**Supplementary material**

**Table S3.** General characteristics of the experimental models used in all studies included in this systematic review.

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| **Study (Author, Year and Country)** | **Design of Study** | **Sample Number/Age** | **Sex and the Incidence** | **Comorbidity Previous** | **Pathogen Infection** | **Infection Mechanism** | **Persistent Symptoms** | **Main Findings** |
| AUGUSTIN et al., 2021; Germany | Prospective and Longitudinal Study. | 958 Patients (female = 43 years, and male = 46 years) | Female = 513  Male = 445 | Hypertension, Chronic Lung Disease, Malignancies, Autoimmune Disease, Diabetes | SARS-CoV-2 | — | Shortness of Breath (86%), Anosmia (12,4%), Ageusia (11,1%), and Fatigue (97%) | The full clinical picture of PCS is complex and far from being understood. However, the viral tropism defined by the entry into cells through a widely expressed ACE2 receptor, makes it highly possible that many organs have the potential to undergo not only acute, but also chronic damage, adding to the very diverse clinical picture of PCS. |
| BARBARA et al., 2022; Malta | Randomized Study | 2646 Patients (18-70 years) | Female = 1360  Male = 1286 | Hypertension, Hyperlipidaemia, Ischaemic Heart Disease, Cerebrovascular Accident/Transient Ischaemic Attack, Peripheral Vascular Disease, Heart Failure, Diabetes Mellitus (Type 1 and 2), Atrial Fibrillation, Chronic Kidney Disease, Obesity BMI > 30, Chronic Respiratory Disease, Dialysis and Liver Cirrhosis | SARS-CoV-2 | — | Shortness of Breath (22.5%), Chest Pain (8.4%), Fatigue (25.6%), Headache (19.6%), Myalgia (14.7%), Abnormal Taste of Food (52.9%) and Anosmia (55.2%) | A significant proportion of post-COVID patients were symptomatic at a median follow-up of 142 days and felt worse than 1 year previously. Hospitalised patients had more deranged lipid and liver parameters as well as elevated RDW and MPV compared to non-hospitalised ones, suggesting ongoing inflammation in subjects who were more severely affected by the disease. It will be important to investigate whether these differences remain after longer follow-up and whether there is persistent liver or cardiac injury. Further studies should also study other populations and ethnic groups. |
| BHATTACHARYYA et al., 2022; India | Observational Study | 25 Patients  (Nonhospitalized  patients - 58.1 ± 8.93)  (Hospitalized patients - 54 ± 12.36) | (Nonhospitalized patients: Male - 8  Female - 2)  (Hospitalized patients -  Male - 11  Female - 4) | Lung Parenchymal Affection | SARS-CoV-2 | — | Cough, Shortness of Breath, Fever, Weakness, Anosmia and Loss of Taste | A good number of subjects recovering from acute COVID-19 continue to have LV dysfunction in terms of GLS even after 3 months of recovery. They show more dyspnea, fatigue, and pulse rate than the other patients and of them, the hospitalized patients had significantly worse LVGLS. The significance of such LV dysfunction in  long term needs to be looked for. |
| BRAGA-PAZ et al., 2022; Brazil | Brief Research Report | 102 Patients  (55.11 ± 4.6 years) | Female = 54  Male = 48 | Diabetes, Obesity, Hypertension and Asthma | SARS-CoV-2 | — | Anosmia (17.6%) and Ageusia (9.8%) | A better understanding of the genes modulated in association with initial anosmia and ageusia may bright light on the signaling pathway alterations that are associated with neurologic symptoms of COVID-19 and the development of long-COVID-19 syndrome and lay the groundwork for pharmacologic therapies that interfere with pathologic signaling changes. |
| BRASSELER et al., 2022; Germany | Single-site Retrospective Cohort Study | 84 Patients  (0-18 years) | Female = 16  Male = 8 | One patient with Depression and Eating Disorder | SARS-CoV-2 | — | Decreased general condition (87.5 %), brain fog/concentration difficulty (37.5%), hyperesthesia (50.0%) and headache (75%). | 24 out of 84 children and adolescents described smell and taste dysfunction after confirmed or suspected SARS-CoV-2 infections. A large number of these patients (6 out of 24) demonstrated increased fixation on their eating behavior post-COVID and over time these patients developed anorexia nervosa. |
