

# Age and subtle cognitive impairment are associated with long-term olfactory dysfunction after COVID-19 infection

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## Next Study group

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**Running Title:** olfactory dysfunction after COVID-19 infection

**Search terms:** COVID-19; hyposmia; olfactory dysfunction; long-covid; neurology.

### **Why does this paper matter?**

This is the first study indicating that geriatric patients with subtle cognitive deficits are at high risk for persistent olfactory dysfunction six months after SARS-CoV-2 infection

### **Introduction**

Severe Acute Respiratory Syndrome coronavirus 2 (SARSCoV-2), the virus responsible for the coronavirus disease 2019 (COVID-19) pandemic, has been widely associated with extra-pulmonary manifestations, including a broad range of neurologic symptoms<sup>1</sup>.

Olfactory and taste disorders have been consistently reported as common non-respiratory symptoms of SARS-CoV-2 infection, although the persistence of neurosensory dysfunctions is still theme of debate<sup>2</sup>. Age and premorbid health status might play a major role in modulating the vulnerability to long-term olfactory recovery after SARS-CoV-2 infection. Indeed, the prevalence of olfactory dysfunction increases in normal ageing but has also been associated with several age-related neurodegenerative conditions<sup>3</sup>.

In this study, we thus evaluated the prevalence and predictors of olfactory dysfunction in a consecutive series of patients hospitalized for COVID-19 and its potential association with features or symptoms suggestive for long-term neurologic involvement.

## RESULTS

One hundred-sixty-eight patients hospitalized for mild to moderate COVID-19 were evaluated at six months after discharge. Of these, 106 patients were assessed in presence through a standardized assessment. Five patients (5.7%) were excluded from the study for allergic rhinitis, resulting in a final dataset of 101 patients.

The Sniffin' Sticks test<sup>4</sup> identified 50 patients with an abnormal score  $\leq 8$ , including 11 patients with severe (score  $<4$ ) hyposmia (4/11 of them reported subjective olfactory dysfunction) (Table 1). Patients with subjective hyposmia exhibited lower Sniffin' Sticks total score ( $5.3 \pm 3.5$  vs  $8.1 \pm 2.4$ ,  $p=0.012$ ) but three of them exhibited normal scores. Conversely, patients with long-term subjective hypogeusia exhibited similar Sniffin' Sticks total scores compared to subjects without complaints ( $7.8 \pm 2.5$  vs  $7.8 \pm 2.8$ , respectively  $p=0.70$ ). Hyposmia and hypogeusia reported during hospitalization did not predict long-term objective hyposmia (OR 1.1; IC95% 0.75-1.7) or subjective hyposmia (OR 1.03; IC95% 0.70-1.5,  $p=0.52$ ).

Compared to patients with normal olfactory function, those with objective hyposmia were older ( $68.2 \pm 11.3$  vs.  $58.2 \pm 12.1$  years;  $p= <0.001$ ) but exhibited similar comorbidity score at admission and during hospitalization and did not differ for duration of hospitalization, oxygen therapy and severity of COVID-19 (OR 1.5; IC95% 0.83-2.7,  $p= 0.10$ ). Age was confirmed as the only predictor of long-term objective hyposmia in logistic regression analyses (Wald 6.4,  $\text{Exp}(B)=0.09$ ,  $p=0.01$ ); subjects older than 65 years exhibited a 1.86 increased risk of hyposmia (IC95%; 1.19-2.9) and subjects older than 75 years of 2.67 (IC95% 1.10-6.5).

No difference of either self-reported neurological symptoms at the neuro-checklist or objective neurological signs was documented between patients with normal olfactory function and hyposmia (Supplementary Table 1). Patients with hyposmia exhibited lower MoCA total score

( $23.2 \pm 3.4$  vs.  $25.7 \pm 2.5$ ) compared to subjects with normal olfactory function in logistic regression analyses adjusted for age, sex and educational levels (Wald 5.8, Exp(B)1.2,  $p=0.01$ ).

## DISCUSSION

The prevalence of objective hyposmia in our cohort of hospitalized patients was fifty percent, definitively higher compared to prevalence of hyposmia in the general population in the sixth decade of age<sup>5</sup>. This prevalence fits well with recent reports adopting sniffing sticks in independent cohorts of SARS-CoV-2 patients<sup>6</sup>.

