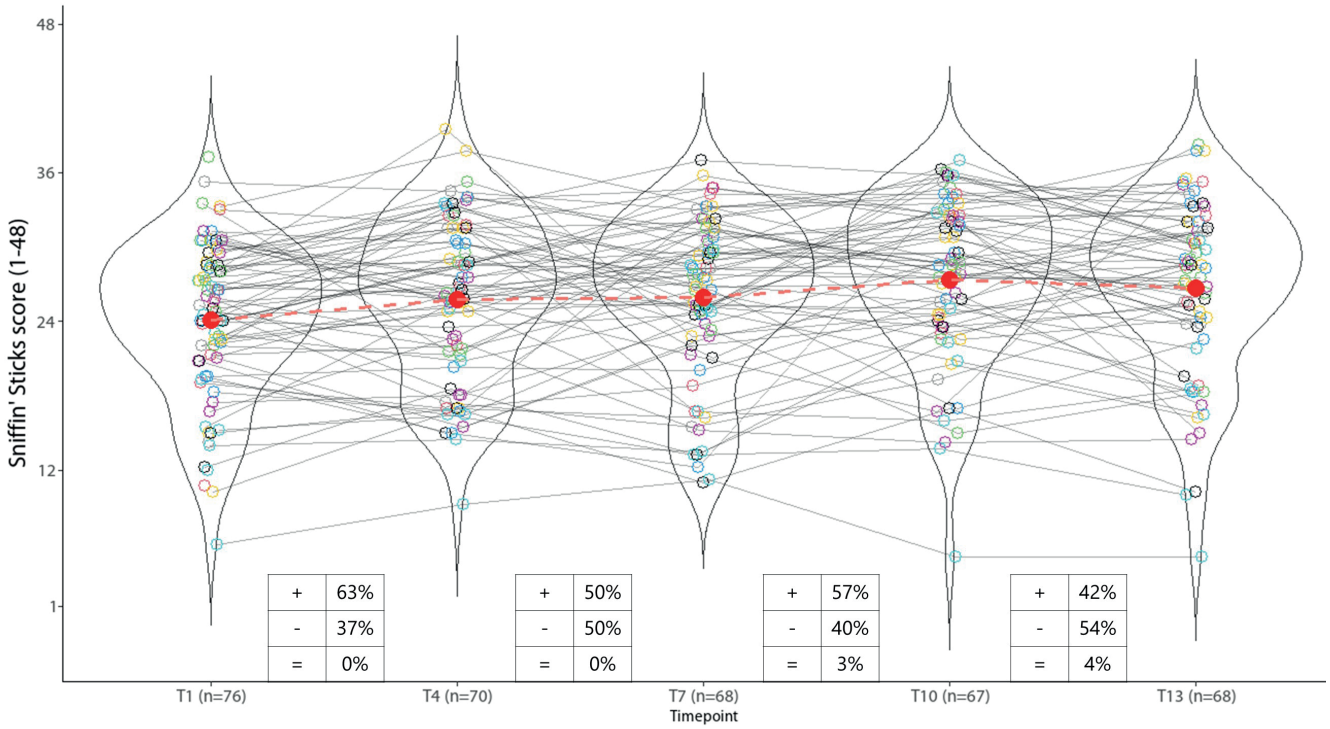


Figure 2. Violin plot representing individual Sniffin' Sticks scores with lines connecting each patient at the five timepoints. Red circle connected by dotted line indicates mean Sniffin' Sticks score at given timepoint. Table between each timepoint indicates the percentage of patients increasing (+), decreasing (-), or not changing (=) in Sniffin' Sticks score between timepoints.

Statistical analysis

Data for subjective overall olfactory functioning that we considered as highly unlikely due to misinterpreting of the question or response scale (i.e., pre-COVID-19 olfactory function <40 on the VAS,) were excluded (n=24 data points). Not all patients filled out the questionnaires every timepoint; these were treated as missing data (ranging from 0-11 per timepoint).

Descriptive statistics are given as means and standard deviations or standard errors for continuous variables, and as frequencies and percentages for categorical variables. Clinical improvement of quantitative olfactory functioning was evaluated as an increase of 5.5 points or more in Sniffin' Sticks score [23]. Recovery of subjective olfactory functioning was defined as a regaining of at least 80% of a patients' pre- COVID-19 olfactory function [7].

Differences over time were evaluated using linear mixed models (LMM) in R (version 4.1.0), with Sniffin' Sticks score (total and separate threshold, discrimination and identification outcomes) and subjective olfactory function as dependent variables, timepoints as fixed factor and patients as random factor. Post-hoc analyses were performed using Tukey's test when the main analyses yielded significant results ($p<0.05$).

Results

Participant characteristics

In total, 85 patients underwent a first test session. Eight of these patients were excluded because they did not meet the set requirements for olfactory dysfunction. Another patient was excluded shortly after baseline due to pregnancy, leaving 76 patients to be included for analysis.

Baseline (T1) measurements were performed on average 83 (range 37-128) days after COVID-19 diagnosis, and the 12-month follow-up (T13) occurred on average 453 (range 405-495) days after diagnosis. Date of infection was between July 2021 and December 2022. The majority of patients (76.3%) tested positive in the period when the Delta variant was most common [24].

Patients' characteristics at T1 can be found in Table 1. One patient that was unvaccinated at T1 received a single dose during the study period. In total, 17 patients reported performing smell training throughout the duration of the study, of which 59% only at one single timepoint. Three patients reported performing smell training at six timepoints or more, with only one patient consistently performing it for the full study duration. Furthermore, one patient used nasal corticosteroids around 6 months after infection, which they used for a period of three weeks with no self-reported effects on their symptoms.

