

# Long COVID, audiovestibular symptoms and persistent chemosensory dysfunction: a systematic review of the current evidence

## *Sindrome “Long COVID”, sintomi otovestibolari e disturbi chemosensoriali persistenti: revisione sistematica delle attuali evidenze scientifiche*

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### SUMMARY

**Objective.** The persistence of auditory, vestibular, olfactory, and gustatory dysfunction for an extended time after COVID-19 has been documented, which represents an emerging challenge of which ENT specialists must be aware. This systematic review aims to evaluate the prevalence of persistent audiovestibular and olfactory/gustatory symptoms in patients with “long-COVID”.

**Methods.** The literature was systematically reviewed according to PRISMA guidelines; PubMed, Scopus and Google Scholar were screened by searching articles on audiovestibular symptoms and olfactory/gustatory dysfunction after SARS-CoV-2 infection. The keywords used were hearing loss, tinnitus, vertigo, smell disorders, parosmia, anosmia, hyposmia, dysgeusia combined with COVID-19 or SARS-CoV-2.

**Results.** 1100 articles were identified. After removal of duplicates (382), 702 articles were excluded, and 16 were included in the systematic review. All articles included identified an association between SARS-CoV-2 infection and persistent hearing or chemosensory impairment. The studies were published over a period of 2 years, between 2019 and 2021.

**Conclusions.** The likelihood of patients with persistent audiovestibular symptoms related to COVID-19 was different among the articles; however, olfactory and gustatory disturbances were more consistently reported. Studies with longer follow-up are required to fully evaluate the long-term impact of these conditions.

**KEY WORDS:** Long-COVID, post-acute COVID, PASC, COVID-19 pandemic, anosmia

### RIASSUNTO

**Obiettivi.** La persistenza di disfunzioni uditive, vestibolari, gustative e olfattive persistenti dopo la risoluzione del COVID-19 è stata documentata in letteratura, e rappresenta una sfida emergente che necessita di una risposta adeguata da parte dello specialista otorinolaringoiatra. Lo scopo di questa revisione sistematica è rivedere le attuali conoscenze sulla persistenza di questi sintomi.

**Metodi.** È stata effettuata una revisione sistematica della letteratura disponibile, in accordo con le linee guida PRISMA; PubMed, Scopus e Google Scholar sono stati sottoposti a screening cercando articoli sui sintomi audiovestibolari e sulla disfunzione olfattiva/gustativa dopo l'infezione da SARS-CoV-2. Le parole chiave utilizzate sono state perdita dell'udito, tinnito, vertigini, disturbi dell'olfatto, parosmia, anosmia, iposmia, disgeusia sempre in combinazione con il termine COVID-19 o Sars-CoV-2. D

**Risultati.** Sono stati identificati 1.110 articoli; dopo la rimozione dei duplicati (382), 702 articoli sono stati esclusi, e 16 articoli, che identificavano l'associazione tra il SARS-CoV-2 e la persistenza di disturbi uditivi, vestibolari e chemosensoriali, e pubblicati tra il 2019 e il 2021, sono stati inclusi nella revisione sistematica.

**Conclusioni.** La percentuale di pazienti che mostrano una persistenza di sintomi audiovestibolari dopo COVID-19 è risultata variabile tra i diversi articoli, mentre le anomalie

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*olfattive e gustative sono riportate più costantemente. In futuro saranno necessari studi con follow-up più lungo, in modo da valutare l'impatto, a lungo termine, di questi disturbi.*

**PAROLE CHIAVE:** Long-COVID, post-acute COVID, PASC, pandemia COVID-19, anosmia

## Introduction

Since February 2020, the SARS-CoV-2 pandemic (COVID-19) has affected tens of millions of people worldwide; although initially identified as respiratory disease, today it is clear that SARS-CoV-2 infection is a multi-organ, multi-systemic disease, which affects organs and apparatus such as the inner ear and cochlea, liver, kidneys, heart and brain <sup>1</sup>. Although symptoms generally disappear in few weeks, about one-third of patients continues to suffer from one or more persistent symptoms for long time after resolution of infection; this condition has been termed “long-COVID” <sup>2</sup>, and recently renamed syndrome of “post-acute sequelae of SARS-CoV-2 infection” (PASC). The pathogenesis of PASC is still unclear, but reasonably it is a multi-factor event (Fig. 1).

