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Cardiorespiratory dysautonomia in post-COVID-19 condition: Manifestations, mechanisms and management

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A significant proportion of COVID-19 patients experience debilitating symptoms for months after the acute infection. According to recent estimates, approximately 1 out of 10 COVID-19 convalescents reports persistent health issues more than 3 months after initial recovery. This 'post-COVID-19 condition' may include a large variety of symptoms from almost all domains and organs, and for some patients it may mean prolonged sick-leave, homestay and strongly limited activities of daily life. In this narrative review, we focus on the symptoms and signs of post-COVID-19 condition in adults – particularly those associated with cardiovascular and respiratory systems, such as postural orthostatic tachycardia syndrome or airway disorders – and explore the evidence for chronic autonomic dysfunction as a potential underlying mechanism. The most plausible hypotheses regarding cellular and molecular mechanisms behind the wide spectrum of observed symptoms – such as lingering viruses, persistent inflammation, impairment in oxygen sensing systems and circulating antibodies directed to blood pressure regulatory components – are discussed. In addition, an overview of currently available pharmacological and non-pharmacological treatment options is presented.

Keywords: autonomous dysfunction, cardiovascular, dysautonomia, post-COVID-19 condition, pulmonary

Introduction

COVID-19 – a disease caused by a novel variant of Coronavirus, SARS-CoV-2 – has affected more than 765 million individuals (6.9 million deaths) worldwide as of May 17, 2023 [1]. Male patients with comorbidities, such as obesity, diabetes and cardiopulmonary diseases are at increased risk of severe disease and death [2]. In contrast, female sex along with age, asthma and previous hospitalization have all been associated with higher risk of long-term symptoms [3]. SARS-CoV-2 enters the cells via the angiotensin-converting enzyme 2 (ACE2) receptor, which is present in numerous cell types throughout the body and therefore facilitates acute multiple organ damage [2, 4]. Important advances have been made in the treatment of the acute phase of COVID-19. Meanwhile, a significant proportion of COVID-19 patients

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experience debilitating symptoms that linger for months after the acute infection. This has been termed 'long COVID' or 'post-acute COVID-19 syndrome' and, more recently, the World Health Organization (WHO) suggested 'post-COVID-19 condition' [5].

Post-COVID-19 condition

According to a consensus statement adopted by the WHO, post COVID-19 condition occurs in individuals with prior confirmed or probable COVID-19 and with remaining symptoms or new onset symptoms at least 3 months after the initial infection and with duration of at least 2 months [5]. The plethora of symptoms reported by patients is striking and includes symptoms from almost all domains (e.g. physiological, psychological and cognitive) and organs (e.g. heart, lungs, gastrointestinal and brain) [6–8]. Prolonged symptoms have been shown to affect formerly hospitalized patients but also those who suffered a milder acute infection without need for hospitalization. In some patients, there are profound effects on functional abilities, such as activities of daily life, work capacity and school/university attendance [2, 3].

A survey by the NHS, UK, reported a 9.9% prevalence of any symptom at 12-week follow-up (UK Office for National Statistics. 2020). A recent Dutch population-based study reported that one out of eight individuals with acute COVID-19 will develop long-term symptoms [7]. Recent data supports the fact that symptoms may persist for several years in a majority of patients with post COVID-19 condition following hospitalization [9]. However, it is problematic with only symptoms as a base for diagnosis [5], as patients suffering sequelae from severe pneumonia and intensive care are defined by the same terminology as those who suffered a milder initial COVID-19 infection but with a prolonged course of debilitating symptoms. In addition, symptoms described as part of post-COVID-19 condition are not classified according to severity, and the impact on individual function and quality of life is at present not properly addressed.

It is therefore fundamental to systemically characterize the various phenotypes of post-COVID-19 condition in order to better understand the long-term effects, underlying pathophysiology and immune mechanisms to enable identification of treatable traits [10, 11]. Patients with post-COVID-19 condition are typically multi-symptomatic, and a common feature is the fluctuating nature of symptom intensity, as well as onset of new conditions, such as neurological or psychiatric diagnosis, dementia, respiratory conditions and sleep disorder [2, 4, 12].

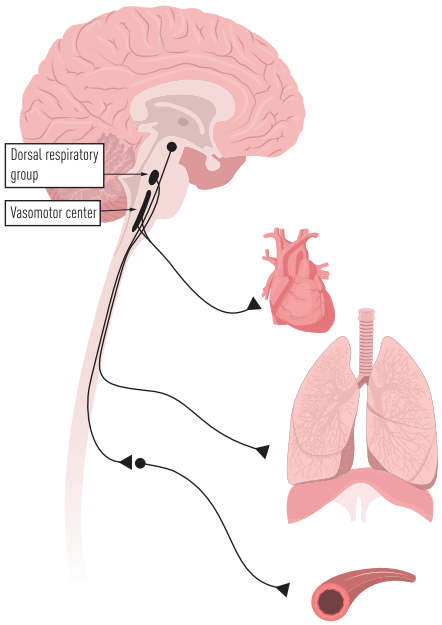
Knowledge gaps regarding the underlying mechanisms of post-COVID-19 condition are still vast [13]. Various hypotheses have been proposed – among others, a state of chronic inflammation in the lungs with sustained production of pro-inflammatory cytokines and reactive oxygen species that are released into the surrounding tissues and bloodstream. Endothelial damage may trigger activation of fibroblasts, which deposit collagen and fibronectin, resulting in fibrotic changes in the lungs and other organs [2]. Other proposed mechanisms include viral persistence as well as immune dysregulation and induction of autoimmunity, the latter a possible explanation of autonomic dysfunction such as COVID-19-triggered postural orthostatic tachycardia syndrome (POTS) [14].

There have been multiple reports on autonomic dysfunction as an important contributing factor behind post-COVID-19 condition, in particular in patients experiencing POTS, inappropriate sinus tachycardia (IST) and microvascular dysfunction, as well as gastrointestinal and respiratory functional disorders [8, 15–20].

In this narrative review, we focus on the symptoms and signs of post-COVID-19 condition – particularly those associated with cardiovascular and respiratory disease – and examine the evidence for autonomic dysfunction as a potential underlying mechanism. We have limited the scope of this review to the discussion of current published research on adult subjects with post-COVID-19 condition.

Autonomic dysfunction

Dysautonomia, or autonomic dysfunction, is a group of disorders that arise from malfunction of the autonomic nervous system (ANS). Dysautonomia may involve either failure or inadequate activation of sympathetic and parasympathetic components of ANS. Different aetiologies of dysautonomia include neurodegenerative disorders such as Parkinson's disease and pure autonomic failure; chronic diseases such as diabetes and renal failure; genetic diseases (e.g. familial dysautonomia,



Symptoms

General
- Fatigue
- Exercise intolerance
- Dyspnoea
- Muscle weakness

Cardiac
- Abnormal tachycardia (postural; post-exercise; resting)
- Chest pain / angina-like
- Palpitations

Pulmonary
- Respiratory muscle weakness
- Alveolar hyperventilation
- Abnormal breathing pattern

Vascular
- Orthostatic intolerance
- Impaired peripheral perfusion
- Venous pooling
- Raynaud-like reaction
- Cold/heat intolerance

Potential mechanisms

- Autoimmunity
- Prolonged inflammatory response
- Virus persistence

- Abnormal adrenergic activity (hyperadrenergic drive)
- Dysfunction of cardiovascular G-protein coupled receptors (autoimmune mechanism)
- Reduced vagal activity

- Autoimmunity
- Abnormal adrenergic activity (hyperadrenergic drive)

- Microvascular endothelial dysfunction
- Capacitance vessel dysfunction
- Leg muscle pump dysfunction

Fig. 1 *Central illustration: Illustration of the plethora of symptoms that has been reported in post-COVID-19 condition, and of the possible mechanisms underlying organ specific symptomatology and autonomic dysfunction. CV, cardiovascular.*

Ehlers-Danlos syndrome); poisoning; viral infections (e.g. AIDS); chronic inflammatory conditions (e.g. multiple sclerosis); and autoimmune diseases (e.g. autonomic autoimmune ganglionopathy, Sjögren's disease and systemic lupus erythematosus) [21, 22].

