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Confronting COVID-19-associated cough and the post-COVID syndrome: role of viral neurotropism, neuroinflammation, and neuroimmune responses

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Cough is one of the most common presenting symptoms of COVID-19, along with fever and loss of taste and smell. Cough can persist for weeks or months after SARS-CoV-2 infection, often accompanied by chronic fatigue, cognitive impairment, dyspnoea, or pain—a collection of long-term effects referred to as the post-COVID syndrome or long COVID. We hypothesise that the pathways of neurotropism, neuroinflammation, and neuroimmunomodulation through the vagal sensory nerves, which are implicated in SARS-CoV-2 infection, lead to a cough hypersensitivity state. The post-COVID syndrome might also result from neuroinflammatory events in the brain. We highlight gaps in understanding of the mechanisms of acute and chronic COVID-19-associated cough and post-COVID syndrome, consider potential ways to reduce the effect of COVID-19 by controlling cough, and suggest future directions for research and clinical practice. Although neuromodulators such as gabapentin or opioids might be considered for acute and chronic COVID-19 cough, we discuss the possible mechanisms of COVID-19-associated cough and the promise of new anti-inflammatories or neuromodulators that might successfully target both the cough of COVID-19 and the post-COVID syndrome.

Introduction

The COVID-19 pandemic, caused by the novel coronavirus SARS-CoV-2, has had an unprecedented effect on global health since its discovery in Wuhan, China.^{1,2} Even in countries where the first pandemic wave of the virus was controlled, second or third waves are happening or have been predicted to occur. With limited availability of effective vaccines, measures to reduce disease spread—such as physical distancing, wearing masks, and avoiding crowds—remain key strategies to combat the infection. Similar to the more common but less serious infections of the common cold or flu, cough is a key symptom of COVID-19 in the acute phase of the infection, and one that persists in the post-infective phase. Cough is not only distressing to patients, but also increases the risk of community transmission by respiratory droplets.³ Stigmatisation of patients with cough can occur, leading to social isolation,⁴ particularly during the COVID-19 pandemic. Identifying ways to control COVID-19-associated cough could help to prevent community transmission and disease spread, as well as removing the stigma of this symptom.

Evidence-based treatment options for COVID-19 cough are needed because patients with cough caused by common viral infections, including cold and flu, frequently resort to over-the-counter cough medicines. Patients with chronic cough also often seek antitussive therapies, but it is unknown whether such approaches are effective in post-COVID cough patients. We propose that it is important to consider cough as a target of intervention in the management of COVID-19 and post-COVID syndrome. However, we currently have little understanding of the mechanisms underlying COVID-19-associated cough. In this Personal View, we review the knowledge that has accumulated on cough in COVID-19, and discuss neuroinflammatory and

neuroimmune mechanisms that could potentially underlie COVID-19-associated cough based on our understanding of the pathogenesis of COVID-19 and of the cough associated with other respiratory viruses. We

Key messages

- Acute COVID-19-associated cough with fever and a loss of taste and smell is common; chronic cough after SARS-CoV-2 infection occurs less frequently, but is common in the so-called post-COVID syndrome (long COVID), in which it is usually associated with other symptoms, including chronic fatigue, dyspnoea, chronic pain, and cognitive impairment (brain fog)
- Optimal management of COVID-19-associated cough remains unclear, although guidelines for current approaches to acute and chronic cough serve as reference
- COVID-19 cough might result from the invasion of vagal sensory neurons by SARS-CoV-2 or a neuroinflammatory response, or both, leading to peripheral and central hypersensitivity of cough pathways
- Studies are needed to provide data on the epidemiology and effect on quality of life of post-COVID chronic cough, together with insights into the cough hypersensitive state
- The hypothesis that the post-COVID syndrome results from a neuroinflammatory response affecting various regions of the brain to induce chronic fatigue, pain, dyspnoea, and cough should be addressed
- Although neuromodulators such as gabapentin or opioids might be considered for COVID-19 cough, new anti-inflammatories or neuromodulators could be considered to treat not only cough, but also the post-COVID syndrome; randomised studies are needed to examine the efficacy and safety of potential treatments during the acute and chronic phases of disease

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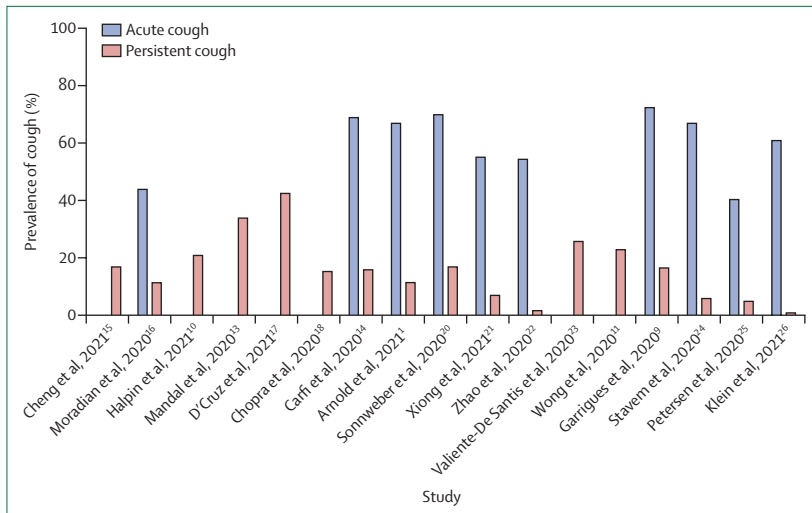


Figure 1: Follow-up studies reporting persistent cough in patients with post-COVID syndrome Studies sorted by follow-up duration in ascending order from left to right. Follow-up duration ranges from 6 weeks to 6 months. Data were retrieved from available publications, including peer-reviewed papers and preprints.^{9-11,13-26} Detailed characteristics of each study are summarised in table 1. Some studies did not report acute cough data.

conclude by discussing the management of acute and chronic COVID-19 cough and future directions for research and clinical practice.

Acute COVID-19-associated cough

Dry cough is one of the most common initial symptoms of COVID-19, reported in about 60–70% of symptomatic patients.^{1,2,5} Using an app-based COVID symptom tracker on smartphones, cough was reported in about 50% of patients who tested positive for SARS-CoV-2, and in combination with a loss of smell (anosmia), loss of taste (ageusia), unusual fatigue, and loss of appetite, was highly predictive of SARS-CoV-2 infection.⁶ A systematic review and meta-analysis⁷ of 21 682 adults infected with SARS-CoV-2 in nine countries reported that cough was present in 57%. A study in Wuhan, China, found that the median time from illness onset to cough was 1 day and that cough persisted for an average of 19 days; cough lasted for 4 weeks or more in approximately 5% of patients.²

The co-presence of cough, anosmia, and ageusia⁶ indicates that neuroinflammatory mechanisms might be operative in COVID-19 pathogenesis. As the cough reflex is mediated by the vagus nerve,⁸ interactions between the virus and the airway vagus nerve, with ensuing neuroinflammation, represent the likely primary events for the initiation of cough.

