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Recovery rates and parosmia in olfactory loss during the COVID-19 era

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ABSTRACT

INTRODUCTION. Olfactory dysfunction (OD) is a common symptom of COVID-19. In some patients, OD persists for many months, fluctuates during recovery or parosmia may occur. Knowledge about the prognosis of these patients is insufficient.

METHODS. Data on chemosensory function and possible prognostic factors were collected through a baseline questionnaire and six follow-up questionnaires answered at 2-3-month intervals.

RESULTS. One year after onset of OD, 42.0% of the respondents reported sustained complete recovery, 41.7% reported partial recovery and 2.4% reported no improvement of olfaction. Follow-up was unavailable for 13.9%. Parosmia, high severity of OD and female sex were associated with lower rates of recovery. Subjects who reported that OD had a high impact on their quality of life were less likely to recover within one month. Smoking, alcohol habits, BMI and physical activity were not associated with persistence of OD.

CONCLUSIONS. High recovery rates were reported within the first months. Recovery of sensory function after more than six months with no prior improvement was reported. After one year, 97.1% of participants with at least one year of follow-up had reported at least some recovery. Recurring OD after initial complete recovery was reported by 24.5% of participants. Parosmia and severity of OD were associated with prolonged recovery rates.

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Chemosensory dysfunction is a common symptom of COVID-19, which has been shown to have a high positive predictive value for COVID-19, making it a valuable clinical predictor of SARS-CoV-2 infection [1]. Meta-analysis found a pooled prevalence of olfactory dysfunction (OD) of 41.0-77.0% and gustatory dysfunction (GD) of 38.2-49.0% in COVID-19 patients [2, 3]. Both measured olfactory and gustatory function may be affected by COVID-19, as initially shown in a Danish publication [4]. Interestingly, studies that objectively measured chemosensory function yielded higher estimates of OD than those which relied on subjective data [5].

Furthermore, parosmia, a qualitative distortion of olfaction, has been reported to affect around one in four of these patients and has been shown to have a negative impact on quality of life (QoL) [6, 7]. Knowledge about the prognosis of OD after COVID-19 is needed to underpin counseling of these patients.

Several studies have been conducted on OD after COVID-19, in general revealing high recovery rates within the

first 2-3 months after OD onset [8, 9]. However, many patients experience OD several months after the initial sensory loss. One study found that 28.6% of patients with OD after mild-moderate COVID-19 still reported OD after 12 months [10]. Furthermore, clinical experience suggests that chemosensory function fluctuates over the course of recovery in some patients who report recurrent OD, either hyposmia or parosmia.