Typical dysautonomia conditions are essential hypertension, orthostatic hypotension, POTS, IST, recurrent reflex syncope, low blood pressure phenotype, dysmotility and dysuria. Importantly, malfunction of ANS may coexist with primary structural or functional organ and system diseases, such as heart failure, ischaemic heart disease, cardiac arrhythmias, diabetes and respiratory and gastrointestinal tract diseases [23, 24]

Manifestations

Cardiovascular manifestations

The primary function of the cardiovascular system is to maintain homeostasis through adaptations of cardiac output and blood flow, in order to transport nutrients, oxygen, carbon dioxide, hormones and cells (e.g. immune cells). Hence, a strict regulation of cardiac output (i.e. heart rate and stroke volume) as well as blood flow (i.e. blood pressure, vascular tone and organ perfusion) is required to match demand and delivery, which is accomplished primarily by the ANS and organ-specific, local auto regulation [24]. The adaptive capacity of the cardiovascular system is well illustrated by the acute transition from rest to exercise (which is clinically evaluated during exercise testing) [25, 26], by a sudden change in body position [27] or by the effects of long-term exercise training [28].

In patients with post-COVID-19 condition, cardiovascular symptoms include heart rhythm abnormalities (palpitations or tachycardia), chest pain, dyspnea and exercise intolerance (Figure 1, central illustration) [17, 29, 30]. In a large study of hospitalized COVID-19 patients, 5% experienced chest pain and 9% experienced palpitations at 6 months follow-up [6].

Several forms of cardiovascular dysautonomia should be considered in patients with suspected

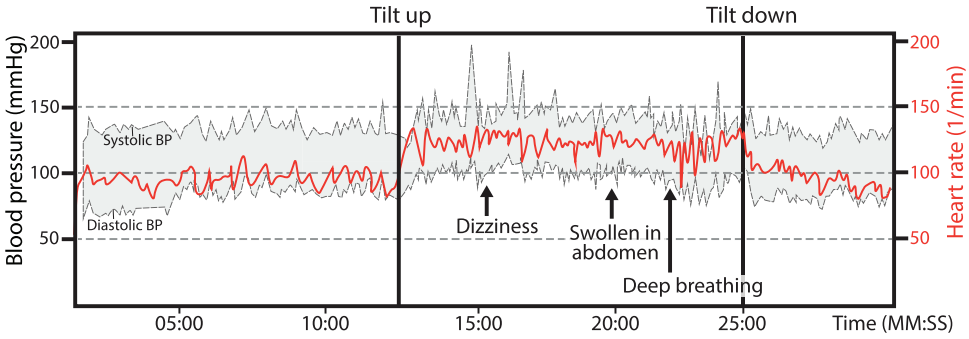


Fig. 2 *The Tilt test: Schematic presentation of Tilt-test results in a patient with postural orthostatic tachycardia syndrome developed after initial COVID-19 infection (woman, 38 years). During the test, heart rate (red) and blood pressure (black/grey) were continuously recorded, as well as potential symptoms (as noted in lower part of figure). Note the steep increase in heart rate after tilt up (70°) associated with reproducible symptoms.*

post-COVID-19 condition. Tests such as active standing or tilt table testing with autonomic function tests, Holter ECG monitoring (mainly for diagnosing IST) [31], 24-h BP monitoring for detection of low-BP phenotype and hypotensive tendency [32], and cardiac imaging such as echocardiography and stress-perfusion magnetic resonance imaging [33] are all of great value in the diagnostic workup.

POTS

According to recent estimates, between 20% and 30% of highly symptomatic post-COVID-19 condition patients (with palpitations, orthostatic intolerance, chest pain and dyspnoea) may meet the diagnostic criteria of POTS, while some also display IST [17, 18].

The definition of POTS endorsed by major autonomic, neurological and cardiological societies is (1) a sustained HR increment of not less than 30 beats/min within 10 min of standing or head-up tilt (for individuals 12–19 years of age, the required HR increment is at least 40 beats/min); and (2) an absence of orthostatic hypotension (i.e. no sustained systolic BP drop of 20 mm Hg or more); and (3) frequent symptoms of orthostatic intolerance (lightheadedness, palpitations, tremulousness, generalized weakness, blurred vision and fatigue) during standing, with rapid improvement upon return to a supine position; and (4) duration of symptoms for at least 3 months; and (5) absence of other conditions explaining sinus tachycardia, such as anorexia nervosa, primary anxiety disorders, hyperventilation, anaemia, fever, pain, infection, dehydration, hyperthyroidism, pheochromocytoma, use of cardioactive drugs (e.g. sympathomimetics and anticholinergics) or severe deconditioning caused by prolonged bed rest.

POTS was first defined in the 1990s by a group from the Mayo clinic [34]. Since then, it has been increasingly recognized as a specific form of cardiovascular dysautonomia, often appearing after viral infection and affecting mainly women of childbearing age (15–45 years) [23, 34].

POTS is a complex disorder of the ANS characterized by orthostatic intolerance with excessive heart rate increase and symptoms upon standing while blood pressure is usually maintained, although some abnormal blood pressure variability may be observed [23, 35] (Figure 2). Apart from the impaired circulatory response to standing, patients with POTS may experience a variety of other persistent symptoms – such as low energy, headache, cognitive impairment, muscle fatigue, chest pain and non-specific generalized weakness – along with numerous gastrointestinal symptoms, to name a few typical POTS correlates [36].

Respiratory manifestations

Dyspnea and cough are common after a COVID-19 infection [37, 38], and studies evaluating patients after discharge from hospital care report new or aggravated dyspnea in 40%–48% of subjects [39, 40]. Although these problems resolve with time in most patients, a significant proportion of patients have remaining symptoms at medium term follow-up, especially in subjects with more severe acute

disease [6]. In a follow-up of approximately 2000 patients who had been discharged from hospital after COVID-19 (of which around 4% had been admitted to intensive care units), the proportion with some level of dyspnea (mMRC $\geq$1) decreased from 26% 6 months after discharge to 14% after 2 years [6]. In another study, the prevalence of chronic cough after 1 year was only 2.5% [41].

Lung function impairment with low total lung capacity, low forced vital capacity and lung diffusion impairment is common after severe COVID-19 requiring hospitalization [37, 42]. Similarly, radiological findings have been found in a significant proportion of patients previously hospitalized [43–46]. Three months after confirmed COVID-19-related pneumonia, ground glass opacities were found in 75% of patients, reticulations in 30% and residual subpleural infiltration in 13% [47]. In another study with ~200 hospitalized patients, 25% still had CT chest abnormalities after 12 months, the most common being residual linear opacities and multifocal reticular or cystic lesions [43, 48].

