

Distorted chemosensory perception and female sex associate with persistent smell and/or taste loss in people with SARS-CoV-2 antibodies: A community based cohort study investigating clinical course and resolution of acute smell and/or taste loss in people with and without SARS-CoV-2 antibodies in London, UK

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Abstract

Background:

Loss of smell and/or taste are cardinal symptoms of COVID-19. 'Long-COVID', persistence of symptoms, affects around one fifth of people. However, data regarding the clinical resolution of loss of smell and/or taste are lacking. We assessed COVID-19 symptoms in a community cohort in London 4-6 weeks after they initially reported acute loss of their sense of smell and/or taste, 78% of whom had SARS-CoV-2 IgG/IgM antibodies. In addition, to assess whether self-reported change in sense of smell was reliable, we compared subjective and objective smell assessments in a subset of participants.

Methods:

467 participants with acute loss of smell and/or taste who had undergone SARS-CoV-2 IgG/IgM antibody testing 4-6 weeks earlier completed a follow-up questionnaire about resolution of their symptoms. A subsample of 50 participants completed an objective olfactory test and results were compared to subjective smell evaluations.

Results:

People with SARS-CoV-2 antibodies with an acute loss of sense of smell and taste were significantly less likely to recover their sense of smell/taste than people who were seronegative (smell recovery: 57.7% vs. 72.1% , $p=0.027$. taste recovery 66.2% vs. 80.3%, $p=0.017$). In SARS-CoV-2 positive participants, a higher percentage of male participants reported full resolution of smell loss (72.8% vs. 51.4%; $p<0.001$) compared to female participants, who were almost 2.5-times more likely to have ongoing smell loss after 4-6 weeks (OR 2.46, 95%CI 1.47-4.13, $p=0.001$). Female participants with SARS-CoV-2 antibodies and unresolved smell loss and unresolved taste loss were significantly older (>40 years) than those who reported full resolution. Participants who experienced parosmia reported lower smell recovery rates and participants with distorted taste perception lower taste recovery rates. Parosmia had a significant association to unresolved smell loss (OR 2.47, 95%CI 1.54-4.00, $p<0.001$).

Conclusion:

Although smell and/or taste loss are often transient manifestations of COVID-19, 42% of participants had ongoing loss of smell, 34% loss of taste and 36% loss of smell and taste at 4-6 weeks follow-up, which constitute symptoms of 'long-COVID'. Females (particularly >40 years) and people with a distorted perception of their sense of smell/taste are likely to benefit from prioritised early therapeutic interventions.

Trials registration:

ClinicalTrials.gov [NCT04377815](https://clinicaltrials.gov/ct2/show/study/NCT04377815)

Introduction

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), which results in coronavirus disease 2019 (COVID-19), emerged in 2019 resulting in a global pandemic with over 85 million cases and 1.8 million deaths reported worldwide[1]. The association between COVID-19 and smell and taste loss was established in March 2020 and has since been identified among the most specific symptoms of COVID-19, with implications for case identification, isolation and tracing[2, 3]. We previously reported seroprevalence of SARS-CoV-2 IgG/IgM antibodies of 78% in a community cohort in London, UK who developed an acute loss of their sense of smell and/or taste during the peak of the first local wave of

the pandemic[4]. We also showed that seropositivity for SARS-CoV-2 antibodies was three times more likely for people with smell loss compared to taste loss.

With the ongoing spread of SARS-CoV-2 globally, COVID-19 and its complications are continuing to affect millions globally. Despite the development of vaccinations resulting in optimism that the pandemic will be contained, healthcare providers worldwide will continue to face the challenge of an unprecedented incidence of COVID-19 related morbidity. It is now evident that symptoms can persist beyond resolution of the acute systemic viral infection and cause a chronic condition, termed 'long-COVID', in up to a quarter of cases[5]. 'Long covid' (> 4 weeks) as well as 'post-acute covid' (> 3 weeks) and 'chronic covid' (> 12 weeks) have been used to describe ongoing symptoms of the disease[6, 7]. Symptoms persisting longer than 5 weeks are estimated to occur in 1 in 5 and symptoms and lasting longer than 12 weeks in 1 in 10 people, according to data published by the UK Office for National Statistics (ONS)[8]. Identifying the people most at risk of long-term symptoms will be key to guide monitoring in order to deliver follow-up care and therapeutic interventions to patients with long COVID-19 disease.

