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Prevalence of olfactory dysfunction and quality of life in hospitalised patients one year after SARS-CoV-2 infection: a cohort study

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ABSTRACT

Objectives: To determine long-term prevalence of olfactory and gustatory dysfunction (OD ± GD) in previously hospitalised COVID-19 patients, associated risk factors and impact on quality of life (QoL).

Design: A single-centre cohort study.

Setting: Patients admitted at a large central London hospital with COVID-19 infection between February 10 and May 22, 2020.

Participants: 150 adult subjects with previously confirmed SARS-CoV-2 infection were recruited between December 10, 2020 and January 29, 2021. Participants were predominantly male (102/150, 68.0%); mean age 58.0 ± 15.9 years, and 41.2% (56/136) were of black and minority ethnic backgrounds.

Main outcome measures: EQ-5D-5L values and Sino-Nasal Outcome Test-22 (SNOT-22) scores.

Results: Long-term prevalence of OD ± GD was 12.8% (19/149) at median time of 264.5 days following SARS-CoV-2 infection onset. Patients with OD ± GD had a significantly higher median total SNOT-22 score (46.1; Q1-Q3: 23.0 - 60.0; CI: 23.0 to 60.0) compared to those without (16.0; Q1-Q3: 5.0 - 30.5; CI: 12.0 to 18.0) (p=0.0002), reflecting poorer QoL, particularly psychological well-being (p=0.0004), which was not alleviated with time (p=0.4977). Median EQ-5D-5L value was not significantly different between patients with OD ± GD (0.70; Q1-Q3: 0.38 - 0.83; CI: 0.38 to 0.83) and those without (0.83; Q1-Q3: 0.61 - 0.94; CI: 0.75 to 0.89) (p=0.0627). Age, sex, ethnicity, smoking status, highest C-reactive protein value, intubation and ventilation, and oxygen supplementation were not found to influence OD ± GD (p>0.05).

Conclusions: 12.8% of previously hospitalised COVID-19 patients in London still report persistent problems with smell or taste up to a year after infection, impacting their QoL. Increased holistic support including psychological therapy for affected patients may help to reduce long-term morbidity.

Strengths and limitations of this study

- To our knowledge, this is the first study to have determined the long-term prevalence of OD ± GD in a cohort of previously hospitalised COVID-19 patients at one year following infection.
- The use of validated measures allows us to conclude that persistent OD ± GD, as a key manifestation of long-COVID, is associated with significant reductions in patient QoL and well-being.
- Prevalence of OD ± GD in this study is based on previously hospitalised COVID-19 patients and may not represent that of mild-to-moderate COVID-19 subjects in the general community, although this allows for important comparisons between different populations.
- The subjective, self-reported questionnaires used have a low correlation with psychophysical measurements but given that psychophysical testing has not been available or feasible in many countries during the pandemic, self-reported scores remain of value.

INTRODUCTION

With over 176 million cases and 3.8 million deaths recorded worldwide so far,[1] the coronavirus disease 2019 (COVID-19) pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is an ongoing global crisis. COVID-19 presentation is highly varied. An estimated 17% to 20% of those infected remain asymptomatic,[2,3] whilst others can develop a mild-to-moderate disease or severe pneumonia.[4]

According to the World Health Organization (WHO), 'loss of smell or taste' is considered a less common symptom of COVID-19. However, findings from many studies conducted worldwide have strongly contradicted this, with several reports depicting high prevalence of olfactory and/or gustatory dysfunction (OD ± GD) amongst infected subjects.[5–10] So far, the long-term prevalence of OD ± GD is unknown, and values determined from the large proportion of studies conducted during the earlier months of the pandemic poorly reflect its persistence and the current proportion of those still affected. Prevalence of OD and GD also vary depending on studied populations, between 70.2% and 54.2% of the general population with mild-to-moderate symptoms (mean 11.5 ± 5.7 days),[11] 73.1% and 69.2% in mild-to-moderate symptomatic healthcare workers (median follow up of 52 days),[9] and 5.1% and 5.6% in acutely hospitalised patients.[12] There also remains conflicting data surrounding associated risk factors. Pre-COVID-19 data show that OD is associated with increased morbidity and mortality,[13–15] and population studies have shown that anosmia is an independent risk factor for a shortened life span.[16-20] In a study of over 3000 adults, olfactory function was reported to be one of the strongest independent predictors of 5-year mortality, surpassing heart failure, lung disease and even cancer.[21] COVID-19-related OD presentation has been extensively investigated, but its impact on quality of life (QoL) in the context of COVID-19 has not been fully explored. Therefore, this represents a key area which needs to be addressed to more effectively reduce long-term morbidity.

We conducted a cohort study on previously hospitalised COVID-19 patients admitted at a central London hospital during the first pandemic wave, to determine the long-term prevalence of OD ± GD, potential risk factors and impact on QoL.

METHODS

A cohort study of previously hospitalised COVID-19 patients was performed between December 10, 2020 and January 29, 2021 at the National Hospital for Neurology and Neurosurgery (*London, UK*).

Study population

358 patients hospitalised at University College London Hospital (UCLH) with a COVID-19 diagnosis between February 10 and May 22, 2020 were identified as potentially eligible for this study. Ethical approval was given by the Research Ethics Committee and the UCL Joint Research Office (REC reference: 14/SC/1180; IRAS project ID: 156511). Sample size was determined pragmatically based on data available within the medical database at the time of collection. Electronic medical records and laboratory findings were reviewed to verify full adherence to the following inclusion criteria: (a) adults ≥18 years of age, and either (b) laboratory-confirmed SARS-CoV-2 infection, defined as a positive result on reverse transcription polymerase chain reaction analysis of nasopharyngeal swab specimens, or (c) clinically-confirmed COVID-19 on the basis of presenting symptoms, in accordance with WHO interim guidance at the time.[22] Considering the lack of widespread testing in the UK during this studied period of the pandemic, both laboratory and clinical diagnostic criteria were initially included to prevent inadvertent exclusion of eligible participants. Prior to commencement of the study, demographic data including age, sex, ethnicity and smoking status were noted to facilitate investigation into any potential associations. Baseline characteristics and medical status were also recorded to identify ineligible patients (death or patient age <18 years).

Outcomes

Eligible subjects were invited to undertake telephone interviews involving a series of standardised questions from validated questionnaires: the EQ-5D-5L[23] and the Sino-Nasal Outcome Test-22 (SNOT-22). Patients reporting decreased sense of smell/taste in the SNOT-22 were subsequently

followed up with an additional smell and taste questionnaire (supplementary figure 1) designed to capture specific details relating to the type(s) of chemosensory dysfunction experienced. All telephone interviews were conducted in English by the same researcher following a standardised procedure in an effort to minimise inter-observer bias. Verbal informed consent was obtained from all participants prior to enrolment in the study.

Statistical analysis

All statistical analyses were performed using GraphPad Prism version 9.0.1 for macOS (GraphPad Software, San Diego, California USA). Qualitative variables were presented as frequency and percentages; quantitative variables were summarised as median and interquartile range (IQR) or mean ± standard deviation (SD) for normally distributed data. Non-parametric variables were compared using the Mann-Whitney test; data following Gaussian distribution were analysed using the unpaired t-test, with Welch's correction applied to adjust for unequal SDs and variances. Fisher's exact test was used to compare associations between variables in patients with OD ± GD and patients without OD or GD. Linear regression analysis was performed to explore whether SNOT-22 scores changed over time. 95% confidence intervals (CI) were provided for the reported data where appropriate, and the level of statistical significance was set at a 2-sided p value of <0.05.

Patient and public involvement

No patients or members of the public were involved in setting the research question or the outcome measures. They were not involved in the study design or conduct, nor were they invited to contribute to the writing, interpretation, reporting or distribution of the results.

RESULTS

358 patients previously hospitalised with a COVID-19 diagnosis were identified as potentially eligible for this study. Figure 1 outlines the selection process. Following screening of electronic medical records for all 358 patients, 156 were subsequently excluded from the study. Of the 202 contacted patients, 51 were excluded in line with the additional exclusion criteria applied. This included unreachable patients (n=13), defined as those unable to be contacted despite >3 separate attempts (n=5) and those with invalid contact details (n=8). Patients with communication difficulties (n=3) referring to aphonic individuals (n=2) or patients with hearing impairments (n=1) preventing completion of the questionnaires. Responses were received from 151/202 invited participants, thereby resulting in a response rate of 74.8%. One patient who did not provide any answers to the SNOT-22 was excluded.

Demographics and characteristics

A final population of 150 subjects (102 male and 48 female, male:female ratio of approximately 2:1) was obtained. Median time from infection was 264.5 days (range 215 - 318). Detailed demographics and baseline characteristics of the population are summarised in Table 1.

Table 1. Detailed characteristics of the population.

	Total population (n = 150)	Patients without OD or GD (n = 129)	Patients with OD ± GD (n = 19)	P value
Age, (mean ± SD), years	58.0 ± 15.9	57.8 ± 16.4	59.6 ± 11.8	0.5773
Age groups, n (%)				
18 – 30	5 (3.3)	5 (3.9)	0 (0)	
31 – 40	20 (13.3)	18 (14.0)	2 (10.5)	
41 – 50	25 (16.7)	21 (16.3)	3 (15.8)	
51 – 60	23 (15.3)	21 (16.3)	2 (10.5)	
61 – 70	48 (32.0)	37 (28.7)	11 (57.9)	
71 – 80	15 (10.0)	14 (10.9)	0 (0)	
81 – 90	12 (8.0)	11 (8.5)	1 (5.3)	
> 90	2 (1.3)	2 (1.6)	0 (0)	
Sex, n (%)				
Male	102 (68.0)	90 (69.8)	11 (57.9)	0.3032
Female	48 (32.0)	39 (30.2)	8 (42.1)	
Ethnicity, n (%)[a]				
White	80 (58.8)	68 (58.6)	11 (61.1)	
BAME	56 (41.2)	48 (41.4)	7 (38.9)	>0.9999
Missing	14	13	1	
Smoking status, n (%)[a]				
Never smoked	72 (65.5)	64 (66.7)	7 (53.8)	
Have smoked	38 (34.5)	32 (33.3)	6 (46.2)	
Current	10 (9.1)	9 (9.4)	1 (7.7)	0.3699
Quit	28 (25.5)	23 (24.0)	5 (38.5)	
Missing	40	33	6	
Highest CRP value (mean ± SD), mg/L	170.9 ± 135.6	174.5 ± 139.5	158.0 ± 109.5	0.9282
Intubation and ventilation, n (%)[a]				
No	52 (57.8)	44 (55.7)	6 (66.7)	
Yes	38 (42.2)	35 (44.3)	3 (33.3)	0.7263
Missing	60	50	10	
Oxygen supplementation, n (%)[a]				
No	20 (17.2)	18 (17.8)	1 (7.1)	0.4599
Yes	96 (82.8)	83 (82.2)	13 (92.9)	
Missing	34	28	5	

[a] Missing data have been reported but were not used in the calculation of percentages (valid percent).

Percentages may not total 100.0% due to rounding.

CRP: C-reactive protein; BAME: Black, Asian and Minority Ethnic.

SNOT-22

150 patients completed the SNOT-22 and the median total score for the whole population was 17.0 (Q1-Q3: 6.0 - 36.3; CI: 13.0 to 22.0). As depicted in Figure 2, the five most prevalent SNOT-22 problems were: *wake up tired* (101/149, 67.8%), *fatigue* (97/147, 66.0%), *lack of a good night's sleep* (98/149, 65.8%), *reduced productivity* (97/148, 65.5%) and *wake up at night* (94/149, 63.1%). *Wake*

up tired, fatigue and *lack of a good night's sleep* were also among the problems most frequently reported to affect patient health the most (Figure 3). 14.1% (21/149) of patients reported to have decreased sense of smell/taste in the SNOT-22 (score ≥1 at the corresponding item), although two individuals were classed as pre-existing OD ± GD based on evidence of iatrogenic causes and age-related olfactory loss predating COVID-19 infection and hospitalisation. This led to a total of 19/149 patients (12.8%) with reported decreased smell/taste in the context of COVID-19. Characteristics of OD and GD are reported in Table 2.