Twenty patients reported a reinfection in the duration of their participation (all occurred when Omicron was most prevalent), of which one patient had two reinfections. Most of these reinfections (66.7%) occurred during the second half of the study, especially between timepoints T10 and T13. Almost half (47.6%)

Table 2. Prevalence of psychophysical quantitative olfactory (dys)function (according to Sniffin' Sticks cut-off points), Sniffin' Stick scores and clinical recovery rate over time (≥5.5 point increase in Sniffin' Sticks score compared to T1). Different superscript letters [(a,b)] in the same row indicate significant different means according to post-hoc testing of LMM.

	T1 n=76	T4 n=70	T7 n=68	T10 n=67	T13 n=68
Prevalence, % (n)					
Anosmia	14.5 (11)	7.1 (5)	13.2 (9)	7.5 (5)	8.8 (6)
Hyposmia	75.0 (57)	67.1 (47)	60.3 (41)	53.7 (36)	60.3 (41)
Normosmia	10.5 (8)	25.7 (18)	26.5 (18)	38.8 (26)	30.9 (21)
Sniffin' Sticks score, mean ± SD					
Total score	24.1 ± 6.4[a]	25.8 ± 6.5[a,b]	25.9 ± 6.6[a,b]	27.4 ± 6.6[b]	26.7 ± 7.1[b]
Threshold	4.7 ± 2.7	5.5 ± 3.0	5.5 ± 2.6	5.6 ± 2.8	5.6 ± 2.7
Discrimination	9.7 ± 2.6	10.1 ± 2.5	10.3 ± 2.6	10.8 ± 2.5	10.6 ± 2.8
Identification	9.7 ± 3.2[a]	10.2 ± 3.0[a,b]	10.1 ± 3.2[a,b]	11.0 ± 3.0[b]	10.5 ± 3.3[a,b]
Clinical recovery rate, % (n)	N/A	18.5 (13)	20.6 (14)	35.8 (24)	29.4 (20)

Table 3. Prevalence of self-reported qualitative olfactory dysfunction over time.

Prevalence rate, % (n)	T1 n=76	T2 n=74	T3 n=70	T4 n=70	T5 n=65	T6 n=67	T7 n=65	T8 n=65	T9 n=66	T10 n=66	T11 n=66	T12 n=67	T13 n=68
Parosmia	52.6 (40)	55.4 (41)	51.4 (36)	62.9 (44)	61.5 (40)	53.7 (36)	63.1 (41)	55.4 (36)	50.0 (33)	53.0 (35)	51.5 (34)	44.8 (30)	50.0 (34)
Phantosmia	43.4 (33)	39.2 (29)	37.1 (26)	34.3 (24)	36.9 (24)	37.3 (25)	40.0 (26)	32.3 (21)	22.7 (15)	31.8 (21)	28.8 (19)	19.4 (13)	23.5 (16)

of reinfected patients reported no change in their olfactory dysfunction, 28.6% reported a worsening of symptoms lasting a few days (of which one reported complete recovery afterwards), and another 23.8% reported a permanent worsening of symptoms.

Psychophysical quantitative olfactory dysfunction

The prevalence of anosmia, hyposmia, and normosmia at the different timepoints, are reported in Table 2. At T1, 89.5% of patients were either anosmic or hyposmic. Interestingly, eight patients already scored normosmic at T1, despite having self-reported olfactory dysfunction. Over time, the percentage of patients with anosmia and hyposmia slowly decreases. At T13, the majority of patients (69.1%) were still classified as having quantitative olfactory dysfunction.

Mixed model analysis showed a significant effect of timepoint on total Sniffin' Sticks score ($F=5.02$, $p=0.001$). Post-hoc testing showed a significant difference in Sniffin' Sticks score between T1 and T10 ($p<0.001$) and T1 and T13 ($p=0.014$), indicating a higher score at T10 and T13 compared to baseline (Table 2). Additional mixed model analyses showed a significant effect of time on separate Sniffin' Sticks scores for Threshold ($F=2.48$, $p=0.044$) and Identification ($F=3.33$, $p=0.011$), but not for Discrimination. Post-hoc analysis revealed a significant difference for Identification between T1 and T10 ($p=0.005$). For Threshold, this same comparison was marginally significant ($p=0.058$).

On an individual level, 29.4% of patients achieved clinically relevant recovery (≥5.5 points increase in Sniffin' Sticks score compared to T1) at T13 (Table 2).