Cough in the post-COVID syndrome

An increasing number of reports describes an array of fluctuating or persistent symptoms experienced by patients for months after recovery from COVID-19. Symptoms include cough, fatigue, dyspnoea, pain, and so-called brain fog (cognitive impairment, including

confusion and memory loss), and are associated with a deleterious effect on activities of daily living.⁹⁻¹¹ This phenomenon has been termed the post-COVID syndrome or long COVID.^{12,13} A study by Carfi and colleagues¹⁴ was the first to describe persistent symptoms in patients after COVID-19. In a post-COVID cohort of 143 patients from a hospital in Italy, 125 (87.4%) reported struggling with symptoms—76 (53.1%) reported fatigue, 62 (43.4%) dyspnoea, and 23 (16.0%) cough—2 months after discharge.¹⁴ Many reports have now described post-COVID symptoms and show that cough can persist for weeks and months after SARS-CoV-2 infection in some patients, with differing severity of acute symptoms (figure 1, table 1).⁹⁻²⁹

What is the prevalence of post-COVID cough?

In a multicentre observational cohort study done in 1250 COVID-19 survivors in Michigan, USA, 75 (15.4%) of those who responded to the telephone survey reported new or worsening cough at 2 months after discharge.¹⁸ Persistent cough was also reported in patients with mild baseline severity,^{24,25} cohort studies in Norway and the Faroe Islands found that about 10% of their non-hospitalised patients had cough at 4 months after symptom onset.^{24,25} In a pooled analysis, we found that the estimated prevalence of persistent cough was 18% (95% CI 12–24%; $I^2=93%$) in 14 studies of hospitalised patients (follow-up duration ranged from 6 weeks to 4 months; figure 2).^{9-11,13-23} However, prevalence varied widely between studies, and is presumably dependent on patient characteristics, treatment, follow-up duration, and outcome definition.

Longitudinal studies in the general population have not been reported so far, but in the UK Office for National Statistics COVID-19 Infection Survey, the proportion of patients who remain symptomatic at 5 weeks after infection was estimated at 21.0% (95% CI 19.9–22.1%), and cough was the second most common persistent symptom (11.4% [10.5–12.2%]), fatigue being the first.³⁰ The estimated prevalence of patients symptomatic at 12 weeks was 9.9% (6.7–14.7%), but a specific rate for cough has not yet been reported.³⁰ In online surveys, cough was reported in 20–30% of still symptomatic patients 2–3 months after the onset of symptoms of COVID-19.^{12,28,29}

Two studies provided information on the prevalence of burdensome cough after COVID-19 (arbitrarily defined as cough with a numerical rating scale ≥ 4) and indicated that 7–10% of patients who recovered from COVID-19 pneumonia might suffer from burdensome cough 2 months after discharge.^{13,17} However, more data are needed on the prevalence, severity, effects, and long-term course of post-COVID cough.

What are the causes of post-COVID cough?

It is not known why the post-COVID syndrome develops in some individuals. There is emerging evidence that

female sex, presence of respiratory comorbidities, and severity of acute COVID-19 presentation might be predictive of post-COVID syndrome.^{9,10,20,24,31} So far, it is unclear whether any factors in the acute phase could specifically determine the persistence of cough. Unlike

cough that persists after the common cold or flu, chronic cough in post-COVID syndrome is usually accompanied by other multisystem manifestations, which might indicate either multifactorial pathogenesis or shared mechanisms underlying these symptoms.

Study design and region	Patients	Follow-up duration	Acute cough (%)	Persistent cough (%)	Other common persistent symptoms	
Clinic-based studies						
Cheng et al, 2021 ¹⁵	Retrospective, multicentre cohort study; London, UK	113 patients discharged from the respiratory unit after COVID-19; median age 65 years	6 weeks after discharge	Not reported	19 of 113 (17%)	Fatigue (67%), breathlessness (38%)
Moradian et al, 2020 ¹⁶	Prospective, single-centre follow-up study; Tehran, Iran	200 patients (160 [80%] men, 40 [20%] women) discharged from hospital after moderate-to-severe COVID-19; mean age 55.6 years	6 weeks after discharge	88 of 200 (44.0%)	23 of 200 (11.5%)	Fatigue (19.5%), dyspnoea (18.5%), weakness (18.0%), anxiety (15.0%), activity intolerance (14.5%)
Halpin et al, 2021 ¹⁰	Prospective, single-centre follow-up study; Leeds, UK	100 patients (56 [56%] men, 44 [44%] women) discharged from hospital after COVID-19; mean age 66.6 years	Mean 48 (SD 10.3) days after discharge	Not reported	21 of 100 (21%) overall; eight of 32 (25%) ICU patients and eight of 68 (12%) ward patients	Fatigue (64%), breathlessness (50%)
Mandal et al, 2020 ¹³	Prospective, multicentre follow-up study; London, UK	384 patients (238 [62%] men, 146 [38%] women) hospitalised with COVID-19; mean age 59.9 years	Median 54 (IQR 47–59) days after discharge	Not reported	131 of 384 (34%) persistent cough (numerical rating scale ≥1); 38 of 384 (10%), burdensome cough (numerical rating scale ≥4)	Fatigue (69.0%), breathlessness (53.1%), depression (14.6%)
D’Cruz et al, 2021 ¹⁷	Prospective, single-centre follow-up study; London, UK	119 patients (74 [62%] men, 45 [38%] women) hospitalised with severe COVID-19 pneumonia; mean age 58.7 years	Median 61 (IQR 51–67) days after discharge	Not reported	49 of 115 (42.6%) persistent cough (numerical rating scale ≥1); eight of 115 (7.0%) burdensome cough (numerical rating scale ≥4)	Fatigue (67.8%), sleep disturbance (56.5%), pain (49.6%)
Chopra et al, 2020 ¹⁸	Prospective, multicentre follow-up survey; MI, USA	488 survivors of COVID-19 hospitalisation (253 [51.8%] men, 235 [48.2%] women); mean age 62 years	60 days after discharge	Not reported	75 of 488 (15.4%) new or worsened cough	Emotional impact (48.8%), breathlessness walking up stairs (23.0%), shortness of breath or chest tightness or wheezing (16.6%), loss of taste or smell (13.1%)
Carfi et al, 2020 ¹⁴	Prospective, single-centre follow-up study; Rome, Italy	143 patients (90 [63%] men, 53 [37%] women) discharged from hospital after COVID-19; mean age 56.5 years	Mean 60.3 (SD 13.6) days after symptom onset	99 of 143 (69%)	23 of 143 (16%)	Fatigue (53.1%), dyspnoea (43.4%), joint pain (27.3%), chest pain (21.7%)
Arnold et al, 2021 ¹⁹	Prospective, single-centre follow-up study; Bristol, UK	110 patients (62 [56%] men, 28 [44%] women) hospitalised with laboratory-confirmed SARS-CoV-2 infection; median age 60 years	Median 90 (IQR 80–97) days after symptom onset	74 of 110 (67%)	13 of 110 (11.8%)	Excessive fatigue (39%), breathlessness (39%), insomnia (24%)
Sonnweber et al, 2020 ²⁰	Prospective, multicentre follow-up study; Austria	145 patients (83 [57%] men, 62 [43%] women) who required hospitalisation (75%) or outpatient care with persisting symptoms; mean age 57 years	Mean 100 (SD 21) days after symptom onset	102 of 145 (70%)	25 of 145 (17%)	Dyspnoea (36%), sleep disorder (28%), night sweat (24%), pain (24%), hyposmia or anosmia (19%)
Xiong et al, 2021 ²¹	Prospective, single-centre follow-up study; Wuhan, China	538 patients (245 [45.5%] men, 293 [54.5%] women) discharged from hospital after COVID-19; median age 52 years	At least 3 months after discharge	297 of 538 (55.2%)	38 of 538 (7.1%)	Alopecia (28.6%), fatigue (28.3%), sweating (23.6%), somniopathy (17.7%), chest distress (14.1%)
Zhao et al, 2020 ²²	Retrospective, multicentre follow-up study; Zhengzhou, China	55 patients (32 [58.2%] men, 23 [41.8%] women) discharged from hospital (51 patients had pneumonia); median age 47.7 years	3 months after discharge	30 of 55 (54.5%)	1 of 55 (1.8%)	Gastrointestinal symptoms (30.9%), headache (18.2%), fatigue (16.4%), exertional dyspnoea (14.6%)