Respiratory muscle strength and dysfunctional breathing

Already early in the pandemic, decreased respiratory muscle strength was found in some patients [49]. A reduced respiratory muscle strength is to be expected after a severe chest infection and immobilization, but reported levels after COVID-19 that did not require hospitalization are not in parity of what could be expected. Both inspiratory and expiratory muscles seem to be affected, and muscle strength may not recover spontaneously [50, 51]. Apart from respiratory muscular impairment following severe pneumonia, a dysfunctional or abnormal breathing pattern has also been reported in patients with post-COVID-19 condition, both at rest and during exercise testing [51–54]. At rest, some patients have been found to have a breathing pattern involving accessory respiratory muscles in the upper part of the chest, increasing the effort of breathing, which may lead to respiratory muscle fatigue and ultimately a sensation of dyspnea [55]. During exercise testing with analysis of breathing gases and/or arterial blood gas sampling, a subset of patients has been found to have an atypical breathing pattern, including disproportionate fluctuations in ventilation and signs of ineffective ventilation [52, 54, 56]. Of note, in most cases, typical signs of alveolar hyperventilation (low pCO_2 or low end-tidal CO_2 pressure) are not present, and lung function testing including diffusion capacity for carbon dioxide is normal [52].

Decreased inspiratory muscle function and dysfunctional breathing pattern are closely connected to other frequently reported symptoms in post-COVID-19 condition, such as the feeling of breathing discomfort, inability to take deep breaths, chest tightness, cough and pain [40, 57, 58].

In summary, some of the respiratory symptoms reported in patients with post-COVID-19 condition seem to be related to radiologically confirmed sequelae following initially severe pneumonia and/or intensive care with mechanical ventilation [6]. In these cases, lung function testing is often at least slightly abnormal, with more advanced abnormalities related to initial severity of disease. In other cases – often following mild initial COVID-19 disease – respiratory symptoms may be severe, while lung function testing is normal. At least in some of these subjects, dysfunctional breathing and/or reduced respiratory muscle strength may play a role, in which autonomic dysfunction could be an important pathophysiological mechanism.

Potential cellular and molecular mechanisms of dysautonomia

The molecular aetiology of post-COVID-19 condition remains obscure. In this section, we will discuss some of the molecular mechanisms that could contribute to the dysautonomia associated with post-COVID-19 condition.

Lingering viruses and persisting inflammation

Several studies have identified evidence for persisting SARS-CoV-2 several months after the acute infection resolved. For example, one study found 5% of subjects to be positive for SARS-CoV-2 RNA in nasopharyngeal swabs 3 months after the infection [59]. Another study found SARS-CoV-2 RNA and protein in intestinal biopsies in a fraction of subjects 6 months after COVID-19 [60]. Post-mortem analysis in patients with worsened clinical status despite negative PCR testing for SARS-CoV-2 indicates that infection can persist much longer than suggested by PCR testing [61]. In fact, persistent replication of other coronaviruses has been demonstrated by numerous studies [62–64]. Proteomic analyses of a cohort of patients with symptoms remaining more than 1 month after confirmed COVID-19 revealed increased levels of circulating tumour necrosis factor α (TNFα)

compared to healthy controls [65, 66]. In-line with this observation, a recent intervention study suggested that TNFα inhibitors relieved symptoms of post-COVID-19 condition [67]. A unique inflammatory response, characterized by interferon-γ and interleukin-2, has been identified using machine-learning approaches that can separate post-COVID-19 condition from acute COVID-19 [68]. This points towards an enhanced effector T cell activation in post-COVID-19 condition, which could be a protective response against the virus but at the same time be associated with a risk of autoimmune cell damage. However, although persisting replicating viruses are likely to drive a general immune activation and inflammatory responses, this does not explain the dysautonomia observed in post-COVID-19 condition.

Impairment of oxygen-sensing systems – Is there a connection to taste receptor dysfunction?

A very widely recognized feature of both acute COVID-19 and post COVID-19 condition is the impairment of smell and taste. Taste bud morphology and the mechanism of chemoreception is highly similar to the carotid artery chemoreceptors, which together with other chemosensory systems maintain oxygen homeostasis throughout the body. The pH of the blood is sensed by glomus cells, and this mechanism involves sensing by acid sensing ion channels. The pH sensing receptors in taste buds are similar to the pH sensing mechanism in the carotid body [69]. Peripherally in the lung, oxygen levels can be sensed via pulmonary neuroendocrine cells (PNECs). These cells form patches in the pulmonary epithelium and, like glomus cells, sense oxygen via a similar mechanism and connect to afferent neurons [70].

The glomus cells and the PNECs also have in common with taste cells that they express ACE2, which is the primary receptor of cell entry of SARS-CoV-2 [71, 72]. The tongue provides an easily accessible organ for biopsies, and it has been demonstrated in ex vivo experiments with COVID-19 patients that SARS-CoV-2 can in fact infect type 2 taste cells [72].

There are several possible ways in which the chemoreceptor systems could be damaged by the virus. First of all, as described by Doyle et al., there is a measurable reduction in taste stem cells, indicating damage caused by viral replication and/or inflammation during the acute phase of COVID-19 [72]. Second, we have discovered that epigenetic alterations to pathways related to odour-sensing can be found in immune cells of healthy recoverees of COVID-19 and in individuals with post-COVID-19 condition months after the acute phase of COVID-19 has resolved [73]. Although highly speculative, the possible correlation between epigenetic modulation of chemoreceptor pathways and dysautonomia is appealing.

Circulating autoantibodies directed to BP regulatory components?

Previous clinical observations associating a recent viral infection with POTS onset – now strengthened by the emerging post-COVID-19 condition-linked POTS – suggest the possibility of an autoimmune aetiology [34, 36]. Positive (though often non-specific) autoantibody tests are frequently seen among POTS patients, and about 20% report a history of an autoimmune disorder such as Hashimoto's thyroiditis, lupus and rheumatoid arthritis or Sjögren's syndrome [23, 35]. In recent years, a focus in POTS research has been on autoantibodies to cardiovascular G-protein coupled membrane receptors, such as adrenergic, muscarinic, angiotensin- and endothelin-related, although only cell-based functional assays have demonstrated positivity [74–76].

Although not yet demonstrated in post-COVID-19 condition, a recent report demonstrated that antibodies from COVID-19 patient sera directed towards the SARS-CoV-2 spike protein receptor-binding region (interacting with the ACE2 receptor) display cross-reactivity to angiotensin II, one of the major BP-regulating hormones of the body [77]. The authors demonstrated that the levels of the angiotensin II cross-reactive antibodies correlated with BP dysregulation. In our recent study, we were able to demonstrate that the angiotensin II signalling pathway was strongly enriched for epigenetic modifications in immune cells in subjects suffering from post-COVID-19 condition, thereby underpinning the possible epigenetic contribution to COVID-19-related disease manifestations [73].

Other possible mechanisms of dysautonomia

Other proposed pathophysiological mechanisms include abnormally increased sympathetic activity and circulating catecholamine excess, peripheral sympathetic noradrenergic denervation leading to venous pooling and relative central hypovolemia, and low blood volume [35]. Recent

reports have suggested the presence of endothelial and microvascular dysfunction as possible contributors to the cardiovascular symptoms in post-COVID-19-condition [14], either in parallel to POTS or as a part of a broader concept of post-COVID-19 cardiovascular dysautonomia. Although this hypothesis is mechanistically very attractive, more studies on well-defined cardiovascular post-COVID phenotypes are needed.