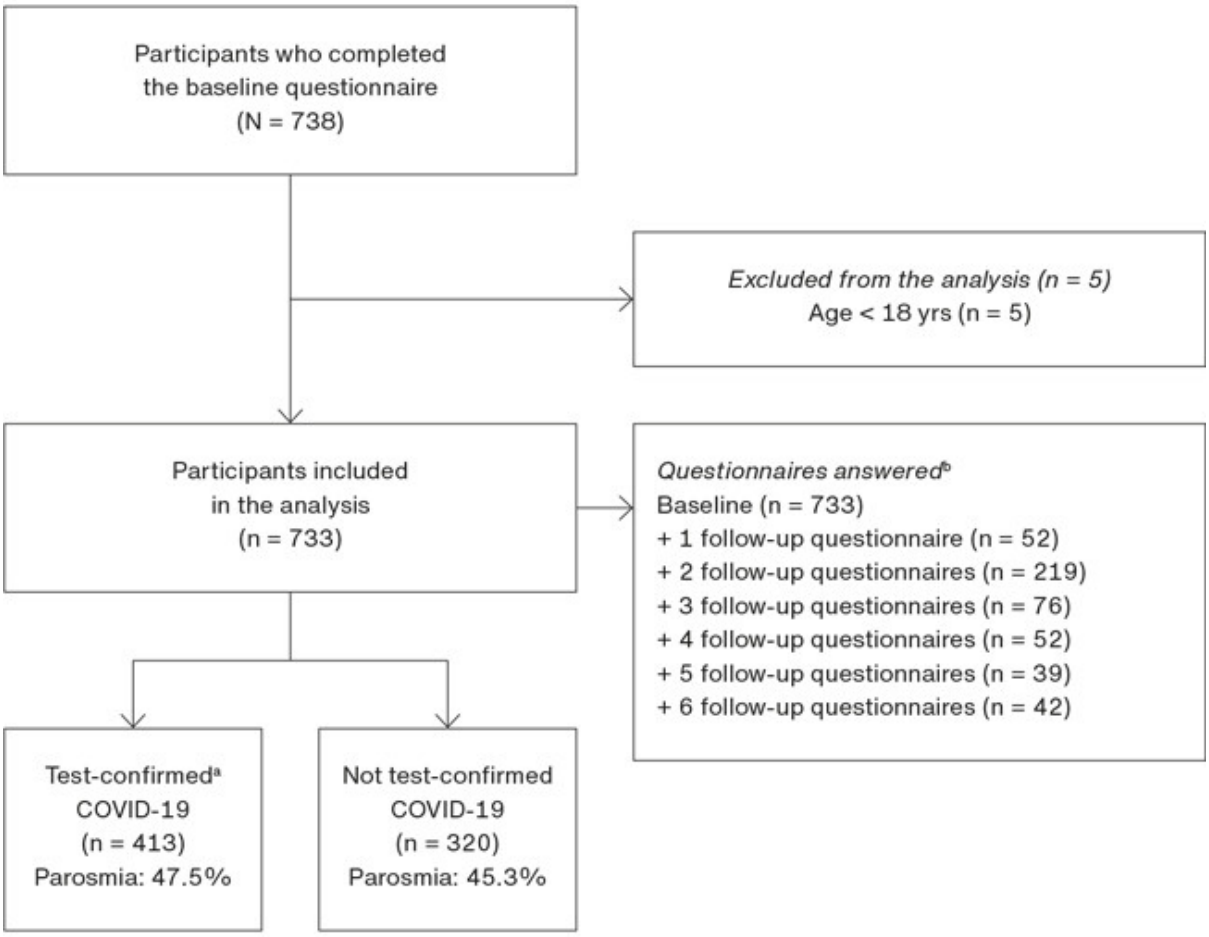
The aim of this study was to determine rates of partial and sustained complete recovery from subjective OD after COVID-19 in a cohort with a continuous follow-up for up to 16 months. The secondary aim was to identify possible prognostic factors for the duration of OD after COVID-19.

METHODS

Study design and population

A baseline questionnaire was designed in REDCap [11] and distributed through social media, national radio, national television and information available in the waiting rooms of general practitioners and hospital outpatient clinics. To be included in the study, respondents needed to be at least 18 years and have experienced a sudden onset of chemosensory loss after the 27th of February 2020, when the first case of COVID-19 in Denmark was confirmed (**Figure 1**). Because OD was not acknowledged as a possible symptom of COVID-19 by the Danish healthcare authorities until the fourth of May 2020, patients with isolated OD were not tested routinely [12, 13] and real-time (RT)-PCR-test-verified COVID-19 was therefore not a criterion for inclusion into the study.

FIGURE 1 Study design and population.



OD = olfactory dysfunction; RT = real-time.
a) Positive RT-PCR-test or SARS-CoV-2 antibody test.
b) Severity of sensory loss was assessed by asking participants to rate olfactory function before and after onset of OD on a visual analogue scale (0-100), and the proportion of sensory loss was calculated by dividing the difference by the sensory function prior to the loss.

The baseline questionnaire included information on subjective olfactory and gustatory function, including the presence of parosmia and time until partial or complete recovery of sensory function. Chemosensory function was assessed by asking participants if they had experienced sudden alterations of their sense of smell or taste since the beginning of 2020. Participants were then asked to rate their level of smell and taste function on a visual analogue scale (VAS) both before and after onset of chemosensory dysfunction. For data analysis, this VAS was transformed into a numerical value ranging from 0 to 100. To reduce the risk of confusion of OD with GD, taste loss was specified to include a loss of basic tastants (sweet, salty, sour and bitter). Data were collected on other common symptoms of COVID-19, medical history, smoking, alcohol consumption, physical activity, QoL and SARS-CoV-2 test results. Severity of OD and the impact of OD on QoL were scored on a VAS which corresponded to a numerical value ranging from 0 to 100. Data from the cohort after 30 and 95 days of follow-up have previously been published [8, 13, 14]. Participants who had not fully recovered their chemosensory function at the time of the baseline questionnaire could sign up to receive follow-up questionnaires. Six rounds of follow-up questionnaires were sent out during follow-up at approximately 2-3-month intervals. In the follow-