| BUONSENSO et al., 2021; Italy | Case Report | 1 Patient  (14 years) | Female = 1 | No comorbidities | SARS-CoV-2 | — | Headache, Chest Pain, Fatigue and Tachycardia | Presentation of the first detailed evaluation of PASC in an adolescent, providing evidence of pulmonary circulation dysfunction with possible lung microvascular or endothelial damage as detected by CPET and chest SPECT/CT. |
| CHU et al., 2021; United Kingdom | Pilot Study | 16 Patients  (20-55 years) | Female = 13  Male = 3 | — | SARS-CoV-2 | — | Anosmia, Ageusia and Parosmia | Patients demonstrate reduced olfaction on quantitative testing and experience significant impacts on their quality of life as a result. More research is needed to demonstrate if olfactory training results in measurable improvements in smell test scores and quality  of life. |
| DA COSTA E SILVA et al., 2023; Brazil | Prospective Cohort Study | 147 Patients  (Mean age = 38.4 years) | Female = 94  Male = 53 | Hypertension, Asthma/Bronchitis, Chronic Cardiac Disease, Chronic Renal Disease, Diabetes Mellitus, Chronic Gastrointestinal Disease, Chronic Liver Disease and Human Immunodeficiency Virus Infection | SARS-CoV-2 | — | Headache (76.9%), Cough (70.7%), Coryza (63.9%), Sore Throat (62.6%), Myalgia (61.9%), Nasal Congestion (59.2%), Fatigue (51.7%), Fever (55.1%), Ageusia (46.3%), Anosmia (43.5%), Diarrhea (40.1%), Respiratory Discomfort (26.5%), Nausea (26.5%), Dyspnea (3.1%), Hair Loss (26.7%), and Memory Loss (26.7%) | The study revealed that three or more symptoms of COVID-19 can persist for up to a year in healthy people with mild COVID-19. Upper tract respiratory symptoms were the most common. Further studies are required to investigate the sequelae of COVID-19 over periods greater than 12 months. |
| EDWARDS et al., 2021; Ukraine | Proof of Concept Studies | Study 1 = 80 Patients  (28 - 84 years)  Study 2 = 20 Patients  (21 - 58 years) | Study 1 (Female = 52, male = 28)  Study 2 (Female = 8, male = 12) | Study 1 (Hypertension, Ischemic Heart Disease, Diabetes, Obesity, Chronic Kidney Disease, Oncopathology)  Study 2 (Hypertension, Diabetes, Obesity) | SARS-CoV-2 | SARS-CoV-2 virus gets into cells using the ACE2 receptor | Study 1 (Loss of Smell, Loss of Taste, Sore Throat, Dyspnea, Dry Cough)  Study 2 (Loss of Smell, Loss of Taste, Sore Throat, Dyspnea, Dry Cough, Fever) | The article suggests that ATP release induced by the SARS-CoV-2 virus plays a key role in the genesis of the major symptoms and complications of COVID-19. |
| FERNÁNDEZ-DE-LAS-PEÑAS et al, 2022; Spain | Multicenter Study | 1593 Patients  61 years (SD: 16 years) | Female = 717  Male = 876 | — | SARS-CoV-2 | — | Ageusia, Anosmia | Post-COVID loss of smell/taste tends to spontaneously recover during the 3 years after COVID-19 in previously hospitalized survivors. The recovery rate is higher than the rate of “again” symptoms. |
| FORTUNATO et al., 2022; Italy | Follow-up Study | 1175 Patients  (Mean age = 45 years) | Female = 633  Male = 542 | — | SARS-CoV-2 | — | Persistent Loss of Taste, Persistent Loss of Smell and Taste and Persistent Loss of Smell | Olfactory and gustatory dysfunctions persist in a substantial portion of patients with previous paucisymptomatic-to-mild clinical COVID-19 up to 12 months after disease onset. As SARS-CoV-2 infection may be associated with long-term smell and/or taste loss that may significantly impact the quality of life, there is a need for a better understanding of the extent and duration of these symptoms. In addition, a better understanding of the physiological mechanisms driving the recovery is required to facilitate the development of effective preventive and therapeutic strategies. |