(Table 1 continues on next page)

	Study design and region	Patients	Follow-up duration	Acute cough (%)	Persistent cough (%)	Other common persistent symptoms	
(Continued from previous page)							
	Valiente-De Santis et al, 2020 (pre-print) ²³	Prospective, single-centre follow-up study; Malaga, Spain	108 patients (48 [44.4%] men, 60 [55.6%] women) discharged from admission or emergency service care; mean age 55.5 years	12 weeks after acute phase	Not reported	28 of 108 (25.9%)	Dyspnoea (55.6%), asthenia (44.9%), chest pain (25.9%), palpitation (22.2%)
	Wong et al, 2020 ²⁴	Prospective, multicentre follow-up study; Vancouver, Canada	78 patients (50 [64%] men, 28 [36%] women) hospitalised with laboratory-confirmed SARS-CoV-2 infection; mean age 62 years	Median 13 (IQR 11–14) weeks after symptom onset	Not reported	18 of 78 (23%)	Dyspnoea (50%)
	Garrigues et al, 2020 ⁹	Prospective, single-centre follow-up study; Paris, France	120 patients (75 [62.5%] men, 45 [37.5%] women) discharged from hospital after COVID-19; mean age 63.2 years	Mean 110.9 days after admission	87 of 120 (72.5%) overall; 69 of 96 (71.9%) ward patients and 18 of 24 (75.0%) ICU patients	20 of 120 (16.7%) overall; 14 of 96 (14.6%) ward patients and six of 24 (25.0%) ICU patients	Fatigue (55.0%), dyspnoea (42.0%), loss of memory (34.0%), sleep disorder (30.8%), concentration disorder (28.0%)
	Stavem et al, 2020 ²⁴	Prospective geographical cohort study; Norway (areas covering 17% of the population)	451 non-hospitalised patients (198 [44%] men, 253 [56%] women) with positive PCR; mean age 49.8 years	Median 117 (range 41–193) days after symptom onset	302 of 451 (67%) dry cough; 12 of 451 (2.8%) productive cough	27 of 451 (6%) dry cough; 18 of 451 (4%) productive cough	Dyspnoea (16%), loss of smell (12%), loss of taste (10%), arthralgia (9%), myalgia (8%)
	Petersen et al, 2020 ²⁵	Prospective geographical cohort study; Faroe Islands	180 non-hospitalised patients (83 [46%] men, 97 [54%] women) with positive PCR; mean age 39.9 years	Mean 125 days after symptom onset	73 of 180 (40.5%) dry cough; 46 of 180 (25.5%) productive cough	Nine of 180 (5%) dry cough; 11 of 180 (6%) productive cough	Fatigue (29%), loss of smell (24%), loss of taste (15%), arthralgia (10%), rhinorrhoea (9%)
	Guler et al, 2021 ²⁷	Prospective, multicentre follow-up study; Switzerland	113 patients (67 [59.3%] men, 46 [40.7%] women) who survived acute COVID-19 (66 patients had severe or critical disease; 47 had mild or moderate disease); mean age 57 years	Median 128 (IQR 108–144) days after symptom onset	Not reported	Not reported; cough VAS median 0 (IQR 0–2)	..
	Klein et al, 2021 ²⁶	Prospective follow-up study of PCR-positive patients with COVID-19 recruited via social media and word of mouth; Israel	112 patients (72 [64.3%] men, 40 [35.7%] women; six hospitalised and 106 ambulatory patients) in recovery after COVID-19; mean age 35 years	6 weeks and 6 months after symptom onset	68 of 112 (61%)	29 of 112 (26%) at 6 weeks; one of 112 (1%) at 6 months	At 6 months: fatigue (23%), smell change (15%), breathing difficulty (10%), taste change (8%), memory disorder (6%)
Online population-based surveys							
	Assaf et al, 2020 ²⁸	Patient-led survey through the Body Politic COVID-19 Support Group on Slack (75.4% of participants) or through social media sites such as Facebook, Twitter, and Instagram; 71.7% from the USA and UK, 12.7% from the USA and UK	640 patients (150 [23.4%] men, 490 [76.6%] women) who had previously experienced or were currently experiencing symptoms consistent with COVID-19 and had suspected or confirmed SARS-CoV-2 infection (23.1% tested positive, 27.5% tested negative, 47.8% not tested); 62.7% between the ages of 30 and 49 years	Up to 8 weeks after symptom onset	At week 1: 301 of 640 (47.0%) dry cough; 141 of 640 (22.0%) persistent uncontrollable cough	At week 8: 179 of 640 (28.0%) dry cough; 57 of 640 (8.9%) persistent uncontrollable cough	Mild shortness of breath (39%), mild chest tightness (34%), mild fatigue (33%), moderate fatigue (32%)
	Sudre et al, 2020 (preprint) ²⁹	Prospective cohort study of users of the COVID Symptom Study app	4182 patients (1192 [28.5%] men, 2990 [71.5%] women) who had tested positive for SARS-CoV-2 by PCR swab testing and logged as “feeling physically normal” before the start of illness (up to 14 days before testing); mean age 42.8 years	56 days after symptom onset	Not reported	920 of 4182 (22%) persistent cough, defined as symptoms lasting more than 56 days	..
	Goërtz et al, 2020 ²⁷	Online survey of individuals with persistent complaints related to COVID-19; the Netherlands and Belgium	2133 members of Facebook groups for COVID-19 patients with persistent complaints and a panel of people who registered at a website of the Lung Foundation Netherlands (309 [14.5%] men, 1824 [85.3%] women); mean age 47 years	Mean 79 (SD 17) days after symptom onset	1450 of 2133 (68.0%)	619 of 2133 (29.0%)	Fatigue (94.9%), dyspnoea (89.5%), headache (76.0%), chest tightness (75.2%), muscle pain (64.7%)
Studies are listed by follow-up duration from 6 weeks to 6 months. ICU=intensive care unit. VAS=visual analogue scale.							
Table 1: Studies reporting cough at follow-up in patients with COVID-19							