up questionnaires, participants were asked if they had experienced partial or complete recovery from OD and how many days had passed from onset of OD to partial or complete recovery. The last four rounds of follow-up questionnaires also inquired about the occurrence of parosmia. Participants could enter the study at any time during the study period by answering the baseline questionnaire. Therefore, not all participants were invited to complete all six follow-up questionnaires. Data collection was initiated on 22 April 2020 and concluded on 10 September 2021.

Statistics

Data were analysed using JMP Pro 16. χ^2-test (Pearson) was performed to screen data for possible associations between possible risk factors and the endpoints of partial, complete or no recovery of olfaction at three time points. Odds ratios (OR) were used to calculate prognostic factors. Student's t-test was used to compare means between groups in parametric data.

Time to partial or complete recovery from OD is displayed on a survival curve (Kaplan-Meyer). Statistical significance was considered at the 5% level ($p \leq 0.05$).

Trial registration: not relevant.

RESULTS

Among the 738 participants who completed the baseline questionnaire, five were excluded due to an age of < 18 years, and thus 733 subjects were included in the analysis.

A total of 654 (89.2%) participants reported combined OD and GD, 46 reported isolated OD and 33 reported isolated GD (**Table 1**). The median age at baseline was 43 years (interquartile range (IQR): 31-52 years) and 74.2% of participants were female. The median time from onset of symptoms to enrollment in the study was 62 days (IQR: 30-85 days).

TABLE 1 Baseline characteristics.