Older age resulted the most important factor associated with long-term hyposmia- as patients older than 75 years of age were at three-fold risk of long-term hyposmia compared to younger subjects. Conversely, we failed to find an association between olfactory dysfunction and severity of COVID-19 disease, thus supporting the claim that hyposmia is independent from the degree of respiratory involvement<sup>7</sup>. Our study went also further, by showing an association between long-term hyposmia and cognitive impairment, after controlling for age, gender and education. These findings corroborate the well-known association between subtle cognitive deficits and olfactory dysfunction in the elderly<sup>8</sup>. Although the mechanisms underlying long-term central nervous system impact of SARS-CoV-2 are still unclear<sup>9,10</sup>, these preliminary results seem to suggest that older subjects with subtle cognitive deficits are a “vulnerable” population with a higher risk of long-term olfactory dysfunction.

We acknowledge that this study entails different limitations. First, we limited the observation to patients presenting with mild to moderate COVID-19 disease; second, patients were evaluated only for orthonasal olfaction, whereas taste disorders were not assessed. Furthermore, no data about pre-existing objective hyposmia or cognitive deficits were available, though we accurately

excluded subjects with pre-morbid cognitive impairment or subjective hyposmia from the analyses.

Despite these limitations, the study underlined the high prevalence of objective hyposmia six months after COVID and identified age and subtle cognitive deficits as factors strongly associated with long-term olfactory dysfunction. Further studies evaluating the nature and progression of cognitive changes and olfactory function would be necessary over time.

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#### **Financial disclosure and conflict of interest regarding the research related to the manuscript:**

All authors have no conflict of interest regarding the research related to the manuscript.

#### **Author contributions**

Conception and design of the study: VC, AP and AP. Acquisition and analysis of data: VC, AP, SCP, NC, GB, SG, DS, MB, ML, AP

Drafting the manuscript and figures: VC, AP and AP.

#### **Declaration of interests**

The authors declare no competing interests.

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Supplementary Table 1

Neurological sign and symptoms in COVID19 patients at 6 months follow-up \*p values were calculated by  $\chi^2$  test or Fisher's exact test, as appropriate.

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**Table 1.:** Demographic and clinical characteristics between previous COVID-19 patients with and without persistent olfactory dysfunction.

\*p values were calculated by T-test or Fisher's exact test, as appropriate.

BCRSS: Brescia-COVID Respiratory Severity Scale; CIRS: Cumulative Illness Rating Scale; MoCA: Montreal Cognitive Assessment.

	Total (n=101)	Normal olfactory function (n=51)	Hyposmia or anosmia (n=50)	p value
<b>Demographic and clinical characteristics</b>				
Age, years	63.62±12.9	58.20 ± 12.1	68.24 ± 11.3	<0.001
Sex, female	28 (27.7%)	17 (33.3%)	11 (22.0%)	0.186
Total days of hospitalization	12.36 ± 10.5	11.14 ± 8.5	12.98 ± 11.7	0.374
BCRSS	0.92 ± 0.90	1.02 ± 0.99	0.82 ± 0.80	0.649
Low-flow oxygen therapy needed	68 (67.3%)	33 (64.7%)	35 (70.0%)	0.830
Non-invasive ventilation	13 (12.9%)	6 (11.8%)	7 (14.0%)	0.796
Orotracheal intubation	2 (1.98%)	1 (1.96%)	1 (2.0%)	0.747
CIRS comorbidity index pre-hospitalization	1.35 ± 0.25	1.35 ± 0.20	1.40 ± 0.21	0.08
CIRS comorbidity index during hospitalisation	1.76 ± 0.28	1.71 ± 0.24	1.81 ± 0.31	0.10
Subjective Hyposmia at follow-up	11 (10.89%)	3 (5.9%)	8 (16.0%)	0.2
Subjective hypogeusia/dysgeusia at follow-up	17 (16.8%)	9 (17.6%)	8 (16.0%)	0.795
MoCA at follow-up	24.4 ± 3.2	25.7 ± 2.5	23.2 ± 3.4	<0.001