

Original Article

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Patient burden of chemosensory dysfunction and long COVID

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ABSTRACT

INTRODUCTION. Chemosensory dysfunction (CD), particularly olfactory and gustatory dysfunction, is a common symptom of SARS-CoV-2 infection. While often transient, some patients develop persistent dysfunction. The long-term relationship between persistent CD, long COVID (LC) and quality of life (QoL) remains unclear. This study aimed to evaluate CD recovery four years after infection and its association with LC symptoms and QoL.

METHODS. In this prospective cohort study, 356 individuals with sudden CD during the COVID-19 pandemic completed a questionnaire four years after symptom onset. The survey assessed CD recovery, LC symptoms and QoL using validated self-report items. Outcomes were compared between participants with recovered versus persistent CD. The study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.

RESULTS. Only 43% reported full recovery of CD after four years. Persistent dysfunction was most common among participants aged 45-59 years (68%). Participants with persistent CD were significantly more likely to report LC symptoms, particularly fatigue (OR = 4.33), memory difficulties (OR = 3.30) and insomnia (OR = 3.39), each affecting more than 30% of this group. QoL scores indicated a greater impact on physical than emotional well-being.

CONCLUSIONS. A substantial proportion of respondents continued to experience CD and other LC symptoms four years after infection. These findings highlight the need for long-term clinical awareness and further research on post-viral CD.

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Chemosensory dysfunction (CD) includes olfactory dysfunction (OD), gustatory dysfunction (GD) and elements of trigeminal dysfunction. OD affects approximately 20% of the population and is more common than GD [1, 2]. Sudden CD became a hallmark symptom of COVID-19 and a strong predictor of SARS-CoV-2 infection [3]. However, recovery does not occur in all patients.

Many patients develop post-acute sequelae after SARS-CoV-2 infection, commonly referred to as long COVID (LC). LC is defined as symptoms persisting ≥ 3 months after infection and may include fatigue, dyspnoea, arthralgia and myalgia, and brain fog [4]. For the full list of LC symptoms, see **Table 1**.

TABLE 1 Reported symptoms in the group experiencing persistent chemosensory dysfunction (CD) and the group reporting a full recovery, adjusted for age and sex. Persistent CD includes participants who did not fully recover, i.e., those who had a partial recovery or no improvement.

Long COVID symptom	Full recovery of CD, n (male/female) (N _f = 152)	Persistent CD, n (male/female) (N _p = 204)	Total participants, n (N _{tot} = 356)	Adjusted OR (95% CI, lower/upper)	p value
Fatigue	22 (5/17)	88 (18/70)	110	4.33 (2.57/7.52)	< 0.0001
Feeling short of breath	10 (0/10)	30 (5/25)	40	2.23 (1.08/4.98)	0.0381
Problems with memory	17 (3/14)	64 (8/56)	81	3.30 (1.86/6.11)	< 0.0001
Problems with concentration	16 (3/13)	64 (9/55)	80	3.61 (2.02/6.78)	< 0.0001
Heart palpitations	11 (2/9)	41 (4/37)	52	2.79 (1.41/5.96)	0.0048
Dizziness	8 (2/6)	33 (4/29)	41	3.10 (1.44/7.46)	0.0062
Joint pain	9 (0/9)	41 (5/36)	50	3.47 (1.68/7.92)	0.0015
Muscle aches	7 (0/7)	36 (6/30)	43	3.94 (1.78/9.96)	0.0016
Insomnia	16 (3/13)	62 (10/52)	78	3.39 (1.89/6.39)	< 0.0001
Symptoms of depression	10 (3/7)	37 (11/26)	47	3.25 (1.61/7.19)	0.0018
Anxiety	5 (2/3)	13 (1/12)	18	2.01 (0.73/6.47)	0.1996
Tinnitus	8 (2/6)	38 (11/27)	46	4.06 (1.90/9.73)	0.0007
Coughing	2 (0/2)	18 (5/13)	20	6.73 (1.87/43.16)	0.0121
Headaches	8 (1/7)	39 (9/30)	47	4.20 (1.98/9.99)	0.0004
Sore throat	1 (0/1)	5 (1/4)	6	3.60 (0.57/69.71)	0.2464

LC symptoms are debilitating, and treatment options vary widely in cost and effect. LC is associated with increased healthcare use and costs [5, 6].