Despite the recognition of loss of smell and/or taste as key symptoms of COVID-19 there remains a paucity of data within the literature regarding the clinical course, recovery rates and demographic risk factors for long-lasting symptoms. Post-viral smell loss from other respiratory pathogens is typically a short-lived phenomenon and recovery usually coincides with resolution of other viral symptoms[9, 10]. In contrast, current data from COVID-19 patients, suggest a wide range of recovery times, from a few days to several months[11–13]. This observation raises concerns of unresolved smell loss as a manifestation of long-COVID. Therefore, identifying risk factors for persistent smell loss will be key to guide therapeutic interventions, such as olfactory rehabilitation and use of corticosteroids, once these are widely available[14, 15]. Furthermore, given the negative impact of these symptoms on quality of life and safety, research on prognostic information is warranted to inform patients, their carers, as well as treatment algorithms[16]. In this follow-up study, we aim to describe and compare the temporal resolution patterns of loss of smell and/or taste in a community cohort with acute smell and/or taste loss with and without SARS-CoV-2 antibodies. This study will focus on smell loss resolution and aim to identify risk factors for persistent smell loss, as well as describe smell loss as a feature of long-COVID. Finally, to address the original study's limitations of reliance on self-reported symptoms, we will correlate self-reported smell function with objective olfactory testing.

Methods

The study was conducted in London, UK, at a time when loss of smell and taste were not recognised as symptoms of COVID-19. People with an acute loss of their sense of smell and/or taste were invited to participate through text messages, sent via primary care centres in London, UK. Recruitment took place over a 4-week period between 23 April and 14 May 2020, during the local first wave of the pandemic. Participants were recruited via an online platform, as previously described[4].

Inclusion criteria were age > 18 years, proficiency in written and spoken English and access to video calling. Exclusion criteria were any pre-existing loss of the sense of smell or taste of longer than one month's duration. Participation was voluntary and written informed consent was obtained electronically. Enrolled participants completed an online questionnaire (see Additional File 1), capturing their sex, age, ethnicity, smoking status, questions about their smell and taste loss, as well as other symptoms of COVID-19. SARS-CoV-2 immunoglobulin G (IgG)/ immunoglobulin M (IgM) antibody testing was carried out via a telemedicine consultation as described previously described[17], using a lateral flow immunoassay detecting IgM and IgG antibodies to SARS-CoV-2 (Wuhan UNscience Biotechnology Co., Ltd. COVID-19 Antibody IgM/IgG) with a relative sensitivity of 98.8% (95% CI 97.3–99.6%) and a relative specificity of 98.0% (95% CI 97.15–98.7%)[18]. A link to a follow-up questionnaire was sent to participants' registered email addresses 4 weeks after they completed their original questionnaire. The follow up questionnaire (see Additional File 1) contained questions

about resolution of their smell and taste loss, as well as resolution of the other symptoms of COVID-19 and admission to hospital. Reminders were sent to participants who did not complete the original questionnaire at 72 hours and 7 days and the platform remained open for questionnaire completion for a further 4 weeks (22 May to 20 July 2020).

In order to correlate participants' questionnaire responses about their loss of smell with objective olfactory testing, a subsample of 50 participants were recruited for objective smell testing. Participants received a separate information sheet and informed consent was obtained electronically using a separate consent form. The University of Pennsylvania Smell Identification Test (UPSIT), a 40-item smell test which is validated to be self-administered, was used[19]. UPSIT kits were sent to recruited participants together with instructions on completing the test. Photographs of the booklet were obtained and the tests were scored by a healthcare professional, who then explained the results to participants.

The study received ethical approval from the National Health Service Queen's Square Research Ethics Committee (IRAS Project ID 282668, ClinicalTrials.gov: NCT04377815) and was conducted in line with the declaration of Helsinki and Good Clinical Practice.

Statistical analysis

A sample size calculation was undertaken in order to determine the study's recruitment target, using the information on reported symptoms from the web-based COVID symptom study app developed by King's College London and symptom reporting between the 24–29 March 2020. To calculate an estimate of 50% (95% CI 45–55%) as the proportion who would test positive amongst those who reported a change in smell or taste, we needed 385 participants in the study [17]. Assuming a 15% attrition, the number increased to 453 participants in the study. The recruitment target was set to 500 participants and was exceeded to allow for larger attrition and increase accuracy.

Data were analyzed using GraphPad Prism version 8 (<https://www.graphpad.com/scientific-software/prism/>) and SPSS version 26 (<https://www.ibm.com/uk-en/products/spss-statistics>).

Descriptive analyses included the calculation of means (plus standard deviation [SD]) for continuous variables and numbers (*n*, with percentages) for categorical variables. Chi-squared tests were performed on categorical data. When performing multiple comparisons, the significance level was adjusted by applying a Bonferroni correction. Parametric and non-parametric tests were used as appropriate on continuous data. Logistic regression analysis was performed to estimate the association between smell loss resolution and additional factors including participant's age, sex, ethnicity, smoking status and smell loss pattern. A Spearman Rank correlation analysis was performed to investigate the association between participants' perceived smell function and an objective assessment of their olfactory function.