Table 2. Prevalence and characteristics of olfactory and gustatory disorders.

	Total responses (n = 149)
Prevalence, n (%)	
Total reporting decreased smell/taste	21 (14.1)
In the context of COVID-19	19 (12.8)
Pre-existing	2 (1.3)
No OD or GD	128 (85.9)
	Analysed population with OD ± GD (n = 19)[a]
Type of dysfunction reported, n (%)	
OD and GD	15 (78.9)
Only OD	4 (21.1)
Only GD	0 (0)
Parosmia[b]	3 (16.7)
Parageusia[b]	5 (27.8)
Phantosmia[b]	2 (11.1)
Phantogeusia[b]	0 (0)
OD ± GD characteristics, n (%)	
Constant[b]	14 (77.8)
Fluctuant[b]	4 (22.2)
Isolated OD[b,c]	1 (5.3)
Isolated GD[b,c]	0 (0)
Treatment, n (%)[b]	
Have not sought treatment	16 (88.9)
Have sought treatment	2 (11.1)

[a] Analyses performed on population following application of exclusion criteria (excludes pre-existing OD ± GD).
[b] Valid percentages calculated based on subjects who provided responses to the question (n = 18).
Missing responses were not included in the calculations.
[c] 'Isolated' OD or GD defined as decreased sense of smell/taste in the absence of any other SNOT-22 problem.

Patients with OD ± GD demonstrated a statistically significant higher median total SNOT-22 score (46.1; Q1-Q3: 23.0 - 60.0; CI: 23.0 to 60.0) than those without (16.0; Q1-Q3: 5.0 - 30.5; CI: 12.0 to 18.0) (p=0.0002), and their scores were higher across all SNOT-22 domains[24] except one (extranasal rhinologic symptoms) (Table 3). Total SNOT-22 scores were found to improve over time in patients without OD or GD (p=0.0327), although this was not observed in patients with OD ± GD (p=0.4977) (Figure 4). Comparisons of the demographics of the two subgroups found no influence of age, sex, ethnicity or smoking status (have smoked versus never smoked) on the development of OD ± GD (p > 0.05) (Table 1). Similarly, no statistically significant association was observed between OD ± GD and other characteristics recorded during hospitalisation, such as highest C-reactive protein (CRP) value, requirement for intubation and ventilation, or oxygen supplementation (p = 0.9282, 0.7263 and 0.4599, respectively).

Table 3. Subgroup differences in median total SNOT-22 score for each domain.

Domain	Median total SNOT-22 score		
	Patients without OD or GD (n = 129)	Patients with OD ± GD (n = 19)	P value
Rhinologic symptoms	2.0	6.0	***0.0189****
Extranasal rhinologic symptoms	0	1.0	0.0524
Ear/facial symptoms	1.0	3.75	***0.0087****
Psychological dysfunction	7.0	22.0	***0.0004*****
Sleep dysfunction	7.0	16.0	***0.0024****

Significant p values in bold. Level of significance *p < 0.05, **p < 0.01, ***p < 0.001

EQ-5D-5L

149 patients completed the EQ-5D-5L and the median value for the total population was 0.80 (Q1-Q3: 0.53 - 0.94; CI: 0.73 to 0.86). Patients with OD ± GD had a lower median EQ-5D-5L value (0.70; Q1-Q3: 0.38 - 0.83; CI: 0.38 to 0.83) compared to those without OD or GD (0.83; Q1-Q3: 0.61 - 0.94; CI: 0.75 to 0.89); however, the difference was not statistically significant (p=0.0627). Time from infection

(the number of days between the date of the patient's first COVID-19 positive swab or their onset of COVID-19 symptoms, and the date at which the questionnaire was administered) was not found to be correlated to EQ-5D-5L value in both patients with OD ± GD (p=0.8693) and those without (p=0.5371) (Figure 5).

DISCUSSION

This is the first study to evaluate the long-term prevalence of OD ± GD in a group of previously hospitalised COVID-19 patients.

The prevalence of OD ± GD in our studied population was 12.8%. This is considerably lower than that of surveys conducted in hospitalised patients in Europe (35.0% to 80.6% for OD and 21.0% to 90.3% for GD within 1 month),[25–27] and in other countries such as Turkey (42.3% for OD ± GD),[28] and Brazil (64.6% and 66.7% for OD and GD, respectively, at follow up of 15-55 days).[29] The longer follow-up at which our study has been conducted could explain the lower rate of observed chemosensory alteration in our population, whereby recovery of OD/GD is expected to happen over time in some patients. This is supported by a recent French study which found that 24.0% of non-severe COVID-19 subjects reported persistent OD/GD 7 months after symptom onset.[30]

Interestingly, our prevalence of 12.8% is similar to that observed by Lee et al.[31] (15.3%) in a large Korean cohort of 3191 patients with varying COVID-19 severity at 1 month, but it is relatively higher than that observed by Mao et al.[12] in a population of 214 acutely hospitalised COVID-19 patients (5.1% and 5.6% with OD and GD, respectively). A selection bias could potentially explain our lower prevalence. Most surveys investigating OD/GD in COVID-19 subjects have been conducted on patients with mild-to-moderate symptoms.[5,11,32–34] In this regard, higher prevalence of anosmia has been noted in milder individuals, along with a significantly increased risk of self-reported olfactory loss in outpatients compared to hospitalised patients.[35] This is reflected in the most recent studies on long-term COVID-19-related OD ± GD. In one study, 48.0% and 38.5% of non-hospitalised COVID-19 subjects reported persistent OD and GD, respectively, at 8 months follow up.[36] Similarly, 21.3% of subjects reported OD ± GD in another study of mild-to-moderate symptomatic patients at one-year.[37] These values were notably higher than our described prevalence despite the longer follow up times, thus suggesting that selection bias may produce the observed disparities in reported long-term OD ± GD prevalence.

In our population, OD was associated with GD in most of the cases (78.9%), while none of the subjects reported GD only. This reflects what has extensively been reported in previous studies[8,30,38,39] and confirms that GD is usually linked to an impairment of retronasal olfaction rather than impairment of gustation itself. Nonetheless, although less common, isolated GD has been described in COVID-19 patients.[40]

Despite the extensive literature available on quantitative changes in smell and taste, qualitative alterations of smell and taste in COVID-19 have been seldom explored. In our study, 16.7% of patients had parosmia (distortions in smell) while 27.8% had parageusia (distortions in taste). A similar prevalence (15.0%) of parosmia was reported by Gorzkowski et al.[41] although a higher rate of 32.4% was previously described by Lechien et al.[5] Prevalence of COVID-19-related parageusia vary widely in the literature, but a recent meta-analysis of 8438 COVID-19 patients from 13 countries revealed a pooled prevalence of 38.2% (95% CI: 24.0% to 53.6%),[42] which is higher than that observed in our study. The differences observed between studies could partly reflect inherent biases in the composition of sampled populations. Additionally, a cultural variability in taste appreciation or perception has been reported to exist in COVID-19 positive subjects with a different cultural background.[43] Phantosmia (the detections of smells not present within the environment) was reported in 11.1% of our study participants. A similar prevalence was reported by Lechien et al.[5] and Gorzkowski et al.[41] No cases of phantogeusia (abnormal taste in the mouth in the absence of any stimulus) were recorded in our population and based on the current published literature, prevalence of phantogeusia in COVID-19 subjects is unknown. In line with previous findings,[5,41] most of our participants (77.8%) reported constant OD ± GD, suggesting that the driving mechanism leading to persistent chemosensory dysfunction is sensorineural.

No statistically significant association between persistent OD ± GD and age, smoking status, highest CRP value, intubation and ventilation, or oxygen supplementation was found in our study, thus corroborating results from multiple studies.[29,30,32,41,44–48] Similarly, sex did not demonstrate any

influence on the prevalence of persistent OD ± GD in our study, which is in line with previous studies conducted worldwide.[7,32,41,45,49,50] Nonetheless, several authors have observed a significantly higher prevalence of OD ± GD in women,[5,31,44,51] with some reports suggesting that being female is a risk factor for prolonged recovery from chemosensory dysfunction.[26,29,46] However, the female predominance observed from such studies may be attributed to the differences in the sampled populations (hospitalised versus mild-to-moderate) or in the gender composition. In fact, previous studies on COVID-19 hospitalised patients have demonstrated a lower prevalence of female patients,[52] which is confirmed by the male:female ratio in our population (2:1). Moreover, women tend to outperform men on olfactory assessment and in their capacity to perceive OD, which could lead to disproportionately increased prevalence seen in females.[53,54]

Our study included a more ethnically diverse population in comparison to more geographically limited studies conducted on cohorts of the same ethnic background. Despite this, we found no statistically significant association between ethnicity and OD ± GD, in contrast to what was reported by Doty[55] before the pandemic that ethnic minorities are more at risk of developing chemosensory dysfunction.

Patients with OD ± GD had a significantly higher median total SNOT-22 score than those without, with the score only improving over time for the latter subgroup. This corresponds to a greater health burden and subsequent poorer QoL among those affected with chemosensory impairments, as exemplified in a recent study by Chary et al.[44] More importantly, it reflects the ongoing health burden in patients with OD ± GD, which has previously been depicted to a similar effect.[49] Analysis of the SNOT-22 items demonstrated intrinsic psychological and sleep dysfunction in our population, where the items *wake up tired*, *fatigue*, and *lack of a good night's sleep* were three of the most commonly ticked "important items" (maximum of five items). While this highlights some of the long-term manifestations of COVID-19, now called 'long-COVID',[8,56] further sub-analysis revealed that OD ± GD significantly reduced QoL in nearly all domains, especially that of psychological

dysfunction, when compared to patients without OD or GD. Recent studies have supported this, with emphasis on both the direct and indirect negative effects of COVID-19-related OD on psychological well-being. In one study, 15.8% of COVID-19 patients with OD reported depression due to their smell loss,[57] whereas in a separate study, 28.2% had increased anger as a secondary effect.[58] Long-lasting fatigue has also been found to be significantly associated with persistent OD ± GD.[33] Taken together, our findings therefore highlight the negative long-term effects of persistent OD ± GD on QoL.

Conversely, based on subgroup analysis of EQ-5D-5L values, we did not observe any difference in health-related QoL between those with OD ± GD and those without. More importantly, EQ-5D-5L value did not improve with time and was not influenced by the presence of a chemosensory alteration. These results are likely due to interpatient variability. Given that the EQ-5D-5L is nonspecific to COVID-19 and captures responses based on overall QoL on the day of questioning, patients' responses could have been influenced by other factors.

Strengths and limitations

To our knowledge, this represents the first study to have determined the prevalence of OD ± GD in a cohort of previously hospitalised COVID-19 patients at one year following infection. We have therefore provided a more current insight into both the persistence and the scale of OD and GD from a long-term perspective, and the impact on patients' QoL and well-being. Our cohort of previously hospitalised COVID-19 patients also adds value by highlighting differences in OD ± GD prevalence in different populations, given that current existing studies have predominantly been based on mild-to-moderately affected patients or healthcare workers.

The prevalence of OD and GD observed in our study refers to a population of previously hospitalised COVID-19 patients and thus, these may not be directly comparable with those reported for mild-to-moderate symptomatic COVID-19 subjects in the general community. As in other COVID-

19 studies, patients with OD ± GD were identified through subjective, self-reported questionnaires which have a low correlation with psychophysical measurements. However, during the pandemic, psychophysical tests have not been available or feasible in many countries. We therefore believe that, in an emergency condition, self-rated symptoms nonetheless remain of value.

Clinical implications of this study

A proportion of previously hospitalised COVID-19 patients continue to experience persistent OD ± GD. With over 4.5 million COVID-19 positive cases in the UK at the time of writing,[59] and with numbers likely to increase including untested asymptomatic individuals and those with milder disease, our study demonstrates the relevance of OD ± GD and its place as a key manifestation of long-COVID. OD ± GD has significant impact on QoL, and potentially substantial long-term burden on patients and healthcare resources.