Recovery rates decline over time [7], but long-term outcomes remain poorly described.

This study aimed to evaluate recovery from CD four years after SARS-CoV-2 infection. The secondary aims were to describe LC symptoms and their association with quality of life (QoL).

Methods

Study design and population

A baseline REDCap questionnaire was distributed via social and general media during the pandemic. Participants were ≥ 18 years with sudden CD after 27 February 2020 - the date of the first confirmed Danish case of COVID-19. Although most participants had test-verified COVID-19, lack of testing was not an exclusion criterion as CD did not qualify for public SARS-CoV-2 testing in this initial phase of the pandemic. Recorded variables included demographics, comorbidities, lifestyle factors and symptoms of upper respiratory tract infections.

Baseline data collection began on 22 April 2020 and concluded on 10 September 2021. Additional questionnaires were sent to the same cohort at 30- to 95-day intervals over six rounds of follow-up, each including an identical CD evaluation, with some also including additional areas of focus. Several studies have previously used questionnaire data [3, 7, 8]. The current questionnaire was designed and distributed in October 2024 and included questions about CD recovery status, LC symptoms and perceived QoL over the past 14 days. The WHO-5 instrument was used to evaluate mental well-being. Upon completing the questionnaire, participants confirmed their consent to this publication. Subgroup analyses and the original questions (translated into English) are available in the [supplementary tables](#).

The primary outcome was self-reported CD recovery. The secondary outcomes were LC symptoms and QoL. LC symptoms were defined according to the NHS definition [4].

This article was prepared in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines for cohort studies.

Ethics

The study was conducted in accordance with the World Medical Association Declaration of Helsinki. Data were collected following regional approval from the Danish Data Protection Agency. The questionnaire-based design of the study did not require ethics approval under Danish law (Danish Act on Research Ethics Review of Health Research Projects, Section 14, Subsection 2).

Statistics

Analyses were performed in RStudio (version 2024.12.0). The Pearson χ^2 test was used to evaluate differences between groups for categorical variables. ORs were used to describe associations between risk factors (persistent CD) and outcomes (LC symptoms). Continuous variables were summarised using median, mean and IQR, whereas counts and percentages were calculated for categorical variables. Inverse probability weighting was used to estimate the risk of bias due to loss to follow-up.

Trial registration: not relevant.

Results

Among 697 invited participants, 363 responded. Six participants were excluded because they did not use the same e-mail address they provided in the baseline questionnaire, and one was excluded because the participant was < 18 years of age at the time of completing the baseline questionnaire, leaving 356 participants for inclusion in the analysis. Inverse probability weighting indicated that neither age (estimate = 0.00042, standard error (SE) = 0.00142, $p = 0.767$) nor sex (estimate = 0.00454, SE = 0.0437, $p = 0.917$) influenced the likelihood of answering the questionnaire in our sample. The mean follow-up was 1,496 days (IQR: 1,398-1,616). The mean time from symptom onset to the baseline questionnaire was 82 days (IQR: 28-103). The median age at enrolment was 46 (range: 18-87, IQR: 36-55). Most participants reported combined OD and GD; see **Table 2**.

TABLE 2 Baseline characteristics.

<i>Participants</i>	
Total, N _{resp}	356
Female, n (%)	259 (73)
Response rate, N _{resp} /N _{inv} (%)	356/697 (51)
Invalid e-mail address, n	32
Age, median (IQR), yrs	46 (36-55)
Total follow-up, mean (IQR), days	1,496 (1,398-1,616)
Time from onset of CD symptoms until baseline completion, mean (IQR), days ^a	82 (28-103)
<i>Type of chemosensory dysfunction, n (%)</i>	
Combined OD and GD	320 (89.9)
Isolated OD	23 (6.5)
Isolated GD	13 (3.7)