Results

Study population

A total of 467 out of the 569 participants who enrolled and underwent a SARS-CoV-2 antibody test completed the follow-up questionnaire, yielding a follow-up rate of 82.1%. The demographics of the entire study cohort can be seen in Additional File 2. Out of the cohort of 467 who completed the follow-up questionnaire, participants with positive and negative SARS-CoV-2 antibodies were comparable in terms of age, gender, smoking status and ethnicity (Table 1). Admission to hospital was reported by 1.6% (*n*=7) of participants in the antibody positive group vs. 3.1% (*n*=4) in the antibody negative group (*p*=0.097).

Table 1: Demographics of participants followed up after 4-6 weeks with positive and negative SARS-CoV-2 antibodies

Demographics	SARS-CoV-2 IgG/IgM positive (n=381)	SARS-CoV-2 IgG/IgM negative (n=86)	p-value (0.05)
Gender			
Female	70.9% (n=270)	66.3% (n=57)	<i>0.382</i>
Male	28.8% (n=110)	33.7% (n=29)	
Other	0.3% (n=1)	0	
Age (years)	39.67±12.12	40.25±12.33	<i>0.689</i>
Ethnicity *			
White	83.7% (n=319)	81.4% (n=70)	<i>0.600</i>
Mixed/Multiple Ethnicities	5.5% (n=21)	4.7% (n=4)	<i>0.749</i>
Asian/Asian British	5% (n=19)	4.7% (n=4)	<i>0.897</i>
Black/African/Caribbean/Black British	1.6% (n=6)	2.3% (n=2)	<i>0.628</i>
'Other'	3.7% (n=14)	3.5% (n=3)	<i>0.933</i>
Smoking status			
Current/ Ex-smoker	42% (n=160)	44.2% (n=38)	<i>0.710</i>
Never smoked	58% (n=221)	55.8% (n=48)	

Figures presented as % with total number (n). SARS-CoV-2, severe acute respiratory syndrome coronavirus 2.

*5 participants opted not to disclose their ethnicity.

Smell and taste loss and resolution at 4 -6 weeks follow-up

The frequency of reported smell and/or taste loss at baseline can be seen in Table 2.

Table 2: Loss of smell and/or taste in SARS-CoV-2 IgG/IgM positive and negative participants

	SARS-CoV-2 IgG/IgM positive (n=443)	SARS-CoV-2 IgG/IgM negative (n=126)	p-value (0.05)
Sense of smell			
Loss of sense of smell (complete and partial)	93.5% (n=414)	79.4% (n=100)	<0.001
Partial loss of smell	24.4% (n=108)	39.7% (n=50)	<0.001
Complete loss of smell	69.1% (n=306)	39.7% (n=50)	
Parosmia (distorted sense of taste)	30% (n=133)	21.4% (n=27)	0.245
Sense of taste			
Loss of sense of taste (complete and partial)	90.1% (n=399)	88.9% (n=112)	0.700
Partial loss of taste	42.7% (n=189)	61.9% (n=78)	<0.001
Complete loss of taste	47.4% (n=210)	27% (n=34)	
Dysgeusia (distorted sense of taste)	44.7% (n=198)	42.9% (n=54)	0.856
Experience of taste without eating/drinking	21.4% (n=95)	24.6% (n=31)	0.374
Only loss of smell	9.9% (n=43)	11.1% (n=14)	0.643
Only loss of taste	6.5% (n=28)	20.6% (n=27)	<0.001
Loss of sense of smell and taste (partial and complete)	83.6% (n=371)	68.3% (n=86)	<0.001

Out of 467 patients followed up at 4-6 weeks, 57.7% (n=206) of participants with positive SARS-CoV-2 antibodies reported full resolution of their smell loss, compared to 72.1% (n=49) of participants with a negative antibody test (p=0.027). Out of the participants with positive SARS-CoV-2 antibodies, 38.4% (n=137) reported partial and 3.9% (n=14) reported no resolution of their smell loss at the time of follow-up. Out of participants with negative SARS-CoV-2 antibodies 25.0% (n=17) reported partial and 2.9% (n=2) no resolution of their smell loss. Figure 1 shows the resolution of smell and taste loss reported at the time of follow-up.