Our study suggests that persistent COVID-19-related chemosensory dysfunction requires increased holistic support: psychological therapy, coping strategies, patient support groups and smell training to aid patients in the management of their OD ± GD.

Conclusions

12.8% of previously hospitalised COVID-19 patients in London reported persistent chemosensory dysfunction, up to a year following infection. COVID-19-related OD ± GD significantly reduces both QoL and psychological well-being, and this does not improve over time, creating an important health burden. With the number of patients seeking treatment expected to rise, developing new therapeutic treatments will be important in the future, as well as providing adequate patient support for now.

Footnotes

Contributors: DC and HQMT conceptualised and designed the study. HQMT and ALP drafted the manuscript. HQMT performed data acquisition, statistical analyses and production of figures and tables. All authors (HQMT, ALP, PJA and DC) contributed to the interpretation of the results and critically revised the manuscript. All authors approved the final manuscript. The corresponding author (HQMT) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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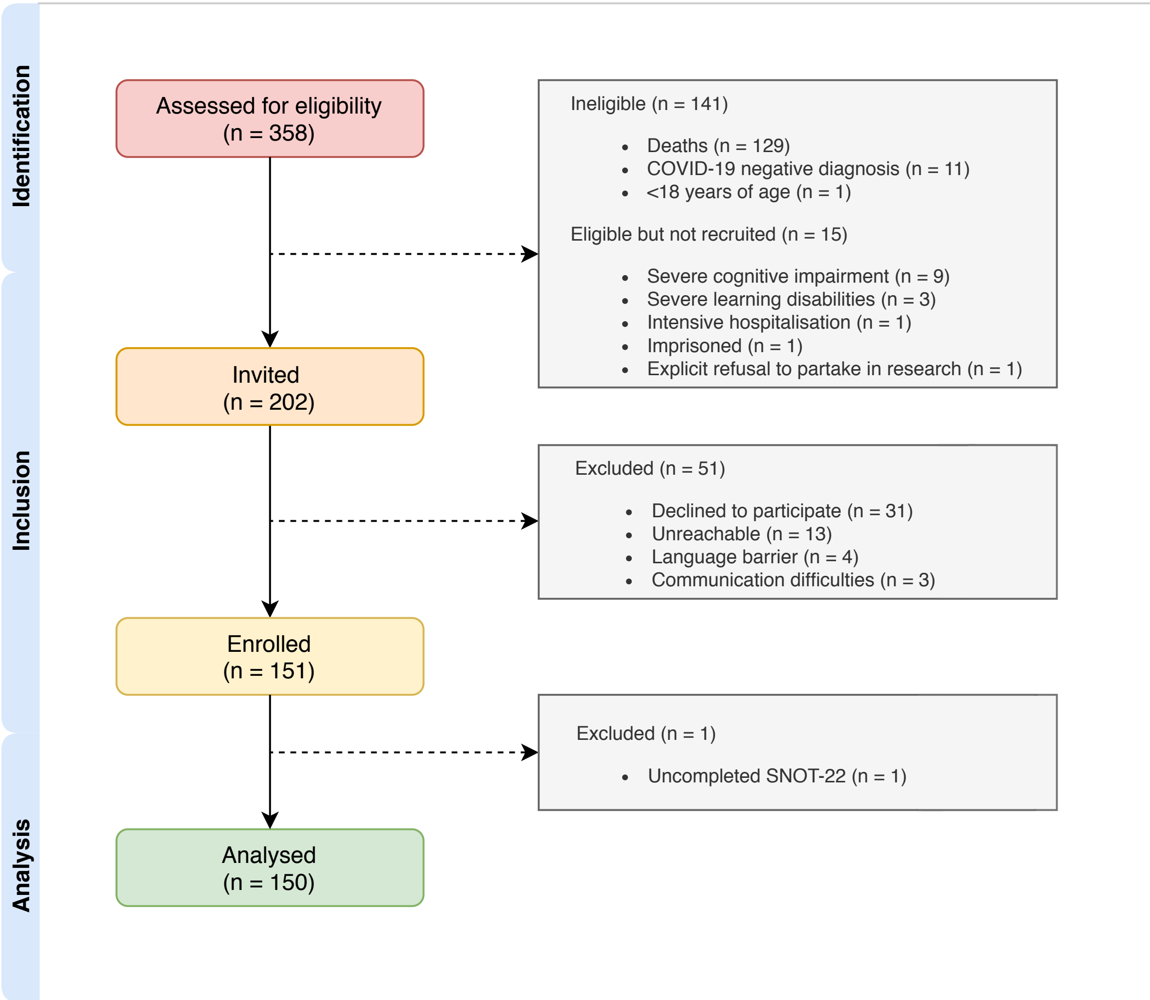

Figure 1. Flowchart depicting stages of patient identification, inclusion and analysis.

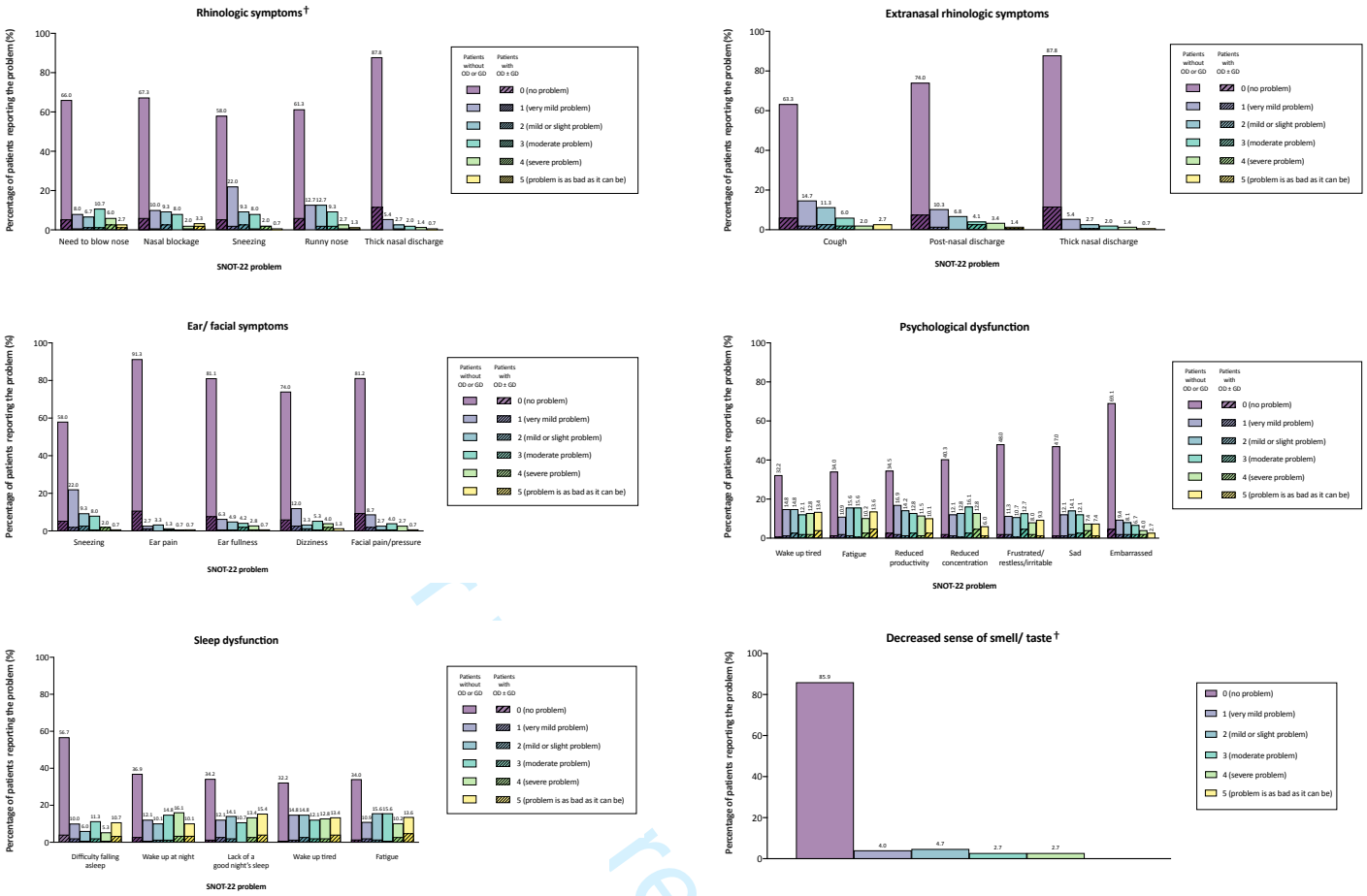

Figure 2. Prevalence of SNOT-22 problems stratified by severity and categorised by domain.

† The item 'decreased sense of smell/taste' was excluded from the rhinologic symptoms domain and presented separately, given OD ± GD status was used as a subgroup in the sub-analysis.

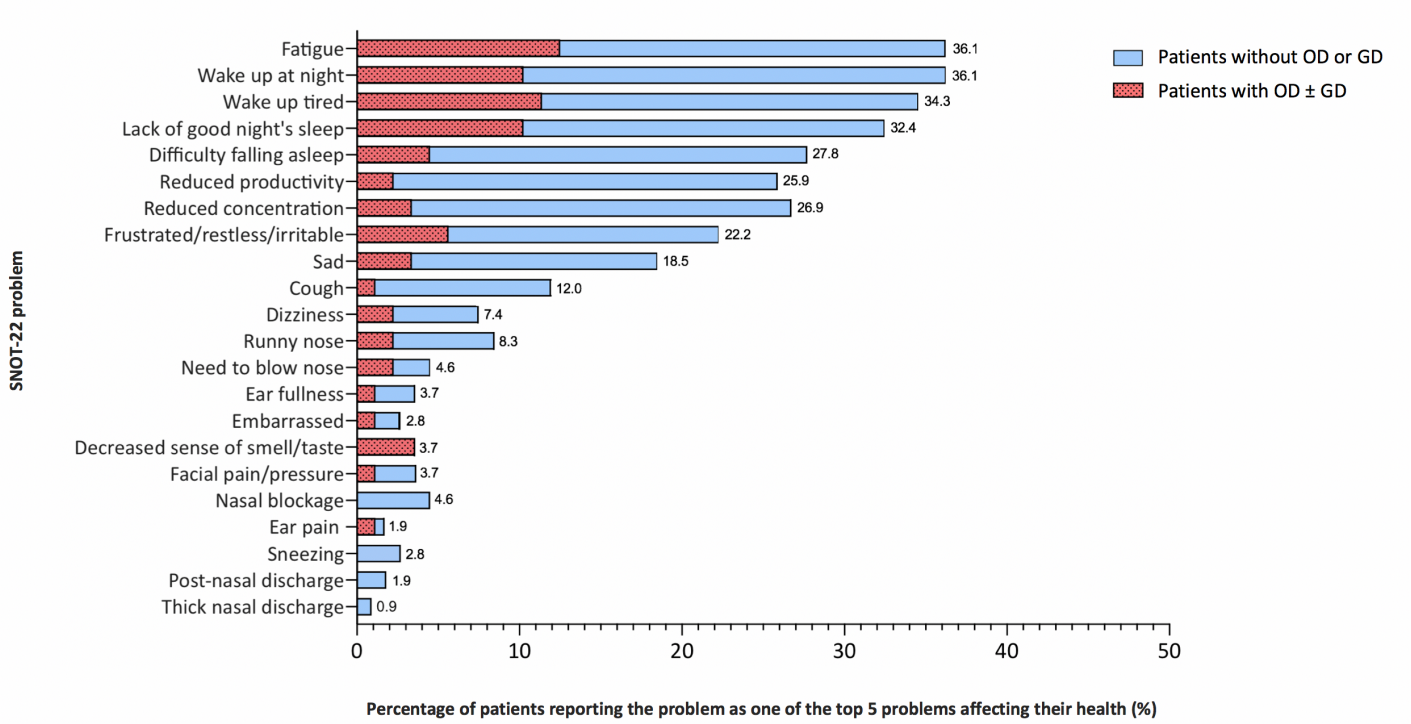

Figure 3. SNOT-22 problems reported to most greatly affect patient health.