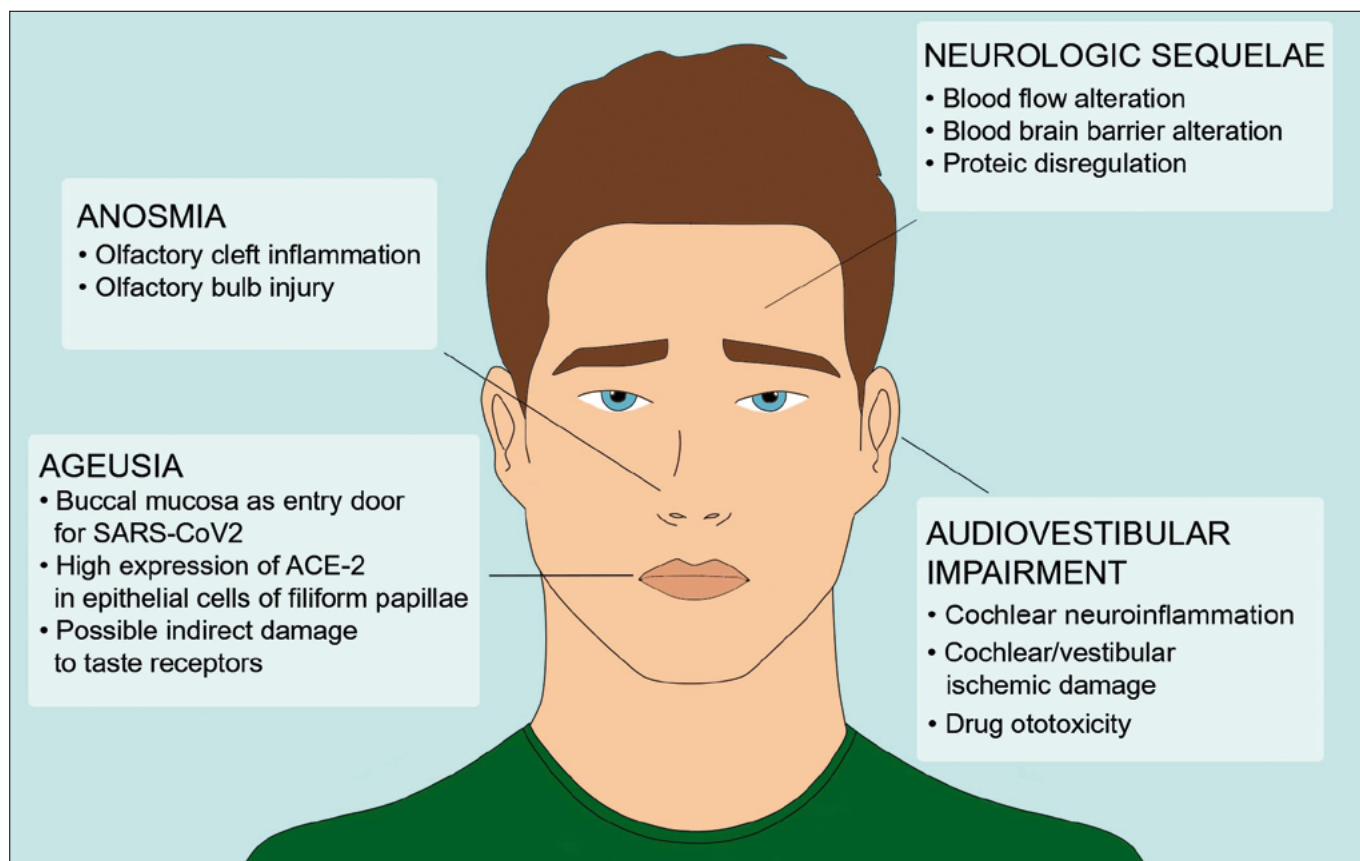
Due to the prominent involvement of the upper respira-