Full resolution of taste loss was reported by 66.2% (n=227) of participants with SARS-CoV-2 antibodies and 80.3% (n=61) of participants with negative SARS-CoV-2 antibodies (p=0.017). Out of participants with positive SARS-CoV-2 antibodies, 31.2% (n=107) reported partial and 2.6% (n=9) no resolution of their taste loss at the time of follow up. Out of participants with negative SARS-CoV-2 antibodies, 19.7% (n=15) reported partial resolution of their taste loss (0 participants reported 'no resolution' of taste loss). Out of participants with positive SARS-CoV-2 antibodies, only 24 experienced a loss of their sense of taste in the absence of a loss of smell. The demographics were comparable to those of the entire SARS-CoV-2 positive cohort, with a mean age of 38.4 ±14.21 years and 70.8% (n=17) of participants of female sex.

For subsequent analyses participants with partial and no resolution were grouped together in order to enable comparison between participants who achieved full resolution versus those who had ongoing smell and/or taste impairment at the time of follow-up. Table 3 shows results regarding resolution vs. no resolution of smell loss, taste loss and combined smell/taste loss in participants with positive and negative SARS-CoV-2 antibodies. A higher percentage of participants without SARS-CoV-2 antibodies fully recovered their sense of smell (72.1% vs 57.7%, p=0.027), their sense of taste (80.3% vs 66.2%, p=0.017) and both their senses of smell and taste (79.6% vs 64.0%, p=0.026).

Table 3: Smell and/or taste loss resolution in SARS-CoV-2 IgG/IgM positive and negative participants

Pattern of resolution	SARS-CoV-2 IgG/IgM positive	SARS-CoV-2 IgG/IgM negative	p-Value (0.05)
Smell loss	Total (n=357)	Total (n=68)	-
No/partial resolution	42.3% (n=151)	27.9% (n=19)	0.027
Full resolution	57.7% (n=206)	72.1% (n=49)	
Taste loss	Total (n=343)	Total (n=76)	-
No/partial resolution	33.8% (n=116)	19.7% (n=15)	0.017
Full resolution	66.2% (n=227)	(80.3%) (n=61)	
Combined smell and taste loss	Total (n=261)	Total (n=54)	-
No/partial resolution	36.0% (n=94)	20.4% (n=11)	0.026
Full resolution	64.0% (n=167)	79.6% (n=43)	

In participants with SARS-CoV-2 antibodies who reported full resolution of their smell loss, a full recovery of the sense of smell was reported to have occurred within one week in 11.7%, within 1-2 weeks in 26%, within 2-4 weeks in 26.5% and within >4 weeks in 35.8%.

The effects of smell loss pattern and presence of parosmia on recovery of the sense of smell in participants with SARS-CoV-2 IgG/IgM antibodies

The effect of complete vs. partial smell loss and the presence of parosmia on smell recovery in participants with positive SARS-CoV-2 antibodies was investigated. In participants who experienced complete loss of their sense of smell, full sense of smell recovery was reported by 54.5% compared to 67.4% in participants who reported a partial loss of their sense of smell (54.5% vs 67.4%, $p=0.032$).

Out of participants who reported parosmia at the time of their smell loss, full recovery was reported by 41.4% compared to 65% in participants with smell loss who did not experience parosmia (41.4% vs. 65%, $p<0.001$).

The effects of taste loss pattern and presence of dysgeusia on recovery of the sense of taste in participants with SARS-CoV-2 IgG/IgM antibodies

The effect of complete vs. partial taste loss and the presence of dysgeusia on smell recovery in participants with positive SARS-CoV-2 antibodies was investigated. There was no significant difference in the reported rates of recovery of taste loss in participant who reported complete vs. partial loss of their sense of taste (64.7% vs. 67.9%, $p=0.525$).

Out of participants who experienced dysgeusia at time of their loss of taste, a significantly lower proportion reported full resolution of their taste loss, compared to participants who did not experience dysgeusia (60.7% vs. 71.4%, $p=0.036$).

Participants who experienced taste sensations in the absence of eating or drinking reported lower resolution rates compared to participants who did not (51.2% vs 71.0%, $p=0.001$).

The effect of sex and age on the recovery of the sense of smell and taste in participants with SARS-CoV-2 IgG/IgM antibodies

Full recovery of sense of smell was more prevalent among males compared to females (72.8% in males vs. 51.4% in females, $p<0.001$). Similarly, full taste loss resolution was more common in males vs. females (80.8% vs. 60.1%, $p<0.001$) as was full resolution of combined smell/taste loss (69.6% vs. 4.1%, $p<0.001$); Table 4.

Table 4: Resolution of loss of smell, loss of taste and combined loss of smell and taste in female vs. male participants with SARS-CoV-2 IgG/IgM antibodies.