Management

Post-COVID-19 condition is a poorly explored multisystem and multiorgan illness with a substantial subset of patients affected by cardiorespiratory autonomic dysfunction. Better diagnostic tests and treatment options are both currently under development, but in many instances circulatory and respiratory symptoms are treated with repurposed methods applied in the pre-COVID era (e.g. for conditions such as POTS and asthma). Although a causal therapy is still lacking, some efforts have been planned or are underway. The main targets in current research are elimination of persistent virus particles (e.g. nirmatrelvir and ritonavir [Paxlovid], ClinicalTrials.gov Identifier: NCT05576662 and NCT05823896), reduction of circulating autoantibodies (e.g. efgartigimod alfa-fcab, ClinicalTrials.gov Identifier: NCT05633407) or inhibition of inflammation (e.g. human immunoglobulin, ClinicalTrials.gov Identifier: NCT05350774) in hope to alleviate debilitating symptoms. The immunomodulating therapy has been long in focus based on the inflammatory and autoimmune hypotheses in post-COVID-19 condition [36, 78]. Although there is evidence of a beneficial effect of corticosteroids on symptoms and recovery during the acute phase in hospitalized patients [79–81], and specifically in patients with concomitant asthma [82–84], similar data on pharmacological treatment options for patients with post-COVID-19 condition is scarce [84]. The selection of an appropriate therapeutic approach to possible inflammatory and autoimmune disorders underlying post-COVID-19 condition is hampered by the fact that positive laboratory findings are unspecific or very limited. For instance, elevated levels of proinflammatory cytokines have been found in some, but not in all, patients [36, 78]. Thus, laboratory tests specifically designed for post-COVID-19 condition are currently not available. In a recently published study on a small patient series who were found to have lower immunoglobulin levels and received empirical long-term intravenous human immunoglobulin therapy, some success was reported [85]. Importantly, that study was non-randomized and without placebo control. Consequently, as there are no established immunological tests for post-COVID-19 condition – including those for antibodies to G-protein coupled receptors – and as randomized controlled trials are underway, no specific immunomodulatory therapy can be currently recommended. If there are strong humanitarian reasons and high clinical suspicion of autoimmune involvement, an experimental ex juvantibus approach might be considered, but a cautious attitude is advised. Another important aspect of disease management is prevention of post-COVID-19 condition by large-scale vaccination programs. Every episode of COVID-19, both de novo and re-infection, increases the risk of post-COVID-19 condition [86, 87]. Prevention of further episodes is therefore important [86]. In a recent publication, 12 studies reported data on vaccination before infection with the SARS-CoV-2 virus, and 10 showed a significant reduction in the incidence of post-COVID-19 condition; the odds ratio of developing post-COVID-19 condition with one dose of vaccine ranged from 0.22 to 1.03; with two doses, odds ratios were 0.25–1; with three doses, 0.16; and with any dose, 0.48–1.01. However, the high heterogeneity between studies precluded any meta-analysis [87, 88]. In summary, there is an urgent need for novel and specific diagnostic assays able to identify the pathophysiological mechanisms of post-COVID-19 condition and its treatable targets.

Management of cardiovascular symptoms

Following proper diagnostic work-up to rule out other underlying cardiovascular diseases, there may be several available treatments, primarily directed at symptom relief. Considering the wide range of cardiovascular symptoms of patients with post-COVID-19 condition, specific treatment will be highly individualized. As there is a considerable overlap with POTS in this group of patients, currently recommended strategies for treatment of POTS are listed in Table 1 [23, 35].

Management of respiratory symptoms

There is no specific pharmacological treatment for respiratory symptoms in post-COVID-19 condition, but evidence is evolving for different rehabilitation strategies, as discussed below. These, and specific recommendations for patients with concomitant asthma, are summarized in Table 2.

Table 1. *Treatments for postural orthostatic tachycardia syndrome.*

Drug	Dosing information	Side effects	Precautions
Non-pharmacological treatments			
Withdraw exacerbating medications	Stop drugs that decrease blood volume or directly increase heart rate such as diuretics or vasoselective calcium channel blockers		The coexisting condition may require treatment with drugs that may worsen POTS symptoms. In such setting, the decision to withdraw medication should be carefully considered and discussed with an appropriate expert
Increased oral water intake	Target 2–3 L/day	Frequent urination	
Increased oral NaCl intake	Target 8–10 g/day	Hypertension, peripheral oedema	Buffered NaCl tablets/solutions if cannot be done with diet alone
Lower body compression garments	20–40 mm Hg compression; focus on abdomen ± legs	Can be hot, tight and itchy	
Exercise training	Aerobic: 30+ min 4 days/week with some leg resistance training	Will initially feel poorly/worse for up to 6 weeks	Initial recumbent exercise (rowing, recumbent cycle or swimming)
Pharmacological treatments			
Blood volume expanders			
Fludrocortisone	0.1–0.2 mg daily	Hypokalaemia, oedema and headache	Electrolytes must be monitored, especially potassium
Desmopressin (DDAVP)	0.1–0.2 mg as needed	Hyponatraemia, oedema	Monitor electrolytes
Acute IV Saline	2 L intravenous over 2–3 h	Venous thrombosis, infection	Acute saline infusion offers short-term relief only
Chronic IV saline	2 L given intravenously once weekly	Infection/thrombosis risk of central venous catheters	Avoid long-term use; avoid placement of central catheters
Erythropoietin	10,000 IU weekly	Increased risk of cardiovascular death	Monitor Haematocrit
Heart rate inhibitors			
Propranolol	10–20 mg orally up to four times daily	Hypotension, bradycardia and bronchospasm	Can worsen asthma or exercise tolerance
Ivabradine	2.5–7.5 mg orally twice daily	headaches, palpitations, hypertension and visual disturbances	Can induce nocturnal bradycardia
Pyridostigmine	30–60 mg orally up to three times daily	Abdominal cramps, diarrhoea	Can worsen asthma
Vasoconstrictors			
Midodrine	2.5–15 mg orally three times daily	Headache, scalp tingling and hypertension	

(*Continued*)

Table 1. *(Continued)*

Drug	Dosing information	Side effects	Precautions
Droxidopa	100–600 mg orally three times daily	Headache, nausea, diarrhoea and supine hypertension	Off-label use only; high cost
Methylphenidate	10 mg orally two to three times a day. Last dose should be avoided before bed	Tachycardia, insomnia, nausea, headache and dizziness	
Sympatholytic drugs			
Alpha-2 adrenergic agonists, such as clonidine	0.1–0.2 mg orally two to three times daily or long-acting patch	Hypotension, fatigue and brain fog	For hyperadrenergic form only (pronounced tachycardia, orthostatic hypertension)
Methyldopa	125–250 mg orally twice daily	Hypotension, fatigue and brain fog	As above
Other			
Modafinil	50–200 mg orally one to two times daily	Tachycardia	Used off-label as a drug counteracting 'brain fog' and fatigue

Source: Table adapted from [23] and [36] with changes.

Pulmonary rehabilitation strategies in post-COVID-19 condition

Several studies and systemic reviews have found that pulmonary rehabilitation after COVID-19 improves 6-min walking distance, health related quality of life, anxiety, depression and dyspnea [89–92].

Effects of treatment for persisting respiratory symptoms have been investigated in several studies. A combination of different breathing exercises for 5 weeks has been found to improve pulmonary function, quality of life and exercise capacity of patients with respiratory symptoms following COVID-19 [93]. A breathing and wellbeing program including singing techniques had minor effects on breathlessness [94].

The decreased respiratory muscle strength may be treated by inspiratory- and/or expiratory muscle training. This has been evaluated after intensive care and in patients with persisting symptoms [50, 95, 96]. These exercises have been shown to significantly improve respiratory muscle strength, dyspnoea, chest symptoms and quality of life, but their effect on pulmonary function and functional performance remains unclear.

Effects of structured pulmonary rehabilitation comprising a variety of combinations of breathing exercises including inspiratory muscle training, exercises to increase thoracic range of motion and general aerobic exercises have been evaluated in different settings [90, 97–101]. The rehabilitation programs were performed in outpatient clinics, were home based or via telemedicine. The results indicate that the interventions had an impact on pulmonary function, hyperventilation, dyspnoea and exercise capacity, even if it is not known which parts of the interventions were most efficient and in which combinations.