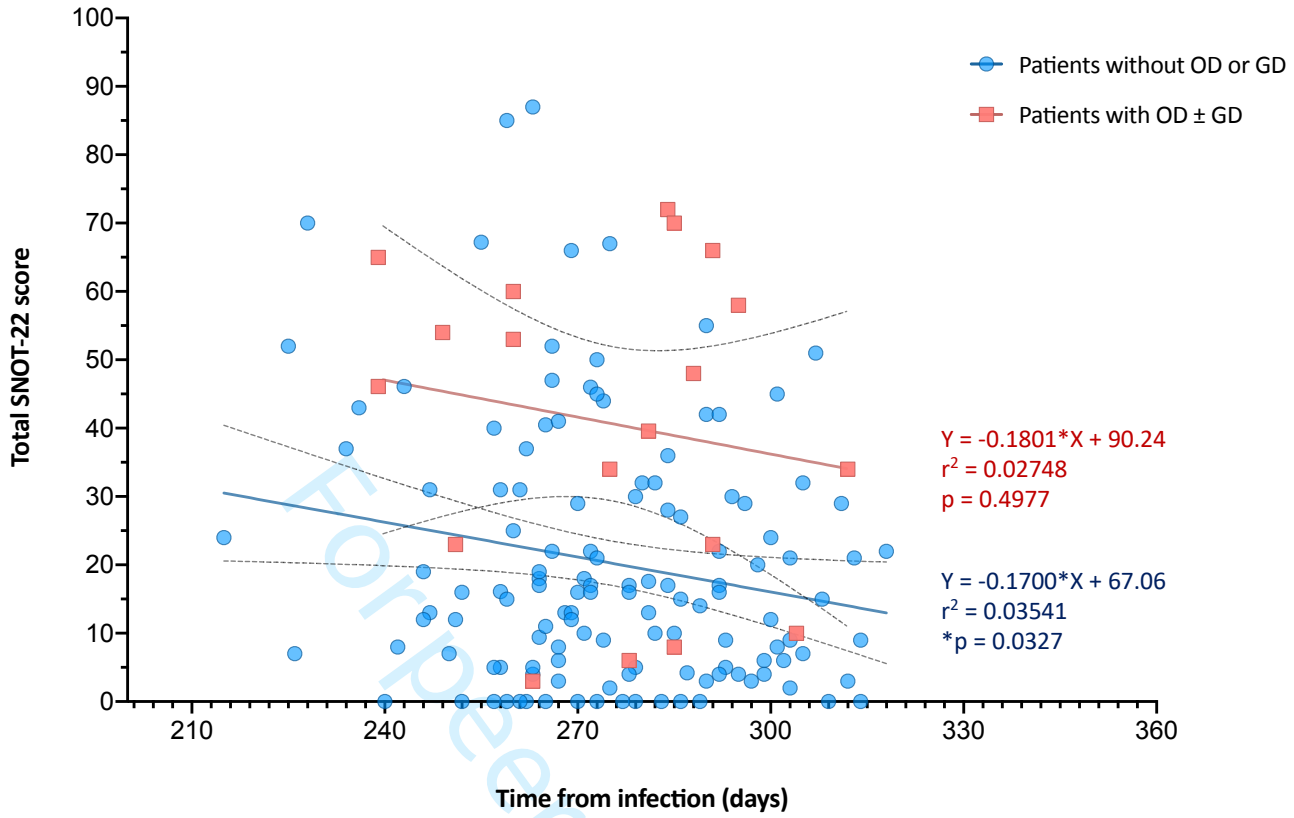

Figure 4. Linear regression analysis of subgroup changes in total SNOT-22 scores over time. Dashed lines denote 95% CI. *Significant p values. Level of significance $p < 0.05$

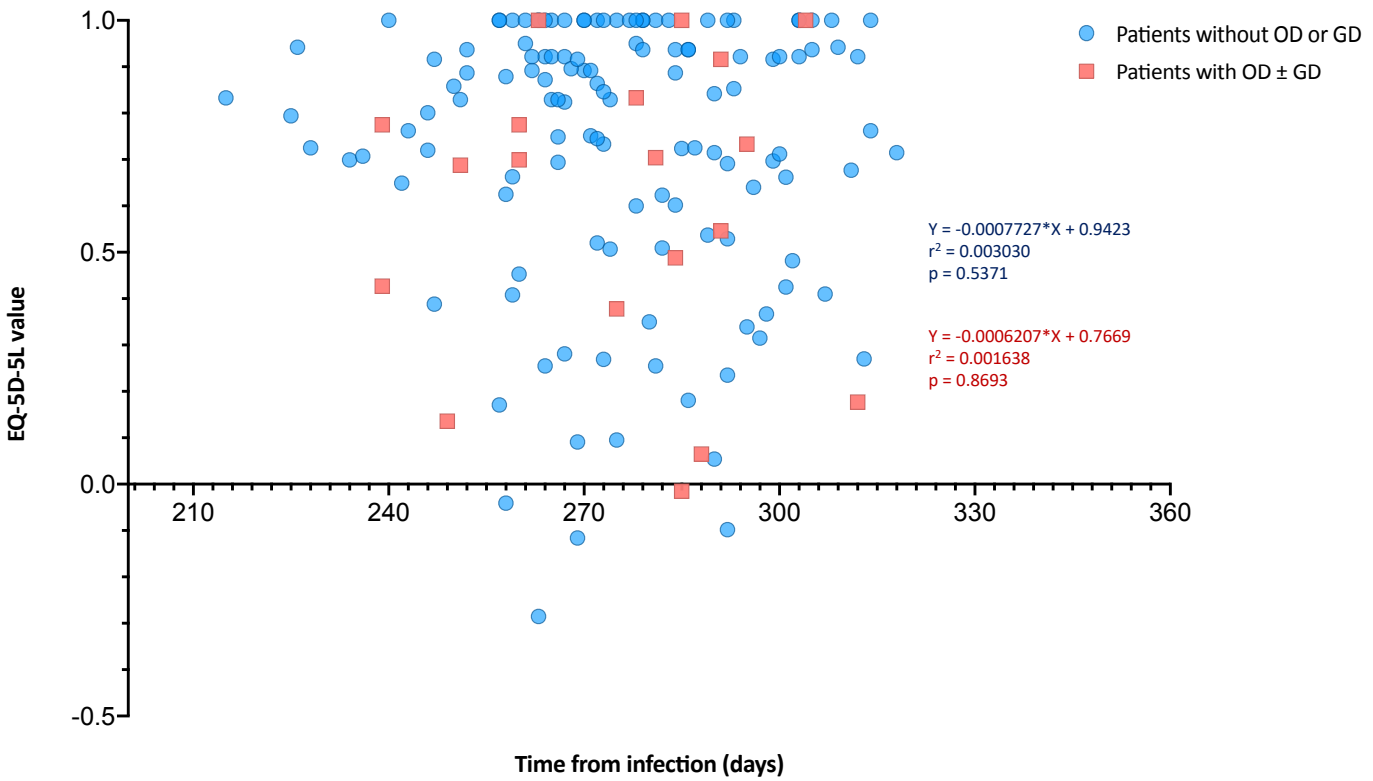

Figure 5. Linear regression analysis of EQ-5D-5L value and time from infection in patients with OD ± GD and patients without OD or GD.

ADDITIONAL SMELL AND TASTE QUESTIONNAIRE Patient study number: _____

For patients reporting decreased sense of smell/taste (in the SNOT-22):

1. Is the problem: decreased sense of smell, decreased taste or both?
   ☐ Smell ☐ Taste ☐ Both

2. How did you first notice you had decreased smell/taste?

3. When did you first notice you had decreased smell/taste?

4. What did you notice about your loss of smell/taste when it was at its worst?

5. What do you notice about your loss of smell/taste now?

6. Is your loss of smell/taste always there or does it come and go?
   ☐ Always there ☐ Comes and goes

7. Have you sought treatment for your smell/taste loss?
   ☐ Yes ☐ No

   a. How long did you wait before seeking treatment?

   b. What treatment(s) did you try?

   c. Has the treatment helped?
      ☐ Yes ☐ No

8. Over the past 2 weeks, have you noticed some things smell/taste different or unpleasant from what they usually smell/taste like? (parosmia/parageusia)

☐ Yes ☐ No

a. Could you please describe how things have smelled/tasted different or unpleasant?

9. Over the past 2 weeks, have you smelled/tasted things when nothing is there? (phantosmia/ phantogeusia)

☐ Yes ☐ No

a. Could you please explain a bit more about this problem?

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	9, 10
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, 10
		(b) Indicate number of participants with missing data for each variable of interest	10, 11
Outcome data	15*	Report numbers of outcome events or summary measures	12, 13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	10, 12
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12, 13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-17
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	17, 18
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-18
Generalisability	21	Discuss the generalisability (external validity) of the study results	17
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	19

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

N/A = Not Applicable

BMJ Open

Prevalence of olfactory dysfunction and quality of life in hospitalised patients one year after SARS-CoV-2 infection: a cohort study

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2021-054598.R1
Article Type:	Original research
Date Submitted by the Author:	10-Nov-2021
Complete List of Authors:	Tan, Hui Qi (Mandy); UCL Medical School; National Hospital for Neurology and Neurosurgery, Department of Neurosurgery Pendolino, Alfonso Luca; Royal National ENT & Eastman Dental Hospitals, Department of Ear, Nose and Throat; UCL Ear Institute Andrews, Peter; Royal National ENT & Eastman Dental Hospitals, Department of Ear, Nose and Throat; UCL Ear Institute Choi, David; National Hospital for Neurology and Neurosurgery, Department of Neurosurgery
Primary Subject Heading:	Ear, nose and throat/otolaryngology
Secondary Subject Heading:	Infectious diseases
Keywords:	COVID-19, OTOLARYNGOLOGY, Adult otolaryngology < OTOLARYNGOLOGY

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Prevalence of olfactory dysfunction and quality of life in hospitalised patients one year after SARS-CoV-2 infection: a cohort study

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ABSTRACT

Objectives: To determine long-term prevalence of olfactory and gustatory dysfunction (OD ± GD), associated risk factors and impact on quality of life (QoL) in previously hospitalised COVID-19 patients one year after infection.

Design: A single-centre cohort study.

Setting: Patients admitted at a large central London hospital with COVID-19 infection between February 10 and May 22, 2020.

Participants: 150 adult subjects with previously confirmed SARS-CoV-2 infection were recruited between December 10, 2020 and January 29, 2021. Participants were predominantly male (102/150, 68.0%); mean age 58.0 ± 15.9 years, and 41.2% (56/136) were of black and minority ethnic backgrounds.

Main outcome measures: EQ-5D-5L values and Sino-Nasal Outcome Test-22 (SNOT-22) scores.

Results: Long-term prevalence of OD ± GD was 12.8% (19/149) at median time of 264.5 days following SARS-CoV-2 infection onset. Patients with OD ± GD had a significantly higher median total SNOT-22 score (46.1; Q1-Q3: 23.0 - 60.0; CI: 23.0 to 60.0) compared to those without (16.0; Q1-Q3: 5.0 - 30.5; CI: 12.0 to 18.0) (p=0.0002), reflecting poorer QoL, particularly psychological well-being (p=0.0004), which was not alleviated with time (p=0.4977). Median EQ-5D-5L value was not significantly different between patients with OD ± GD (0.70; Q1-Q3: 0.38 - 0.83; CI: 0.38 to 0.83) and those without (0.83; Q1-Q3: 0.61 - 0.94; CI: 0.75 to 0.89) (p=0.0627). Age, sex, ethnicity, smoking status, highest C-reactive protein value, intubation and ventilation, and oxygen supplementation were not found to influence OD ± GD (p>0.05).

Conclusions: 12.8% of previously hospitalised COVID-19 patients in London still report persistent problems with smell or taste up to a year after infection, impacting their QoL. Increased holistic support including psychological therapy and olfactory rehabilitation for affected patients may help to reduce long-term morbidity.