	Female	Male	p-value (0.05)
Smell loss resolution			
Full resolution	51.4% (n=130)	72.8% (n=75)	<0.001
No/partial resolution	48.6% (n=123)	27.1% (n=28)	
Taste loss resolution			
Full resolution	60.1% (n=146)	80.8% (n=80)	<0.001
No/partial resolution	39.9% (n=97)	19.2% (n=19)	
Combined smell and taste loss resolution			
Full resolution	45.1% (n=102)	69.6% (n=64)	<0.001
No/partial resolution	54.9% (n=124)	30.4% (n=28)	

The effect of age on resolution of smell and taste loss was evaluated. Mean age of male and female participants was comparable for participants who experienced full resolution of the loss in their sense of smell (40.4 ± 13.2 years in males vs. 38.1 ± 11.3 in females, $p=0.333$), their sense of taste (40.3 ± 13.4 vs. 37.1 ± 10.7 $p=0.153$) and combined loss of smell and taste (40.0 ± 12.6 vs. 37.1 ± 11.0 , $p=0.122$). In participants with loss of their sense of taste that did not resolve at the time of follow-up, mean age was significantly higher in females compared to males (42.7 ± 12.5 years vs. 37.6 ± 12.6 years, $p=0.030$). Mean age was also significantly higher in female participants with unresolved combined loss of smell and taste loss compared to male participants (42.8 ± 12.5 vs. 34.6 ± 10.4 , $p=0.001$). Mean age of female participants with unresolved smell loss was 41.6 ± 11.7 years compared to 37.4 ± 12.7 years in male participants, however this borderline difference did not reach statistical significance ($p=0.053$) (Figure 2).

In light of the above findings, we further evaluated the effect of age on smell and/or taste loss resolution in female participants. A significantly higher age was observed in female participants without resolution compared to those with full resolution of the loss of their sense of smell (41.6 ± 11.7 yrs vs. 38.1 ± 11.3 yrs, $p=0.010$), their sense of taste (42.7 ± 12.5 yrs vs. 37.1 ± 10.7 yrs, $p<0.001$) and combined smell and taste (42.8 ± 12.5 yrs vs. 37.1 ± 11.0 yrs, $p<0.001$).

Predictors of persisting smell loss in a community population with SARS-CoV-2 antibodies and acute loss of their sense of smell

Logistic regression was used to explore the relative importance of participant's age, sex, ethnicity, smoking status, presence of parosmia and smell loss pattern as risk factors for persistent smell loss at >4 weeks from onset.

Female participants were almost 2.5 times more likely to have ongoing smell loss after 4 weeks compared to participants of male sex (OR 2.46, 95% CI 1.47 to 4.13, $p=0.001$). Parosmia was also shown to have a significant association with unresolved smell loss at 4-6 week follow-up (OR 2.47, 95%CI 1.54 to 4.00, $p<0.001$), in a model adjusting for the age, ethnicity, patterns of smell loss (complete vs partial) and smoking; Table 5.

Table 5: Logistic regression exploring the association between age, sex, ethnicity, smoking status, presence of parosmia and smell loss pattern (complete vs partial) and no resolution of smell loss at 4 weeks follow up.

Variable	B	OR	95% CI (lower)	95% CI (upper)	p value
Age	0.13	1.013	.994	1.032	<i>0.172</i>
Ethnicity	0.96	1.101	.595	2.034	<i>0.760</i>
Complete anosmia	0.529	1.697	0.998	2.884	<i>0.051</i>
Parosmia	0.904	2.470	1.539	3.966	<0.001
Sex (Female)	0.901	2.461	1.468	4.126	0.001
Smoking	0.303	1.355	0.604	3.038	<i>0.462</i>

Persistent smell and/or taste loss as a manifestation of long COVID.

At the end of the 4-6 week follow-up period 42.3% (n=151) of participants with positive SARS-CoV-2 antibodies had ongoing smell loss, 33.8% experienced ongoing taste loss and 36% had ongoing taste and smell loss. We also evaluated the resolution of other symptoms of COVID-19 at the end of the follow-up period in participants positive for SARS-CoV-2 antibodies. Out of 134 participants with unresolved smell loss who reported additional COVID-19 symptoms on their original questionnaire, 29.1% (n=39) had at least 1 additional unresolved symptom at the time they completed their follow-up questionnaire, compared to 19.9% (n=35) of participants with full resolution of their smell loss (29.1% vs 19.9%, p=0.059). The most commonly reported unresolved symptoms were shortness of breath, chest pain and muscle/joint pains.