Knowledge gaps and future directions

During the last 2 years, much effort has been put into illuminating the prevalence, risk factors and underlying mechanisms for post-COVID-19 condition, generating several definitions [102] and hypotheses [36]. Although much has been learned about dysautonomia in post-COVID-19 condition, there are still important gaps in our understanding of mechanisms underlying observed cardiovascular and respiratory alterations. First, the overlap between dysautonomia and other debilitating chronic conditions (e.g. concurrence of POTS and myalgic encephalomyelitis/chronic fatigue syndrome) needs to be further elucidated in the search for what is common and what separates various post-COVID-19 phenotypes. Second, it is possible or even likely that different subtypes of cardiorespiratory dysautonomia may coexist (e.g. IST and microvascular dysfunction), requiring

Table 2. *Treatments for respiratory symptoms in post-COVID-19 condition*

Non-pharmacological treatments		
Symptom	Treatment	Precautions
Hypoventilation	Mobilization, deep breathing exercises with or without breathing devices	Nocturnal symptoms
Hyperventilation	Regimen and instructions	Anxiety
Dysfunctional breathing pattern	Retraining of a normal breathing pattern	Neurological reasons
Decreased respiratory muscle strength/endurance	Inspiratory/expiratory muscle training	Neurological reasons
Productive cough	Forced expiration techniques	Haemorrhage
Non-productive cough	Regimen how to avoid coughing	Aspiration
Musculoskeletal pain in the ribcage and adjacent joints	Stretching, exercises to increase range of motion and circulation and manual treatment	Osteoporosis
Decreased thoracic expansion	Stretching, exercises to increase range of motion, manual treatment and retraining of a normal breathing pattern	
Chest tightness	Stretching, exercises to increase range of motion and circulation, manual treatment and retraining of a normal breathing pattern	Cardiac reasons
Low physical capacity	Physical training, preferably in intervals	Post exertion malaise POTS
Hypoxia	Depending on the cause, see above	
Dyspnoea	Depending on the cause, see above	
Obstructive sleep apnoea	Continuous positive airway pressure (CPAP)	Nasal congestion, rhinorrhoea and pharyngeal irritation
Excessive dynamic airway collapse (EDAC)	Continuous positive airway pressure (CPAP)	Nasal congestion, rhinorrhoea and pharyngeal irritation

Pharmacological treatments			
Drug	Dosing information	Indication	Side effects
Inhaled corticosteroids			
Budesonide	200–400 μg twice daily	Asthma	Oral and pharyngeal side effects
Ciclesonide	160 μg once daily	Asthma	Oral and pharyngeal side effects
Mometasone	200–400 μg once daily	Asthma	Oral and pharyngeal side effects
Fluticasone propionate	125–250 μg twice daily	Asthma	Oral and pharyngeal side effects
Inhaled corticosteroids and long acting beta-2-agonists			
Budesonide and formoterol	160/4.5 μg twice daily and/or when needed	Asthma	Oral and pharyngeal side effects
Beclomethasone and formoterol	100/6 or 200/6 μg 2 inhalations twice daily and/or when needed	Asthma	Oral and pharyngeal side effects
Fluticasone furoate and vilanterol	92/22 or 184/22 μg once daily	Asthma	Oral and pharyngeal side effects
Inhaled corticosteroids, long acting beta-2-agonists and long acting muscarinic antagonist			
Beclomethasone, formoterol and glycopyrronium	87/5/9 or 172/5/9 μg 2 inhalations twice daily	Asthma	Oral and pharyngeal side effects
Mometasone, indacaterol and glycopyrronium	114/46/136 μg once daily	Asthma	Oral and pharyngeal side effects

(*Continued*)

Table 2. *(Continued)*

Pharmacological treatments			
Drug	Dosing information	Indication	Side effects
Montelukast	10 mg orally once daily.	Asthma	Sleep disturbances and depression
Short acting bronchodilators			
Salbutamol	0.2–1.5 mg given through a spacer	Asthma attack or acute bronchial obstruction	Tachycardia
Ipratropium	20–120 μg given through a spacer	Asthma attack or acute bronchial obstruction	Mouth dryness
Oral corticosteroids			
Prednisolone	25–50 mg orally	Asthma attack or acute bronchial obstruction	Anxiety, sleep disturbances and hyperglycaemia
Betamethasone	4–6 mg orally	Asthma attack or acute bronchial obstruction	Anxiety, sleep disturbances and hyperglycaemia

different therapeutic approaches and clinical follow-up, which needs to be systematically studied. Third, clinical trials are crucial in order to test the robustness of hypotheses explaining pathophysiological mechanisms of post-COVID-19 condition, such as viral persistence or autoimmune process. These trials should be carefully designed to include precise characterization of dysautonomia subtypes, which hitherto has been largely missing. Fourth, there is an obvious need for novel treatment options to relieve the most vexing symptoms of post-COVID-19 condition, such as brain fog or exercise intolerance. Although several studies are ongoing, as outlined above, more clinical trials are needed to improve symptom alleviation, perspectives for return to work, long-term prognosis and – in the best-case scenario – to offer a curative treatment. Such a goal may seem unattainable today, but a decisive breakthrough may not be far away.

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Conflict of interest statement

The authors declare no conflict of interests.

References

1 World Health Organization. WHO Coronavirus (COVID-19) Dashboard. Accessed 17 May, 2023. https://covid19.who.int/2023
2 Crook H, Raza S, Nowell J, Young M, Edison P. Long Covid-mechanisms, risk factors, and management. *BMJ*. 2021;**374**:n1648.
3 Hedberg P, Granath F, Bruchfeld J, Askling J, Sjöholm D, Fored M, et al. Post COVID-19 condition diagnosis: a

