

High prevalence of persistent smell loss and qualitative smell dysfunction during the COVID-19 pandemic in the United States: urgent need for clinical trials

Running Title: Persistent COVID-19 associated smell dysfunction

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The COVID-19 pandemic has put unprecedented strains on healthcare systems across the globe and this is thought to continue with the advent of long COVID. Long COVID is a condition of persistent sequelae for longer than one month after initial infection and may involve any body system.¹ The associated disability and long-term morbidity has placed an immense burden across communities, from the impact on daily living and interpersonal relationships to reduced workforce capacity and the consequent economic cost. One presentation that can be regarded as part of the long COVID spectrum is persistent smell and taste dysfunction.^{2,3} However, the burden and prevalence of this problem is still not fully recognized, especially within the United States. In an attempt to estimate the burden of persistent smell loss in the US, we interviewed a gender and age-matched representative sample of the US population, comprising 4,534 adults across all fifty states, using a previously reported questionnaire (supplemental material).⁴

Twenty percent (872/4,369, 95% CI: 18.8%-21.1%) of responders reported having experienced a loss of sense of smell since January 2020; extrapolated to the entire US population (World Bank, 2020, estimated 329.5 million), this is equivalent to 65.8 million (95% CI: 61.9 million to 69.7 million) individuals having experienced smell loss during the COVID-19 pandemic. For those who reported a loss of sense of smell, roughly half recovered their smell within one month (47.5%, 360/757). Subjective smell loss persisted for 1-3 and 3-6 months for 16.4% (124/757) and 20.2% (153/757), respectively. For the remaining 15.5% (120/757), smell loss persisted beyond 6 months. Taking a rate of persistent smell loss of 2.7% (120/4,369; 95% CI: 2.3%-3.2%), this is equivalent to 9.0 million individuals in the US (95% CI: 7.4 million to 10.6 million).

Participants were asked to rate their sense of smell and taste on a scale of 0 (completely absent) to 10 (normal) both at its worst and at the time of the survey. For sense of smell, the mean scores at its worst and at the time of survey were 6.49 (Std. Dev. 3.31) and 6.96 (Std. Dev. 3.04) in those who reported smell loss, respectively. For sense of taste, the mean scores were 6.72 (Std. Dev. 3.09) and 6.95 (Std. Dev. 2.93), respectively.

Parosmia and phantosmia were reported in 17.9% (148/829) and 21.1% (175/829) of participants, who initially reported smell loss, respectively. For these participants who reported parosmia, 29.3% (43/147) had fully recovered on the date of the survey with improvements observed in 38.8% (57/147). Parosmia remained unchanged or worsened in 9.5% (14/147) and 18.4% (27/147) respectively. When considering all survey responders, unchanged or worsened parosmia (i.e. persistent) has a rate of 0.9% (95% CI: 0.7-1.2%), which is equivalent to 3.1 million individuals in the US (95% CI: 2.1 million to 4.0 million). For those who reported phantosmia,

26.3% (46/175) had fully recovered, whilst 40.6% (71/175) had seen improvements. Phantosmia remained unchanged or worsened in 15.4% (27/175) and 14.3% (25/175), respectively. Seventy one percent (589/831) reported having experienced sensations of burning, cooling, or tingling in their nose or mouth (chemesthesis).

Regarding participants' sense of taste, 33.1% (276/834) reported absent or diminished perception of sweet flavors, 42.6% (354/831) for salty flavors, 41.9% (349/834) for sour flavors and 37.5% (312/832) for bitter flavors. The perception of these flavors was distorted in 12.5% (104/834), 14.2% (118/831), 13.7% (114/834) and 16.7% (139/832), respectively.

69.8% (579/829) of responders with smell loss reported that their smell dysfunction had adversely impacted their quality of life. These participants were further asked to answer a series of quality of life (QoL) -related items, pertaining to the impact of smell dysfunction on daily life, eating habits and mental health. Responses for these were on a 7-point Likert scale where a higher score indicated a worse perceived impact on the corresponding item. For each of the fifteen QoL items, there was a statistically significant difference in scores between participants who either experienced anosmia, hyposmia, parosmia or a heightened sense of smell. When comparing parosmia to anosmia (i.e. severe smell loss), a higher combined QoL score (scale 15 – 105, where 105 indicates the worst overall QoL) was observed in the anosmic group (median_{anosmic}= 96 (range = 15 – 105) vs. median_{parosmic}= 69 (range = 15 – 105), $p<0.001$). Comparing parosmia to hyposmia, the combined QoL score was higher in the parosmic (i.e. mild smell loss) group (median_{parosmic}= 69 (range = 15 – 105) vs. median_{hyposmic}= 57 (range = 15 – 95), $p=0.001$).

Although there was no psychometric testing to corroborate the subjective self-reporting in this specific population, the smell questionnaire utilized has already been compared with and tested against validated psychometric measures in a UK trial⁵, and has been further utilized in a study of the UK general public⁴, demonstrating its use as an effective means of ascertaining patterns of olfactory dysfunction in a large population.

In summary, our findings show that a large proportion of a sample from the US general population have experienced some degree of smell loss since the start of the COVID-19 pandemic. Although many of these individuals experience spontaneous recovery, there is still a significant number of patients with persistent smell dysfunction beyond 6 months, and that this number is greater than prior estimates.^{6,7} Importantly, this work has shed light on an extremely challenging aspect of COVID-19 related smell dysfunction, that of distorted smells, i.e. parosmia. This was reported to have either remained unchanged or worsened in 0.9% of respondents, indicating that roughly 3 million US adults may have persistent parosmia. Adding to the 9 million individuals with long term hyposmia or anosmia, this is a huge burden and aligns with recent

evidence of its emerging role in the overall symptomology of long COVID.^{8,9} Crucially, few treatments for parosmia are available in clinical practice, most of which rely on anecdotal evidence or small case series. This is of particular importance as the impact of parosmia on patient quality of life appears to be substantial. Through this study and what the authors' own clinical observations, there is a significant psychological and emotional consequence related to parosmia, and other qualitative smell disorders, that should not be overlooked. As such, there remains an urgent need to address the therapeutic gap in their management, with studies currently underway.

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