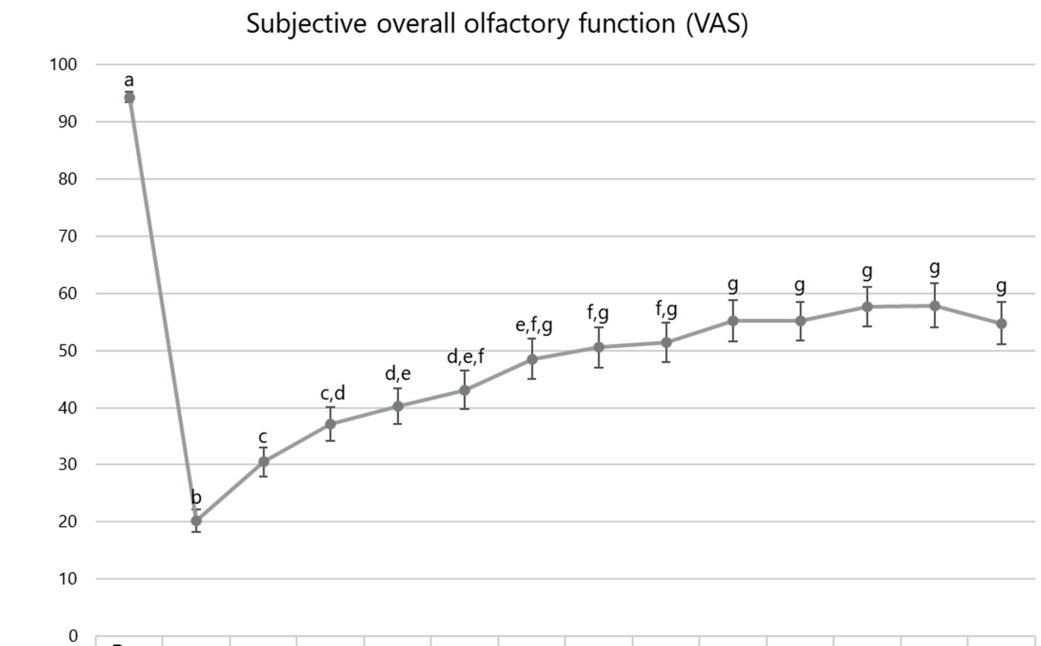
Despite an upward trend in the overall amount of normosmic patients and clinically relevant recovery, the decline both from T10 to T13 indicate that recovery is not always stable. On an individual level, we observed frequent fluctuation in Sniffin' Sticks score (Figure 2, and more details in S1).

Qualitative olfactory dysfunction

The prevalence of self-reported parosmia complaints remained around 50% for the majority of the timepoints, although some fluctuation can be seen (Table 3). Phantosmia was reported by 43.3% of patients at T1, and remains roughly around 40% until T8, whereafter it slowly decreases to around 24% at T13. However, frequent individual fluctuations in the presence and absence of qualitative dysfunctions were observed (details in S2), indicating that recovery for qualitative symptoms is not stable.

Subjective overall olfactory functioning

The development of subjective overall olfactory functioning over time is visualized in Figure 3. Mixed model analysis showed a significant effect of time on self-reported olfactory function ($F=79.9$, $p<0.001$). Post-hoc analysis showed that patients' pre-



	Pre-COVID (n=74)	T1 (n=74)	T2 (n=69)	T3 (n=67)	T4 (n=69)	T5 (n=65)	T6 (n=66)	T7 (n=63)	T8 (n=64)	T9 (n=64)	T10 (n=64)	T11 (n=66)	T12 (n=64)	T13 (n=66)
Recovery rate %(n)	N/A	1.4 (1)	8.7 (6)	10.4 (7)	15.9 (11)	15.4 (10)	21.2 (14)	27.0 (17)	28.1 (18)	39.1 (25)	35.9 (23)	37.9 (25)	43.8 (28)	37.9 (25)

Figure 3. Means and standard errors of subjective olfactory function pre- COVID-19 and over time measured on a VAS, 0-100 (anchored "no sense smell at all" to "excellent sense of smell"). Different letters indicate significant different means according to post-hoc testing of LMM. Recovery rates for each time point are calculated as an improvement of at least 80% of pre-COVID-19 function as measured on VAS.

COVID-19 subjective olfactory functioning was scored significantly higher compared to each measured timepoint. Subjective olfactory functioning did improve over time, especially between T1 and T6. After a year of follow-up, subjective olfactory functioning was rated on average around 55 on the 100-unit VAS.
At T13, 37.9% of patients are considered subjectively recovered (computed as an improvement of at least 80% of pre-COVID-19 functioning), but this percentage fluctuates over time.
When looking at individual scores over time, again fluctuations were observed (see S3 for details). Furthermore, prevalence of self-reported fluctuations in olfactory functioning was between 44% and 60% throughout all measured timepoints (see S4 for details).

Discussion

This study investigated the prevalence and recovery rate of persistent COVID-19-related olfactory dysfunction up to 15 months after infection, measured as 1) psychophysical quantitative olfactory dysfunction, 2) presence of qualitative complaints, and 3) subjective overall functioning. Individual fluctuations in between timepoints were observed, indicating that olfactory recovery is not always stable. For all three measurement methods, prevalence of olfactory dysfunction remains high after a year of follow-up, and recovery rate is low.

The results of this article are based on data from the COVORTS cohort, which exclusively included patients with persistent (>1 month) self-reported olfactory dysfunction after COVID-19 infection. The prevalence and recovery rates discussed here are thus only applicable for patients experiencing long-term symptoms.
A striking clinical result from this study is the frequent individual fluctuation in prevalence and recovery rate between timepoints for all three measurement methods, as well as indicated by self-report. This is especially important as the vast majority of studies on this topic only measure at one or two timepoints [7,12,13,25,26], and if they include more follow-up, they are usually months apart [4,5]. Both psychophysical and subjective fluctuations have been reported before in this patient group [27–29], but only for a small percentage of patients and not specifically for qualitative complaints. Olfactory fluctuation is commonly associated with sinonasal disorders [29,30], but it is unlikely that sinonasal inflammation is the (main) reason for persistent olfactory dysfunction in COVID-19 patients [31]. We evaluated the presence of qualitative complaints and subjective overall olfactory functioning monthly for a period of one year, and our psychophysical measurements were repeated every three months. Our study indicates that – although one might expect an increasing line in individual recovery – olfactory function can improve over time but subsequently decrease again in this patient group.