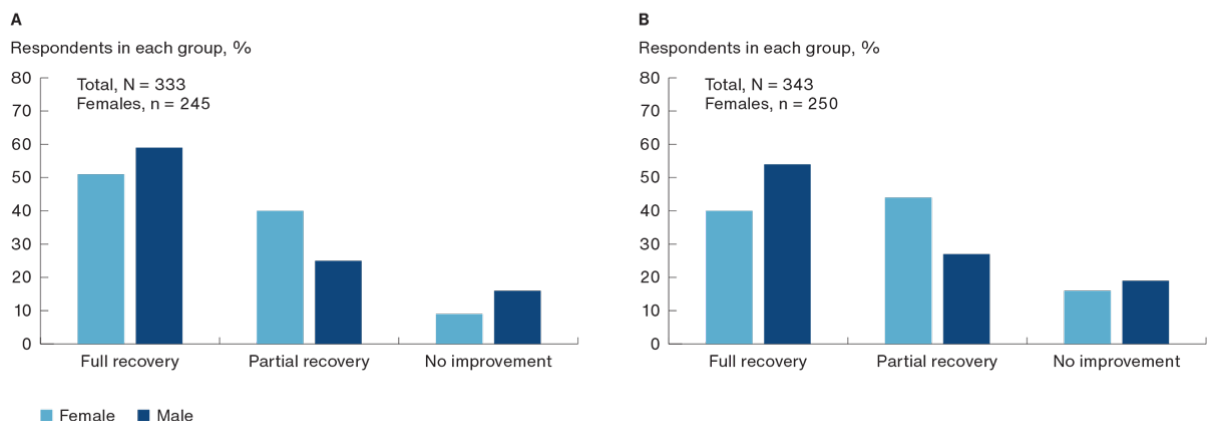
CD = chemosensory dysfunction; OD = olfactory dysfunction; GD = gustatory dysfunction

a) 8 participants reported symptom onset *after* the date of filling out the baseline questionnaire, so for the analysis of time from onset until filling out the baseline questionnaire, they were omitted.

Factors related to improvement

Male participants reported significantly higher recovery rates: 59% achieved full GD recovery, compared with 51% of females (p = 0.028). A similar pattern was observed among participants reporting OD (p = 0.013), as shown in **Figure 1**. Overall, 43% of participants reported a full recovery from CD.

FIGURE 1 Self-reported improvement of chemosensory function by sex. The distribution of respondents in each group as percentages. For gustatory dysfunction (**A**), 245 female participants reported having any degree of gustatory dysfunction at any point, and 88 male participants reported it as well, among a total of 333. For olfactory dysfunction (**B**), 250 female participants reported this symptom at any point, and 93 male participants, among a total of 343 participants. χ^2 for gustatory dysfunction = 7.1291, and χ^2 for olfactory dysfunction = 8.7578.



Secondary outcomes

Participants reporting partial recovery or no improvement (Persistent CD group) were compared with those reporting full recovery (Full recovery group). Participants with persistent CD were significantly more likely to experience all LC symptoms, except for the less frequently reported symptoms of anxiety and sore throat (ORs of

2.01 (95% CI: 0.73-6.47, $p = 0.200$) and 3.60 (95% CI: 0.57-69.71, $p = 0.246$), respectively). In the persistent CD group, self-reported fatigue (43%), problems with memory and concentration (31%), and insomnia (30%) were common. See Table 1.

In a subgroup analysis, the proportion of participants reporting persistent CD was highest in individuals aged 45-59 years (68.3%), compared with 52.4% and 49.1% in the 30-44 and ≥ 60 age groups, respectively, and lowest in the 18-29 age group (45.3%). For QoL, persistent CD was associated with feeling less active and vigorous ($p = 0.001$). A substantial proportion of participants reported feeling active and vigorous less than half the time over the 14 days preceding completion of the questionnaire. Similar trends were observed for feeling rested and restored ($p = 0.013$) and experiencing daily life as interesting ($p = 0.039$). No significant group differences were found in feeling cheerful and in good spirits or feeling calm and relaxed (see Table 3).

TABLE 3 Quality of life for participants who made a full recovery versus participants still experiencing any form of chemosensory dysfunction, partial recovery or no improvement at all. $N_{\text{tot}} = 355^a$: 151 full recovery, 204 persistent chemosensory dysfunction.