Strengths and limitations of this study

- To our knowledge, this is the first study to have determined the long-term prevalence of OD ± GD in a cohort of previously hospitalised COVID-19 patients at one year following infection.
- The use of validated measures allows us to conclude that persistent OD ± GD, as a key manifestation of long-COVID, is associated with reductions in patient QoL and well-being.
- Prevalence of OD ± GD in this study is based on previously hospitalised COVID-19 patients and may not represent that of mild-to-moderate COVID-19 subjects in the general community, although this allows for important comparisons between different populations.
- Patient-reported outcome measures (PROMs) poorly correlate with psychophysical tests. However, given their good discriminative ability to predict an impaired olfactory function, PROMs still remain of value when psychophysical testing cannot be conducted.

INTRODUCTION

With over 250 million cases and 5 million deaths recorded worldwide so far,[1] the coronavirus disease 2019 (COVID-19) pandemic caused by Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is an ongoing global crisis. COVID-19 presentation is highly varied. An estimated 17% to 20% of those infected remain asymptomatic,[2,3] whilst others can develop a mild-to-moderate disease or severe pneumonia.[4]

According to the World Health Organization (WHO), 'loss of smell or taste' is considered a less common symptom of COVID-19. However, findings from many studies conducted worldwide have strongly contradicted this, with several reports depicting high prevalence of olfactory and/or gustatory dysfunction (OD ± GD) amongst infected subjects.[5–10] So far, the long-term prevalence of OD ± GD is unknown, and values determined from the large proportion of studies conducted during the earlier months of the pandemic poorly reflect its persistence and the current proportion of those still affected. Prevalence of OD and GD also vary depending on studied populations, between 54.2% and 70.2% of the general population with mild-to-moderate symptoms (mean 11.5 ± 5.7 days),[11] 69.2% and 73.1% in mild-to-moderate symptomatic healthcare workers (median follow up of 52 days),[9] and 5.1% and 5.6% in acutely hospitalised patients.[12] There also remains conflicting data surrounding associated risk factors. Pre-COVID-19 data show that OD is associated with increased morbidity and mortality,[13–15] and population studies have shown that anosmia is an independent risk factor for a shortened life span.[16-20] In a study of over 3000 adults, olfactory function was reported to be one of the strongest independent predictors of 5-year mortality, surpassing heart failure, lung disease and even cancer.[21] COVID-19-related OD presentation has been extensively investigated, but its impact on quality of life (QoL) in the context of COVID-19 has not been fully explored. Therefore, this represents a key area which needs to be addressed to more effectively reduce long-term morbidity.

We conducted a cohort study on previously hospitalised COVID-19 patients admitted at a central London hospital during the first pandemic wave, to determine the long-term prevalence of OD ± GD, potential risk factors and impact on QoL.

METHODS

A cohort study of previously hospitalised COVID-19 patients was performed between December 10, 2020 and January 29, 2021 at the National Hospital for Neurology and Neurosurgery (*London, UK*).

Study population

Three hundred fifty-eight patients hospitalised at University College London Hospital (UCLH) with a COVID-19 diagnosis between February 10 and May 22, 2020 were identified as potentially eligible for this study. Ethical approval was given by the Research Ethics Committee and the UCL Joint Research Office (REC reference: 14/SC/1180; IRAS project ID: 156511). Sample size was determined pragmatically based on data available within the medical database at the time of collection. Electronic medical records and laboratory findings were reviewed to verify full adherence to the following inclusion criteria: (a) adults ≥18 years of age, and either (b) laboratory-confirmed SARS-CoV-2 infection, defined as a positive result on reverse transcription polymerase chain reaction analysis of nasopharyngeal swab specimens, or (c) clinically-confirmed COVID-19 on the basis of presenting symptoms, in accordance with WHO interim guidance at the time.[22] Considering the lack of widespread testing in the UK during this studied period of the pandemic, both laboratory and clinical diagnostic criteria were initially included to prevent inadvertent exclusion of eligible participants. Prior to commencement of the study, demographic data including age, sex, ethnicity and smoking status were noted to facilitate investigation into any potential associations. Baseline characteristics and medical status were also recorded to identify ineligible patients (death or patient age <18 years).

Outcomes

Eligible subjects were invited to undertake telephone interviews involving a series of standardised questions from validated questionnaires: the EQ-5D-5L[23] and the Sino-Nasal Outcome Test-22 (SNOT-22). Patients reporting decreased sense of smell/taste in the SNOT-22 were subsequently

followed up with an additional smell and taste questionnaire (supplementary figure 1) designed to capture specific details relating to the type(s) of chemosensory dysfunction experienced. All telephone interviews were conducted in English by the same researcher following a standardised procedure in an effort to minimise inter-observer bias. Verbal informed consent was obtained from all participants prior to enrolment in the study.

Statistical analysis

All statistical analyses were performed using GraphPad Prism version 9.0.1 for macOS (GraphPad Software, San Diego, California USA). Qualitative variables were presented as frequency and percentages; quantitative variables were summarised as median and interquartile range (IQR) or mean ± standard deviation (SD) for normally distributed data. Non-parametric variables were compared using the Mann-Whitney test; data following Gaussian distribution were analysed using the unpaired t-test, with Welch's correction applied to adjust for unequal SDs and variances. Fisher's exact test was used to compare associations between variables in patients with OD ± GD and patients without OD or GD. Linear regression analysis was performed to explore whether SNOT-22 scores changed over time. 95% confidence intervals (CI) were provided for the reported data where appropriate, and the level of statistical significance was set at a 2-sided p value of <0.05.

Patient and public involvement

No patients or members of the public were involved in setting the research question or the outcome measures. They were not involved in the study design or conduct, nor were they invited to contribute to the writing, interpretation, reporting or distribution of the results.

RESULTS

Three hundred fifty-eight patients previously hospitalised with a COVID-19 diagnosis were identified as potentially eligible for this study. Figure 1 outlines the selection process. Following screening of electronic medical records for all 358 patients, 141 were classed as ineligible and subsequently excluded. This comprised patients who had either died (n=129) or those <18 years of age (n=1), as well as patients with a COVID-19 negative diagnosis (n=11), defined as individuals with presenting complaints initially ascribed to SARS-CoV-2 infection, but which were later attributed to non-COVID-19 causes. The remaining 217 patients were deemed eligible for this study. However, 15 were not invited to participate due to overarching causes for exclusion. This included patients who were unable to consent, such as those with severe cognitive impairment (n=9), severe learning disabilities (n=3) or patients under intensive hospitalisation (n=1). Additionally, imprisoned individuals (n=1) and those with explicit refusal to partake in research as recorded in the patient notes (n=1) were excluded. Of the 202 patients contacted and invited to participate, 51 were excluded. This included unreachable patients (n=13), defined as those unable to be contacted despite >3 separate attempts (n=5) and those with invalid contact details (n=8). Patients with communication difficulties (n=3) referring to aphonic individuals (n=2) or patients with hearing impairments (n=1) preventing completion of the questionnaires. Responses were received from 151/202 invited participants, thereby resulting in a response rate of 74.8%. One patient who did not provide any answers to the SNOT-22 was excluded.

Demographics and characteristics

A final population of 150 subjects (102 male and 48 female, male:female ratio of approximately 2:1) was obtained. The majority of patients had laboratory-confirmed COVID-19 (n=147) and three patients had a presumptive diagnosis based on clinical criteria. Median time from infection was 264.5 days (range 215-318). Detailed demographics and baseline characteristics of the population are summarised in Table 1.

Table 1. Detailed characteristics of the population.

	Total population (n = 150)	Patients without OD or GD (n = 129)	Patients with OD ± GD (n = 19)	P value
Age, (mean ± SD), years	58.0 ± 15.9	57.8 ± 16.4	59.6 ± 11.8	0.5773
Age groups, n (%)				
18 – 30	5 (3.3)	5 (3.9)	0 (0)	
31 – 40	20 (13.3)	18 (14.0)	2 (10.5)	
41 – 50	25 (16.7)	21 (16.3)	3 (15.8)	
51 – 60	23 (15.3)	21 (16.3)	2 (10.5)	
61 – 70	48 (32.0)	37 (28.7)	11 (57.9)	
71 – 80	15 (10.0)	14 (10.9)	0 (0)	
81 – 90	12 (8.0)	11 (8.5)	1 (5.3)	
> 90	2 (1.3)	2 (1.6)	0 (0)	
Sex, n (%)				
Male	102 (68.0)	90 (69.8)	11 (57.9)	0.3032
Female	48 (32.0)	39 (30.2)	8 (42.1)	
Ethnicity, n (%)[a]				
White	80 (58.8)	68 (58.6)	11 (61.1)	
BAME	56 (41.2)	48 (41.4)	7 (38.9)	>0.9999
Missing	14	13	1	
Smoking status, n (%)[a]				
Never smoked	72 (65.5)	64 (66.7)	7 (53.8)	
Have smoked	38 (34.5)	32 (33.3)	6 (46.2)	
Current	10 (9.1)	9 (9.4)	1 (7.7)	0.3699
Quit	28 (25.5)	23 (24.0)	5 (38.5)	
Missing	40	33	6	
Highest CRP value (mean ± SD), mg/L	170.9 ± 135.6	174.5 ± 139.5	158.0 ± 109.5	0.9282
Intubation and ventilation, n (%)[a]				
No	52 (57.8)	44 (55.7)	6 (66.7)	
Yes	38 (42.2)	35 (44.3)	3 (33.3)	0.7263
Missing	60	50	10	
Oxygen supplementation, n (%)[a]				
No	20 (17.2)	18 (17.8)	1 (7.1)	0.4599
Yes	96 (82.8)	83 (82.2)	13 (92.9)	
Missing	34	28	5	

[a] Missing data have been reported but were not used in the calculation of percentages (valid percent).

Percentages may not total 100.0% due to rounding.

CRP: C-reactive protein; BAME: Black, Asian and Minority Ethnic.

SNOT-22

150 patients completed the SNOT-22 and the median total score for the whole population was 17.0 (Q1-Q3: 6.0 - 36.3; CI: 13.0 to 22.0). As depicted in Figure 2, the five most prevalent SNOT-22 problems were: *wake up tired* (101/149, 67.8%), *fatigue* (97/147, 66.0%), *lack of a good night's sleep* (98/149, 65.8%), *reduced productivity* (97/148, 65.5%) and *wake up at night* (94/149, 63.1%). *Wake up tired, fatigue* and *lack of a good night's sleep* were also among the problems most frequently reported to affect patient health the most (Figure 3). 14.1% (21/149) of patients reported to have decreased sense of smell/taste in the SNOT-22 (score ≥1 at the corresponding item), of which the severity was very mild in 4.0%, mild in 4.7%, moderate in 2.7% and severe in 2.7%. Two individuals were classed as pre-existing OD ± GD based on evidence of iatrogenic causes and age-related olfactory loss predating COVID-19 infection and hospitalisation. This led to a total of 19/149 patients (12.8%) with reported decreased smell/taste in the context of COVID-19. Only 2/19 (11.1%) had sought treatment: one patient did olfactory training and the other patient did not specify. Characteristics of OD and GD are reported in Table 2.

Table 2. Prevalence and characteristics of olfactory and gustatory disorders.

	Total responses (n = 149)
Prevalence, n (%)	
Total reporting decreased smell/taste	21 (14.1)
In the context of COVID-19	19 (12.8)
Pre-existing	2 (1.3)
No OD or GD	128 (85.9)
	Analysed population with OD ± GD (n = 19)[a]
Type of dysfunction reported, n (%)	
OD and GD	15 (78.9)
Only OD	4 (21.1)
Only GD	0 (0)
Parosmia[b]	3 (16.7)
Parageusia[b]	5 (27.8)
Phantosmia[b]	2 (11.1)
Phantogeusia[b]	0 (0)
OD ± GD characteristics, n (%)	
Constant[b]	14 (77.8)
Fluctuant[b]	4 (22.2)
Isolated OD[b,c]	1 (5.3)
Isolated GD[b,c]	0 (0)
Treatment, n (%)[b]	
Have not sought treatment	16 (88.9)
Have sought treatment	2 (11.1)

[a] Analyses performed on population following application of exclusion criteria (excludes pre-existing OD ± GD).
[b] Valid percentages calculated based on subjects who provided responses to the question (n = 18).
Missing responses were not included in the calculations.
[c] 'Isolated' OD or GD defined as decreased sense of smell/taste in the absence of any other SNOT-22 problem.