One explanation for these fluctuations could be the reinfections reported by 26% of patients in the cohort. The observed fluctuations were especially present in reported qualitative symptoms. A reinfection with the virus could induce another period of acute anosmia [8], thus influencing both quantitative functioning as well as (temporarily) eliminate any qualitative complaints that were previously present. However, the fluctuations in prevalence and recovery were observed throughout the duration of the study, whilst most reinfections took place in the second half of patient follow-up (and only half of reinfected patients reported a change in symptoms). It might well be that these fluctuations are a normal part of the course of persistent COVID-19-related olfactory dysfunction which had not been previously reported due to a low frequency of follow-up.

Prevalence of COVID-19-related olfactory dysfunction remained high at all timepoints, and recovery rate remained low. Psychophysically measured, we found a high prevalence of quantitative olfactory dysfunction after a year of follow-up (69.1% after mean 453 days since infection), similar to previous reports [12,13]. Although prevalence remained high, we did observe small increases in the number of patients scoring normosmic on the Sniffin' Sticks test between the measured timepoints. AAround 30% of individual patients achieved clinically relevant recovery when comparing their score at baseline to their score at the final measurement. Nonetheless, due to the observed fluctuations, these patients might not continue to improve or even decline again. However, recovery of psychophysical quantitative olfactory dysfunction has been reported to continue over two years after original infection [13].

The prevalence of parosmia remained around 50% for all measured timepoints, whereas for phantosmia it slowly decreased from 43% to 24% over time. It has been reported that the incidence of qualitative complaints is low during the acute phase of the infection and tends to increase with longer follow-up [7,12,25,32]. In our study, we observed a stable prevalence of parosmia, and a decrease in phantosmia complaints over time. These results might be explained by our inclusion outside of the acute phase of illness, as well as a longer follow-up as compared to other studies. Notably, we observed high individual fluctuations in the presence of qualitative complaints, with a small group of patients reporting multiple occurrences of developing qualitative complaints, followed by recovery, only to subsequently report symptoms again (or vice versa).

There was a sharp and significant decrease in subjective overall olfactory functioning between pre-COVID-19 and the baseline measurement. Similar to a previous report [12], we observed a steady increase in subjective functioning, especially in the first six months, although all timepoints were scored significantly lower compared to patients' pre-COVID-19 olfactory function. After a year of follow-up, average subjective olfactory function was scored at 55 on a 100-unit VAS, where it was almost at 95 pre-COVID-19 infection. While 38% of patients were considered recovered at the final measurement, this is lower than the study who used the same measurement method [7], although this can be explained through the inclusion of only patients with persistent complaints in our cohort. Again, fluctuations were observed between timepoints, indicating that patients might not continue to improve their subjective olfactory functioning. However, in the hitherto longest follow-up of subjectively measured COVID-19-related chemosensory dysfunction, it was found that the group of patients that still reported complaints two years after original infection, about one-third experienced complete recovery after 3 years [4].

Although we did not directly compare measurement methods in this article, we observed a bigger improvement in subjective olfactory functioning compared to the psychophysical and qualitative measures. This could be explained by a habituation effect, where patients suffering from persistent symptoms rate their olfactory functioning better over time without actual recovery taking place, or some form of recall bias, where over time it becomes harder for patients to remember their previous olfactory abilities. Our subjective measure can include information on both quantitative and qualitative complaints, and it has been suggested that patients also incorporate experiences of symptom-related disability and effect on quality of life in these self-reported measures [33]. The three methods discussed in this article measure different aspects of olfactory dysfunction and should therefore all be considered when assessing recovery. In follow-up studies, it is however advised to include questions on the severity and frequency of qualitative symptoms [34,35], to better evaluate the prevalence and fluctuations over time.

Although spontaneous recovery has been reported up to two and three years after infection [4,12], we have shown here that recovery is not necessarily stable. Even with the possibility of spontaneous recovery, this seems to only occur in a minority of patients with persistent complaints, resulting in many patients still suffering from olfactory dysfunction to this day. It is important that patients receive recognition of their symptoms, and to inform them of the possibility of fluctuations in their recovery. The current insight of the existence of possible fluctuations in recovery is important in research on the pathophysiology of persistent chemosensory dysfunction in COVID-19 patients, as well as in studies on possible treatments, suggesting frequent follow-up of patients is necessary. The persistence of olfactory dysfunction in the larger context of the post-COVID syndrome is worrisome, due do its known effects on patients' emotional and physical wellbeing, as well as its relationship with neurodegenerative diseases [36,37]. Overall, more research is needed focussing on patients with persistent COVID-19-related chemosensory dysfunction, both independent from and within the larger context of post-COVID syndrome to improve patient management and health outcomes.

Conclusion

This study investigated the prevalence and recovery rate of persistent COVID-19-related olfactory dysfunction up to 15 months after infection, measured as psychophysical quantitative olfactory dysfunction, presence of qualitative symptoms, and subjective overall olfactory functioning. Irrespective of measurement method, prevalence of olfactory dysfunction remains high up to 15 months after infection, and recovery rate is low. Our results reveal individual fluctuations between timepoints, indicating that recovery is not always stable. Acknowledgement of symptoms, information on possible fluctuations, and longer follow-up to evaluate recovery rates, are crucial to improve patient management.

Acknowledgements

The authors want to thank all patients who took part in the COVORTS cohort, as well as the Dutch Organization for Health Research and Development (ZonMW) and the Netherlands Organization for Scientific Research (NWO). Special thanks to students Nienke Steenstra, Maureen Coolbergen, Laudine de Bever, Carla Meijer, Catoo Krale, Femke Bootsma, Tesse van der Struijk, Amy Kroeze, Sam Kreuk, Pien Velthuijs, Saskia Markerink, and Puck Smit, and especially to research assistant Louise Leenders, for their assistance in data collection and cohort management.