tory tract in COVID-19, otolaryngologists have assumed a prominent role in both the early fighting of the disease <sup>3</sup> and in treatment of post-COVID-19 sequelae <sup>4</sup>. Considering the increase of post-COVID-19 symptoms and that most of these are in the ENT district, the awareness of the different and possible symptoms related to SARS-CoV-2 is something to keep in mind.

The present systematic review aims to summarize and discuss the evidence regarding the presence of audio, vestibular and chemosensory sequelae of COVID-19, of which the otolaryngologist should be aware for correct management and treatment of such patients.

## Materials and methods

This study was performed in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-analy-



**Figure 1.** Multi-factorial pathogenesis of post-acute sequelae of SARS-CoV-2 infection (PASC).

sis (PRISMA) <sup>5</sup> checklist and statement recommendations (Fig. 2).

#### Search strategy

A comprehensive search strategy, developed in partnership with a medical librarian, was performed on PubMed, Scopus, and Google Scholar without time restrictions. The keywords used were: “persistent”, OR “persistence”, AND “hearing loss,” OR “hearing impairment”, OR “tinnitus”, OR “audio and vestibular symptom”, OR “sudden hearing loss”, OR “olfactory symptoms”, OR “smell symptoms”, OR “anosmia”, OR “hyposmia” OR “parosmia OR “gusta-

tory symptoms”, OR “ageusia” AND “SARS-CoV-2” OR “COVID-19”. Only articles in English were considered for the analysis.

Two independent investigators (P.D.L. and A.D.S.) reviewed the articles extracted from the literature review. Duplicates were removed, and each reviewer then individually filled in an Excel data sheet (Microsoft Corporation, USA) including information extracted from the articles in agreement with inclusion and exclusion criteria (see below). The datasheets were compared, and disagreements were debated until complete agreement by both researchers. Only papers that received full consensus were considered.