| FUMAGALLI et al., 2022; Italy | Prospective Cohort Study | 254 Patients  (> 18 years) | Female = 102  Male = 152 | Allergies, Chronic Obstructive, Pulmonary Disease, Diabetes Mellitus, History of Cancer, Hypertension and Ischemic Heart Disease | SARS-CoV-2 | — | Fatigue, Exertional Dyspnea, Cough, Bowel Complaints, Insomnia, Confusion, Fear and Depression | Almost one-in-two patients reported COVID-19-related symptoms at 12 months after hospital discharge. Fatigue, exertional dyspnea, insomnia, confusion, fear, depression, cough, and bowel symptoms were the most common symptoms at 12-month contact. Age, gender, COPD, >2 symptoms at baseline and frailty at baseline were associated with a higher probability of symptoms, highlighting potential patient categories who may benefit from specific follow up strategies. |
| GAYLIS et al., 2022; Israel/USA | Single Arm Open Label Study | 51 Patients  (21-73 years) | Mouse Study: Male (Alone)/ Human Study: Female to male ratio was approximately 2 to 1 | — | SARS-CoV-2 | — | Fatigue, Weakness, Cardiac and Neurological Symptoms, Shortness of Breath, Gastrointestinal Disorders, Ageusia or Anosmia, Anxiety, Joint Pain, Rash, Cough and Insomnia. | The data indicate that the use of the nutraceutical product is a safe and significantly efficient option to reduce multiple symptoms of long COVID. |
| GRISANTI et al., 2022; Italy | Prospective Study | 109 Patients  (Mean Age = 57.17 years) | Female to Male Ratio - 1:1 | — | SARS-CoV-2 | — | Anosmia, Ageusia, Cough, Rhinitis, Fever, Myalgia, Gastrointestinal Symptoms | The analysis showed the presence of two subtypes of neurological long-COVID in our population: i) a type 1 long-COVID consisting mostly of patients with memory impairment, psychological disorders, headache, anosmia and ageusia; i) a type 2 long-COVID consisting mostly of patients with symptoms attributable to PNS involvement. An analysis of demographic and clinical risk factors showed a correlation between the severity of acute infection and the risk of developing a type 2 long-COVID (i.e., PNS involvement). |
| HERNDON et al., 2022; USA | Cross-sectional Study | 1065 Patients  (Mean Age = 33.95) | Female = 459  Male = 598  Nonbinary = 8 | — | SARS-CoV-2 | — | Sore Throat, Fatigue, Ageusia and Anosmia | Arthropathy and myalgia are common symptoms experienced during and following COVID-19. After controlling for self-reported, pre-existing conditions, we found approximately one-fifth to one-quarter of patients reported experiencing arthralgia or myalgia, respectively. More noteworthy was new onset joint pain or myalgia following resolution of COVID-19 symptoms. Additionally, COVID-19 vaccination may also contribute to the onset of these symptoms making causal inferences difficult. Viral arthropathy due to COVID-19 infection should be considered in a differential diagnosis when encountering patients with new onset polyarthropathy or myalgia. |
| KAATZ et al., 2022; Germany | Analysis of Online Search Trends | - | - | — | SARS-CoV-2 | — | Ageusia, Anosmia, Shortness of Breath, Clouding of Consciousness (Cognitive Impairment), Fatigue and Fatigue Syndrome | While interest in some relevant symptoms has declined again after an initial peak at the beginning of the pandemic, long COVID shows a relatively steady increase during the pandemic period under investigation, intermittently punctuated by a significant dip towards the end of 2021. Although the relative interest in long COVID is low in relation to the search volumes for other diseases, it nonetheless demonstrates the growing public concern and sustained interest for the disease. As a consequence, this clinical condition should also be given lasting consideration in the healthcare system. |
| KALAK et al., 2022; Israel | Single-center Cohort Study | 166 Patients  (19-86 years) | Female = 83  Male = 83 | Hypertension Diabetes, Asthma, Obstructive Sleep Apnea, Ischemic Heart Disease, Connective Tissue Disease, Chronic Heart Failure, Chronic Renal Failure, Immunosuppressive Disease, Solid Tumor, Lymphoma, Interstitial Lung Disease and other Respiratory | SARS-CoV-2 | — | Weakness (21.2%), Dyspnea (15.8%), Cough (7.9%), Brain Fog (7.3%), Generalized Pain (5.5%), and Chest Pain (0.6%) | Our results confirm the fluctuating pattern of post-COVID-19 symptoms over time; the prevalence of some symptoms decreasing or remaining stable and that of others increasing in the medium and long term. These data provide useful information for the clinical management of patients recovering from COVID-19. Longer follow-up studies in larger populations are needed to fully characterize the time course of symptoms in COVID-19 survivors. |