Authorship contribution

BD, EP and SB were responsible for trial design and analysis. BD and EP were responsible for data acquisition. All authors contributed to data interpretation and all authors reviewed drafts and approved the final version of the manuscript before submission.

Conflict of interest

The authors declare no conflicts of interest.

Funding

This research was funded by the Dutch Organization for Health Research and Development (ZonMW, 10430102110001) and by an Aspasia grant of the Netherlands Organization for Scientific Research (NWO; 015.013.052), awarded to SB.

Availability of data and materials

The dataset analysed during the current study will be available in the DANS-Easy repository once the cohort project has completed, [https://doi.org/10.17026/LS/YZHHK7].

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Rhinology 63: 3, 0 - 0, 2025
https://doi.org/10.4193/Rhin24.331

Received for publication:
September 12, 2024
Accepted: March 20, 2025

Associate Editor:
Michael Soyka

This manuscript contains online supplementary material

SUPPLEMENTARY MATERIAL

S1. Fluctuations in individual Sniffin' Sticks scores.

Table S1. Changes in individual Sniffin' Sticks scores, and total number of patients increasing or decreasing in score between timepoints. Increases of ≥5.5 points (regarded as clinically relevant recovery) are marked in green, and decreases of ≤5.5 are marked in red.

	T1 – T4 (n=70)	T4 – T7 (n=68)	T7 – T10 (n=67)	T10 – T13 (n=67)
Change in Sniffin' Sticks score per participant				
1	+6.3	-5.0	+4.3	+2.5
2	+5.3	-4.8	-4.5	+18.3
3	+12.3	-16.8	+1.8	+2.5
4	-7.8	-2.0	+3.8	+6.3
5	-5.8	+7.0	+2.0	-4.5
6	-2.0	+1.8	+5.5	+4.3
7	-4.3	+1.5	-0.3	-0.3
8	+9.3	-5.0	+0.3	+0.5
9	-2.8	-3.3	+0.5	-3.8
10	+2.8	+0.8	-1.0	+11.0
11	+9.5	-4.5	-1.5	-1.8
12	-0.5	+1.0	+11.8	-4.3
13	+8.8	-15.8	+6.3	+2.5
14	-12.0	+5.0	-4.0	+5.8
15	+0.5	N/A	N/A	N/A
16	-5.8	-0.3	-1.8	+5.3
17	+1.5	-2.3	+0.3	+5.0
18	-0.8	-1.5	+2.3	-1.0
19	+6.3	-5.3	+10.3	+1.8
20	-1.5	+2.0	+5.3	-4.0
21	-4.5	-2.8	+22.0	-0.8
22	+10.0	-8.8	-0.8	+2.5
23	-3.5	-7.3	-1.0	+0.3
24	+2.8	-2.3	+1.5	-4.0
25	+5.0	-8.3	+6.3	-3.0
26	+6.0	-7.8	+11.3	-5.5
27	+0.8	-0.3	+5.8	-7.5
28	+3.3	+4.3	-1.3	-2.5
29	+2.3	-6.0	+9.0	+1.0
30	+0.5	-1.0	+8.8	-4.0
31	+6.0	+9.5	+3.5	-5.5
32	-5.0	+10.3	-3.3	-2.3
33	+2.0	-6.0	+6.0	-6.8
34	+0.8	N/A	N/A	N/A
35	+0.3	+3.5	+2.5	-5.3
36	-1.0	-2.8	N/A	N/A
37	-0.5	-1.0	-0.3	-3.3
38	+0.5	+5.8	+5.3	+2.3
39	+6.8	-0.8	+4.3	-4.3

Table S1. *continued*

	T1 – T4 (n=70)	T4 – T7 (n=68)	T7 – T10 (n=67)	T10 – T13 (n=67)
40	+2.0	-1.8	+6.8	-8.5
41	+1.3	+1.5	+4.0	-13.5
42	-0.8	+10.3	-3.0	+9.8
43	-1.5	+16.5	+0.8	-2.0
44	-2.3	+4.3	+10.8	-5.3
45	-7.8	+12.5	+2.0	-17.5
46	+3.0	+1.8	+3.5	-6.0
47	+2.0	+4.8	-4.5	-5.0
48	-4.0	+2.5	+0.5	-5.3
49	-3.0	+8.5	-2.8	0.0
50	-2.8	+2.0	0.0	-5.3
51	+3.3	+2.0	-6.3	0.0
52	-5.5	+7.3	+3.5	-9.0
53	+1.8	+0.5	-4.3	+0.8
54	+4.5	-0.3	-0.8	+3.8
55	-2.8	+3.8	+1.8	+2.3
56	+2.0	+5.8	0.0	+1.0
57	+6.8	-6.3	-8.3	+3.3
58	+3.8	-3.8	-9.5	+5.5
59	+1.3	+8.3	-4.0	-4.3
60	+4.3	+1.0	-2.8	+1.3
61	+4.5	-4.5	+0.3	+4.3
62	+3.5	-10.5	+8.5	-3.8
63	-1.3	+3.0	-2.3	0.0
64	+7.3	-5.8	-0.8	-2.5
65	+11.8	-3.3	+1.0	-3.5
66	+4.5	+1.3	+7.3	-7.3
67	-3.0	+4.0	-3.8	-1.0
68	+2.3	+6.8	-9.0	+1.8
69	+3.3	-2.8	-2.8	+2.8
70	+4.8	+3.5	-6.5	+5.8
Increase in Sniffin' Sticks score, % (n)	62.9 (44)	50.0 (34)	56.7 (38)	41.8 (28)
Decrease in Sniffin' Sticks score, % (n)	37.1 (26)	50.0 (34)	40.3 (27)	53.7 (36)
No change in Sniffin' Sticks score, % (n)	N/A	N/A	3.0 (2)	4.5 (3)
Increase of ≥5.5 in Sniffin' Sticks score, % (n)	18.6 (13)	17.6 (12)	22.4 (15)	10.4 (7)
Decrease of ≤5.5 in Sniffin' Sticks score, % (n)	8.6 (6)	16.2 (11)	7.5 (5)	14.9 (10)

S2. Fluctuations in the presence of qualitative olfactory dysfunction.