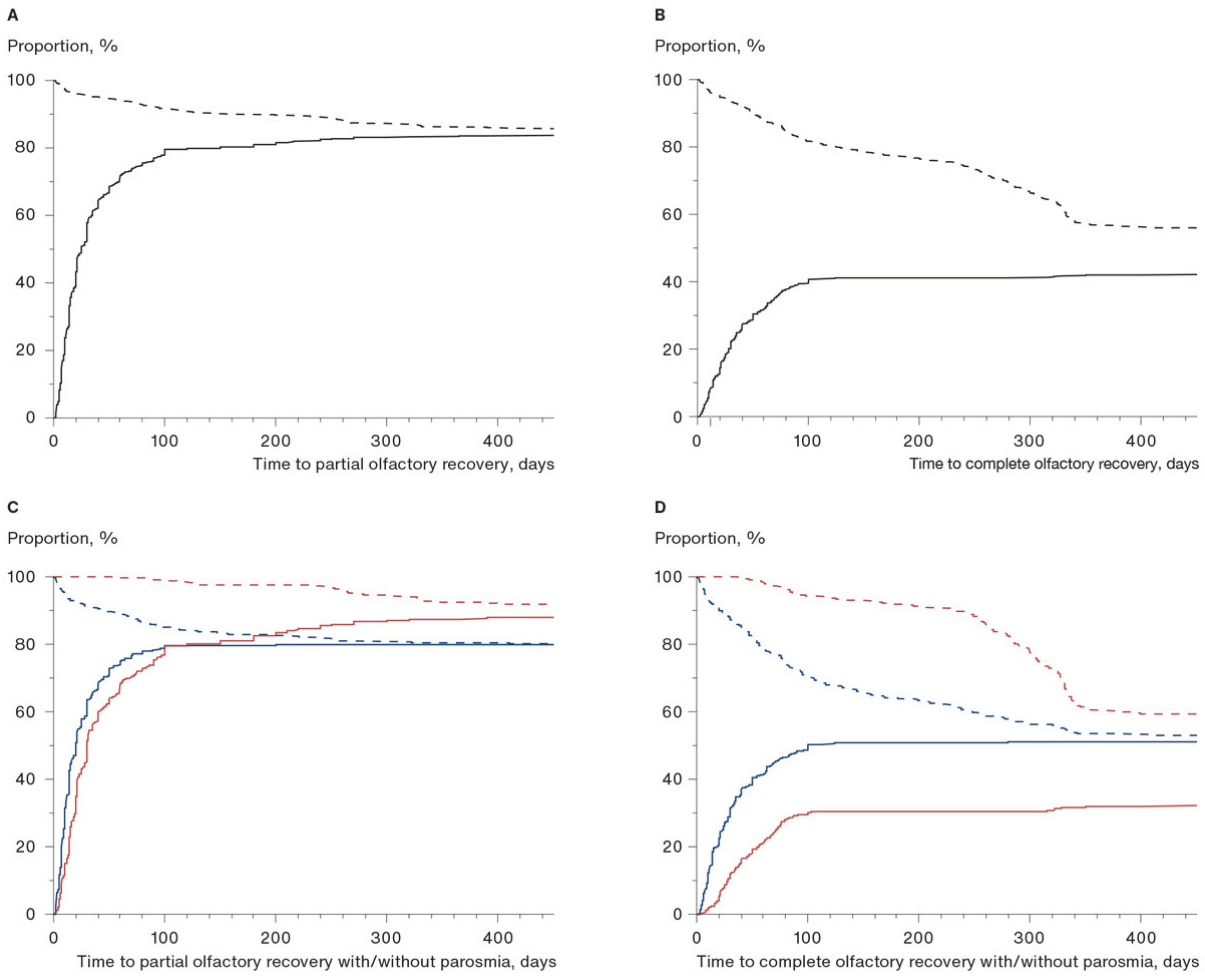
Female, n (%)	544 (74.2)
Age, median (IQR), yrs	43 (31-52)
Type of CD, n (%)	
Combined olfactory and gustatory dysfunction	654 (89.2)
Isolated olfactory dysfunction	46 (6.3)
Isolated gustatory dysfunction	33 (4.5)
Confirmed SARS-CoV-2 infection[a], n (%)	413 (56.3)
Severity of sensory loss[b], % (IQR)	
Olfactory dysfunction	97.9 (88.4-100)
Gustatory dysfunction	91.2 (72.5-100)
Time from onset of CD to baseline questionnaire, median (IQR), days	62 (30-85)

CD = chemosensory dysfunction; IQR = interquartile range.
a) Positive real-time-PCR-test or SARS-CoV-2 antibody test.
b) Severity of sensory loss was assessed by asking participants to rate olfactory function before and after onset of olfactory dysfunction on a visual analogue scale (0-100), and the proportion of sensory loss was calculated by dividing the difference by the sensory function prior to the loss.

Recovery rates

At 30 days from onset of OD, 22.2% of participants had complete subjective recovery of olfactory function, 36.9% had partial recovery and 37.6% reported no improvement of olfactory function. At 180 days from onset of OD, 41.1% of participants had complete subjective recovery of olfactory function, 40.1% had partially recovered, whereas 10.0% reported no improvement of olfactory function. At this time point, no follow-up data were available for 8.7% of the participants. One year from onset of OD, 42.0% of participants reported complete subjective recovery of olfactory function, 41.7% had partially recovered, and only 2.4% of participants reported no improvement of olfactory function. At this time point, no follow-up data were available for 13.9% of the participants. Recurring OD after initial complete recovery was reported by 24.5% of participants (**Figure 2**).

FIGURE 2 Kaplan-Meier plot of time to partial and sustained complete recovery of olfactory function. The accumulated proportion of participants (N = 700) who reported partial (**A**) or sustained complete (**B**) recovery of olfactory function. **C** + **D.** The effects of parosmia. The accumulated proportion of participants who recovered olfactory function (blue: participants without parosmia (n = 368), red: participants with parosmia (n = 332)). For all figures, the space between the dotted and continuous lines are confirmed lack of recovery, whereas the area above the dotted line represents timepoints beyond follow-up for the given percentage of participants, which increases over time. See supplementary material (https://ugeskriftet.dk/files/a04220271_-_supplementary.pdf) for a Kaplan-Meier plot of recovery of gustatory function.