Objective smell testing in a subsample of participants and correlation with perceived smell function

A subsample of 50 participants underwent objective olfactory testing using the UPSIT. 84% were female (n=42) and 16% (n=8) male. The mean age was 39.6 ±13.5 years and mean duration of test date from the onset of symptoms was 21.6 ±4.7 weeks. 76% (n=38) participants had complete loss of their sense of smell at the time of the original questionnaire and 24% (n=12) partial loss of smell. At the time of the follow-up questionnaire 16% (n=8) reported their smell loss 'did not resolve', 42% (n=21) reported their smell loss 'resolved partially' and 42% (n=21) reported their smell loss 'resolved fully'.

The mean UPSIT test score was 29.1 ±7.5 points. In view of the time elapsed between the completion of the follow-up questionnaire and the UPSIT testing, prior to testing, participants were asked how they perceived their smell function. Their answers were grouped into: 'No or minimal sense of smell', 'Sense of smell improved but not fully recovered' or 'Sense of smell fully recovered'. Table 6 illustrates a comparison of participants' perceived smell function and their UPSIT test result, by test result category. A Spearman rank correlation analysis found a significant correlation between perceived smell function and UPSIT test result category (r=0.84 ± 0.71 to 0.90, p<0.001).

Table 6: Comparison between UPSIT test result and perceived smell function in a study subgroup of 50 participants

	Minimal/no sense of smell (n=11)	Improved sense of smell, not fully recovered (n=9)	Fully recovered (n=30)
Total anosmia	45.5% (5)	0%	0%
Severe microsmia	45.5% (5)	0%	0%
Moderate microsmia	9.0% (1)	77.8% (7)	0%
Mild microsmia	0%	11.1% (1)	16.7% (n=5)
Normosmia	0%	11.1% (1)	83.3% (n=25)
Spearman r	0.95	-0.63	-0.89

Discussion

We report longitudinal data from a community cohort with a new loss in their sense of smell and/or taste and resolution of these symptoms both in people with positive and negative SARS-CoV-2 IgG/IgM antibodies. Our data come from an entirely community based cohort with a low hospital admission rate where loss of taste and/or smell are the predominant symptoms. 77.9% of our cohort had positive SARS-CoV-2 antibodies and the study had a follow-up completion rate of 82.2%. We report a higher rate of recovery of smell loss (72.1% vs. 57.7%; $p = 0.027$), taste loss (80.3% vs. 66.2%; $p = 0.017$) and combined smell and taste loss (79.6% vs. 64%; $p = 0.026$) in participants who tested negative compared to participants who tested positive for SARS-CoV-2 antibodies.

Importantly, our study highlights the high percentage of patients with ongoing smell loss (42.3%), ongoing taste loss (33.8%) and combined smell and taste loss (36.0%). The observed smell loss resolution rate of 57.7% in participants with SARS-CoV-2 antibodies within 4–6 weeks in our study is in line with existing literature[12, 20]. Dell’Era *et al.* similarly reported that in 355 participants with COVID-19, 70% reported either smell loss and/or taste loss during infection[21]. 49.5% of participants reported full resolution of both sense of smell/taste after 14 days since the onset of symptoms, increasing to 62.9% at time of interview (23 days median, range 15-31), with a median recovery time of 10 days. In contrast to our community-based study, their findings come from a hospitalised patient cohort. Resolution rates in the literature currently range from 29-92.8%[11, 12, 22]. Discrepancies are likely due to differences in study populations, sample size, location and duration of follow up since onset of symptoms.

Furthermore, we report higher rates of smell loss resolution in participants with partial compared to complete smell loss (67.4% vs. 54.5%, $p = 0.032$). This is compatible with Kosugi *et al.* [14] who reported that the full resolution from ‘partial loss of smell’ in COVID-19 positive patients takes place more frequently than that from ‘complete loss of smell’. Supportively, using an objective approach, Lechien *et al.* also found that higher baseline severity of smell loss, measured by ‘Sniffin-Sticks’ was strongly predictive of persistent smell loss[23]. Beltrán-Corbellini *et al.* compared smell loss recovery in 70 COVID-19 and 40 influenza participants[24]. 40% of COVID-19 positive participants reported full resolution after 7.4 ± 2.3 days and 16.7% reported partial resolution after 9.1 ± 3.6 days, whereas 100% of influenza participants fully recovered their sense of smell. The fact that participants with SARS-CoV-2 antibodies also had higher rates of complete anosmia, suggests a more severe spectrum of COVID-19 related smell loss compared to post-viral smell loss from other respiratory pathogens.