population-based cohort study of occurrence, associated factors, and healthcare use by severity of acute infection. *J Intern Med.* 2023;**293**(2):246–58.
4 Nalbandian A, Sehgal K, Gupta A, Madhavan MV, Mcgroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. *Nat Med.* 2021;**27**(4):601–15.
5 Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV. Condition WHOCCDWGoP-C-. A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect Dis.* 2022;**22**(4):e102–7.
6 Huang L, Li X, Gu X, Zhang H, Ren L, Guo Li, et al. Health outcomes in people 2 years after surviving hospitalisation with COVID-19: a longitudinal cohort study. *Lancet Respir Med.* 2022;**10**(9):863–76.
7 Ballering AV, Van Zon SKR, Olde Hartman TC, Rosmalen JGM. Lifelines Corona Research I. Persistence of somatic symptoms after COVID-19 in the Netherlands: an observational cohort study. *Lancet.* 2022;**400**(10350):452–61.
8 Greenhalgh T, Knight M, A'court C, Buxton M, Husain L. Management of post-acute COVID-19 in primary care. *BMJ.* 2020;**370**:m3026.
9 Wahlgren C, Forsberg G, Divanoglou A, Östholm Balkhed Å, Niward K, Berg S, et al. Two-year follow-up of patients with post-COVID-19 condition in Sweden: a prospective cohort study. *Lancet Reg Health Eur.* 2023:100595.
10 Brodin P. SARS-CoV-2 infections in children: understanding diverse outcomes. *Immunity.* 2022;**55**(2):201–9.
11 Yelin D, Wirtheim E, Vetter P, Kalil AC, Bruchfeld J, Runold M, et al. Long-term consequences of COVID-19: research needs. *Lancet Infect Dis.* 2020;**20**(10):1115–7.
12 Taquet M, Sillett R, Zhu L, Mendel J, Camplisson I, Dercon Q, et al. Neurological and psychiatric risk trajectories after SARS-CoV-2 infection: an analysis of 2-year retrospective cohort studies including 1 284 437 patients. *Lancet Psychiatry.* 2022;**9**(10):815–27.
13 Brodin P, Casari G, Townsend L, O'farrelly C, Tancevski I, Löffler-Ragg J, et al. Studying severe long COVID to understand post-infectious disorders beyond COVID-19. *Nat Med.* 2022;**28**(5):879–82.
14 Oikonomou E, Souvaliotis N, Lampsas S, Siasos G, Poulakou G, Theofilis P, et al. Endothelial dysfunction in acute and long standing COVID-19: a prospective cohort study. *Vascul Pharmacol.* 2022;**144**:106975.
15 Johansson M, Ståhlberg M, Runold M, Nygren-Bonnier M, Nilsson J, Olshansky B, et al. Long-Haul Post-COVID-19 symptoms presenting as a variant of postural orthostatic tachycardia syndrome: the Swedish experience. *JACC Case Rep.* 2021;**3**(4):573–80.
16 Ståhlberg M, Reistam U, Fedorowski A, Villacorta H, Horiuchi Yu, Bax J, et al. Post-COVID-19 tachycardia syndrome: a distinct phenotype of post-acute COVID-19 syndrome. *Am J Med.* 2021;**134**(12):1451–6.
17 Raman B, Bluemke DA, Lüscher TF, Neubauer S. Long COVID: post-acute sequelae of COVID-19 with a cardiovascular focus. *Eur Heart J.* 2022;**43**(11):1157–72.
18 Bisaccia G, Ricci F, Recce V, Serio A, Iannetti G, Chahal AA, et al. Post-acute sequelae of COVID-19 and cardiovascular autonomic dysfunction: what do we know? *J Cardiovasc Dev Dis.* 2021;**8**(11):156.
19 Greenhalgh T, Sivan M, Delaney B, Evans R, Milne R. Long COVID – an update for primary care. *BMJ.* 2022;**378**:e072117.
20 Meringer H, Mehandru S. Gastrointestinal post-acute COVID-19 syndrome. *Nat Rev Gastroenterol Hepatol.* 2022;**19**(6):345–6.
21 Feigofsky S, Fedorowski A. Defining cardiac dysautonomia – different types, overlap syndromes; case-based presentations. *J Atr Fibrillation.* 2020;**13**(1):2403.
22 Goldstein DS. Dysautonomias: clinical disorders of the autonomic nervous system. *Ann Intern Med.* 2002;**137**(9):753–63.
23 Fedorowski A. Postural orthostatic tachycardia syndrome: clinical presentation, aetiology and management. *J Intern Med.* 2019;**285**(4):352–66.
24 Biaggoni IBK, Fink G, Jordan J, Low PA, Paton JFR. *Primer on the autonomic nervous system.* 4th ed. Amsterdam, the Netherlands: Elsevier Academic Press; 2022.
25 Schwendinger F, Knaier R, Radtke T, Schmidt-Trucksass A. Low cardiorespiratory fitness post-COVID-19: a narrative review. *Sports Med.* 2022;**53**:51–74.
26 Fletcher GF, Ades PA, Kligfield P, Arena R, Balady GJ, Bittner VA, et al. Exercise standards for testing and training: a scientific statement from the American Heart Association. *Circulation.* 2013;**128**(8):873–934.
27 Eldokla AM, Ali ST. Autonomic function testing in long-COVID syndrome patients with orthostatic intolerance. *Auton Neurosci.* 2022;**241**:102997.
28 Utomi V, Oxborough D, Whyte GP, Somauroo J, Sharma S, Shave R, et al. Systematic review and meta-analysis of training mode, imaging modality and body size influences on the morphology and function of the male athlete's heart. *Heart.* 2013;**99**(23):1727–33.
29 Jiang DH, Roy DJ, Gu BJ, Hassett LC, Mccoy RG. Postacute sequelae of severe acute respiratory syndrome coronavirus 2 infection: a state-of-the-art review. *JACC Basic Transl Sci.* 2021;**6**(9):796–811.
30 Long Q, Li J, Hu X, Bai Y, Zheng Y, Gao Z. Follow-ups on persistent symptoms and pulmonary function among post-acute COVID-19 patients: a systematic review and meta-analysis. *Front Med (Lausanne).* 2021;**8**:702635.
31 Mayuga KA, Fedorowski A, Ricci F, Gopinathannair R, Dukes JW, Gibbons C, et al. Sinus tachycardia: a multidisciplinary expert focused review. *Circ Arrhythm Electrophysiol.* 2022;**15**(9):e007960.
32 Rivasi G, Groppelli A, Brignole M, Soranna D, Zambon A, Bilo G, et al. Association between hypotension during 24 h ambulatory blood pressure monitoring and reflex syncope: the SynABPM 1 study. *Eur Heart J.* 2022;**43**:3765–76.
33 Puntmann VO, Martin S, Shchendrygina A, Hoffmann J, Ka MM, Giokoglu E, et al. Long-term cardiac pathology in individuals with mild initial COVID-19 illness. *Nat Med.* 2022;**28**:2117–23.
34 Schondorf R, Low PA. Idiopathic postural orthostatic tachycardia syndrome: an attenuated form of acute pandysautonomia? *Neurology.* 1993;**43**(1):132–7.
35 Vernino S, Bourne KM, Stiles LE, Grubb BP, Fedorowski A, Stewart JM, et al. Postural orthostatic tachycardia syndrome (POTS): state of the science and clinical care from a 2019 National Institutes of Health Expert Consensus Meeting – Part 1. *Auton Neurosci.* 2021;**235**:102828.
36 Davis HE, Mccorkell L, Vogel JM, Topol EJ. Long COVID: Major findings, mechanisms and recommendations. *Nat Rev Microbiol.* 2023;**21**(3):133–46.