| LENNOL et al., 2023; Spain | Clinical Follow-up Study | 45 Patients  (21-89 years) | Female = 18  Male = 27 | Diabetes, Hypertension and Obesity | SARS-CoV-2 | — | Headache (26.9 %), Memory Loss (23.1%), Asthenia (50.0%), Myalgia/Arthralgia (26.9%), Anosmia/Ageusia (26.9%), and Vision Impairment (3.8 %) | The study demonstrated altered plasma GFAP, NfL and T-tau levels in COVID-19 patients without substantial neurological manifestation at the acute phase of the disease, providing a suitable indication of CNS vulnerability; but these biomarkers fail to predict the occurrence of delayed minor neurological symptoms. |
| LIU et al., 2022; USA | Case Report | 2 patients, a  (42-44 years) | Female = 2 | — | SARS-CoV-2 | — | Fatigue, Dyspnea, Cough, Chest Pain, Memory/Concentration Issues, Sleep Problems, Muscle Pain and Headache, Fast/Pounding Heartbeat, Loss of Smell or Taste, Depression or Anxiety, Fever, Dizziness upon Standing, and Post-exertional Malaise | The lack of effective treatments for Long COVID/PASC makes the SGB an attractive therapeutic modality that deserves further investigation. |
| LUCKOS et al., 2021; Poland | Case Study | 1 Patient  (48 years) | Female = 1 | Rheumatoid Arthritis | SARS-CoV-2 | — | Brain Fog, Word Finding Problem, Speaking with Strange Speech Prosody  (Foreign Accent Syndrome), Motor Symptoms, Cognitive Difficulties | EEG neurofeedback and goal-oriented cognitive training might be helpful in the reduction of neurocognitive dysfunctions in patients following the infection of SARS-CoV-2 and long-term side effects after the contraction of COVID-19. |
| MAIORANA et al., 2023; Italy | Follow-up Study | 376 Patients  (18-65 years) | Female = 277  Male = 99 | Parkinson’s Disease, Multiple Sclerosis, Epilepsy, Hashimoto Disease and Panic Attack Disorder. | SARS-CoV-2 | — | Fatigue (87.84%), Headache (65.74%), Mood Disorders (64.91%), Sleep Disorders (63.81%), Concentration and Attention Problems (59.94%), Anxiety (58.56%), Memory Impairment (58.56%), Musculoskeletal Pain (57.18%), and Sensitivity to External Auditory Stimuli (52.48%) | The results suggest that RTs recorded by an online-managed VDT could be an effective way to study post-COVID-19 syndrome from a neuropsychological perspective. |
| MÉNDEZ et al., 2021; Spain | Longitudinal Study | 179 Patients  (23-82 years) | Female = 75  Male = 104 | Arterial Hypertension, Diabetes, Dyslipidaemia, Chronic Heart Disease,  Chronic Renal Disease,  Chronic Liver Disease, Chronic Respiratory Disease, Cancer | SARS-CoV-2 | — | Fatigue (48.5%), Memory Complaints (32.2%), Arthromyalgia (26.9%), Dyspnoea (25.7%), Headache (15.8%), Chest Pain (7.6%), Paraesthesia (7%), Sputum Production (7%), Cough (5.3%), Anosmia (5.3%), Ageusia/Dysgeusia (2.3%), Fever (1.2%), and Tremors (1.2%) | Declined cognitive function, psychiatric morbidity and low QoL are prevalent in moderate to severe COVID‐19 survivors 1 year after hospital discharge. These data await confirmation by further prospective studies in other regions. Meanwhile, health policies should be designed to address these long‐term problems. A multidisciplinary approach that includes neurocognitive rehabilitation and psychiatric evaluation and treatments should be offered to indicated patients. |
| MERA-CORDERO et al., 2022; Spain | Double-blind Study | 284 Patients  (18-80 years) | (-) | — | SARS-CoV-2 | — | — | — |