Table S2 reports the number of patients switching between the presence and absence of qualitative complaints between timepoints. Between almost each timepoint, a few patients recover or report the development of qualitative complaints.

Table S2. Number of patients "switching" qualitative olfactory dysfunction complaints between timepoints. Only patients where data for all 13 time-points were available were included in table (n=58/76).

Symptom switch (n=58)		T1-T2	T2-T3	T3-T4	T4-T5	T5-T6	T6-T7	T7-T8	T8-T9	T9-T10	T10-T11	T11-T12	T12-T13
Parosmia (n)	Yes-no	9	8	3	5	7	2	5	4	4	3	6	2
	No-yes	10	5	10	2	3	7	1	2	4	3	2	6
Phantosmia (n)	Yes-no	5	6	4	0	4	2	5	6	0	4	6	3
	No-yes	4	4	3	1	4	3	1	2	5	1	1	5

When looking at the course of an individual patient, we might expect that some patients have no qualitative complaints throughout the study or qualitative complaints at all timepoints (which would indicate no "switches" in diagnosis). Some patients might start with no qualitative complaints but develop them at a later timepoint, and perhaps even recover from them again later, or vice versa (which would indicate one to two "switches" in diagnosis). For the majority of patients, this was indeed the case. However, for parosmia, 35.5% of patients reported more than two "switches" in diagnosis, with a range from three to seven. For phantosmia, this was the case for 19.0% of patients, with a range of diagnosis "switches" from three to eight times. These frequent fluctuations in the presence and absence of qualitative symptoms demonstrates the instability of recovery of this type of olfactory dysfunction in COVID-19 patients.

S3. Fluctuations in individual subjective overall olfactory functioning.

Table S3. Changes in individual subjective overall olfactory functioning scores, and total number of patients increasing or decreasing in score between timepoints. Increases of ≥20 are marked in green and decreases of ≤20 are marked in red (minimum clinically relevant difference on VAS in pain research [38]).

	T1 – T2 (n=68)	T2 – T3 (n=64)	T3 – T4 (n=65)	T4 – T5 (n=64)	T5 – T6 (n=64)	T6 – T7 (n=62)	T7 – T8 (n=60)	T8 – T9 (n=61)	T9 – T10 (n=62)	T10 – T11 (n=62)	T11 – T12 (n=62)	T12 – T13 (n=63)
Change in subjective overall olfactory functioning per participant												
1	+15.2	+11.8	+5.5	+13.5	+10.2	-1.8	+14.4	+15.8	+1.7	+4.4	+0.8	+1.2
2	+15.7	-9.7	-3.0	+1.0	+6.2	+9.7	-20.3	+23.7	+8.9	+7.7	N/A	N/A
3	+31.6	-15.6	-11.1	+0.2	-4.2	+22.7	+25.2	-25.0	+4.2	-3.7	+23.0	-21.3
4	-0.4	+1.0	-3.0	+0.5	-7.4	+50.9	-19.3	-23.4	+30.8	+14.6	-40.9	+46.2
5	-3.4	N/A	N/A	N/A	N/A	-17.3	+24.5	-11.1	+16.2	+15.6	+4.6	-18
6	+7.2	-11.1	+25.9	+6.5	-3.0	+15.5	+6.2	+8.6	-10.3	+15.7	-1.6	-16.8
7	+12.6	+12.9	-13.0	+3.2	-11.3	+17.4	-15.8	-6.9	-17.4	+33.2	-10.5	-6.5
8	+11.5	+18.0	-4.1	+3.2	-1.4	+10.8	-14.8	+7.6	+0.5	+4.9	+0.9	-17.0
9	-2.0	+0.4	-0.8	+4.5	+7.7	-6.0	N/A	N/A	+6.3	+4.2	-1.7	-15.6
10	+14.2	+0.2	+19.5	-18	+26.4	-14.3	+10.3	-9.1	+13.6	-13.8	+6.7	+0.4
11	+3.7	+13.0	+5.6	+9.1	-0.7	+16.5	-8.3	+3.2	-0.4	+9.1	-4.4	+0.3
12	+5.4	+12.6	+12.1	+3.7	+23.2	-0.1	-3.4	+16.9	-7.7	-5.9	+18.3	+4.4
13	+6.6	+5.7	+5.7	-5.0	-8.9	-14	-0.8	+48.2	-17.8	-2.0	-8.1	-2.5
14	+7.6	-2.1	+10.6	+3.4	+29.3	-20.4	+3.2	+8.0	+0.5	-10.6	16.0	-14.4
15	+46.7	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
16	-18.0	-0.7	+4.7	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
17	+54.6	+14.7	-7.0	+7.4	-9.1	+12.8	-8.5	+1.0	-11.9	+16.1	+0.7	-10.0
18	+14.5	+22.6	+21.9	+19.6	-26.2	+26.6	+4.5	-13.1	+7.2	+2.6	+1.8	-17.8
19	+6.3	-21.0	+9.3	+24.3	+5.4	-5.4	+16.2	+3.2	-10.6	+0.2	+10.8	-3.3
20	+0.7	-0.4	-0.1	-0.4	+49.8	-48.3	+47.2	-47.2	+17.4	+10.5	-12.3	+1.1
21	-18.3	+16.2	-11.0	+0.3	+12.9	-9.2	+14.6	+2.4	+22.3	-16.6	+29.6	-63.1
22	-0.3	N/A	N/A	+0.2	+0.8	0.0	-0.8	+29.2	-8.4	-19.3	+0.2	N/A
23	+1.5	+0.7	-1.9	+3.4	-2.4	+1.8	-2.9	+0.5	+0.7	N/A	N/A	-8.0
24	+6.3	-10.6	+8.1	+11.4	-10	-1.1	+21.7	-6.9	+3.7	-6.9	-35.3	+42.4
25	+1.5	-2.9	-0.3	+1.1	+4.7	-4.3	+10.2	-5.9	+7.2	-5.0	+4.3	+1.1
26	+8.1	+30.6	+6.2	+20.8	-6.2	-0.5	+19.2	-1.1	+1.1	+1.1	+1.3	+3.5
27	N/A	N/A	+0.8	-3.7	+6.7	N/A	N/A	-8.4	+26.1	-1.9	-19.3	+13.9
28	+68.6	-70.7	N/A	N/A	+19.7	+1.7	-25.8	+24.4	+15.1	+9.1	+15.3	-45.6
29	+0.9	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
30	+8.5	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
31	+48.3	+23.0	-10.1	-3.0	+9.6	+3.2	0.0	-2.3	-2.6	+5.4	-30.6	+26.2
32	-0.5	+33.9	-14.8	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
33	+24.5	-12.2	+5.0	+17.3	-18.1	+2.5	+15.1	-10.9	+16.0	-2.5	-3.4	0.0
34	+3.3	+1.2	-3.6	-1.1	-1.0	+3.8	-1.1	+4.2	-3.1	-2.1	N/A	N/A
35	+40.8	+12.3	-1.1	+4.0	+16.8	+8.5	+3.2	-2.1	+8.2	-2.1	-20.0	+19.0
36	-3.0	+11.8	-17.3	+7.9	+19.3	+26.7	N/A	N/A	N/A	N/A	+1.9	-19.0
37	0.0	+2.2	0.0	-0.2	+1.0	+5.1	-5.5	+3.6	+9.7	-1.3	+0.2	-11.2