37 Montani D, Savale L, Noel N, Meyrignac O, Colle R, Gasnier M, et al. Post-acute COVID-19 syndrome. *Eur Respir Rev.* 2022;**31**(163):210185.
38 Chudzik M, Babicki M, Kapusta J, Kałuzińska-Kołat Ż, Kołat D, Jankowski P, et al. Long-COVID clinical features and risk factors: a retrospective analysis of patients from the STOP-COVID Registry of the PoLoCOV study. *Viruses.* 2022;**14**(8):1755.
39 Larsson AC, Engwall M, Palstam A, Persson HC. Self-assessed aspects of health 3 months after COVID-19 hospitalization – a Swedish cross-sectional study. *Int J Environ Res Public Health.* 2022;**19**(13):8020.
40 Wahlgren C, Divanoglou A, Larsson M, Nilsson E, Östholm Balkhed Å, Niward K, et al. Rehabilitation needs following COVID-19: Five-month post-discharge clinical follow-up of individuals with concerning self-reported symptoms. *EClinicalMedicine.* 2022;**43**:101219.
41 Fernández-De-Las-Peñas C, Guijarro C, Plaza-Canteli S, Hernández-Barrera V, Torres-Macho J. Prevalence of post-COVID-19 cough one year after SARS-CoV-2 infection: a multicenter study. *Lung.* 2021;**199**(3):249–53.
42 Ekbom E, Frithiof R, Emilsson O, Larson I, Lipcsey M, Rubertsson S, et al. Impaired diffusing capacity for carbon monoxide is common in critically ill Covid-19 patients at four months post-discharge. *Respir Med.* 2021;**182**:106394.
43 Tarraso J, Safont B, Carbonell-Asins JA, Fernandez-Fabrellas E, Sancho-Chust JN, Naval E, et al. Lung function and radiological findings 1 year after COVID-19: a prospective follow-up. *Respir Res.* 2022;**23**(1):242.
44 Lee JH, Yim J-J, Park J. Pulmonary function and chest computed tomography abnormalities 6-12 months after recovery from COVID-19: a systematic review and meta-analysis. *Respir Res.* 2022;**23**(1):233.
45 Katzenstein TL, Christensen J, Lund TK, Kalhauge A, Rönsholt F, Podlekareva D, et al. Relation of pulmonary diffusing capacity decline to HRCT and VQ SPECT/CT findings at early follow-up after COVID-19: a prospective Cohort Study (the SECURe Study). *J Clin Med.* 2022;**11**(19):5687.
46 Yu JZ, Granberg T, Shams R, Petersson S, Sköld M, Nyrén S, et al. Lung perfusion disturbances in nonhospitalized post-COVID with dyspnea – a magnetic resonance imaging feasibility study. *J Intern Med.* 2022;**292**(6):941–56.
47 Frija-Masson J, Debray M-P, Boussouar S, Khalil A, Bancal C, Motiejunaite J, et al. Residual ground glass opacities three months after Covid-19 pneumonia correlate to alteration of respiratory function: the post Covid M3 study. *Respir Med.* 2021;**184**:106435.
48 Pan F, Yang L, Liang Bo, Ye T, Li L, Li L, et al. Chest CT patterns from diagnosis to 1 year of follow-up in patients with COVID-19. *Radiology.* 2022;**302**(3):709–19.
49 Thomas P, Baldwin C, Bissett B, Boden I, Gosselink R, Granger CL, et al. Physiotherapy management for COVID-19 in the acute hospital setting: clinical practice recommendations. *J Physiother.* 2020;**66**(2):73–82.
50 Mcnarry MA, Berg RMG, Shelley J, Hudson J, Saynor ZL, Duckers J, et al. Inspiratory muscle training enhances recovery post-COVID-19: a randomised controlled trial. *Eur Respir J.* 2022;**60**(4):2103101.
51 Fagevik Olsén M, Lannefors L, Nygren-Bonnier M, Johansson E-L. Long COVID – respiratory symptoms in non-hospitalised subjects – a cross-sectional study. *Eur J Physiother.* 2022:1–8.
52 von Gruenewaldt A, Nylander E, Hedman K. Classification and occurrence of an abnormal breathing pattern during cardiopulmonary exercise testing in subjects with persistent symptoms following COVID-19 disease. *Physiol Rep.* 2022;**10**(4):e15197.
53 Frizzelli A, Di Spigno F, Moderato L, Halasz G, Aiello M, Tzani P, et al. An impairment in resting and exertional breathing pattern may occur in long-COVID patients with normal spirometry and unexplained dyspnoea. *J Clin Med.* 2022;**11**(24).
54 Frésard I, Genecand L, Altarelli M, Gex G, Vremaroiu P, Vremaroiu-Coman A, et al. Dysfunctional breathing diagnosed by cardiopulmonary exercise testing in 'long COVID' patients with persistent dyspnoea. *BMJ Open Respir Res.* 2022;**9**(1):e001126.
55 McConnell A. *Respiratory muscle training: theory and practice.* London: Churchill Livingstone; 2013.
56 Van Voorthuizen EL, Van Helvoort HAC, Peters JB, Van Den Heuvel MM, Van Den Borst B. Persistent exertional dyspnea and perceived exercise intolerance after mild COVID-19: a critical role for breathing dysregulation? *Phys Ther.* 2022;**102**(10):pzac105.
57 Zhu J, Ji P, Pang J, Zhong Z, Li H, He C, Zhang J, Zhao C. Clinical characteristics of 3062 COVID-19 patients: a meta-analysis. *J Med Virol.* 2020;**92**(10):1902–14.
58 Ladds E, Rushforth A, Wieringa S, Taylor S, Rayner C, Husain L, et al. Persistent symptoms after Covid-19: qualitative study of 114 "long Covid" patients and draft quality principles for services. *BMC Health Serv Res.* 2020;**20**(1):1144.
59 Vibholm LK, Nielsen SSF, Pahus MH, Frattari GS, Olesen R, Andersen R, et al. SARS-CoV-2 persistence is associated with antigen-specific CD8 T-cell responses. *EBioMedicine.* 2021;**64**:103230.
60 Gaebler C, Wang Z, Lorenzi JCC, Muecksch F, Finkin S, Tokuyama M, et al. Evolution of antibody immunity to SARS-CoV-2. *Nature.* 2021;**591**(7851):639–44.
61 Bussani R, Zentilin L, Correa R, Colliva A, Silvestri F, Zacchigna S, et al. Persistent SARS-CoV-2 infection in patients seemingly recovered from COVID-19. *J Pathol.* 2023;**259**(3):254–63.
62 Arbour N, CôTé Geneviè, Lachance C, Tardieu M, Cashman NR, Talbot PJ. Acute and persistent infection of human neural cell lines by human coronavirus OC43. *J Virol.* 1999;**73**(4):3338–50.
63 Chan PKS, To Ka-F, Lo AWI, Cheung JoLK, Chu I, Au FWL, et al. Persistent infection of SARS coronavirus in colonic cells in vitro. *J Med Virol.* 2004;**74**(1):1–7.
64 Murray RS, Brown B, Brain D, Cabirac GF. Detection of coronavirus RNA and antigen in multiple sclerosis brain. *Ann Neurol.* 1992;**31**(5):525–33.
65 Zoodsma M, De Nooijer AH, Grondman I, Gupta MK, Bonifacius A, Koeken VACM, et al. Targeted proteomics identifies circulating biomarkers associated with active COVID-19 and post-COVID-19. *Front Immunol.* 2022;**13**:1027122.
66 Queiroz MAF, Neves PFMD, Lima SS, Lopes JC, Torres MKS, Vallinoto IMVC, et al. Cytokine profiles associated with acute COVID-19 and long COVID-19 syndrome. *Front Cell Infect Microbiol.* 2022;**12**:922422.
67 Shafiee G, Arastou T, Heshmat R, Jamshidi AR, Larijani B, Arzaghi SM. Post COVID-19 neuropsychiatric complications