| PACHALSKA et al., 2022; Poland | Case Study | 1 patient  (62 years) | Male n = 1 | Untreated Hypercholesterolaemia | SARS-CoV-2 | — | Weakness, Intense Fatigue, Brain Fog and Headache | ERPs can be useful in the diagnosis and treatment of patients following infection  by SARS-CoV-2 who contracted COVID-19, developed long COVID and  additionally PD. It allows for the detection of the functional neuromarker of PD  (e.g., hypoactivation of the dorsolateral prefrontal cortex, DLPFC) and enabled  the choosing of a proper tDCS protocol with the anode over these region of the  brain, and also the selection of effective neurostimulation. The proposed protocol  of tDCS tailored by the neuromarker offered to our patient, was effective in the  reduction of long COVID symptoms as well as early PD symptoms. |
| PARANHOS et al., 2022; Brazil | Cross-sectional Study | 219 Patients  (18-59 years) | Female = 164  Male = 55 | Allergic Rhinitis, Smoking, Diabetes | SARS-CoV-2 | — | Ageusia, Fatigue, Cognitive Disorder, Headache, Weakness, Dyspnea, Paresthesias, Sleep Disorder, Anxiety and Depression | The olfactory dysfunction is one of the most important long-term neurologic symptoms of COVID-19, with the highest prevalence among women, adults, and outpatients. Patients with olfactory dysfunction may experience persistent severe hyposmia or anosmia more than 1 year from the onset of symptoms, suggesting the possibility of permanent sequelae. |
| SAID et al., 2022; Saudi Arabia | Retrospective Cross-sectional Study | 998 Patients  (19-29 years) | Female = 785  Male = 213 | — | SARS-CoV-2 | — | Shortness of Breath (20%), Bruises or Bleeding (18%), Inattention (18%), GIT Symptoms (17.6%), Skin Irritation (8.6%), Anosmia and Ageusia (8%) | The absence of significant difference in symptoms between substantially different geographic regions and the seemingly independent dose and onset timings of region, age, sex, education, and nationality implied a common response to a universal vaccine component(s). |
| SALIHEFENDIC et al., 2021; Bosnia and Herzegovina | Case Report | 2 Patients  (31 years) | Female = 2 | — | SARS-CoV-2 | — | Fever, Cough, Back Pain, Dizziness, Muscle Pain, Weight Loss, and Muscle Aches | Neuropsychiatric disorders in Post COVID-19 syndrome are common and they vary. Two cases of young adults who developed signs of brain disorders in the post COVID-19 period were presented, and CT scans of the brain showed signs of ischemic vasculitis. In the future, it is necessary to develop and implement guidelines for management of brain disorders in younger COVID-19 patients. |
| SUGÁR et al., 2022; Hungary | Cross-sectional  Descriptive Study | 501 Patients  (11.05-40.09 years) | Female = 422  Male = 79 | Allergy and Chronic Diseases | SARS-CoV-2 | — | Fatigue/Weakness (59.8%), Anosmia (57.3%), Tachycardia (37.8%), Post-traumatic Stress Disorder (33.9%), Dysgeusia (28.1%) and Dyspnoea (25.6%) | The most important finding of the study was that the most common type of food that people would reject after the COVID-19 disease was meat. |
| VAIRA et al., 2022; Italy | Retrospective Cohort Study | 431 Patients  (12-71 years) | Female = 329  Male = 102 | — | SARS-CoV-2 | — | Fatigue (42.9%), Olfactory Dysfunction (29.5%), Gustatory Dysfunction (22.3%), and Muscle Pain (19.3%) | POD and PGD are a frequent symptom of the long-COVID-19 syndrome and significantly reduce QoL, specifically in the mental health component. |

ACE2: Angiotensin-converting Enzyme 2; BMI: Body Mass Index; CNS: Central Nervous System; COPD: Chronic Obstructive Pulmonary Disease CPET: Cardiopulmonary Exercise Testing; DLPFC: Dorsolateral Prefrontal Cortex; EEG: Electroencephalogram; ERPS: Event-Related Potentials; GFAP: Glial Fibrillary Acidic Protein; GIT: Gastrointestinal; GLS: Global Longitudinal Strain; HADS-D: Hospital Anxiety and Depression Scale - D: Depression; LV: Left Ventricular; LVGLS: Left Ventricular Global Longitudinal Strain; MPV: Mean Platelet Volume; NfL: Neurofilament Light Chain; PASC: Post-acute Sequelae of COVID-19; PCS: Post-COVID Syndrome; PD: Parkinson’s Disease; PGD: Persistent Gustatory Dysfunction; POD: Persistent Olfactory Dysfunction; QoL: Quality of Life; CT: Computerized Tomography; RDW: Red Cell Distribution Width; RT: Reaction Times; VDT: Visual Detection Task; SD: Standard Deviation; SGB: Stellate Ganglion Block; SPECT: Single Photon Emission Computed Tomography; tDCS: Transcranial Direct Current Stimulation.