Patients with OD ± GD demonstrated a statistically significant higher median total SNOT-22 score (46.1; Q1-Q3: 23.0 - 60.0; CI: 23.0 to 60.0) than those without (16.0; Q1-Q3: 5.0 - 30.5; CI: 12.0 to 18.0) (p=0.0002), and their scores were higher across all SNOT-22 domains[24] except one (extranasal rhinologic symptoms) (Table 3). Total SNOT-22 scores were found to improve over time in patients without OD or GD (p=0.0327), although this was not observed in patients with OD ± GD (p=0.4977) (Figure 4). Comparisons of the demographics of the two subgroups found no influence of age, sex, ethnicity or smoking status (have smoked versus never smoked) on the development of OD ± GD (p > 0.05) (Table 1). Similarly, no statistically significant association was observed between OD ± GD and

other characteristics recorded during hospitalisation, such as highest C-reactive protein (CRP) value, requirement for intubation and ventilation, or oxygen supplementation (p = 0.9282, 0.7263 and 0.4599, respectively).

Table 3. Subgroup differences in median total SNOT-22 score for each domain.

Domain	Median total SNOT-22 score		
	Patients without OD or GD (n = 129)	Patients with OD ± GD (n = 19)	P value
Rhinologic symptoms	2.0	6.0	***0.0189****
Extranasal rhinologic symptoms	0	1.0	0.0524
Ear/facial symptoms	1.0	3.75	***0.0087****
Psychological dysfunction	7.0	22.0	***0.0004*****
Sleep dysfunction	7.0	16.0	***0.0024****

Significant p values in bold. Level of significance *p < 0.05, **p < 0.01, ***p < 0.001

EQ-5D-5L

149 patients completed the EQ-5D-5L and the median value for the total population was 0.80 (Q1-Q3: 0.53 - 0.94; CI: 0.73 to 0.86). Patients with OD ± GD had a lower median EQ-5D-5L value (0.70; Q1-Q3: 0.38 - 0.83; CI: 0.38 to 0.83) compared to those without OD or GD (0.83; Q1-Q3: 0.61 - 0.94; CI: 0.75 to 0.89); however, the difference was not statistically significant (p=0.0627). Time from infection (the number of days between the date of the patient's first COVID-19 positive swab or their onset of COVID-19 symptoms, and the date at which the questionnaire was administered) was not found to be correlated to EQ-5D-5L value in both patients with OD ± GD (p=0.8693) and those without (p=0.5371) (Figure 5).

DISCUSSION

This is the first study to evaluate the long-term prevalence of OD ± GD in a group of previously hospitalised COVID-19 patients.

The prevalence of OD ± GD in our studied population was 12.8%. This is considerably lower than that of surveys conducted in hospitalised patients in Europe (35.0% to 80.6% for OD and 21.0% to 90.3% for GD within 1 month),[25–27] and in other countries such as Turkey (42.3% for OD ± GD),[28] and Brazil (64.6% and 66.7% for OD and GD, respectively, at follow up of 15-55 days).[29] The longer follow-up at which our study has been conducted could explain the lower rate of observed chemosensory alteration in our population, whereby recovery of OD/GD is expected to happen over time in some patients. This is supported by a recent French study which found that 24.0% of non-severe COVID-19 subjects reported persistent OD/GD 7 months after symptom onset.[30] Interestingly, our prevalence of 12.8% is similar to that observed by Lee et al.[31] (15.3%) in a large Korean cohort of 3191 patients with varying COVID-19 severity at 1 month, but it is relatively higher than that observed by Mao et al.[12] in a population of 214 acutely hospitalised COVID-19 patients (5.1% and 5.6% with OD and GD, respectively). A selection bias could have potentially influenced the observed lower prevalence. Most surveys investigating OD/GD in COVID-19 subjects have been conducted on patients with mild-to-moderate symptoms.[5,11,32–34] In this regard, higher prevalence of anosmia has been noted in milder individuals, along with a significantly increased risk of self-reported olfactory loss in outpatients compared to hospitalised patients.[35] This is reflected in the most recent studies on long-term COVID-19-related OD ± GD. In one study, 48.0% and 38.5% of non-hospitalised COVID-19 subjects reported persistent OD and GD, respectively, at 8 months follow up.[36] Similarly, 21.3% of subjects reported OD ± GD in another study of mild-to-moderate symptomatic patients at one-year.[37] These values were notably higher than our described prevalence despite the longer follow up times, thus suggesting that selection bias may produce the observed disparities in reported long-term OD ± GD prevalence.

Additionally, it is important to consider the possible contribution of COVID-19 variants to such disparities due to their potential differing effects on olfaction. Genetic, structural and epidemiological data have shown that a single nucleotide polymorphism from D614 to G614 (D614G mutation) in the spike protein of SARS-CoV-2 may enhance chemosensory impairment, resulting in increased prevalence of COVID-19-related OD ± GD.[38,39] With the presence of different viral strains and potentially uncharacterised host and viral variants, such factors may have therefore contributed to the different incidences of OD ± GD observed between countries.

In our population, OD was associated with GD in most of the cases (78.9%), while none of the subjects reported GD only. This reflects what has extensively been reported in previous studies[8,30,40,41] and confirms that GD is usually linked to an impairment of retronasal olfaction rather than impairment of gustation itself. Nonetheless, although less common, isolated GD has been described in COVID-19 patients.[42]

Despite the extensive literature available on quantitative changes in smell and taste, qualitative alterations of smell and taste in COVID-19 have been seldom explored. In our study, 16.7% of patients had parosmia (distortions in smell) while 27.8% had parageusia (distortions in taste). A similar prevalence (15.0%) of parosmia was reported by Gorzkowski et al.[43] although a higher rate of 32.4% was previously described by Lechien et al.[5] Prevalence of COVID-19-related parageusia vary widely in the literature, but a recent meta-analysis of 8438 COVID-19 patients from 13 countries revealed a pooled prevalence of 38.2% (95% CI: 24.0% to 53.6%),[44] which is higher than that observed in our study. The differences observed between studies could partly reflect inherent biases in the composition of sampled populations. Additionally, a cultural variability in taste appreciation or perception has been reported to exist in COVID-19 positive subjects with a different cultural background.[45] Phantosmia (the detections of smells not present within the environment) was reported in 11.1% of our study participants. A similar prevalence was reported by Lechien et al.[5] and Gorzkowski et al.[43] No cases of phantogeusia (abnormal taste in the mouth in the absence of any stimulus) were recorded in

our population and based on the current published literature, prevalence of phantogeusia in COVID-19 subjects is unknown. In line with previous findings,[5,43] most of our participants (77.8%) reported constant OD ± GD, suggesting that the driving mechanism leading to persistent chemosensory dysfunction is sensorineural.

No statistically significant association between persistent OD ± GD and age, smoking status, highest CRP value, intubation and ventilation, or oxygen supplementation was found in our study, thus corroborating results from multiple studies.[29,30,32,43,46–50] Similarly, sex did not demonstrate any influence on the prevalence of persistent OD ± GD in our study, which is in line with previous studies conducted worldwide.[7,32,43,47,51,52] Nonetheless, several authors have observed a significantly higher prevalence of OD ± GD in women,[5,31,46,53] with some reports suggesting that being female is a risk factor for prolonged recovery from chemosensory dysfunction.[26,29,48] However, the female predominance observed from such studies may be attributed to the differences in the sampled populations (hospitalised versus mild-to-moderate) or in the gender composition. In fact, previous studies on COVID-19 hospitalised patients have demonstrated a lower prevalence of female patients,[54] which is confirmed by the male:female ratio in our population (2:1). Moreover, women tend to outperform men on olfactory assessment and in their capacity to perceive OD, which could lead to disproportionately increased prevalence seen in females.[55,56]

Our study included a more ethnically diverse population in comparison to more geographically limited studies conducted on cohorts of the same ethnic background. Despite this, we found no statistically significant association between ethnicity and OD ± GD, in contrast to what was reported by Doty[57] before the pandemic that ethnic minorities are more at risk of developing chemosensory dysfunction.

In this study, the majority of patients reporting *decreased sense of smell/taste* had very mild or mild impairment as opposed to moderate or severe impairment. *Decreased sense of smell/taste* was also not frequently ranked within the top five of their most important items, suggesting that

chemosensory impairment was not of their greatest concern, if compared to other residual symptoms listed in the SNOT-22. This is an expected finding, considering previous studies which show that hospitalised patients are less likely to report olfactory loss compared to patients with milder course,[35] possibly due to the presence of more prominent symptoms. However, while OD ± GD severity was not largely found to be profound in this study, it should be noted that patients with OD ± GD had a significantly higher median total SNOT-22 score than those without, with the score only improving over time for the latter subgroup. This corresponds to a greater health burden and subsequent poorer QoL among those affected with chemosensory impairments, as exemplified in a recent study by Chary et al.[46] More importantly, it reflects the ongoing health burden in patients with OD ± GD, which has previously been depicted to a similar effect.[51] Analysis of the SNOT-22 items demonstrated intrinsic psychological and sleep dysfunction in our population, where the items *wake up tired*, *fatigue*, and *lack of a good night's sleep* were three of the most commonly ticked "important items" (maximum of five items). While this highlights some of the long-term manifestations of COVID-19, now called 'long-COVID',[8,58] further sub-analysis revealed that OD ± GD reduced QoL in nearly all domains, especially that of psychological dysfunction, when compared to patients without OD or GD. Recent studies have supported this, with emphasis on both the direct and indirect negative effects of COVID-19-related OD on psychological well-being. In one study, 15.8% of COVID-19 patients with OD reported depression due to their smell loss,[59] whereas in a separate study, 28.2% had increased anger as a secondary effect.[60] A more recent study reported that chemosensory disturbance in mildly symptomatic COVID-19 patients was associated with emotional distress and depression, despite over a year since the onset of their COVID-19 infection.[61] Interestingly, long-lasting fatigue has also been found to be significantly associated with persistent OD ± GD.[33] Taken together, our findings therefore highlight the negative long-term effects of persistent OD ± GD on QoL.

Conversely, based on subgroup analysis of EQ-5D-5L values, we did not observe any difference in health-related QoL between those with OD ± GD and those without. More importantly,

EQ-5D-5L value did not improve with time and was not influenced by the presence of a chemosensory alteration. One possible explanation for these results is interpatient variability. Given that the EQ-5D-5L is nonspecific to COVID-19 and captures responses based on overall QoL on the day of questioning, patients' responses could have been influenced by other factors. The questionnaire also may not have been sensitive enough to differentiate the problems experienced by patients with OD ± GD. Alternatively, the lack of any significant difference in EQ-5D-5L values between these two subgroups may reflect the residual difficulties of long-COVID which are common to many COVID-19 patients, regardless of anosmia status.

Strengths and limitations

To our knowledge, this represents the first study to have determined the prevalence of OD ± GD in a cohort of previously hospitalised COVID-19 patients at one year following infection. We have therefore provided a more current insight into both the persistence and the scale of OD and GD from a long-term perspective, and the impact on patients' QoL and well-being. Our cohort of previously hospitalised COVID-19 patients also adds value by highlighting differences in OD ± GD prevalence in different populations, given that current existing studies have predominantly been based on mild-to-moderately affected patients or healthcare workers.