The concomitant presence of fatigue, dyspnoea, pain, and cough could point to a derangement of the CNS. Therefore, documentation of the extent and quality of these co-existing symptoms is an important goal. From the point of view of cough, detailed characterisation—including frequency, severity, urge to cough, hyper-sensitivity, or cough suppressibility—using clinical tools that are already available could improve our understanding of its clinical implications and relationship to the other post-COVID symptoms.

In the clinical management of post-COVID chronic cough, it is important to exclude any pathological or structural causes, such as fibrotic damage to the lung parenchyma³² or damage to the airways caused by either SARS-CoV-2 or the treatment provided in critical care. Lung parenchymal changes are commonly found on CT scans of adult patients with COVID-19, and lung fibrotic changes can occur in 10–20% of patients.³² Lung fibrosis could increase cough reflex sensitivity in response to mechanical stimulation of the chest wall, as reported in patients with idiopathic pulmonary fibrosis.³³

Neuronal mechanisms of cough

There have been great advances in our understanding of the pathways underlying cough and cough hyper-sensitivity. Cough is a reflex that requires minimum conscious control, occurring through the activation of peripheral sensory nerves into the vagus nerves, which provide input to the brainstem at the solitary nucleus and the spinal trigeminal nucleus.⁸ In chronic cough, the concept of cough hypersensitivity has been developed with the notion that the cough pathways have been sensitised by amplification of the afferent signals to the brainstem.³⁴ In this Personal View, we postulate that neuronal mechanisms of hypersensitivity are central to the cough of COVID-19. We consider the possibility that SARS-CoV-2 infects the sensory nerves mediating cough, leading to neuroinflammation and neuroimmune interactions as mechanisms of cough hypersensitivity (figure 3). We also examine whether the neurotropism of SARS-CoV-2 could explain the other accompanying symptoms of COVID-19 and post-COVID syndrome.

Does SARS-CoV-2 infect sensory nerves?

Angiotensin-converting enzyme 2 (ACE2) receptors and proteases such as transmembrane serine protease 2 (TMPRSS2) and furin are important for viral entry into host cells for coronaviruses such as SARS-CoV-2.³⁵ SARS-CoV-2 might interact directly with sensory neurons, given that sensory dysfunction—including cough, and olfactory and taste impairments—are frequent in infected patients.⁶ However, it is not known whether human airway vagal sensory neurons express ACE2 or TMPRSS2, or can be infected by SARS-CoV-2. In mice, single-cell sequencing of bronchopulmonary vagal sensory neurons showed no expression of murine ACE2.³⁶ Additional viral entry factors might also have a

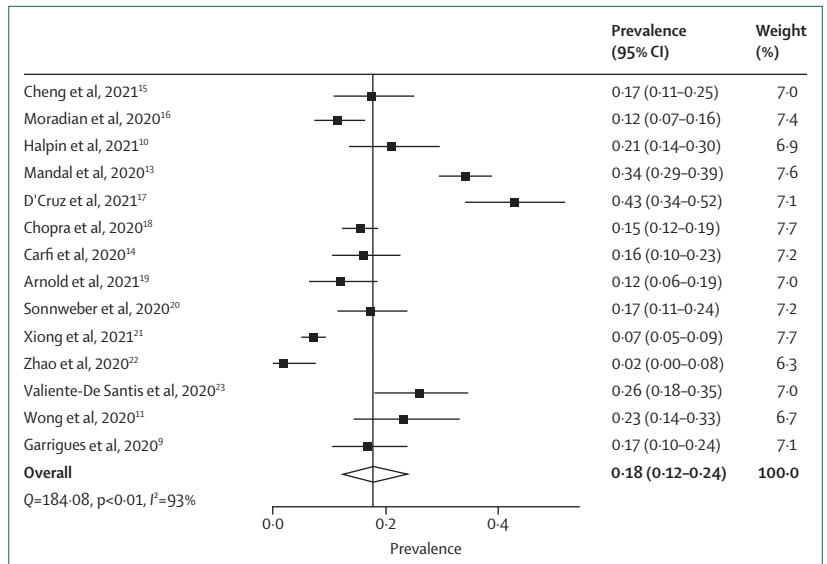


Figure 2: Prevalence of post-COVID cough in 14 studies of patients who required hospitalisation

Follow-up duration ranges from 6 weeks to 4 months. Detailed characteristics of included studies are summarised in table 1.^{9–21,23–25} We conducted a random-effects meta-analysis to estimate the pooled prevalence and standard errors for post-COVID-cough in previously hospitalised patients, and quantified the degree of heterogeneity between studies using the I^2 in the MetaXL 5.3 software (EpiGear International Pty, Sunrise Beach, QLD, Australia).

