

# Post - Long - Covid 19 und Schmerz: Gibt es einen Zusammenhang?

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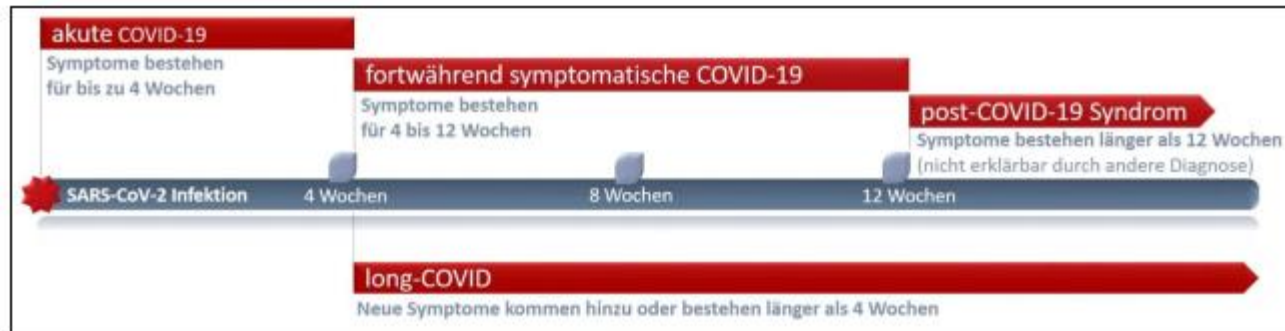
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# KABEG

KLINIKUM KLAGENFURT  
AM WÖRTHERRSEE

# Überblick über COVID-19 Nomenklatur (in Anlehnung an NICE 2020)



Sivan M, Taylor S. NICE guideline on long covid. BMJ 2020; 371: m4938.  
DOI:10.1136/bmj.m4938

## Was ist „Long Covid“?

Eine verlässliche Definition fehlt nach wie vor

Die WHO<sup>1</sup> schlägt folgende 3 Hauptsymptome vor

- **Fatigue**
- **Kurzatmigkeit**
- **Kognitive Dysfunktion**

<sup>1</sup> [https://www.who.int/publications/i/item/WHO-2019-nCoV-Post\\_COVID-19\\_condition-Clinical\\_case\\_definition-2021.1](https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1)

Prevalence, intensity and associated disability of spontaneously reported new onset persistent symptoms related to coronavirus disease 2019 (COVID-19) in 162 survivors at one year after hospital discharge (order according to frequency)

Symptom	Prevalence N (%)	Intensity (1 = slight ... 4 = severe) Mean (SD)	Disability (0 = none; 4 = very severe) Mean (SD)
Fatigue	40 (24.7)	2.3 (0.9)	2.3 (0.9)
Cognitive dysfunction	24 (14.8)	2.4 (1.4)	2.2 (1.2)
Shortness of breath	14 (8.6)	1.9 (0.6)	1.6 (1.1)
Pain in muscles and joints	11 (6.8)	2.3 (0.8)	2.0 (1.1)
Headache	10 (6.2)	2.4 (0.7)	1.3 (1.2)
Cough	3 (1.8)	2.3 (0.6)	1.3 (1.2)
Altered smell/taste	3 (1.8)	1.7 (1.2)	0.3 (0.6)
Posttraumatic stress symptoms	2 (1.2)	3.0 (1.0)	3.0 (1.0)
Sleep problems	2 (1.2)	3.0	1.5 (1.5)
Anxiety	1 (0.6)	3.0	3.0
Depression	1 (0.6)	3.0	3.0
Disturbance of sensitivity in one leg	1 (0.6)	1.0	1.0
Loss of appetite and weight	1 (0.6)	2.0	2.0
Nausea	1 (0.6)	3.0	1.0
Pain in hands and feet	1 (0.6)	3.0	3.0
Pruritus	1 (0.6)	2.0	2.0
Thoracic burning	1 (0.6)	2.0	2.0
Vertigo	1 (0.6)	1.0	2.0
Weakness of forefoot	1 (0.6)	1.0	1.0
<i>SD</i> standard deviation			