The prevalence of OD and GD observed in our study refers to a single-centre population of previously hospitalised COVID-19 patients. Our findings therefore may not be directly comparable or generalisable to those reported for mild-to-moderate symptomatic COVID-19 subjects in the general community. There is also the possibility of misdiagnosis, especially with the three clinically-confirmed COVID-19 patients, although this is unlikely considering the surging number of COVID-19 cases at the time of their presentation. Without baseline data, we were unable to determine the extent to which the impairments in OD ± GD patients were new-onset or more chronic, or whether there was any previous improvement of chemosensory function. Lastly, as in other COVID-19 studies, patients with

OD ± GD were identified through subjective, self-reported questionnaires. These have a low correlation with psychophysical measurements,[62] and findings derived from these surveys cannot be compared with studies which have used objective tests, such as Sniffin' sticks. However, given that psychophysical testing has not been available or feasible in many countries during the pandemic, we believe that, in an emergency condition, self-rated symptoms remain of value.[63]

Clinical implications of this study

A proportion of previously hospitalised COVID-19 patients may continue to experience persistent OD ± GD long-term, especially when this is not treated. With over 9.3 million COVID-19 positive cases in the UK at the time of writing,[64] and with numbers likely to increase including untested asymptomatic individuals and those with milder disease, our study demonstrates the relevance of OD ± GD and its place as a key manifestation of long-COVID. OD ± GD impacts QoL and can have a potentially substantial long-term burden on patients and healthcare resources.

Our study suggests that persistent COVID-19-related chemosensory dysfunction requires increased holistic support. This includes safety counselling, psychological therapy, coping strategies and patient support groups to aid patients in the management of their OD ± GD, but concurrent rehabilitation such as olfactory training should also be considered, given the evidence base supporting its effectiveness in post-viral olfactory loss.[65-68] It should also be noted that there are currently ongoing clinical trials assessing other interventions such as anti-inflammatory agents, nasal/oral steroids and even intranasal photobiomodulation therapy.[69,70] However, while these could play supportive roles in the potential recovery of COVID-19-related OD ± GD, further research regarding their safety and efficacy will be needed, alongside additional studies investigating the impact of such modalities on patient QoL.

CONCLUSIONS

Up to a year following infection, 12.8% of previously hospitalised COVID-19 patients in London reported persistent chemosensory dysfunction. COVID-19-related OD ± GD reduces both QoL and psychological well-being, and this does not improve over time, creating an important health burden. With the number of patients seeking treatment expected to rise, developing new therapeutic treatments will be important in the future, as well as providing adequate patient support for now.

Footnotes

Contributors: DC and HQMT conceptualised and designed the study. HQMT and ALP drafted the manuscript. HQMT performed data acquisition, statistical analyses and production of figures and tables. All authors (HQMT, ALP, PJA and DC) contributed to the interpretation of the results and critically revised the manuscript. All authors approved the final manuscript. The corresponding author (HQMT) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Figure captions

Figure 1. Flowchart depicting stages of patient identification, inclusion and analysis.

Figure 2. Prevalence of SNOT-22 problems stratified by severity and categorised by domain.

† The item 'decreased sense of smell/taste' was excluded from the rhinologic symptoms domain and presented separately, given OD ± GD status was used as a subgroup in the sub-analysis.

Figure 3. SNOT-22 problems reported to most greatly affect patient health.

Figure 4. Linear regression analysis of subgroup changes in total SNOT-22 scores over time. Dashed lines denote 95% CI. *Significant p values. Level of significance $p < 0.05$

Figure 5. Linear regression analysis of EQ-5D-5L value and time from infection in patients with OD ± GD and patients without OD or GD.

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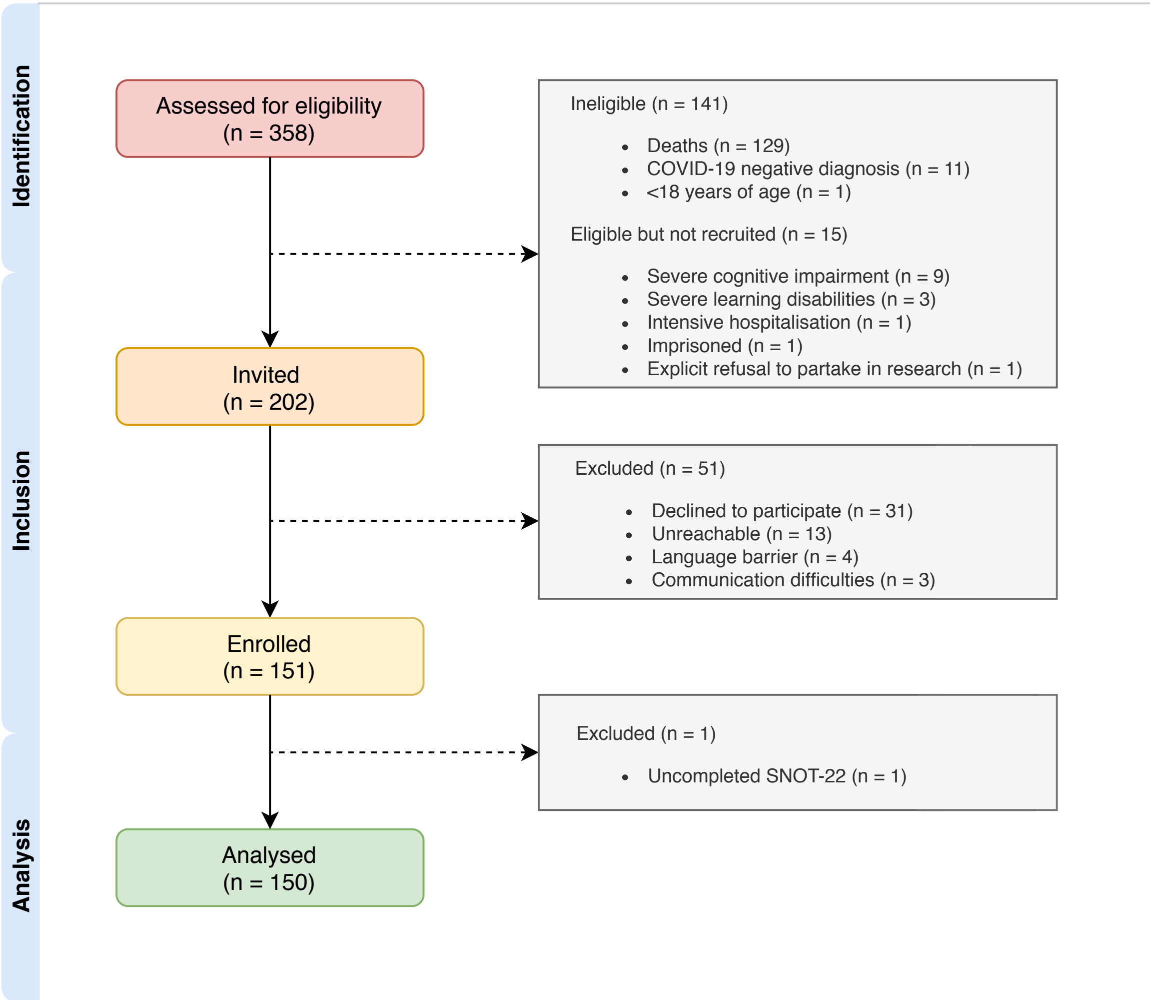

Figure 1. Flowchart depicting stages of patient identification, inclusion and analysis.

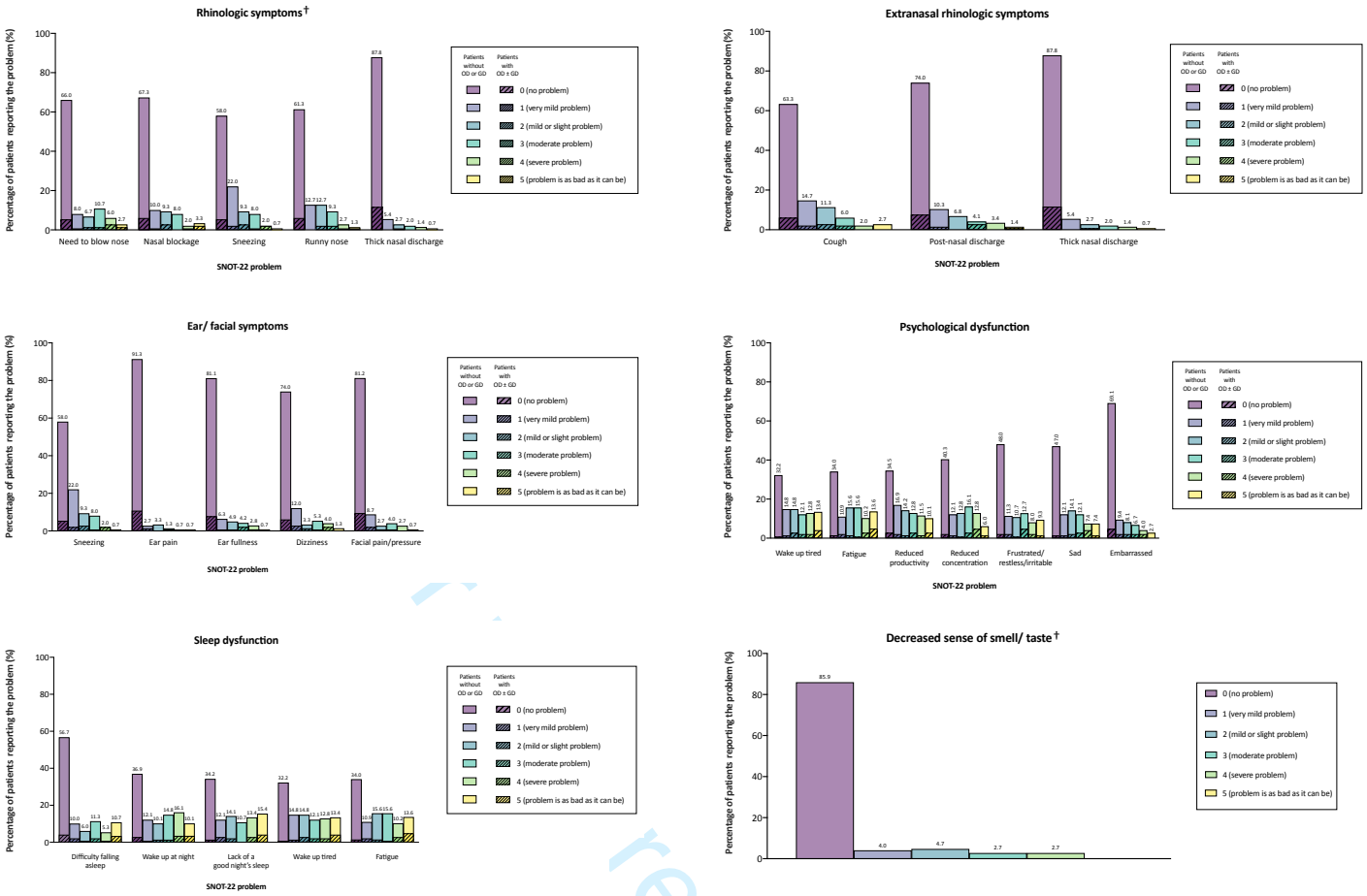

Figure 2. Prevalence of SNOT-22 problems stratified by severity and categorised by domain.