role in the interactions of SARS-CoV-2 with neurons, including neuropilin-1, which is expressed by vagal and other sensory neurons.³⁷ In a sequencing study of human olfactory mucosal cells, ACE2 and TMPRSS2 were not found in olfactory epithelial neurons, but were abundantly expressed in olfactory epithelial support cells and stem cells.³⁸ The findings were confirmed by cellular histological localisation of ACE2 in the specialised neuroepithelium of supporting cells around neuronal dendritic projections; the neuroepithelium contains odour-sensing cilia.³⁹ Therefore, anosmia induced by SARS-CoV-2 infection might be caused by the effect of the infected epithelium on neuronal activity. However, the ACE2 gene has been reported in a subset of human dorsal root ganglion sensory neurons in the thoracic ganglia, some of which also innervate the lungs. Notably, expression was reported in a subset of nociceptive neurons co-expressing CALCA (calcitonin related polypeptide alpha) or P2RX3 (purinergic receptor P2X3),⁴⁰ and comparable neuronal subtypes of the vagal sensory ganglia are important for the induction of coughing. The fact that some vagal sensory neurons, including those involved in cough, have a developmental lineage and molecular phenotype that is very similar to dorsal root ganglion neurons⁴¹ means that ACE2 expression in human vagal sensory neurons might be predicted.

Although the infection of dorsal root ganglion neurons containing nociceptors might provide an explanation for the post-COVID symptoms of joint and chest pain, headache, and dyspnoea, the basis for sustained cough after SARS-CoV-2 infection remains unclear. A

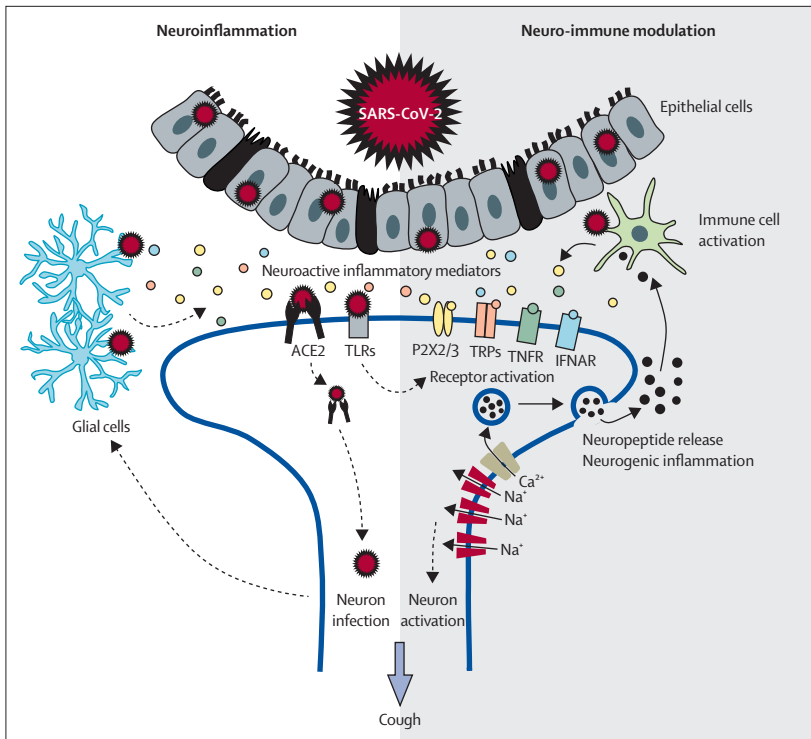


Figure 3: Proposed mechanisms of cough in SARS-CoV-2 infection

SARS-CoV-2 might induce cough via neuroinflammatory and neuroimmune mechanisms. (Left) Direct infection or viral recognition by vagal sensory neurons or sensory neuron-associated glial cells could promote a neuroinflammatory state, characterised by neuronal or glial release of neuroactive inflammatory mediators. Neuroinflammation could occur at the level of the nerve terminal in the airways and lungs, within the vagus nerve containing the neuronal axons, at the level of the vagal sensory ganglia containing neuronal cell bodies, or at sites within the CNS responsible for integrating vagal sensory inputs. Neuroinflammatory mediators include neuronally released interferons and glial-derived ATP, which are important for antiviral responses within the nervous system. (Right) Traditional inflammatory cells, including dendritic cells, macrophages, neutrophils, and epithelial cells, involved in SARS-CoV-2 infection and viral recognition can also release a broad range of inflammatory mediators, including antiviral interferons, cytokines, prostanoids, lipid mediators, and ATP. Many of these mediators can activate or sensitise vagal sensory nerves via cognate receptors or gating ion channels, providing a neuroimmune axis for alterations in vagal sensory neuron activity. Sensory neuron activation could enhance inflammation via the release of neuropeptides, which facilitate inflammatory cell recruitment and activation in a process known as neurogenic inflammation. Collectively, these cascades could upregulate sensory neuron activation and input to brain circuits mediating cough. ACE2=angiotensin-converting enzyme 2 (or other viral entry factors). IFNAR=interferon receptor. P2X2/3=purinergic receptors. TLRs=toll-like receptors. TNFR=tumour necrosis factor receptor. TRPs=transient receptor potential channels.

post-mortem study⁴² of individuals who died with COVID-19 has reported the presence of SARS-CoV-2 RNA and protein in the olfactory mucosa, confirming entry of the virus into the CNS at a neural–mucosal surface. In the same study,⁴² the trigeminal sensory ganglia, which innervate the corneal, nasal, and oral epithelium, also contained virus, suggesting that sensory neurons can offer an entry point for SARS-CoV-2 to the CNS. SARS-CoV-2 has also been shown to infect brain organoids *in vitro*, and the brains of human ACE-expressing transgenic mice after *in-vivo* intranasal inoculation.⁴³ There is evidence in animals that some respiratory viruses can reach the brainstem and the brain by the retrograde route, through infection of the sensory vagal fibres from the respiratory tract.⁴⁴ Alternatively, mechanisms might exist that trigger responses in the

brain independent of intact viral particles, as shed S1 spike protein of SARS-CoV-2 can cross the blood–brain barrier in mice via absorptive transcytosis.⁴⁵ Further work is needed to investigate these possible direct viral–neural interactions in the pathogenesis of cough and other sensory symptoms during SARS-CoV-2 infection.

Does SARS-CoV-2 alter sensory neuronal function?