## Was ist „Long Covid“?

Zum Beispiel: Studie, die verschiedene Cluster beschreibt<sup>1</sup>:

- Neurokognitive (brain fog, Benommenheit, Gedächtnisprobleme)
- Kardiorespiratorisch (Kurzatmigkeit, Husten, Herzpalpationen, Brustschmerz)
- NB: Anxiety/Depression hier gering ausgeprägt vor allem bei milder Infektion

<sup>1</sup> Caspersen IH et al. Excess risk and clusters of symptoms after COVID-19 in a large Norwegian cohort. *Eur J Epidemiol* 2022;  
[doi.org/10.1007/s10654-022-00847-8](https://doi.org/10.1007/s10654-022-00847-8)

# Study sample characteristics. Data are numbers (%)

	No COVID-19 (n = 72,953) <sup>a</sup>	COVID-19 cases (n = 774) <sup>b</sup>
Male	29,658 (40.7)	325 (42.0)
Female	43,295 (59.3)	449 (58.0)
<i>Age (years)</i>		
25–34	489 (0.7)	6 (0.8)
35–39	5386 (7.4)	58 (7.5)
40–44	19,525 (26.8)	201 (26.0)
45–49	27,492 (37.7)	292 (37.7)
50–54	15,245 (20.9)	150 (19.4)
55–59	3836 (5.3)	53 (6.8)
60–64	758 (1.0)	10 (1.3)
65 +	222 (0.3)	4 (0.5)
Missing	0 (0)	0 (0)
<i>Educational level</i>		
<High school	4230 (5.8)	33 (4.3)
High school	21,144 (29.0)	220 (28.4)
College ≤ 4 years	26,486 (36.3)	298 (38.5)
College > 4 years	18,401 (25.2)	195 (25.2)
Missing	2692 (3.7)	28 (3.6)
<i>BMI</i>		
< 18.5	449 (0.6)	2 (0.3)
18.5–24.9	26,973 (37.0)	287 (37.1)
25–29.9	23,861 (32.7)	263 (34.0)
30–34.9	8219 (11.3)	93 (12.0)
≥ 35.0	2794 (3.8)	31 (4.0)
Missing	10,657 (14.6)	98 (12.7)
<i>Current smoking</i>		
No	58,254 (79.9)	645 (83.3)
Yes, occasional	2000 (2.7)	26 (3.4)
Yes, daily	2861 (3.9)	9 (1.2)
Missing	9838 (13.5)	94 (12.1)
<i>Chronic illness<sup>c</sup></i>		
No	45,564 (62.5)	480 (62.0)
Yes	18,981 (26.0)	197 (25.5)
Missing	8408 (11.5)	97 (12.5)

<sup>a</sup>Participants not registered with a COVID-19 diagnosis before February 1st, 2021. Participants with COVID-19 diagnosis in February or March 2021 were excluded from the study sample

<sup>b</sup>Participants who were registered with a COVID-19 diagnosis in MSIS before February 1st, 2021

<sup>c</sup>Asthma or other lung disease, cancer, heart disease, hypertension, diabetes, other disease reported in March/April 2020

**Caspersen IH, Magnus P, Trogstad L. Excess risk and clusters of symptoms after COVID-19 in a large Norwegian cohort. *Eur J Epidemiol.* 2022 May;37(5):539-548. doi: 10.1007/s10654-022-00847-8. Epub 2022 Feb 25. PMID: 35211871; PMCID: PMC8872922.**