Table S3. continued

	T1 – T2 (n=68)	T2 – T3 (n=64)	T3 – T4 (n=65)	T4 – T5 (n=64)	T5 – T6 (n=64)	T6 – T7 (n=62)	T7 – T8 (n=60)	T8 – T9 (n=61)	T9 – T10 (n=62)	T10 – T11 (n=62)	T11 – T12 (n=62)	T12 – T13 (n=63)
38	+13.7	+31.0	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
39	+9.5	-3.9	+20.2	-1.4	-5.8	+7.6	+4.4	-4.0	+4.3	+1.1	+7.6	-12.3
40	+1.7	-4.5	+15.3	+30.9	+11.9	N/A	N/A	N/A	N/A	N/A	-3.6	-4.7
41	-5.0	+10.1	+6.4	+5.7	-4.7	-9.4	+10.6	-2.2	-0.9	0.0	-6.5	-2.9
42	+29.0	+13.3	-8.3	-30.5	+48.2	-7.1	-8.2	+9.4	-12.3	+2.9	+9.7	-3.2
43	N/A	N/A	-7.1	-0.9	+7.5	-13.4	+6.3	+5.1	-9.7	+22.7	-36.5	+6.2
44	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	+38.1
45	+8.6	+0.2	+7.2	+5.4	+25.0	-21.8	-22.7	+35.5	-39.8	+27.4	-1.5	-19.2
46	N/A	+20.8	+11.3	+9.6	-2.4	+19.6	-12.8	+26.7	-2.8	-7.5	+1.9	-1.3
47	+14.7	-21.4	+13.4	+34.8	-14.2	N/A	N/A	+0.1	-13.5	+13.9	+8.8	+5.0
48	+18.4	+45.3	+6.7	-5.7	+5.4	-0.7	-22.0	+3.5	+7.7	-8.6	-61.9	+44.6
49	+2.1	0.0	+2.7	N/A	N/A	+5.0	-4.1	+92.8	-93.4	-4.0	+3.2	-0.3
50	N/A	N/A	+16.3	+8.9	+17.6	+0.6	N/A	N/A	-6.0	-43.6	+86.4	-100.0
51	-8.3	+16.6	+73.1	-66.8	+66.8	-46.3	-10.0	+56.3	-37.7	-6.3	+7.4	-5.6
52	-10.7	+6.5	-1.2	+11.9	+45.6	-28.2	-0.5	+17.5	N/A	N/A	+9.2	-6.6
53	+14.3	-8.2	+5.1	+17.7	+0.3	+8.9	-41.8	+26.4	+20.3	-19.3	-8.4	+5.9
54	-9.4	+17.8	+10.2	-11.0	+32.9	+11.7	-0.8	-3.7	+8.5	-0.5	+2.4	-12.3
55	+15.9	-4.2	-3.7	-7.9	+9.5	+9.6	+10.2	-5.0	+1.9	-10.3	-0.5	-5.6
56	+2.1	+5.9	+1.7	+5.0	-2.7	N/A	N/A	-6.9	+6.2	-0.9	-4.2	0.0
57	+3.0	+10.3	-4.2	+0.9	+8.5	-11.1	+12.4	-51.9	+41.1	+9.9	+8.4	-9.4
58	+8.2	+29.0	+20.1	+8.4	+5.1	+8.8	+0.4	-18.5	+11.4	+2.5	+5.0	-2.5
59	+12.1	-5.2	+13.2	+5.1	-30.0	+55.9	+3.2	-6.5	+2.3	+8.0	+4.7	-3.1
60	-10.9	+32.3	-1.3	-7.5	-22.4	+41.3	-7.2	-6.9	+21.6	+0.8	-0.8	+9.9
61	+22.0	-28.5	-1.8	+32.7	-5.8	-1.3	+10.2	N/A	N/A	-14.8	-1.8	-4.5
62	-5.3	+19.2	+3.6	+11.4	N/A	N/A	+8.8	N/A	N/A	N/A	N/A	N/A
63	-26.4	+29.7	+2.2	-16.2	+31.4	-6.7	+2.8	-7.7	+11.7	-31.3	+37.2	-2.7
64	+21.4	-15.2	+13.0	-12.0	+11.5	+9.3	+30.7	+23.5	+6.1	+4.0	-4.5	+4.5
65	+16.5	+18.2	+20.5	-24.3	+23.5	-10.2	-8.5	+27.0	+2.4	+7.2	-6.4	+9.8
66	-9.8	+6.6	-3.3	-6.8	+3.2	+1.9	-5.7	+10.2	-0.7	-0.8	+4.5	+2.6
67	+14.0	-5.7	+21.6	-4.6	-1.6	+10.7	+2.1	+5.9	+4.5	-10.6	+9.8	+2.2
68	-3.5	+24.3	+2.2	+27.3	+9.5	-3.3	-16.8	+10.1	+10.0	-22.6	+17.4	-2.6
69	-12.5	-11.8	+9.4	-8.0	+36.5	-28.5	-0.5	+19.4	-0.4	-3.0	-3.0	+17.9
70	+9.8	+67.9	-23.4	+18.8	-12.2	-6.5	+9.7	-16.2	+26.9	-10.4	-29.1	+18.0
71	+9.1	+2.3	-1.9	-5.9	-1.2	+1.7	-6.0	+7.2	+3.2	+0.7	-4.6	+8.8
72	N/A	N/A	N/A	-5.9	+12.2	5.0	+6.8	-7.2	-11.3	-8.0	N/A	N/A
73	+15.6	+11.4	+16.4	+2.2	-8.3	-0.7	+8.5	-8.1	-36.4	+35.2	+1.7	-6.3
74	+61.2	-7.8	-39.7	-3.6	-9.4	-1.3	+10.3	+3.4	+2.6	-10.4	+2.5	-5.1

