Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Letter to the Editor

Olfactory dysfunction after COVID-19: metanalysis reveals persistence in one-third of patients 6 months after initial infection

Dear editor,

Recently, Deng et al. reported a significant proportion of patients having persistent olfactory dysfunction (OD) even 2 years after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection.[1] Moreover, the prevalence of OD evaluated by psychophysical tests was higher than that estimated based on self-reported information. We had a valuable opportunity to carefully read this interesting manuscript and additional published studies to further explore the persistent OD after the coronavirus disease 2019 (COVID-19) infection.

COVID-19 was caused by SARS-CoV-2 infection, and it was listed as a global pandemic by the World Health Organization on March 11, 2020. The virus is mainly transmitted through respiratory droplets and physical contact. Besides respiratory symptoms, the most common symptom is dysfunction of smell and taste.

Post-acute COVID-19 syndrome, also known as long COVID, is a prolonged illness after the acute phase of COVID-19. It is defined as "the collection of symptoms that develop during or following a confirmed or suspected case of COVID-19 and continue for more than 28 days."[2] The OD associated with COVID-19 is usually transient, and it tends to subside spontaneously within a few weeks after the infection, especially in mild-to-moderate patients. However, some patients still complain of persistent OD 6 months after infection. Lechien et al. found the prevalence of OD significantly decreased from 50.8% (baseline) to 18.7% (1 year) and 3.5% (2 years) according to the psychophysical olfactory evaluations.[3] Some authors reported significantly higher rates of persistent OD, but only a few of them investigated the prevalence of OD after 6 months or even more than 1 year of infection using objective methods.

Loss of smell can have a serious impact on quality of life as it can negatively affect food enjoyment, nutritional balance, social communication, cognitive skills, and psychological functioning. In addition, it can expose patients and their families to dangerous situations.[4] Given the above-mentioned harms, there is an urgent need to develop effective treatments. We sought to explore the prevalence of persistent OD after COVID-19 infection, which is essential to understand the chronic symptoms of long COVID and to guide treatments.

For this reason, PubMed, Web of Science, Embase, and Cochrane Library databases were extensively searched for all compliant studies published from January 1, 2020, to December 27, 2022. The inclusion criteria were as follows: (1) adult patients with COVID-19 confirmed by reverse transcriptase–polymerase chain reaction; (2) peer-reviewed original studies in English; (3) OD after COVID-19 persisting for more than 6 months after infection; and (4) normal cognitive function before COVID-19 and no severe nasal injuries. Twelve studies report persistent OD after COVID-19 infection. General information about the included studies is summarized in Supplementary Material (Table 1). We focused on recording the number of patients with COVID-19 having OD for more than 6 months; especially those in which the dysfunction persisted for more than 1 year were of more concern to us. The results of 12 studies listed in Fig. 1 showed among patients with COVID-19, OD lasted for more than 6 months in about 30% of patients (95% CI, 0.20–0.40; $P < 0.01$). The heterogeneity (I^2) was 97.4% and the Begg's test P-value was 0.631, indicating no publication bias. To further

Table 1
The basic information of the included literature. OD: olfactory dysfunction. N: no data.

Author	Country	Age	Duration	Total No. of persistent OD	Total No. of OD
María	Spain	46.8 ± 13.9	12 months	43	78
Jerome	Multicenter	45.0 ± 12.0	24 months	6 (4 anosmia, 2 hyposmia)	123
Can	France	50.4 ± 18.9	9.5 months	93 (11 anosmia, 82 hyposmia)	229
Constantin	Germany	49.0 ± 14.4	8 months	85 (55 hyposmia)	212
Luigi	Italy	38.4 ± 12.5	253.4 ± 70.5 days	127 (18 anosmia, 109 hyposmia)	306
Francesca	Italy	N	12 months	46	176
Luigi	Multicenter	39.9 ± 0.5	419.8 days	45 (8 anosmia, 37 hyposmia)	119
Ameen	Israel	37.5 (19–74)	229 days	31	65
Martin	Germany	45 ± 2.06	201 days	1	26
JR	Multicenter	44.5 ± 16.4	6 months	11 (6 anosmia, 5 hyposmia)	233
Nhu	France	45	6 months	136	584
Mads	Multicenter	43.3	6 months	12	34