Risks, excess risks (risk difference, RD) and relative risks (RR) for reporting current symptoms among cohort participants who acquired a COVID-19 diagnosis 11–12 months ago compared with controls with no COVID-19

	n <sup>a, b</sup>	No COVID-19, n (%) with symptoms <sup>b</sup>	COVID-19 diagnosis 11–12 months ago, n (%) with symptoms <sup>b</sup>	RD	RR (95% CI), unadjusted	RR (95% CI), adjusted <sup>c</sup>
<i>Cardiorespiratory</i>						
Chest pain	73,512	606 (0.8)	9 (5.4)	4.6	6.4 (3.4, 12.2)	6.7 (3.6, 12.7)
Cough	73,231	1611 (2.2)	8 (4.8)	2.6	2.1 (1.1, 4.2)	2.2 (1.1, 4.4)
Shortness of breath	73,257	963 (1.3)	19 (11.2)	9.9	8.4 (5.5, 12.9)	8.7 (5.7, 13.3)
Heart palpitations	72,735	1478 (2.1)	13 (7.7)	5.6	3.8 (2.2, 6.4)	3.9 (2.3, 6.6)
Myocarditis	73,718	5 (0)	0 (0)	0	NA	NA
Reduced lung function	73,311	234 (0.3)	13 (7.7)	7.4	23.8 (13.9, 40.8)	24.9 (14.6, 42.7)
<i>Neurocognitive</i>						
Anxiety	72,401	963 (1.3)	6 (3.5)	2.2	2.6 (1.2, 5.8)	2.8 (1.3, 6)
Brain fog	71,516	2780 (3.9)	20 (12)	8.1	3.0 (2, 4.6)	3.2 (2.1, 4.8)
Depression	72,364	2046 (2.9)	7 (4.1)	1.2	1.4 (0.7, 3.0)	1.5 (0.7, 3.1)
Dizziness	72,652	2212 (3.1)	10 (6)	2.9	1.9 (1.1, 3.6)	2.1 (1.1, 3.7)
Fatigue	70,956	2634 (3.8)	29 (17.4)	13.6	4.6 (3.3, 6.5)	4.8 (3.5, 6.7)
Headache	70,742	4970 (7.1)	20 (12)	4.9	1.7 (1.1, 2.6)	1.8 (1.2, 2.6)
Mood swings	72,571	3835 (5.3)	11 (6.5)	1.2	1.2 (0.7, 2.1)	1.3 (0.7, 2.2)
Poor memory	71,578	2517 (3.6)	30 (18.2)	14.6	5.1 (3.7, 7.1)	5.3 (3.8, 7.3)
Sleep problems	69,702	4436 (6.4)	15 (9.3)	2.9	1.4 (0.9, 2.3)	1.5 (0.9, 2.4)
<i>Joint and muscle</i>						
Joint pain	69,583	1855 (2.7)	7 (4.3)	1.6	1.6 (0.8, 3.3)	1.7 (0.8, 3.4)
Muscle pain	69,655	2623 (3.8)	10 (6.1)	2.3	1.6 (0.9, 2.9)	1.7 (0.9, 3.0)
<i>Other</i>						
Altered smell or taste	73,655	249 (0.3)	28 (16.9)	16.6	49.4 (34.5, 70.8)	51.4 (36, 73.5)
Fever	73,580	344 (0.5)	2 (1.2)	0.7	2.5 (0.6, 9.9)	2.6 (0.7, 10.5)
Hair loss	73,268	416 (0.6)	1 (0.6)	0	1.0 (0.1, 7.4)	1.1 (0.2, 8.0)
Kidney disease	73,537	32 (0)	0 (0)	0	NA	NA
Skin rash	72,784	1117 (1.6)	6 (3.5)	1.9	2.3 (1.0, 5.0)	2.4 (1.1, 5.2)

<sup>a</sup>Number of subjects included in regression model

<sup>b</sup>Participants with symptom duration > 12 months were excluded from both case and control groups

<sup>c</sup>Adjusted for age and chronic illness

## Was ist „Long Covid“?

Zum Beispiel: Studie, die verschiedene Cluster beschreibt<sup>1</sup>:

- Pain predominant (Gelenksschmerz, Myalgie, Kopfschmerz)
- Kardiovaskulär (thorakaler Schmerz, Kurzatmigkeit, Palpitationen)
- NB: relativ deutliche funktionelle Beeinträchtigung in diesen Clustern