Interestingly, one of our key findings shows that parosmia was more common in the group of participants with unresolved smell loss and was also a predictor of non-remission in the logistic regression analysis, which is novel in COVID-19. Parosmia has been associated with post-viral smell loss prior to the COVID-19 pandemic[25]. A potential

explanation for our finding may be that parosmia has been associated with decreased number and disordered regrowth of olfactory axons into existing neural circuits and a preponderance of immature neurons[26]. Comparatively, Liu *et al.* found that in 153 participants with post-infectious smell loss the presence of parosmia was associated with clinically significant recovery in suprathreshold olfactory function discrimination in patients receiving olfactory training[27]. Parosmia in the context of post-viral smell loss is associated with ongoing smell impairment, and although has been viewed as a sign of recovery, its role as a prognostic marker remains largely unclear. However, our data suggest that parosmia is a marker of poor prognosis in COVID-19. Similarly, our finding show that dysgeusia and experiencing taste sensations in the absence of eating and drinking were associated with lower reported taste loss resolution rates. Together, these findings suggest that distorted chemosensory perception is a risk factor for prolonged smell and/or taste loss and long-COVID.

With regard to full resolution of smell and/or taste loss, a significant sex difference was evident. Females had a lower full resolution rate of smell loss (51.4% vs. 72.8%; $p < 0.001$), taste loss (60.1% vs. 80.8%; $p < 0.001$) and combined smell and taste loss (45.1% vs. 69.6%; $p < 0.001$), compared to males, respectively. These findings are supported by several studies who also report the recovery of sense of smell was longer in females[10, 21]. Although Meini *et al.* found that the recovery rate did not differ significantly between males and females, they however, the mean recovery time from smell loss or taste loss was significantly longer for females than for males (26 vs. 14 days, $p = 0.009$), even though the mean age of males was significantly higher than that of females (66 vs. 57 years, $p = 0.04$)[20].

Notably, in our study, female participants who reported no/partial resolution of smell loss were significantly older (41.6 ± 11.7 years) than female participants who reported full resolution of smell loss (38.1 ± 11.3 years, $p = 0.010$). The same was also found to be true for taste loss (42.7 ± 12.5 vs. 37.1 ± 10.7 , ($p < 0.001$) and combined smell and taste loss (42.8 ± 12.5 vs. 37.1 ± 11.0 , $p < 0.001$). In contrast, Lee *et al.* reported that young age, particularly the age group of 20–39 years, showed a tendency to be associated with a longer persistence of anosmia[28]. Interestingly, oestradiol has been shown to increase olfactory epithelial cell density and to have a protective role against olfactory function decline[29]. Additionally, in animal models of neurodegenerative diseases oestradiol replacement prevents olfactory dysfunction[30]. This study was not powered to estimate the effect of menopause-driven differences in this subgroup. Nevertheless, a link between prolonged or reduced recovery of smell function and a post-menopausal state appears plausible.

Loss of smell and taste have been demonstrated to persist beyond resolution of the infectious phase of COVID-19[31]. In light of evidence from the clinical course of smell loss from other viruses, smell loss after COVID-19 could persist for two or more years[32, 33]. Arguably, our study follow-up window still only represents a relatively short-term observation and it is reasonable to predict that a number of participants will have further recovered their sense of smell and taste over additional weeks. Nevertheless, loss of smell and taste undoubtedly constitute a manifestation of long-COVID, which may result in significant psychological morbidity and adversely impact quality of life of the subset of patients with long-term unresolved smell and taste loss[8, 16, 34]. Given the limitations in accuracy and accessibility to testing during particularly the earlier phases of the pandemic, further patient populations may present with olfactory and gustatory impairment and features of long-COVID, indicative of previous COVID-19 infections. Of note, current proposed diagnostic criteria for long-COVID or chronic COVID-19 do not necessitate a positive test at time of symptom onset. The magnitude of the pandemic and the potential for SARS-CoV-2 to cause long-term smell and/or taste loss in relatively small cohorts therefore suggest that the overall prevalence of long-COVID with smell loss within the general population will be considerable[5, 9].