Full recovery vs persistent CD		All of the time, n (%) ^b	Most of the time, n (%) ^b	$\geq 1/2$ the time, n (%) ^b	$< 1/2$ the time, n (%) ^b	Some of the time, n (%) ^b	At no time, n (%) ^b	χ^2 (df), p value
"I have felt cheerful and in good spirits"	Full recovery	22 (14.57)	98 (64.90)	16 (10.60)	9 (5.96)	6 (3.97)	0	9.2244 (5), 0.1004
	Persistent CD	18 (8.82)	117 (57.35)	34 (16.67)	20 (9.80)	14 (6.86)	1 (0.49)	
"I have felt calm and relaxed"	Full recovery	20 (13.25)	73 (48.34)	32 (21.19)	17 (11.26)	9 (5.96)	0	7.6538 (5), 0.1764
	Persistent CD	15 (7.35)	90 (44.12)	46 (22.55)	30 (14.71)	21 (10.29)	2 (0.98)	
"I have felt active and vigorous"	Full recovery	17 (11.26)	64 (42.38)	31 (20.53)	19 (12.58)	17 (11.26)	3 (1.98)	23.296 (5), 0.0003
	Persistent CD	17 (8.33)	44 (21.57)	54 (26.47)	44 (21.57)	32 (15.69)	13 (6.37)	
"I woke up feeling fresh and rested"	Full recovery	10 (6.62)	57 (37.75)	31 (20.53)	27 (17.88)	20 (13.25)	6 (3.97)	14.489 (5), 0.0128
	Persistent CD	11 (5.39)	53 (25.98)	39 (19.12)	36 (17.65)	36 (17.65)	29 (14.22)	
"My daily life has been filled with things that interest me"	Full recovery	24 (15.89)	81 (53.64)	25 (16.56)	13 (8.61)	8 (5.30)	0	11.726 (5), 0.0387
	Persistent CD	16 (7.84)	97 (47.55)	51 (25.00)	22 (10.78)	15 (7.35)	3 (1.47)	

CD = chemosensory dysfunction; df = degrees of freedom; QoL = quality of life.

a) 1 participant (female) did not answer the QoL questions.

b) % are for full recovery and persistent CD separately.

Participants who reported testing positive for SARS-CoV-2 by PCR were compared with participants who reported no positive PCR test, including those with negative tests or no test results. Full recovery was reported significantly less often among participants with a positive PCR ($n = 221$; 36.7%) than among those with no positive PCR ($n = 135$; 52.6%) (χ^2 (df 1) = 8.704, $p = 0.003$).

Discussion

This study provides one of the longest follow-ups of CD experienced after SARS-CoV-2 infection. It indicates that a substantial proportion of individuals continue to experience persistent CD and associated LC symptoms four years after infection.

Persistent CD had a negative effect on several QoL parameters and was significantly associated with LC symptoms compared with participants who had a full recovery of CD. This is clinically important, as persistent CD remains debilitating and affects daily functioning years after infection. The implications extend beyond symptom persistence, influencing overall QoL and long-term patient well-being.

Recovery rates and risk factors

Only 152 (43%) reported full subjective recovery. Female sex was associated with lower recovery rates than male sex in this longitudinal cohort. Patients with OD showed higher recovery rates than those reported in earlier studies of this cohort. In the latest 2022 study, complete recovery rates ranged from 35% in the 18-29 age group to 50.7% in participants ≥ 60 , after a mean OD duration of 365 days [8]. In the same study, however, 40.8% of female participants reported complete OD recovery, compared with 40% in the present study. This may reflect the non-participation of recovered individuals. Relapsing OD may have occurred for some participants, which could also be an explanation. Spontaneous recovery of complete anosmia has been documented even up to 2.5

years after infection [9]. However, most recoveries occur within the first few months, with recovery rates remaining stagnant thereafter [8]. In the present study, 72% of respondents were female. This sex distribution is consistent with previous studies reporting a higher prevalence of LC and related chronic conditions among females. However, this imbalance should be considered when interpreting the findings, as it may influence the observed outcomes and limit the transferability of the results to male populations. Females have also been shown to be more likely to seek healthcare [10].

A study by Boscolo-Rizzo et al. found that 92.1% of participants reported complete CD recovery three years after symptom onset [11]. Notably, the participants in this study were exclusively mild symptomatic patients, with 267 (66.3%) of 403 respondents at baseline reporting any form of CD. This is substantially different from the present study, in which only 43% of respondents reported a full recovery from CD after four years. Another factor to consider is that greater baseline disease severity is generally a negative prognostic indicator, which complicates direct comparisons across studies [12].