Viral infection of neurons, including herpes virus infection of primary sensory neurons, leads to the activation of neuronal antiviral signalling, which can include the production of interferons and other cytokines traditionally involved in cellular defence against viral infection.⁴⁶ Additionally, neuronal support cells (such as glial cells) respond to neuronal infection by generating a local inflammatory environment.⁴⁷ It is now clear that release of cytokines—the so-called cytokine storm—can occur in severe COVID-19 infection, characterised by increased levels of inflammatory cytokines including tumour necrosis factor (TNF) and interleukin (IL)-6, which are associated with increased mortality.^{1,48}

In the peripheral nervous system, traditional immune cells, including macrophages and dendritic cells, infiltrate nerves and neuronal tissues to assist with inflammatory reactions.⁴⁹ Collectively, these neuroinflammatory processes would be expected to dramatically alter sensory neuron activity and potentially underpin cough induction and persistence.⁵⁰ Alternatively, as sensory neurons commonly express Toll-like receptors (TLRs) and other receptors for recognition of pathogenic organisms, direct functional interactions between viral particles and nerves might occur in the absence of neuronal infection. Indeed, in dorsal root ganglion neurons, TLR activation leads to gating of transient receptor potential (TRP) channels, offering a mechanism by which pathogens can directly change neuronal activity independent of viral entry.⁵¹ Further studies are warranted to explore the interactions between SARS-CoV-2 and vagal sensory neurons with their supportive cells.

The very rapid onset of cough after SARS-CoV-2 infection² might suggest a mechanism independent of a direct nerve–virus interaction. For example, an initial epithelium-derived mechanism could evolve to be sustained by dysregulated inflammation. In addition to TLRs, cytokines released through dysregulated inflammation caused by SARS-CoV-2 activation of the innate immune response (eg, through inflammasome activation) are likely candidates driving acute cough via neuroimmune interactions. These cytokines include IL-1 β , TNF, and interferons, because their receptors are commonly present on immune cells and peripheral neurons.⁵² Type I and type II interferons, such as interferon- γ , might cause cough hyper-responsiveness through depolarisation of vagal sensory neurons.^{53,54} Neuropeptides released from sensory nerves through activation of TRPV1, such as substance P, neurokinin A, and calcitonin gene-related peptide, can recruit and activate immune cells (eg, lymphocyte and

dendritic cells) and inflammatory cells (eg, mast cells and macrophages), and increase vascular permeability, thereby aggravating lung inflammation.^{52,55} Various ligand–receptor interactions after SARS-CoV-2 infection at the level of the dorsal root ganglion have been proposed to induce a neurogenic inflammation.⁵⁶ Support cells of peripheral sensory neurons (myelinating and non-myelinating glia) can additionally contribute to viral recognition and inflammation, and alter sensory neuron responsiveness.^{57,58} One product of inflammasome activation is ATP, which might activate or sensitise cough receptors directly.^{52,59}

Is COVID-19 cough the result of sensory hypersensitive pathways?

The mechanisms of cough in the context of other respiratory viruses might provide further insight into the mechanisms of acute COVID-19 cough. Human rhinovirus (HRV)-16, a major pathogen for the common cold and asthma exacerbations, can infect sensory neurons and upregulate TRP channels,⁶⁰ which could explain the heightened cough reflex and urge-to-cough sensations in patients with common cold.⁶¹ In A549 alveolar epithelial cells, HRV-16 infection significantly increased not only intracellular ATP concentrations, but also the extracellular release of ATP,⁶² which is a highly relevant mediator for chronic refractory cough.⁶³ In guinea pigs, infection with parainfluenza type 3 virus caused phenotypic changes of sensory neuronal hypersensitivity in the tracheal nodose neurons, including de-novo expression of substance P or TRPV1.^{64,65} Therefore, sensory hypersensitivity is likely to underlie virus-associated cough in general, although specific mechanisms might vary between different respiratory viruses (figure 3).

Urge to cough, frequently seen in subjects with common cold and possibly also in those with acute COVID-19-associated cough, has been linked to altered central processing of sensory input and cough reflex (termed central sensitisation).⁶⁶ Substance P, which might be upregulated in the nodose ganglionic neurons by viral infection,⁶⁴ can drive central sensitisation in virus-associated cough. Murine pneumovirus infection induced inflammatory glial cell activation and altered neuronal responsiveness in the brainstem nucleus tractus solitarius of mice, the primary site of vagal sensory inputs.⁶⁷ Therefore, increased inflammatory activation of sensory neurons could induce altered reflex processing in the brain. In *ACE2* transgenic mice infected with SARS-CoV, brain areas that have first-order or second-order connections with the olfactory bulb were heavily infected, including the dorsal vagal complex, area postrema, and dorsal motor nucleus of the vagus, which are also implicated in cough regulation.⁶⁸ SARS-CoV-2 can be found in the brain and cerebrospinal fluid of patients with COVID-19,⁶⁹ suggesting that this virus is likely to be detectable by microglia and macrophage-like immune

cells, which might orchestrate inflammation in the brain and provide a central basis for hypersensitivity. This response could, in turn, influence peripheral mechanisms of hypersensitivity. A post-mortem analysis of individuals who died of COVID-19 found the pro-inflammatory cytokines IL-6, IL-18, and C-C motif chemokine 2 (CCL2) in the cerebrospinal fluid, and SARS-CoV-2 virus in the brainstem medulla.⁴² Notably, SARS-CoV-2 was detected in brainstem regions involved in respiratory control, perhaps a neuroanatomical basis for effects on breathing and associated reflexes in COVID-19.

Is the post-COVID syndrome due to a generalised neuronal hypersensitivity?