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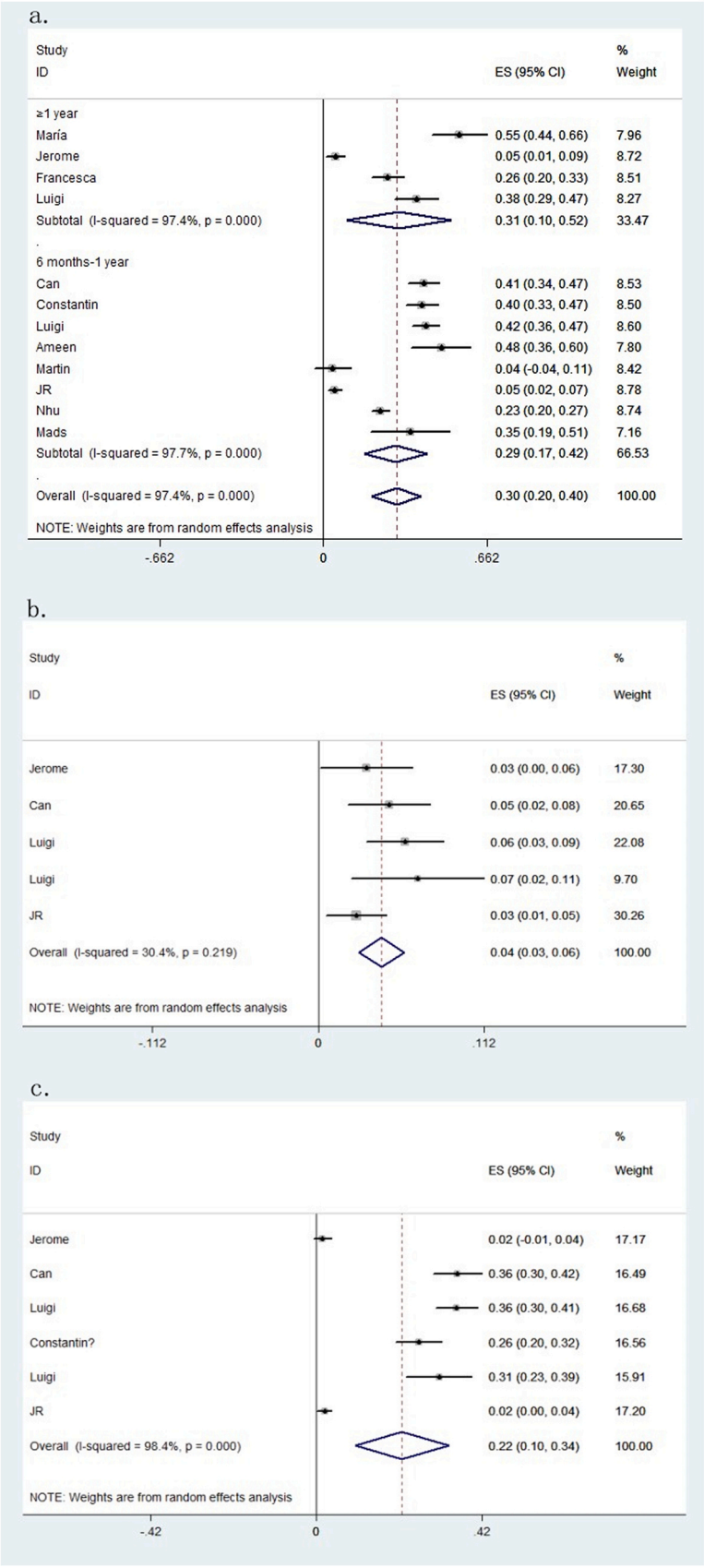

Fig. 1. (a) The pooled prevalence of persistent olfactory dysfunction after 6 months of infection in COVID-19 can be divided into 6 months to 1 year and more than 1 year. (b) The pooled prevalence of persistent anosmia after 6 months of infection in COVID-19. (c) The pooled prevalence of persistent hyposmia after 6 months of infection in COVID-19.

explore the persistence of olfactory impairment, we categorized the duration into 6 months to 1 year and more than 1 year. Similar rates were found for those in which the dysfunction lasted more than 1 year. The estimated prevalence rate was 31% (95% CI, 0.10–0.52; $P < 0.01$). OD can be subdivided into anosmia and hyposmia. In five studies, patients had anosmia 6 months after being infected with COVID-19, and the proportion was 4% (95% CI, 0.03–0.06; $P < 0.01$). Also, in six studies, the rate of patients having hyposmia was 22% (95% CI, 0.10–0.34; $P < 0.01$).

Within 50 days after COVID-19 diagnosis, acute symptoms such as diarrhea, stomach pain, and cold-like symptoms develop. However, what make people suffer more physically and mentally are the persistent cardiopulmonary symptoms, musculoskeletal symptoms, sensory symptoms (taste loss or olfactory disturbance), and general symptoms within 90–150 days after diagnosis.[5] It is estimated that as many as 1.6 million people in the United States have chronic OD due to COVID-19.[6] Chronic olfactory disorders may lead to eating behavior disorders, depression, and a general decrease in quality of life. However, little is known about the long-term course of OD associated with COVID-19. Previously, it was thought that SARS-CoV-2 caused anosmia by affecting the olfactory epithelium, the peripheral organ for olfaction that lines the olfactory cleft of the nasal cavity. The olfactory epithelium houses the primary olfactory sensory neurons responsible for detecting odors. Transient gene expression changes in olfactory sensory neurons, alterations in the characteristics of the mucus layer surrounding their cilia, and inflammation are thought to cause acute anosmia in animal models of SARS-CoV-2 infection.[7] Recent findings indicate that acute SARS-CoV-2 infection drives a proinflammatory reprogramming that is thought to induce long-term alterations in the function of other immune cells. T cell-mediated inflammation persists in the olfactory epithelium long after SARS-CoV-2 has been eliminated from the tissue, suggesting a mechanism for long-term post-COVID-19 smell loss.[8]

These mechanisms suggest therapeutic strategies. The persistent COVID-19-related chemical sensory dysfunction, a harmful sequela, needs to be treated physically and psychologically. For example, oral and intranasal corticosteroids, olfactory training, and oral vitamin–mineral supplementation are all feasible treatments. The olfactory scores indicate that the effect of rehabilitation combined with drugs may not be significantly different from that of single olfactory training therapy. However, there is an improvement in olfactory function after olfactory training.[9] Therefore, olfactory training cannot be ignored as an easy-to-administer, low-cost treatment with negligible side effects.

In conclusion, one-third of the patients still have OD 6 months after the first COVID-19 infection. Even after recovery from COVID-19, persistent symptoms still deserve our attention. In the future, large-scale long-term follow-ups of patients with OD may provide continuous insights into the etiology and treatment of OD.

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Declaration of Competing Interest

The authors declare no competing interests.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2023.01.041.

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