<sup>1</sup> *Kenny G et al. Identification of Distinct Long COVID Clinical Phenotypes Through Cluster Analysis of Self-Reported Symptoms. Open Forum Infectious Diseases 2022; 9:ofac060*



# Proportion of Patients Experiencing Symptoms

**KABEG**

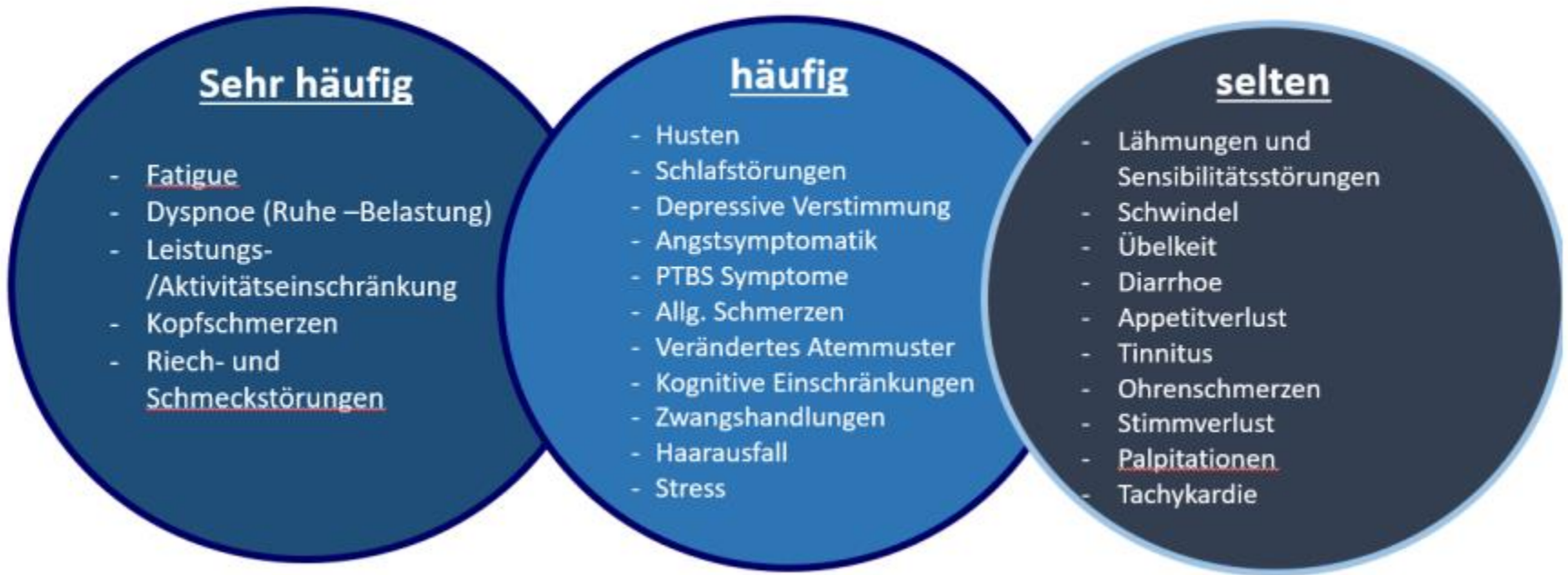
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Symptom	No. (%) of Patients Reporting Symptom
Fatigue	190/231 (81.9)
Respiratory	
Shortness of breath	160/231 (69)
Cough	37/231 (15.9)
Cardiovascular	
Chest pain	96/232 (41)
Palpitations	78/231 (33.6)
Neurological	
Poor concentration	82/232 (35.3)
Headache	48/232 (20.7)
Dizziness	28/227 (12.1)
Anosmia/hyposmia	27/231 (11.6)
Gastrointestinal	
Nausea/vomiting	13/231 (5.6)
Abdominal pain	11/229 (4.7)
Diarrhea	6/231 (2.6)
Musculoskeletal	
Joint pain	53/230 (22.8)
Myalgia	36/232 (15.5)
Other	
Rash	11/232 (4.7)
Sore throat	13/230 (5.6)
Fever	9/226 (4)
Coryza	2/228 (0.9)
Conjunctivitis	2/231 (0.9)

Percentage reflects the proportion of individuals experiencing symptoms within those with complete information for each symptom. For analysis, all gastrointestinal symptoms were collapsed into a single variable; other symptoms present in <10% of individuals were excluded from analysis.