An important consideration is whether the post-COVID syndrome is the result of a generalised hypersensitivity state that underlies the panoply of symptoms associated with this condition. Key symptoms reported in post-COVID syndrome (dyspnoea, pain, and cough) have similarities in terms of the control and peripheral sensitisation of their respective afferent pathways.⁷⁰ We have shown that idiopathic chronic cough, now often described as the cough hypersensitivity syndrome, is dominated by the presence of a hypersensitivity with both peripheral and central components.³⁴ The central neurobiology of cough hypersensitivity has been supported by functional brain imaging of airway stimulation with a tussive TRPV1 agonist, capsaicin, which showed elevated neural activity in the midbrain of individuals with this syndrome.⁷¹ Chronic fatigue syndrome (also called myalgic encephalomyelitis) and fibromyalgia, in which patients complain of fatigue and musculoskeletal pain, have also been associated with alterations in pain and sensory processing in both peripheral and central neurogenic sensitisation.^{72,73} Functional MRI studies have shown that the insular and cingulate cortices are key areas in the nociceptive processing of dyspnoea, which are the same areas activated by pain and cough.^{70,71,74} Therefore, we need to gather evidence to explore shared or common features in the pathways of central hypersensitivity, encompassing not only post-COVID hypersensitive cough, but also the whole post-COVID syndrome. Indeed, brain MRI imaging of patients with neurological complications of COVID-19 infection have shown cortical signal abnormalities and neuroinflammatory features,⁷⁵ and brain PET imaging suggests hypometabolism in the olfactory gyrus and connected limbic and paralimbic regions, extending to the brainstem and the cerebellum in patients with long COVID.⁷⁶

Management of COVID-19-associated cough

The advice for treating the acute and chronic cough of COVID-19 is based on available treatments and guidelines.^{77,78} Although many drugs are on the market or in development for the relief of cough,⁷⁹ there is no good evidence for their benefits in the treatment of cough associated with acute viral infection or pneumonia.^{80,81} In

	Unanswered questions	Potential research studies
Mechanistic studies		
Some sensory neurons (eg, those arising from the dorsal root ganglia) express entry factors for SARS-CoV-2, providing a route for neuronal infection; bronchopulmonary (vagal) sensory neuron terminals are in close apposition to airway epithelia and are probably exposed to SARS-CoV-2; bronchopulmonary (vagal) sensory neurons express innate viral recognition receptors and receptors for many cytokines	How does SARS-CoV-2 infection modify the activity of vagal sensory neurons mediating cough?	<ul style="list-style-type: none"> • Investigations of SARS-CoV-2 interaction with vagal bronchopulmonary sensory nerves, including neural expression of ACE2 and other entry factors, involvement of neural innate viral recognition factors, and role of resident and recruited airway and lung cells (and their mediators) in sensory neuronal activation. • Assessment of bronchopulmonary sensory neuron sensitivity in COVID-19, including use of animal models to evaluate cough response pathways and pathological changes following SARS-CoV-2 infection and treatment • Mechanistic studies in humans to assess peripheral and central processing to cough challenge with functional MRI, particularly with respect to post-COVID syndrome • Airway sampling to study inflammatory phenotype or effect of SARS-CoV-2 infection on airway nerve architecture or deformity
	What are the pathological consequences, within peripheral and central cough processing pathways, of SARS-CoV-2 infection?	
	What is the inflammatory (neural and airway) profile of individuals with COVID-19-related cough?	
	What is the impact of modulating neuroinflammation and neuroimmune processes on cough in COVID-19?	
Acute COVID-19-related cough		
Cough is a key symptom of acute infection and an important mode of SARS-CoV-2 transmission	What are the characteristics of acute COVID-19-related cough? Can these characteristics aid diagnosis or prognosis?	<ul style="list-style-type: none"> • Subjective and objective cough evaluation, with sound recording, and studies of relationship with health outcomes, with appropriate prospective comparator groups • Assessment of utility of cough sound analysis based on artificial intelligence algorithm to facilitate early detection of COVID-19 • Initial evaluation and re-evaluation of data from randomised clinical trials with cough documentation; future establishment of robust cough measures to monitor cough outcome and clinical responses • Randomised controlled trials of existing or emerging antitussive therapies with robust primary outcome measures in patients with COVID-19 and cough • Inclusion of validated cough endpoint measures in future viral inoculation models for optimisation of vaccine development
	How does acute COVID-19-related cough respond to anti-inflammatory drugs (eg, corticosteroids) or SARS-CoV-2-targeted treatments?	
	How does the presence of comorbid conditions or diagnoses influence the presence of COVID-19-related cough?	
	Is antitussive therapy during the acute phase of COVID-19 safe and effective in treating morbidity or reducing SARS-CoV-2 transmission?	
Chronic or post-COVID cough		
Cough persists in a subgroup of patients after resolution of acute disease; cough in post-COVID syndrome is usually associated with chronic fatigue and dyspnoea	What are the prevalence, longitudinal course, clinical features, and effect on quality of life of post-COVID cough? Are they similar to those encountered in cough hypersensitivity syndrome?	<ul style="list-style-type: none"> • Cross-sectional evaluation of prevalence of cough in those with co-existing pulmonary infiltrates, documented reflux, or history of airways disease, or in those taking ACE inhibitors; evaluation of changes with treatment response • Longitudinal follow-up and robust phenotyping with cough hypersensitivity testing (eg, cough challenge testing) and validated measures of cough (eg, cough-related quality of life); evaluation of sequelae and impact on quality of life (eg, incontinence and social exclusion) • Randomised controlled trials of novel cough therapies in patients with post-COVID cough using robust cough outcome measures (eg, ambulatory cough count); response of concomitant symptoms of post-COVID syndrome
	Do treatments for cough hypersensitivity help in post-COVID cough management? Are novel treatments (eg, P2X3 antagonists) beneficial? Does cough modulation treatment (eg, speech pathology therapy) help?	
	Should the treatment to post-COVID syndrome be a global approach to tackling all symptoms?	

ACE=angiotensin-converting enzyme. ACE2=angiotensin-converting enzyme 2. P2X3= P2X purinoceptor 3.

Table 2: Future research in COVID-19-associated cough

the UK National Institute for Health and Care Excellence guidelines for managing acute symptoms of COVID-19, only taking honey or opioid-derived antitussives are recommended for cough.⁸² Opiates (such as codeine or low-dose morphine) could exert antitussive effects by acting on the cough reflex network in the brainstem,⁸³ and might have some effects in suppressing cough, particularly in the early stages. However, opiates are not universally effective and have associated risks of dependence, abuse, or central side-effects.⁸³

Oral corticosteroids are often prescribed for acute lower respiratory tract infection and have been used by many centres to treat patients with post-COVID interstitial lung changes. Oral corticosteroids were not

better than placebo in reducing cough duration in non-asthmatic adults with acute lower respiratory tract infection.⁸⁴ However, the situation with SARS-CoV-2 infection might be different, with the likely presence of an early inflammatory response and neuroimmune interactions underlying the acute cough. The report that dexamethasone reduces the mortality rate of hospital-treated patients with COVID-19 provides some support for the use of corticosteroids.^{85,86} However, cough was not assessed in these trials,^{85,86} nor was it measured in any other trials of therapies for COVID-19, such as the study of the antiviral replicating agent remdesivir.⁸⁷ Cough measurements should be incorporated into future trials.