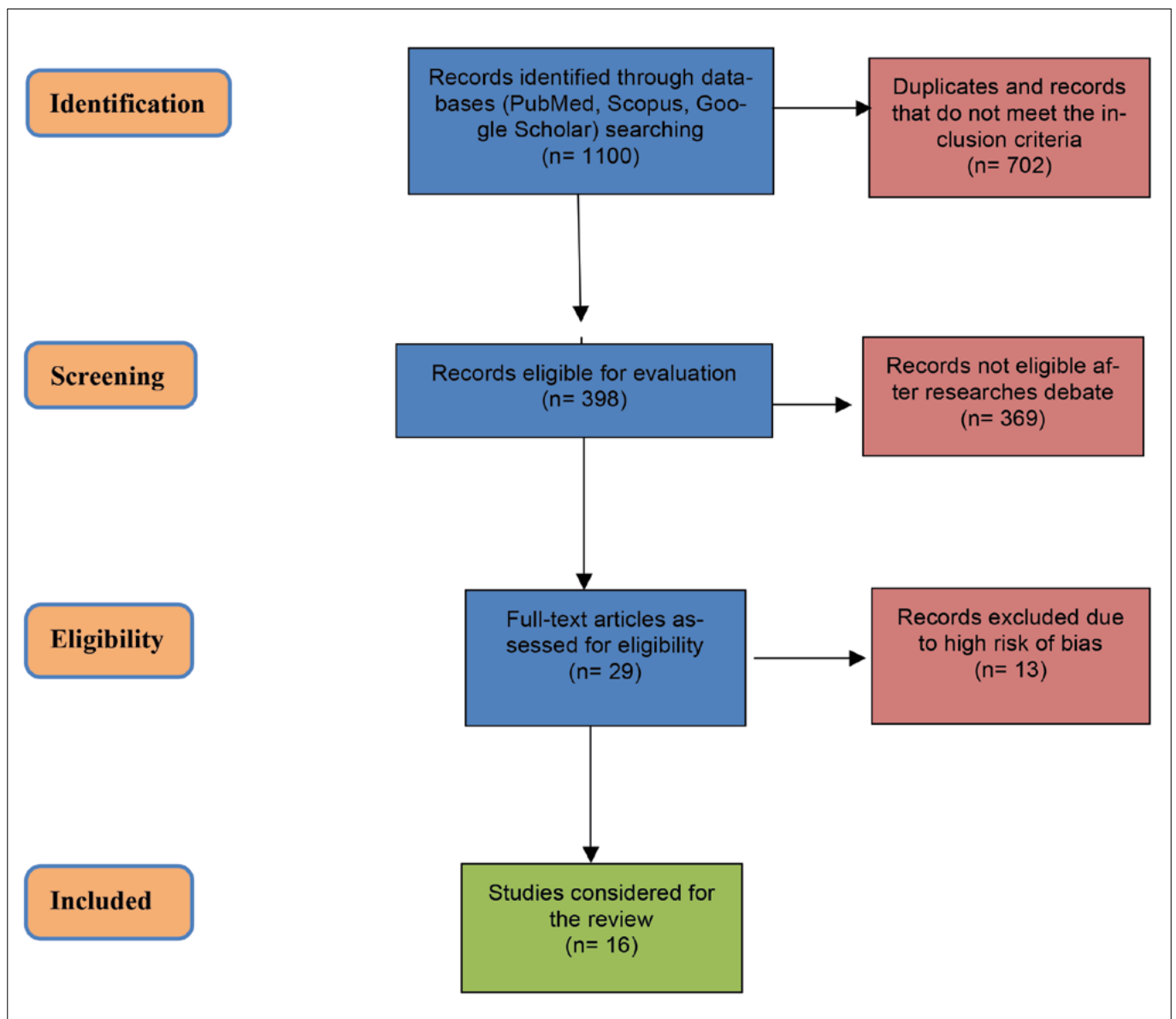


Figure 2. Systematic reviews and meta-analysis (PRISMA) diagram.

PRISMA guidelines were followed to conduct the systematic review and the full list of references was screened for potentially relevant articles. Selected articles were read in full to assess the study objectives and the level of evidence.

*Inclusion criteria:* patients (0-99 years) affected by persistent hearing deterioration, gustatory or olfactory symptoms after SARS-CoV-2 infection, written in English language, with full-text available. There were no restrictions in terms of diagnostic tools used to detect SARS-CoV-2.

*Exclusion criteria:* studies that contain information about suspected/unconfirmed COVID-19, articles that included patients affected by auditory/vestibular/ olfactory/taste disorders before COVID-19 infection or lacked previous clinical history and case reports.

## Results

### *Study selection*

A total of 1100 articles were identified (Tab. I). After removal of duplicates, 702 articles were excluded. Twenty-nine full-text articles matched the inclusion/exclusion criteria; of these 13 were excluded because at high-risk of bias and the remaining 16 were included in the systematic review<sup>4-19</sup>. The articles identified an association between SARS-CoV-2 and persistent hearing or chemosensory impairment. All studies were published over a period of 2 years, between 2019 and 2021. Across the studies, 5582 patients recovered from SARS-CoV-2 infection were evaluated.

### *Audio and vestibular symptoms*

The presence and the persistence of audiovestibular disorders in COVID-19 were reported in 7 studies.