and therapeutic role for TNF-alpha inhibitors: a case series study. *J Diab Metab Disord.* 2022;**21**(2):2013–6.
68 Patterson BK, Guevara-Coto J, Yogendra R, Francisco EB, Long E, Pise A, et al. Immune-based prediction of COVID-19 severity and chronicity decoded using machine learning. *Front Immunol.* 2021;**12**:700782.
69 Tan Z-Y, Lu Y, Whiteis CA, Benson CJ, Chapleau MW, Abboud FM. Acid-sensing ion channels contribute to transduction of extracellular acidosis in rat carotid body glomus cells. *Circ Res.* 2007;**101**(10):1009–19.
70 Youngson C, Nurse C, Yeger H, Cutz E. Oxygen sensing in airway chemoreceptors. *Nature.* 1993;**365**(6442):153–5.
71 Villadiego J, Ramírez-Lorca R, Cala F, Labandeira-García JL, Esteban M, Toledo-Aral JJ, et al. Is carotid body infection responsible for silent hypoxemia in COVID-19 patients? *Function (Oxf).* 2021;**2**(1):zqaa032.
72 Doyle ME, Appleton A, Liu Q-R, Yao Q, Mazucanti CH, Egan JM. Human type II taste cells express angiotensin-converting enzyme 2 and are infected by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). *Am J Pathol.* 2021;**191**(9):1511–9.
73 Nikesjö F, Sayyab S, Karlsson L, Apostolou E, Rosén A, Hedman K, et al. Defining post-acute COVID-19 syndrome (PACS) by an epigenetic biosignature in peripheral blood mononuclear cells. *Clin Epigenetics.* 2022;**14**(1):172.
74 Fedorowski A, Li H, Yu X, Koelsch KA, Harris VM, Liles C, et al. Antiadrenergic autoimmunity in postural tachycardia syndrome. *Europace.* 2017;**19**(7):1211–9.
75 Hall J, Bourne KM, Vernino S, Hamrefors V, Kharraziha I, Nilsson J, et al. Detection of G protein-coupled receptor autoantibodies in postural orthostatic tachycardia syndrome using standard methodology. *Circulation.* 2022;**146**(8):613–22.
76 Kharraziha I, Axelsson J, Ricci F, Di Martino G, Persson M, Sutton R, et al. Serum activity against g protein-coupled receptors and severity of orthostatic symptoms in postural orthostatic tachycardia syndrome. *J Am Heart Assoc.* 2020;**9**(15):e015989.
77 Briquez PS, Rouhani SJ, Yu J, Pyzer AR, Trujillo J, Dugan HL, et al. Severe COVID-19 induces autoantibodies against angiotensin II that correlate with blood pressure dysregulation and disease severity. *Sci Adv.* 2022;**8**(40):eabn3777.
78 Mehandru S, Merad M. Pathological sequelae of long-haul COVID. *Nat Immunol.* 2022;**23**(2):194–202.
79 Utrero-Rico A, Ruiz-Ruigómez M, Laguna-Goya R, Arrieta-Ortubay E, Chivite-Lacaba M, González-Cuadrado C, et al. A short corticosteroid course reduces symptoms and immunological alterations underlying long-COVID. *Biomedicines.* 2021;**9**(11):1540.
80 Isaka Y, Hirasawa Y, Terada J, Shionoya Yu, Takeshita Y, Kinouchi T, et al. Preliminary study regarding the predicted body weight-based dexamethasone therapy in patients with COVID-19 pneumonia. *Pulm Pharmacol Ther.* 2022;**72**:102108.
81 Cheng W, Li Y, Cui L, Chen Y, Shan S, Xiao D, et al. Efficacy and safety of corticosteroid treatment in patients with COVID-19: a systematic review and meta-analysis. *Front Pharmacol.* 2020;**11**:571156.
82 Ramakrishnan S, Nicolau DV, Langford B, Mahdi M, Jeffers H, Mwasuku C, et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. *Lancet Respir Med.* 2021;**9**(7):763–72.
83 Izquierdo JL, Almonacid C, González Y, Del Rio-Bermudez C, Ancochea J, Cárdenas R, et al. The impact of COVID-19 on patients with asthma. *Eur Respir J.* 2021;**57**(3):2003142.
84 Carson E, Hemenway AN. A scoping review of pharmacological management of postacute sequelae of severe acute respiratory syndrome coronavirus 2 infection in 2021. *Am J Ther.* 2022;**29**(3):e305–21.
85 Thompson JS, Thornton AC, Ainger T, Garvy BA. Long-term high-dose immunoglobulin successfully treats long COVID patients with pulmonary, neurologic, and cardiologic symptoms. *Front Immunol.* 2022;**13**:1033651.
86 Bowe B, Xie Y, Al-Aly Z. Acute and postacute sequelae associated with SARS-CoV-2 reinfection. *Nat Med.* 2022;**28**(11):2398–405.
87 Byambasuren O, Stehlik P, Clark J, Alcorn K, Glasziou P. Effect of Covid-19 vaccination on long Covid: systematic review. *BMJ Med.* 2023;**2**(1):e000385.
88 Richard SA, Pollett SD, Fries AC, Berjohn CM, Maves RC, Lalani T, et al. Persistent COVID-19 symptoms at 6 months after onset and the role of vaccination before or after SARS-CoV-2 infection. *JAMA Netw Open.* 2023;**6**(1):e2251360.
89 Chen H, Shi H, Liu X, Sun T, Wu J, Liu Z. Effect of pulmonary rehabilitation for patients with post-COVID-19: a systematic review and meta-analysis. *Front Med (Lausanne).* 2022;**9**:837420.
90 Liu K, Zhang W, Yang Y, Zhang J, Li Y, Chen Y. Respiratory rehabilitation in elderly patients with COVID-19: a randomized controlled study. *Complement Ther Clin Pract.* 2020;**39**:101166.
91 Fugazzaro S, Contri A, Esseroukh O, Kaleci S, Croci S, Massari M, et al. Rehabilitation interventions for post-acute COVID-19 syndrome: a systematic review. *Int J Environ Res Public Health.* 2022;**19**(9):5185.
92 Jimeno-Almazán A, Franco-López F, Buendía-Romero Á, Martínez-Cava A, Sánchez-Agar JA, Sánchez-Alcaraz Martínez BJ, et al. Rehabilitation for post-COVID-19 condition through a supervised exercise intervention: a randomized controlled trial. *Scand J Med Sci Sports.* 2022;**32**(12):1791–1801.
93 Okan F, Okan S, Duran Yücesoy F. Evaluating the efficiency of breathing exercises via telemedicine in post-Covid-19 patients: randomized controlled study. *Clin Nurs Res.* 2022;**31**(5):771–81.
94 Philip KEJ, Owles H, Mcvey S, Pagnuco T, Bruce K, Brunjes H, et al. An online breathing and wellbeing programme (ENO Breathe) for people with persistent symptoms following COVID-19: a parallel-group, single-blind, randomised controlled trial. *Lancet Respir Med.* 2022;**10**(9):851–62.
95 Abodonya AM, Abdelbasset WK, Awad EA, Elalfy IE, Salem HA, Elsayed SH. Inspiratory muscle training for recovered COVID-19 patients after weaning from mechanical ventilation: a pilot control clinical study. *Medicine (Baltimore).* 2021;**100**(13):e25339.
96 Del Corral T, Fabero-Garrido R, Plaza-Manzano G, Fernández-De-Las-Peñas C, Navarro-Santana M, López-De-Uralde-Villanueva I. Home-based respiratory muscle training on quality of life and exercise tolerance in long-term post-COVID-19: Randomized controlled trial. *Ann Phys Rehabil Med.* 2022;**66**(1):101709.

97 Bouteleux B, Henrot P, Ernst R, Grassion L, Raherison-Semjen C, Beaufils F, et al. Respiratory rehabilitation for Covid-19 related persistent dyspnoea: a one-year experience. *Respir Med.* 2021;**189**:106648.
98 Li J', Xia W, Zhan C, Liu S, Yin Z, Wang J, et al. A telerehabilitation programme in post-discharge COVID-19 patients (TERECO): A randomised controlled trial. *Thorax.* 2022;**77**(7):697–706.
99 Dun Y, Liu C, Ripley-Gonzalez JW, Liu P, Zhou N, Gong X, et al. Six-month outcomes and effect of pulmonary rehabilitation among patients hospitalized with COVID-19: a retrospective cohort study. *Ann Med.* 2021;**53**(1):2099–109.
100 Nopp S, Moik F, Klok FA, Gattinger D, Petrovic M, Vonbank K, et al. Outpatient pulmonary rehabilitation in patients with long COVID improves exercise capacity, functional status, dyspnea, fatigue, and quality of life. *Respiration.* 2022;**101**(6):593–601.
101 Gloeckl R, Leitl D, Jarosch I, Schneeberger T, Nell C, Stenzel N, et al. Benefits of pulmonary rehabilitation in COVID-19: a prospective observational cohort study. *ERJ Open Res.* 2021;**7**(2):00108-2021.
102 Chaichana U, Man KKC, Chen A, Wong ICK, George J, Wilson P, Wei L. Definition of post-COVID-19 condition among published research studies. *JAMA Netw Open.* 2023;**6**(4):e235856.

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