Anatomical diagnostic protocols for chronic cough⁷⁷ should be applied for the management of cough in the post-COVID syndrome; such approaches could identify any contributing causes to chronic cough—such as gastro-oesophageal reflux disease, ACE inhibitor therapy, lung fibrosis, or airway inflammation—that might have resulted from COVID-19 infection.

Persistent cough in post-COVID syndrome might be driven by neuroinflammation leading to a state of laryngeal and cough hypersensitivity, which is the basis for chronic refractory or unexplained cough. Gabapentin and pregabalin, which are neuromodulators, have been shown to be effective in controlling chronic refractory cough.^{88,89} This approach could be considered for the post-COVID syndrome, because these drugs might also be useful for other symptoms accompanying cough, such as pain, although they have the potential to worsen any cognitive dysfunction. Antimuscarinic drugs, such as tiotropium, could be used to control COVID-19 cough, because they can decrease cough sensitivity in acute viral upper respiratory tract infection.⁹⁰ Similarly, speech and language therapy⁹¹ might help patients to recover, delivered as part of a multimodal therapy and recovery model in synergy with other aspects of pulmonary rehabilitation for the post-COVID syndrome.

Investigation of novel therapeutic interventions that interfere with the neuroinflammatory pathways could be advantageous, such as inhibitors of TRP channels, ATP-gated P2X3 receptors, neurokinin-1 receptors (NK1Rs), or sodium channels. A P2X3 receptor antagonist, gefapixant, substantially reduced cough in patients with chronic refractory cough,⁶³ and its use in COVID-19-associated cough is supported by the report that ACE2 is frequently co-expressed with P2X3 in dorsal root ganglion sensory neurons.⁴⁰ Substance P and NK1R might also be a potential target for intervention, because NK1R antagonists such as aprepitant or orvepitant have shown antitussive potential in patients with lung cancer-associated cough or chronic refractory cough, possibly through blocking of central NK1Rs.^{92,93} Although TRPV1 antagonists have not been shown to reduce cough in patients with refractory cough,^{94,95} they should be tested in COVID-19 cough because TRPV1 in sensory neurons is upregulated by viral infections such as human rhinovirus.⁶⁰ The charged sodium channel blocker NTX-1175, which silences nociceptor neurons, is a new neuromodulator that is being trialled (EuraCT 2020-004715-27) for chronic cough, but could also be considered for acute and chronic COVID-19 cough.

Conclusions and future directions

Little is known about the cough associated with COVID-19, apart from details of the frequency, prevalence, and persistence of cough. We need to understand more about the mechanisms by which the vagal sensory neurons are activated by the virus and sensitised through the process of neuroinflammation

Search strategy and selection criteria

We searched PubMed and Google Scholar for articles published in English from database inception until Jan 31, 2021, with the search terms “COVID-19” or “SARS-CoV-2” combined with “cough”, “neuro-immune”, “neuron” or “nerve”. We also searched *MedRxiv* for relevant preprints using these terms. The concept of cough hypersensitivity and neuroinflammation came from the authors’ personal collection of articles. The final list of references was selected on the basis of relevance to the focus of this Personal View.

and neuroimmunity. To better understand the characteristics of COVID-19-associated cough, evidence for both peripheral and central sensitisation should be obtained. Chronic cough should be considered together with the other symptoms of the post-COVID syndrome, and evidence sought to address the question of whether they reflect the process of central sensitisation. Table 2 summarises research studies that could be considered. These studies might lead to the consideration of antiviral or anti-inflammatory drugs or neuromodulators for the treatment of acute and chronic COVID-19-associated cough, in addition to the treatment of the post-COVID syndrome as a whole. Steps need to be taken to identify therapies that target the central sensitisation process.

Practical steps have already been taken to address the range of symptoms associated with the post-COVID syndrome. Clinics are currently being set up to manage the many patients with long COVID, and research efforts are underway to better understand the long-term health effects of COVID-19. In the UK, the National Institute for Health Research and UK Research and Innovation are already focusing on long COVID in hospitalised patients—for example, in the ISARIC 4C (ISARIC Coronavirus Clinical Characterisation Consortium) and PHOSP-COVID (Post-Hospitalisation COVID-19 study) research initiatives—to understand and improve the long-term health outcomes of this challenging condition. In addition, a £20m joint research call has been made to fund research into the longer-term physical and mental effects of COVID-19 in non-hospitalised individuals.

We hope that the questions we have addressed in this Personal View will soon be answered. As we learn more about the mechanisms of acute and chronic cough associated with COVID-19, we hope that strategies for improved management and prevention emerge so that the effects of COVID-19-associated cough on the health and wellbeing of patients and on the transmission of SARS-CoV-2 can be reduced. Moreover, identification of shared mechanisms underlying components of the post-COVID syndrome could point to treatment options for debilitating long-term effects of COVID-19.

Contributors

W-JS, SSB, SBM, and KFC did the literature search. W-JS, SBM, and KFC wrote the first draft, with later contributions by CKMH, JHH, and

For more on **NHS England long COVID clinics** see <https://www.nationalhealthexecutive.com/articles/nhs-england-long-covid-clinics>

For more on **ISARIC 4C** see <https://isaric4c.net/>

For more on the **joint research call** see <https://www.nihr.ac.uk/news/new-20m-call-for-research-into-physical-and-mental-effects-of-long-covid/26163>

LM. All authors discussed the scope and focus of the article at the start of the writing process, and all reviewed the advanced version of the article, providing suggestions, edits, and corrections.

Declaration of interests

KFC has received honoraria for participating in advisory board meetings for GlaxoSmithKline, AstraZeneca, Novartis, Merck, Boehringer Ingelheim, Nocien, Shionogi, Roche, and TEVA Pharmaceutical regarding treatments for asthma and chronic obstructive pulmonary disease; he has received honoraria for participating on the scientific advisory board of the Clean Breathing Institute, supported by GlaxoSmithKline Health Care Consumer Products; and he has been remunerated for speaking engagements by AstraZeneca, Novartis, and Merck. SBM reports grants from Merck and personal fees from Merck and NeRRe Therapeutics. SSB reports personal fees from Nocien, Merck, Nerre, Bayer, Bellus, and Shionogi; and grants from Merck, all outside the submitted work. LM reports personal fees from GlaxoSmithKline, Merck, Shionogi, Bayer, Bellus Health, Nocien, Chiesi, and Applied Clinical Intelligence; and grants from Merck and Chesi, all outside the submitted work. JHH has received grant funding and advisory fees from MSD pharmaceuticals and is a member of the advisory board for Bellus health. The other authors declare no competing interests.

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