Vertigo prevalence was 7.2%<sup>1</sup>. In a questionnaire administered to 185 patients who recovered from COVID-19, Viola et al.<sup>6</sup> found that 34 patients (18.4%) reported equilibrium disorders after COVID-19 diagnosis. Of these, 32 patients reported dizziness (94.1%) and 2 (5.9%) reported acute vertigo attacks; 14 (7.6%) patients reported equilibrium disorders associated with tinnitus.

Regarding the persistence of audio and vestibular dysfunction, Bhatta et al.<sup>7</sup> evaluated 331 COVID patients at the time of diagnosis and at 3 months follow-up, and failed to show any significant change in hearing status of COVID-19 patients compared to a control group. Moreover, 3.2% patients had mild conductive hearing loss correlated with nasopharyngeal inflammation, which improved over the course of follow-up. In a cross-sectional study by Dror et al.<sup>8</sup>, no cochlear or retrocochlear dysfunction was found in recovered COVID-19 patients analysing auditory brainstem response (ABR), transiently evoked otoacoustic emissions (TEOAE) and and distortion product otoacoustic

emissions (DPOAE) responses. One limitation of this study is that among admission criteria there was current normal hearing and absence of audiological complaints.

In assessing the presence of persistent audio and vestibular damage in healed COVID-19 patients, Gallus et al.<sup>9</sup> tested 48 patients within 2 weeks from the second negative swab with pure tone audiometry (PTA), video-Head Impulse Test (vHIT) and suppression head impulse test (SHIMP) and compared them with 28 age-sex matched voluntary controls. The difference between the two groups appeared to be minimal, and all patients fell within the normal range for the explored frequencies. Moreover, in this study most vestibular symptoms reported were transient and resolved at the time of the screening and vHIT gain was within the normal range. One only case reported a persistent sensation of isolated static imbalance.

Kökoğlu et al.<sup>10</sup> in 101 healed COVID-19 patients who did not require hospitalization, identified the following as otologic symptoms during mild and moderate COVID-19: ear fullness (20%), otalgia (11%), tinnitus (10%), dizziness (6%) and hearing loss (5%). However, none of the neuro-otological symptoms was permanent, and audiological evaluation via PTA found no persistent impairment. Thrane et al.<sup>11</sup> administered an ear-symptom questionnaire to a group of healed COVID-19 patients with reported audiological symptoms (mean follow-up range 209-318 days). Of the 17 patients with hearing loss, two reported normalised hearing, 10 reported improvements but not yet at the same level as before COVID-19, and 5 patients had not experienced improved function at the time of follow-up. Of the 21 patients with tinnitus, 7 reported recovery, 7 reported reduction of symptoms, and 7 reported no decrease in tinnitus since onset at the time of follow-up.

In another study<sup>12</sup>, the authors investigated the effects of COVID-19 on the hearing system by administering PTA, speech audiometry, extended high-frequency audiometry, otoacoustic emissions (OAE) testing and auditory brainstem response (ABR) testing. This study enrolled 27 patients diagnosed with COVID-19 at least one month (mean  $3.81 \pm 2.11$  months) earlier and treated at home and a control group of 20 individuals without history of COVID-19. A small but significant difference was observed in air and bone conduction thresholds between the two groups in terms of mean low and high frequencies. Speech audiometry recognition thresholds were significantly higher in both ears in patients with COVID-19 compared to the control group at 2 kHz only, in the right ear. The ABR results demonstrated that only the interpeak latencies of waves III-V were significantly longer in the study group compared to the control group. The authors noted that even if further research is needed there is the possibility that SARS-CoV-2



infection may cause damage to the hearing system, particularly in high frequencies.