Evidence regarding the association between age and recovery rates remains limited. A review suggests that older age may be associated with lower recovery rates, and older age is a known risk factor for CD, which may contribute to poorer outcomes [13, 14]. In contrast, previous studies on this cohort found no association between older age and lower recovery rates [7, 8, 15]. However, a subgroup analysis in the present study revealed that the 44-59-year age group most often reported persistent CD, with 68.3% still experiencing it to varying degrees. For comparison, only 49.1% of participants aged 60 years and older experienced persistent CD.

Participants with persistent CD reported significantly poorer outcomes on three of five QoL measures related to mental well-being (Table 3). While most studies on QoL and LC symptoms use different assessment tools, they consistently find that QoL is adversely affected when one or more LC symptoms are present [15]. The observed impact on QoL in this study and others highlights the need for further research examining the association between specific LC symptoms and QoL.

Potential treatments or preventative measures

Few treatment options have demonstrated efficacy in preventing LC, and even fewer improve LC symptoms once they appear. However, vaccination against SARS-CoV-2 has been associated with a lower risk of developing LC and with milder symptoms during and after the acute phase. A systematic review examining vaccine status and dose number found that ORs for LC slightly favoured vaccinated individuals (OR: 0.48-1.01 overall) [16]. The same review included studies that examined vaccination after infection, with reduced odds in the vaccinated group (OR: 0.38-0.91).

Prior studies have shown that adherence to olfactory training (OT) can improve olfactory test scores in post-COVID-19 olfactory loss. In one study, 57% of participants who adhered to OT showed improvement, compared with 22% of those who did not [17]. As reduced enjoyment of food is generally the most common complaint in patients with OD, the negative consequences of OD can also be reduced by multisensory culinary guidance for patients [18].

Other treatment options, including nasal and oral steroids, as well as various medications and interventions, have shown inconsistent efficacy in alleviating LC symptoms [19]. Further research is necessary to optimise the treatment of persistent symptoms.

Limitations

Self-selection bias may have influenced the results, as participants experiencing persistent or severe symptoms were likely more motivated to participate at both baseline and follow-up. Conversely, non-responders may have recovered fully and felt less inclined to engage, potentially causing an overestimation of persistent CD. However,

if it were hypothesised that all 334 non-responders had fully recovered, the CD non-recovery rate in the baseline cohort would still be 29.3%.

Not all participants had reverse transcription-PCR-confirmed SARS-CoV-2 infection, as CD symptoms in the early pandemic did not qualify for PCR testing in Denmark. We compared participants with PCR-confirmed COVID-19 (62%) with those without (38%) and found that those with PCR-confirmed COVID-19 had even lower recovery rates. This highlights the high occurrence of CD as part of LC syndrome.

This study relied entirely on self-reported data, with no psychophysical measurement of olfactory or gustatory function. This introduces uncertainty, as subjective olfactory loss may not align with objective testing, and reported taste loss may reflect impaired flavour perception rather than true GD. Validated methods, such as taste strips and “Sniffin’ Sticks”, would offer a more comprehensive evaluation. The present result reflects subjective complaints but does not quantify or validate them. However, these results and their impact on QoL may influence healthcare-seeking behaviour [6, 10], making them relevant to both patients and healthcare professionals.

Recall bias is another limitation of retrospective surveys, potentially affecting participants’ recollection of symptom onset, duration and severity. However, the baseline questionnaire was administered shortly after symptom debut, likely minimising this effect.

Overall, this study highlights the prolonged impact of CD in a subset of COVID-19 patients, emphasising the need for further research and targeted interventions. Importantly, those affected continue to report persistent CD, which negatively affects their QoL.

Conclusions

This study demonstrates that a substantial proportion of individuals continue to experience persistent CD and associated LC symptoms four years after infection. Furthermore, QoL measures of mental well-being were shown to be negatively affected for these individuals. However, limitations such as a lack of psychophysical testing and potential responder bias should be considered when interpreting the findings. The findings highlight the need for further research and continued clinical support for affected individuals.

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