Prognostic factors

Female sex was associated with a lower recovery rate from OD one year after onset of OD ($p = 0.003$). Parosmia at any time during data collection was strongly associated with lower rates of complete recovery from OD ($p < 0.001$). Among the participants who reported parosmia, 31.9% reported a sustained complete recovery of olfaction at one year after onset of OD compared with 51.1% of participants without parosmia (OR = 0.35 (95% confidence interval (CI): 0.25-0.46), $p < 0.001$). However, after 180 and 365 days, no parosmia-related difference was observed in the proportion of participants who had not reported any improvement (9.0% and 10.9% at 180 days and 1.8% and 3.0% at 365 days for subjects with and without parosmia, respectively).

Age affected recovery times in our cohort as a larger proportion of the oldest subgroup (> 60 years of age) had reported complete and sustained recovery of olfaction after 30 and 180 days. No difference was observed in complete recovery in different age groups after one year. Subjective high severity of OD at baseline was strongly

associated with prolonged recovery rates (p < 0.001). Participants who reported that OD had a high impact on their QoL immediately after onset of OD were less likely to recover from OD within 30 days (p = 0.005). This association did not reach statistical significance when respondents who had only answered the baseline questionnaire were excluded from the analysis in order to counter any recall bias (p = 0.249). The trend, however, was present also at 180 and 365 after onset of OD but did not reach statistical significance.

No associations between rates of partial or complete recovery from OD were found for smoking status, BMI, alcohol consumption or physical activity (see **Table 2**).

TABLE 2 Possible prognostic factors for the duration of olfactory dysfunction. Participants were grouped to assess associations with rates of partial and complete recovery.