### *Smell and taste alterations*

Spontaneous recovery rates of smell and taste symptoms were found to be very high, with a 60-day recovery rate ranging from 75% to 85% and a 6-month recovery rate of 95.3%<sup>13,14</sup>, suggesting a remarkable capacity of regeneration for these structures. Nonetheless, a minority of patients will continue to suffer from anosmia and will be referred to an ENT specialist, requiring some sort of management. This was confirmed by the study from Riestra-Ayora et al.<sup>15</sup> in which, at 6-months follow-up, 11% of patients did not experience recovery, and partial resolution was reported in 30% of patients. The work from Bussiere et al.<sup>16</sup> and Petrocelli et al.<sup>17</sup> also described a similar percentage (respectively, 27% and 19.5%) of persistent smell alterations at 6 and 7 months after testing negative for infection. A higher rate of smell alterations was reported by Biadsee et al.<sup>18</sup> who reported that 48% of subjects experienced smell alterations at 8 months after the primary infection, and by the work from Zayet et al.<sup>19</sup> in which persistent loss of smell was the most prevalent symptom, at 9 months of follow-up in a group of 354 long-COVID French patients. On the other hand, the small cohort (only 26 patients) described by Otte et al.<sup>20</sup> showed a high percentage (97%) of olfactory function improvement after 6 months of COVID-19 infection. An Italian study led by Boscolo-Rizzo<sup>21</sup> reported the longest follow-up (one-year) in a cohort of 100 patients who were previously home-isolated for moderate symptomatic COVID-19; in this study, 46% of patients showed persistent olfactory dysfunction, and the authors hypothesised that this could be associated with emotional distress and depression.

## **Discussion**

The etiopathogenesis of persistence of audio, vestibular and gustatory symptoms in PASC is still unclear. A series of hypotheses have been made. The first idea is the crucial role of inflammatory cytokines and their over-production (cytokine storm) during COVID-19 infection; their increase and excessive circulating levels are responsible for the short effects and perhaps even for the long-term symptoms. These effects are exemplified by interleukin 6, the main interleukin produced by lymphocytes, fibroblasts, and bronchial epithelium during SARS-CoV-2 infection, which can regulate synaptic plasticity and change brain blood flow and local tissue metabolism<sup>22</sup>. There is also evidence that the SARS-CoV-2 spike protein can directly alter the blood-brain barrier and cause direct brain inflammation,

from which both auditory and smell disorders can arise depending of the areas suffering from neuroinflammation<sup>23</sup>. Another possible mechanism is an abnormal immune response, with the production of a large number of autoantibodies, including those directed to cells of the blood vessels, which can potentially cause autoimmune thrombocytopenia, and those directed against phospholipids, which can later result in antiphospholipid antibody syndrome. In addition, the molecular mimicry of some proteins, such as OR7DAm, SLC12A6, and PARP9, has been hypothesised to be responsible for anosmia, vascular damage, and multi-organ damage<sup>24</sup>.

Another hypothesis, specifically focused on the audio and vestibular symptoms, is neuro-inflammation in the inner ear<sup>23</sup>. The thrombotic and transient-ischaemic mechanisms, and the consequent prolonged hypoxia of the auditory pathways, could be responsible for persistent audiological symptoms in long-COVID-19 patients. Although vertigo and dizziness are very uncommon, the same aetiopathogenesis of audiological disorders, especially a thrombosis in the audio-vestibular artery, could be held accountable for the persistence of these symptoms. However, to date the most valid theory is the one focusing on the neuroinflammation<sup>5</sup>. The inflammation of the auditory, vestibular, olfactory and gustatory areas following the spread of the virus from the nose (olfactory bulbs) or the extension of the inflammation from this area to the part of the brain, might explain the presence of all these otolaryngological symptoms.

Acute olfactory dysfunction (OD) is a key symptom in COVID-19 disease, and since the first phases of the pandemic it has been considered a potential discriminatory symptom, indicating triaging for COVID-19 and allowing early identification.