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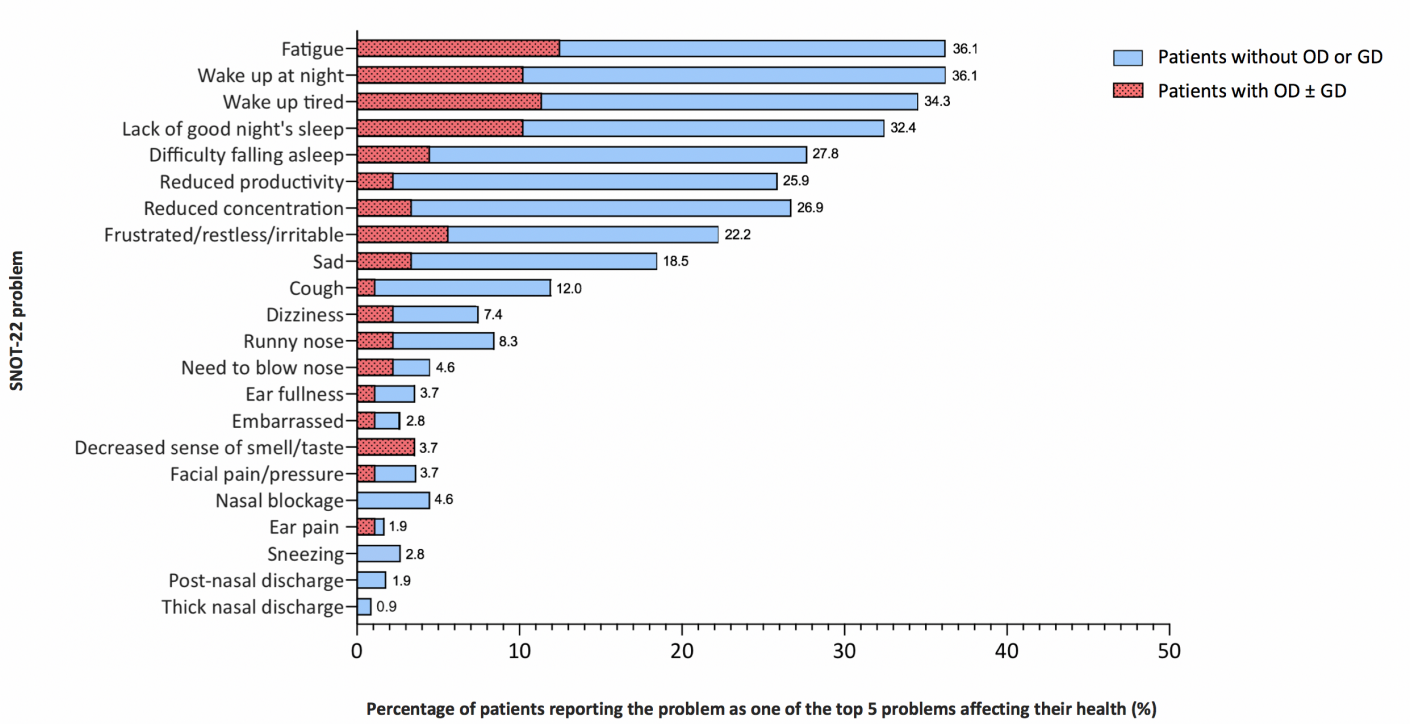

Figure 3. SNOT-22 problems reported to most greatly affect patient health.

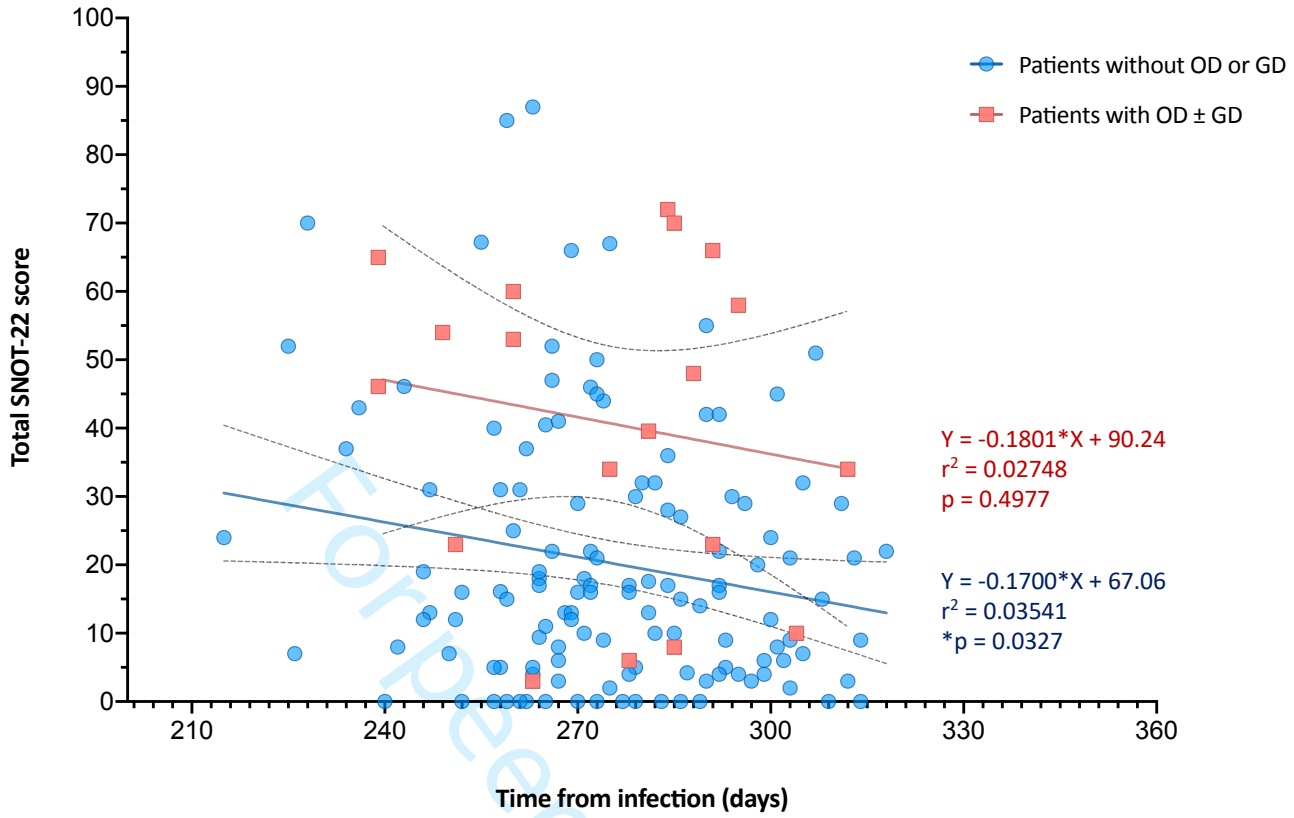

Figure 4. Linear regression analysis of subgroup changes in total SNOT-22 scores over time. Dashed lines denote 95% CI. *Significant p values. Level of significance $p < 0.05$

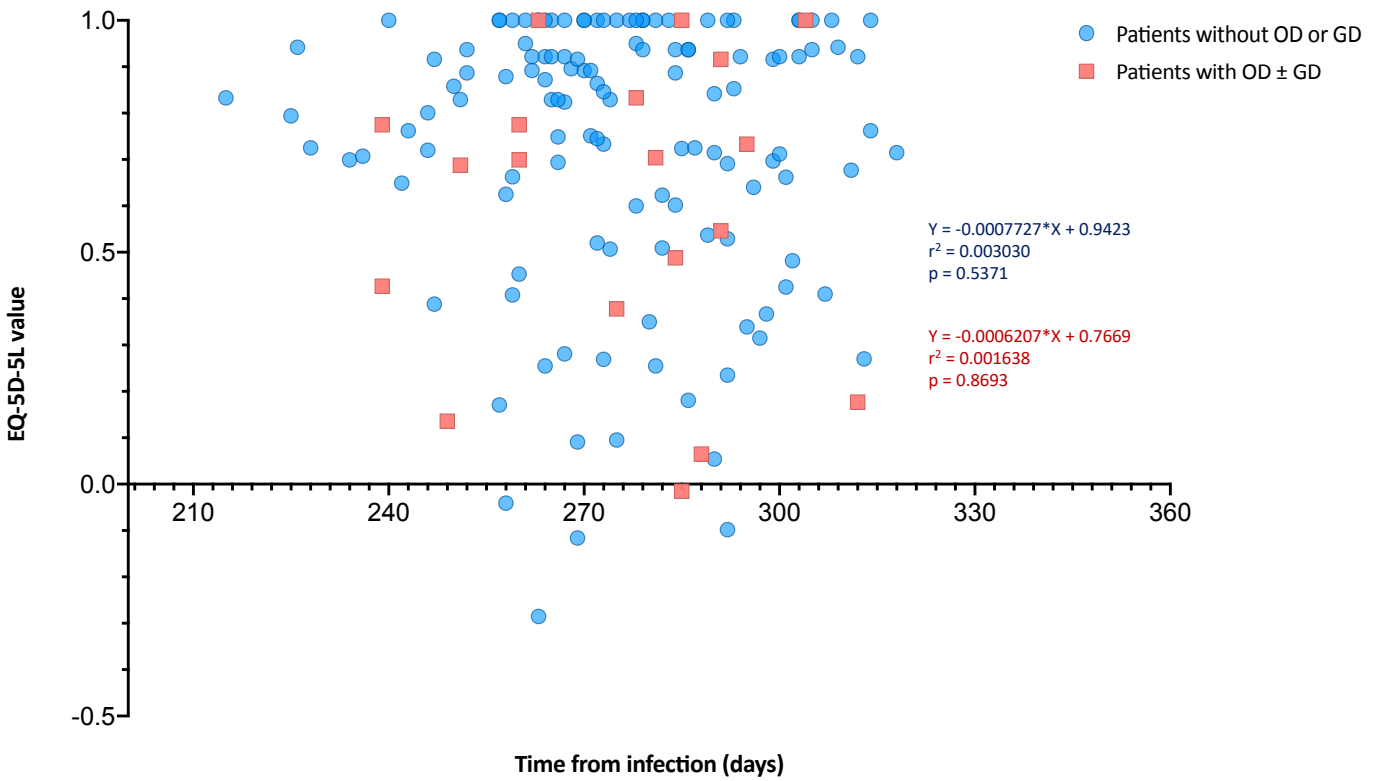

Figure 5. Linear regression analysis of EQ-5D-5L value and time from infection in patients with OD ± GD and patients without OD or GD.

ADDITIONAL SMELL AND TASTE QUESTIONNAIRE Patient study number: _____

For patients reporting decreased sense of smell/taste (in the SNOT-22):

1. Is the problem: decreased sense of smell, decreased taste or both?
   ☐ Smell ☐ Taste ☐ Both

2. How did you first notice you had decreased smell/taste?

3. When did you first notice you had decreased smell/taste?

4. What did you notice about your loss of smell/taste when it was at its worst?

5. What do you notice about your loss of smell/taste now?

6. Is your loss of smell/taste always there or does it come and go?
   ☐ Always there ☐ Comes and goes

7. Have you sought treatment for your smell/taste loss?
   ☐ Yes ☐ No

   a. How long did you wait before seeking treatment?

   b. What treatment(s) did you try?

   c. Has the treatment helped?
      ☐ Yes ☐ No

8. Over the past 2 weeks, have you noticed some things smell/taste different or unpleasant from what they usually smell/taste like? (parosmia/parageusia)

☐ Yes ☐ No

a. Could you please describe how things have smelled/tasted different or unpleasant?

9. Over the past 2 weeks, have you smelled/tasted things when nothing is there? (phantosmia/ phantogeusia)

☐ Yes ☐ No

a. Could you please explain a bit more about this problem?

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cross-sectional studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	2, 3
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	3
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	5
Objectives	3	State specific objectives, including any prespecified hypotheses	6
Methods			
Study design	4	Present key elements of study design early in the paper	7
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants	7
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	7
Bias	9	Describe any efforts to address potential sources of bias	8
Study size	10	Explain how the study size was arrived at	7
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8
		(*b*) Describe any methods used to examine subgroups and interactions	8
		(*c*) Explain how missing data were addressed	9, 10
		(*d*) If applicable, describe analytical methods taking account of sampling strategy	N/A
		(*e*) Describe any sensitivity analyses	N/A
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	9
		(b) Give reasons for non-participation at each stage	9
		(c) Consider use of a flow diagram	Figure 1
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	9, 10
		(b) Indicate number of participants with missing data for each variable of interest	10, 11
Outcome data	15*	Report numbers of outcome events or summary measures	12, 13
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11-13
		(*b*) Report category boundaries when continuous variables were categorized	N/A
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	12, 13
Discussion			
Key results	18	Summarise key results with reference to study objectives	14-18
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	18, 19
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	14-20
Generalisability	21	Discuss the generalisability (external validity) of the study results	18
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	21

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

N/A = Not Applicable