	30 days after onset of OD					180 days after onset of OD					365 days after onset of OD				
	complete recovery	partial recovery	no recovery	difference, p- value	no follow-up	complete recovery	partial recovery	no recovery	difference, p- value	no follow-up	complete recovery	partial recovery	no recovery	difference, p- value	no follow-up
Total, N (%)	156 (22.2)	258 (36.9)	263 (37.6)	-	23 (3.3)	288 (41.1)	281 (40.1)	70 (10.0)	-	61 (8.7)	294 (42.0)	292 (41.7)	17 (2.4)	-	97 (13.9)
Sex, n (%)															
Female	107 (20.7)	203 (39.3)	191 (36.9)	0.062	16 (3.1)	207 (40.0)	223 (43.1)	48 (9.3)	0.054	39 (7.5)	211 (40.8)	232 (44.9)	8 (1.6)	0.003	66 (12.8)
Male	49 (26.8)	55 (30.1)	72 (39.3)		7 (3.8)	81 (44.3)	58 (31.7)	22 (12.0)		22 (12.0)	83 (45.4)	60 (32.8)	9 (4.9)		31 (16.9)
Age, n (%)															
18-29 yrs	32 (20.0)	53 (33.1)	69 (43.1)	0.005	6 (3.8)	55 (34.4)	57 (35.6)	26 (16.3)	0.004	22 (13.8)	56 (35.0)	62 (38.8)	4 (2.5)	0.915	38 (23.8)
30-44 yrs	52 (23.2)	103 (46)	62 (27.7)		7 (3.1)	95 (42.4)	103 (46)	11 (4.9)		15 (6.7)	97 (43.3)	101 (45.1)	4 (1.8)		22 (9.8)
45-59 yrs	51 (29.8)	81 (33.1)	103 (42.0)		10 (4.1)	102 (41.6)	94 (38.0)	28 (11.4)		21 (8.6)	105 (42.9)	100 (30.8)	7 (2.9)		33 (13.5)
≥ 60 yrs	21 (29.6)	21 (29.6)	29 (40.9)		0	36 (50.7)	27 (38.0)	5 (7.0)		3 (4.2)	36 (50.7)	29 (40.9)	2 (2.8)		4 (5.6)
Parosmia at any time during follow-up, n (%)															
Yes	40 (12.1)	138 (41.6)	142 (42.8)	< 0.001	12 (3.6)	101 (30.4)	174 (52.4)	30 (9.0)	< 0.001	27 (8.1)	106 (31.9)	185 (55.7)	6 (1.8)	< 0.001	35 (10.5)
No	116 (31.5)	120 (32.6)	121 (32.9)		11 (3.0)	187 (50.8)	107 (29.1)	40 (10.9)		34 (9.2)	188 (51.1)	107 (29.1)	11 (3.0)		62 (16.9)
Severity of OD at baseline[a], n (%)															
Loss 100%	52 (17.6)	117 (39.7)	114 (38.6)	0.001	12 (4.1)	97 (32.9)	138 (46.8)	33 (11.2)	< 0.001	27 (9.2)	102 (34.6)	141 (47.8)	5 (1.7)	< 0.001	47 (15.9)
Loss ≥ 50% quartile	6 (11.3)	18 (34.0)	26 (49.1)		3 (6.7)	13 (24.5)	24 (45.3)	9 (17.0)		7 (13.2)	13 (24.5)	26 (49.1)	4 (7.6)		10 (18.9)
Loss ≥ 25% quartile	36 (20.6)	64 (36.6)	70 (40.0)		5 (2.9)	71 (40.6)	72 (41.1)	17 (9.7)		15 (8.6)	72 (41.1)	78 (44.6)	5 (2.9)		20 (11.4)
Loss < 25% quartile	61 (35.1)	58 (33.3)	52 (29.9)		3 (1.7)	106 (61.3)	46 (26.6)	11 (6.4)		10 (5.8)	106 (61.3)	46 (26.6)	3 (1.7)		18 (10.4)
Impact of OD on QoL, VAS score[b, c], n (%)															
1-24	33 (36.3)	28 (30.8)	29 (31.9)	0.005	1 (1.1)	42 (46.2)	37 (40.7)	4 (4.4)	0.176	8 (8.8)	43 (47.3)	37 (40.7)	2 (2.2)	0.131	9 (9.9)
25-49	22 (29.7)	27 (36.5)	24 (32.4)		1 (1.4)	35 (47.3)	31 (41.9)	4 (5.4)		4 (5.4)	35 (47.3)	31 (41.9)	1 (1.4)		7 (9.5)
50-74	56 (23.4)	87 (36.4)	87 (36.4)		9 (3.8)	105 (43.9)	91 (38.1)	24 (10.0)		19 (8.0)	108 (45.2)	97 (40.6)	2 (0.8)		32 (13.4)
75-100	45 (15.3)	116 (39.2)	123 (41.6)		12 (4.1)	106 (35.8)	122 (41.2)	38 (12.8)		30 (10.1)	108 (36.5)	127 (42.9)	12 (4.1)		49 (16.6)
BMI, n (%)															
< 25 kg/m²	88 (22.1)	153 (38.4)	144 (36.2)	0.757	13 (3.3)	160 (40.2)	166 (41.7)	39 (9.8)	0.396	33 (8.3)	164 (41.2)	172 (43.2)	8 (2.0)	0.739	54 (13.6)
25-29 kg/m²	42 (23.6)	60 (33.7)	72 (40.5)		4 (2.3)	76 (42.7)	63 (35.4)	22 (12.4)		17 (9.6)	76 (42.7)	68 (38.2)	5 (2.8)		29 (16.3)
≥ 30 kg/m²	19 (19.2)	38 (38.4)	37 (37.4)		5 (5.1)	40 (40.4)	46 (46.5)	7 (7.1)		6 (6.1)	42 (42.4)	46 (46.5)	4 (4.0)		7 (7.1)
Physical activity, weekly time of hard physical training, n (%)															
0 h	75 (41.9)	60 (33.5)	35 (19.6)	0.456	9 (5.0)	22 (12.3)	75 (41.9)	66 (36.9)	0.277	16 (8.9)	4 (2.2)	79 (44.1)	66 (36.9)	0.125	30 (16.8)
1-3 h	108 (34.6)	121 (38.8)	74 (23.7)		9 (2.9)	26 (8.3)	123 (39.4)	137 (43.9)		26 (8.3)	5 (1.6)	128 (41.0)	141 (45.2)		38 (12.2)
4-7 h	67 (40.1)	61 (36.5)	34 (20.4)		5 (3)	19 (11.4)	70 (41.9)	62 (37.1)		16 (9.6)	25 (15)	8 (4.8)	70 (41.9)		25 (15)
≥8 h	13 (30.1)	16 (38.1)	13 (31)		0	3 (7.1)	13 (31.0)	23 (54.8)		3 (7.1)	0	15 (35.7)	23 (54.8)		4 (9.5)
Alcohol, weekly consumption, n (%)															
0-5 IU	198 (39.4)	179 (36.0)	101 (20.3)	0.232	19 (3.8)	57 (11.5)	206 (41.5)	195 (39.2)	0.114	39 (7.9)	13 (2.6)	216 (43.5)	199 (40.0)	0.399	69 (13.9)
6-10 IU	45 (31.7)	55 (38.7)	39 (27.5)		3 (2.1)	7 (4.9)	50 (35.2)	67 (47.2)		18 (12.7)	2 (1.4)	51 (35.9)	68 (47.9)		21 (14.8)
> 10 IU	20 (32.8)	24 (39.3)	16 (26.2)		1 (1.6)	6 (9.8)	25 (41)	26 (42.6)		4 (6.6)	2 (3.3)	25 (41)	27 (44.3)		7 (11.5)
Smoking status, n (%)															
Current smokers	11 (27.5)	11 (27.5)	18 (45.0)	0.572	0	15 (37.5)	17 (42.5)	4 (10.0)	0.339	4 (10.0)	16 (40.0)	18 (45.0)	0	0.627	6 (15.0)
Former smokers	34 (19.8)	68 (39.5)	61 (35.5)		9 (5.2)	68 (39.5)	80 (46.5)	12 (7.0)		12 (7.0)	69 (40.1)	81 (47.1)	4 (2.3)		18 (10.5)
Non-smokers	104 (22.8)	169 (37.0)	171 (37.4)		13 (2.8)	192 (42.0)	175 (38.3)	51 (11.2)		39 (8.5)	195 (42.7)	185 (40.5)	13 (2.8)		64 (14.0)