Table S3. continued

	T1 – T2 (n=68)	T2 – T3 (n=64)	T3 – T4 (n=65)	T4 – T5 (n=64)	T5 – T6 (n=64)	T6 – T7 (n=62)	T7 – T8 (n=60)	T8 – T9 (n=61)	T9 – T10 (n=62)	T10 – T11 (n=62)	T11 – T12 (n=62)	T12 – T13 (n=63)
Increase in subjective overall olfactory functioning, % (n)												
	72.1 (49)	64.1 (41)	56.9 (37)	62.5 (40)	57.8 (37)	51.6 (32)	51.7 (31)	55.7 (34)	62.9 (39)	46.8 (29)	56.5 (35)	39.7 (25)
Decrease in subjective overall olfactory functioning, % (n)												
	26.5 (18)	34.4 (22)	41.5 (27)	37.5 (24)	42.2 (27)	46.8 (29)	46.7 (28)	44.3 (27)	37.1 (23)	51.6 (32)	43.5 (27)	57.1 (36)
No change in subjective overall olfactory functioning, % (n)												
	1.5 (1)	1.6 (1)	1.5 (1)	N/A	N/A	1.6 (1)	1.7 (1)	N/A	N/A	1.6 (1)	N/A	3.2 (2)
Increase of ≥20 in subjective overall olfactory functioning, % (n)												
	16.2 (11)	18.8 (12)	10.8 (7)	9.4 (6)	18.8 (12)	9.7 (6)	8.3 (5)	18.0 (11)	11.3 (7)	6.5 (4)	6.5 (4)	7.9 (5)
Decrease of ≤ 20 in subjective overall olfactory functioning, % (n)												
	1.5 (1)	6.3 (4)	3.1 (2)	4.7 (3)	4.7 (3)	9.7 (6)	8.3 (5)	6.6 (4)	6.5 (4)	4.8 (3)	11.3 (7)	6.3 (4)

S4. Self-reported presence of fluctuation in olfactory functioning.

Table S4 reports the prevalence of patients' self-reported fluctuations in olfactory functioning over time. The presence of these fluctuations was determined by the selection of the answer option "Sense of smell fluctuates (comes and goes)" in the Check-All-That-Apply question in the monthly questionnaire.

Table S4. Prevalence of patients' self-reporting fluctuations in their olfactory functioning.

Prevalence rate, % (n)	T1 n=76	T2 n=74	T3 n=70	T4 n=70	T5 n=65	T6 n=67	T7 n=65	T8 n=65	T9 n=66	T10 n=66	T11 n=66	T12 n=67	T13 n=68
Self-reported fluctuation	47.4 (36)	56.8 (42)	60.0 (42)	50.0 (35)	58.5 (38)	55.2 (37)	60.0 (39)	55.4 (36)	43.9 (29)	48.5 (32)	48.5 (32)	44.8 (30)	47.1 (32)