It will be vital to develop a better understanding of the pathophysiology causing smell loss as well as the physiological processes driving smell recovery, in order to facilitate development of effective treatments for smell loss. Angiotensin-converting enzyme-2 receptors (ACE-2) present on olfactory epithelial cells and neuropilin-1 receptors (NRP1), abundant on all olfactory cell lines, are known entry routes for SARS-CoV-2 and damage to these cells have been proposed as

potential mechanisms for smell loss[35–37]. Viral entry via NRP1 could result in direct damage to olfactory sensory neurons[35]. Furthermore, the distribution of these two receptors may form a plausible explanation for the spectrum of smell loss, with mild and typically short-lived smell loss from ACE-2 invasion versus more longstanding smell loss via NRP1 mediated sensory neuronal damage, following COVID-19. Therapeutic strategies including olfactory rehabilitation and corticosteroids are already in use to aid recovery of smell function following COVID-19, with further therapeutic strategies in clinical trials [14, 15]. With emerging treatments for COVID-19 related anosmia and the high predicted prevalence of long covid with long-standing smell loss, identifying those at risk of long-COVID with smell loss will be key. We highlight female sex (and increasing age within female cohorts) as well as the presence of parosmia as key risk factors for a prolonged clinical course of COVID-19 related smell loss.

Finally, in this study, we addressed the limitation of using subjective assessment of smell by recruiting a subset of participants who underwent objective UPSIT testing. Our results show that objectively assessed smell function using UPSIT correlates well with perceived smell function in this population, which highlights the reliability of our subjective patient-reported data on smell function following COVID-19. This finding is in line with a study conducted in ambulatory COVID-19 patients using the 12-item Brief Smell Identification Test (BSIT) which also concluded that self-reported olfactory loss is a strong predictor of abnormal olfactory function[38]. Furthermore, this highlights that in this subsample, tested 21.6 ± 4.7 weeks since the onset of their symptoms, 20% of participants had ongoing loss of their sense of smell, who would meet diagnostic criteria for both long-COVID and chronic COVID-19.

Limitations

The main limitation of this study remains the lack of a general population control group without loss of smell/taste. Our selection criteria enabled us to study acute smell and taste loss as presentations of COVID-19 as well as their resolution in people both with and without SARS-CoV-2 antibodies. Coupled with the web-based delivery of the study, this leads to susceptibility to a degree of selection and age bias, which required proficiency with computers and smartphones and may have resulted in under-representation of older adults. Furthermore, the majority of our participants were female; this may reflect previous findings that females are more likely to engage in research and also have a higher frequency of loss of smell and/or taste with COVID-19 than males. Through recruiting a subset of participants for objective testing we addressed the previous limitation of lack of objective testing, and demonstrated a strong correlation between perceived and assessed smell function.

Conclusions

We followed up a community cohort of people who had reported acute loss of their sense of smell and/or taste and had undergone SARS-CoV-2 IgG/IgM antibody testing 4–6 weeks earlier in order to investigate the clinical course of smell and/or taste loss. We also aimed to identify factors that were associated with persistent smell loss at 4–6 weeks of follow-up. In line with existing literature, we can offer reassurance that smell and/or taste loss is a transient phenomenon in most SARS-CoV-2 cases. However, persistent smell and taste loss constitute a feature of long-COVID. The population of patients with longstanding smell and/or taste loss as a manifestation of long-COVID will continue to grow during and following the pandemic; given the impact of these symptoms on quality of life and safety, it will be imperative to devise support and treatment pathways. We identified the presence of parosmia and female sex as risk factors for persistent smell loss, as well as increasing age within the female sub-cohort. Similarly, female sex and increasing age as well as distorted taste perception were associated with persistent taste loss. Our findings highlight that female patients over the age of 40, who experience with a distorted perception of their sense of smell and/or taste are likely to benefit from therapeutic interventions to prevent persistent smell and/or taste loss and should be prioritized when targeted therapies for post-covid smell and taste loss become available.

Abbreviations

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

Coronavirus disease 2019 (COVID-19)

Immunoglobulin G (IgG)

Immunoglobulin M (IgM)

University of Pennsylvania Smell Identification Test (UPSIT)

Angiotensin-converting enzyme-2 receptors (ACE-2)

Neuropilin-1 receptors (NRP1)

Brief Smell Identification Test (BSIT)

Declarations

Ethics approval and consent to participate

The study received ethical approval from the National Health Service Queen's Square Research Ethics Committee (IRAS Project ID 282668, ClinicalTrials.gov: NCT04377815) and was conducted in line with the declaration of Helsinki and Good Clinical Practice.

Consent for publication

Not applicable

Availability of data and materials

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Competing interests

The authors declare no competing interests.

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Authors' contributions

JM: Conceptualization, Data curation, Participant recruitment, Formal analysis, Investigation, Validation, Writing

CF: Data curation, Formal analysis, Investigation, Writing

CM: Investigation, Methodology, Writing

JMok: Investigation, Methodology, Writing

NB: Data curation, Investigation, Writing

ML: Investigation, Writing

AC: Conceptualization, Formal analysis, Investigation, Methodology, Project administration, Writing

RLB: Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Methodology, Resources, Writing

All authors read and approved the final manuscript.

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