IU = international standardized units; OD = olfactory dysfunction; QoL = quality of life; VAS = visual analogue scale.
a) Ordered by quartiles of subjective severity of olfactory loss.
b) Participants were divided into 4 groups according to the negative impact of OD on QoL.
c) Assessed through a VAS, which corresponds to a score of 0-100, where 0 was the least and 100 was the most negative impact.

No statistical difference was seen in BMI, alcohol and smoking habits or in the distribution of most symptoms from COVID-19 (i.e., dry cough, productive cough, congested nose, runny nose, dyspnoea, myalgia or sore throat) between subjects with and without a confirmed SARS-CoV-2 infection. Participants with a confirmed SARS-CoV-2 infection were slightly older (mean 44.0 years (95% CI: 42.4-45.5 years) versus 41.8 years (95% CI: 40.5-43.0 years)), more likely to be women (p = 0.021) and reported fever and headache more often than those without a positive test. Fever and headache were not found to be risk factors for persistent OD. No difference was observed in the prevalence of known risk factors for OD such as chronic rhinosinusitis (CRS), head trauma, dental treatment, hay fever or any condition that alters air flow through the nose (e.g., congestion or nasal discharge), depression and neurological disease in participants with or without test-confirmed SARS-CoV-2 infection.

DISCUSSION

Our findings showed that OD after COVID-19 can persist for more than one year. Some previous studies found higher rates of recovery within the first month [10, 15]. This might be due, in part, to the continuous enrollment process into the present study as selection bias is inevitable. Participants with a more persistent OD may have

been more likely to sign up for the study and thus have increased the mean time to recovery. Due to the median time from symptom onset to enrollment in the questionnaire, the findings of this study more accurately reflect the prognosis for recovery of olfactory function in patients with continuous OD two months or more after OD onset. Despite the high awareness of OD as a symptom of COVID-19, patients often have a delay of several weeks to months before consulting a physician with OD. As such, we argue that the prognosis in the present study provides a fairly accurate estimation of recovery rates for these patients.