The mechanism by which SARS-CoV-2 could cause long anosmia is not completely defined and is probably related to the injury caused by the virus on neuro-olfactory epithelium, in which the sustentacular cells express the ACE 2 receptor 200-700 times more than in nasal or tracheal epithelia, and consequential spreading to the olfactory bulb. Neuroradiologic findings are consistent with this hypothesis and MRI studies of patients suffering from olfactory dysfunction after COVID-19 noted a high percentage of olfactory cleft opacification, reduction of olfactory bulb volumes, change in bulb shape and signal abnormalities suggesting direct/indirect injury to olfactory neuronal pathways<sup>5,25</sup>.

Although OD in most cases resolves completely within 30 days, a consistent number of patients may experience longer symptoms. The risk of developing a long-lasting anosmia is related to the severity of the baseline OD, with

highly severe cases more likely to experience a persistent deficit<sup>13</sup>; moreover, some authors have speculated that the viral load (very high) might cause the persistence of symptoms.

Unfortunately, the therapeutic approach for the treatment of post-COVID-19 smell alteration is not well defined yet. Current strategies include olfactory training (deliberate sniffing of a set of odourants 20 sec each at least twice a day for at least 3 months), alpha-lipoic acid and systemic omega-3 supplementation. Oral and topical corticosteroids are used to treat inflammatory component in post-infective OD, but data regarding their efficacy in COVID-19 related anosmia is currently lacking and their usage is not recommended. Recently, D'Ascanio et al. proposed the combination of anti-neuroinflammatory drugs and olfactory training for treating persistent olfactory disease; the authors, in their pilot study, showed that patients treated by combining olfactory training and PeaLut recovered 100% more than patients who did olfactory rehabilitation only<sup>5</sup>. The rationale of the study was focused on the treatment of neuro-inflammation to support the recovery of smell. Even if preliminary, the results of this study are very promising. Gustatory impairment is the most common oral manifestation in COVID-19, affecting 45% of patients. The estimated pooled prevalence of loss of taste in a systematic review was 41.47%<sup>26</sup>. The mean duration of these conditions was found to be 15 days, and most patients seemed to fully recover. Long-lasting gustatory impairment is often attributed to concomitant impaired retronasal olfaction (flavour) rather than impaired gustation (sweet, salty, sour, bitter). However isolated gustatory impairment is described in long-COVID patients, although its mechanism is not completely understood. Since epithelial cells of the oral cavity, including taste buds, widely express ACE2 receptors, this could again represent the key to cellular damage; it is reasonable to assume that in some cases this damage is irreversible or slow to heal, thus leading to long lasting ageusia. Also, neuronal impairment of the gustatory afferents and nuclei could play a role, similarly to how it happens elsewhere. Data regarding medical treatments specifically aimed at hypogeusia are limited and no specific recommendations can be made.

## Limits of the study

This study presents several limitations. First, the quality rating of the studies was not always satisfactory; in fact, there are several case reports and the cross-sectional, prospective observational, and case control studies have uncontrolled designs or provide insufficient details on the control groups. Second, some of these studies described

“self-reported symptoms” without objective assessment of hearing or olfactory/gustatory symptoms.

## Conclusions

The available evidence indicates that an inconsistent percentage of patients show persistence of audio and vestibular symptoms after COVID-19 infection, while notable numbers of long-COVID subjects present lasting olfactory and consequent gustatory disturbances. Further studies with longer (more than one-year) follow-up will be required to fully understand the percentage of COVID-19 ‘long haulers’ who will spontaneously recover from these symptoms.

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## Conflict of interest statement

The authors declare no conflict of interest.

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## Authors' contributions

PDL: design, acquisition of data, data analysis and interpretation, drafting, accountability of the work; ADS: data analysis and interpretation, drafting, accountability of the work; VC: design, drafting, figure editing; PM: design, drafting, table editing; AS: data analysis and interpretation, table editing; FR: data analysis and interpretation, revising the manuscript for important intellectual content; CC: data analysis and interpretation, accountability of the work; AC: revising the manuscript for important intellectual content, final approval; EC: design, accountability of the work, final approval.

## Ethical consideration

Because of the nature of this work, Institutional Review Board approval was not requested.

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