Boscolo-Rizzo et al. found that 69.5% of patients with chemosensory dysfunction reported complete recovery after one year from onset of symptoms, whereas 8.6% reported unchanged or worsened dysfunction [10]. Compared with the findings of this study, more participants from our cohort reported some improvement but not complete and sustained recovery.

We found that severity of OD was associated with longer recovery rates, which seems logical as the severity of OD may be associated with a more severe damage to olfactory structures. However, participants with a persistent OD may also be prone to overestimating the severity of their OD due to recall bias. A study by Amer et al. reported that female sex may increase the risk of persistent OD, which is in line with our findings [15]. In this study, high age negatively impacted the prognosis, whereas our data indicate that age > 60 years is a predictor of rapid recovery. However, drop-out rates were strongly associated with young age, which may have led to an underestimation of recovery rates in the younger participants.

Persistent OD and parosmia after COVID-19 have been shown to negatively impact patient QoL [7], highlighting the importance of being aware of treatment and supportive options. Currently, only little evidence exists on treatment and improving recovery from post-viral OD. The cornerstone for patients with persistent OD is to engage in systematic olfactory training. This intervention was shown to improve post-viral OD caused by other infections and is both safe and inexpensive [16]. However, persistence and compliance are important, especially with the long possible duration of post-COVID OD. Olfactory training should be conducted twice daily using four different stimuli (scented oils), which may be replaced by four new odorants after three months for optimal results [17]. The efficacy of intranasal corticosteroids is well established for the treatment of CRS. However, evidence is insufficient to support the use of systemic or topical corticosteroids in the treatment of post-viral OD. Therefore, corticosteroids are not recommended as standard treatment due to the potential side effects of corticosteroids. More research is needed to elucidate the potential beneficial effect of topical corticosteroids in OD after COVID-19 [18]. Systemic omega-3 may have a positive effect on the regeneration of olfactory neurons and may thus be a promising option [19]. As such, the general recommendations from the health authorities on consumption of fish should be followed in patients suffering from OD in particular.

Limitations

RT-PCR-test-verified COVID-19 was not a criterion for inclusion into the study, and we chose to include participants without test-confirmed COVID-19 in the analysis as recent OD has been shown to be the best clinical predictor of a SARS-CoV-2 infection [1]. Furthermore, data collected prior to the pandemic show that sudden-onset OD is rare in a population resembling the present study population [13]. Even so, we cannot be entirely sure that no participants suffered from OD due to other viral infections or non-viral causes of OD. Another limitation of this study may be the lack of a validated questionnaire for the assessment of olfactory function. Our study relies on subjective data with no clinical assessment or testing of olfactory function conducted and may therefore underestimate the true prevalence of persistent OD after COVID-19; thus, a meta-analysis of 34 studies (six with objective and 28 with subjective evaluation of olfactory function) found that the incidence of OD after COVID-19 was higher when assessed by clinical testing [5]. However, subjective chemosensory dysfunction has been shown to have a negative impact on patient QoL and it is likely that individuals whose QoL was affected will seek help [7]. Furthermore, as sustained subjective OD reflects patients' experienced complaint, the high

proportion of participants who have not regained complete olfactory function indicates a prolonged demand for olfactory assessments and consultations after COVID-19.

Although this study is among those with the longest follow-up times to date, our findings should be viewed as intermediate results as spontaneous recovery from OD after several years has been reported [20].

CONCLUSIONS

Most subjects with OD after COVID-19 recovered at least some olfactory function within the first months after their infection. Recovery of olfactory function after more than six months without any prior improvement was reported. One year after onset of OD, 42.0% of participants reported complete subjective recovery of olfactory function, 41.7% had partially recovered, 2.4% reported no improvement of olfactory function and no follow-up was reported for 13.9%. Recurring OD after initial complete recovery was reported by 24.5% of participants. Female sex, parosmia and subjective severity of OD were associated with a prolonged duration of recovery from OD. Participants who reported that OD had a high impact on their QoL immediately after onset of OD were less likely to report recovery from OD at 30 days past OD onset.

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Conflicts of interests Potential conflicts of interest have been declared. Disclosure forms provided by the authors are available with the full text of this article at ugeskriftet.dk/dmj

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