***Kenny G, McCann K, O'Brien C, Savinelli S, Tinago W, Yousif O, Lambert JS, O'Broin C, Feeney ER, De Barra E, Doran P, Mallon PWG; All-Ireland Infectious Diseases (AIID) Cohort Study Group. Identification of Distinct Long COVID Clinical Phenotypes Through Cluster Analysis of Self-Reported Symptoms. Open Forum Infect Dis. 2022 Mar 7;9(4):ofac060. doi: 10.1093/ofid/ofac060. PMID: 35265728; PMCID: PMC8900926.***

## Häufigkeit von long-COVID Symptomen



Pragmatische Einteilung der Symptommhäufigkeit nach aktueller Literatur ohne Anspruch auf Vollständigkeit nach

Wong AW, Shah AS, Johnston JC et al. Patient-reported outcome measures after COVID-19: a prospective cohort study. European Respiratory Journal 2020; 56.

Huang C, Huang L, Wang Y et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. Lancet 2021; 397: 220-232. DOI: 10.1016/S0140-6736(20)32656-8

Carfi A, Bernabei R, Landi F et al. Persistent Symptoms in Patients After Acute COVID-19. JAMA 2020; 324: 603-605. DOI: 10.1001/jama.2020.12603

Goërtz YM, Van Herck M, Delbressine JM et al. Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome? ERJ open research 2020; 6.

Halpin S, O'Connor R, Sivan M. Long COVID and chronic COVID syndromes. J Med Virol 2021; 93: 1242-1243. DOI: 10.1002/jmv.26587

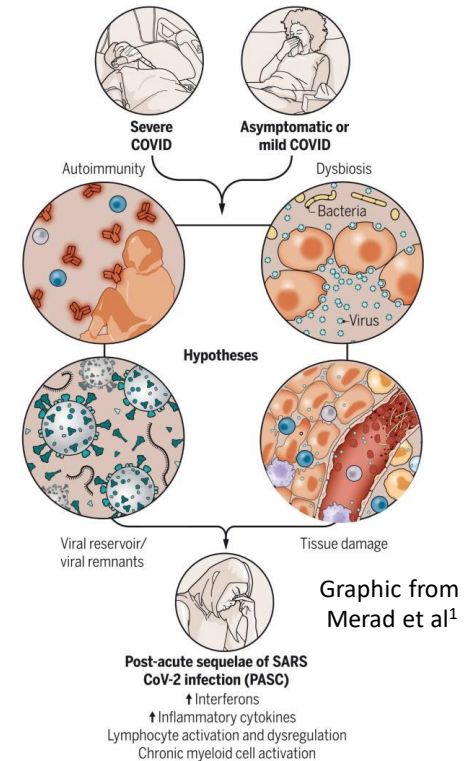
Cares-Marambio K, Montenegro-Jimenez Y, Torres-Castro R et al. Prevalence of potential respiratory symptoms in survivors of hospital admission after coronavirus disease 2019 (COVID-19): A systematic review and meta-analysis. Chron Respir Dis 2021; 18: 14799731211002240. DOI:

10.1177/14799731211002240

## Was sind die Ursachen für „Long Covid“?

Hypothesen<sup>1</sup>:

- Autoimmunität
- Virale Reservoirs
- Gewebsschäden/Vaskuläre Schäden<sup>2</sup>/Microclots<sup>3</sup>
- Eine Kombination?



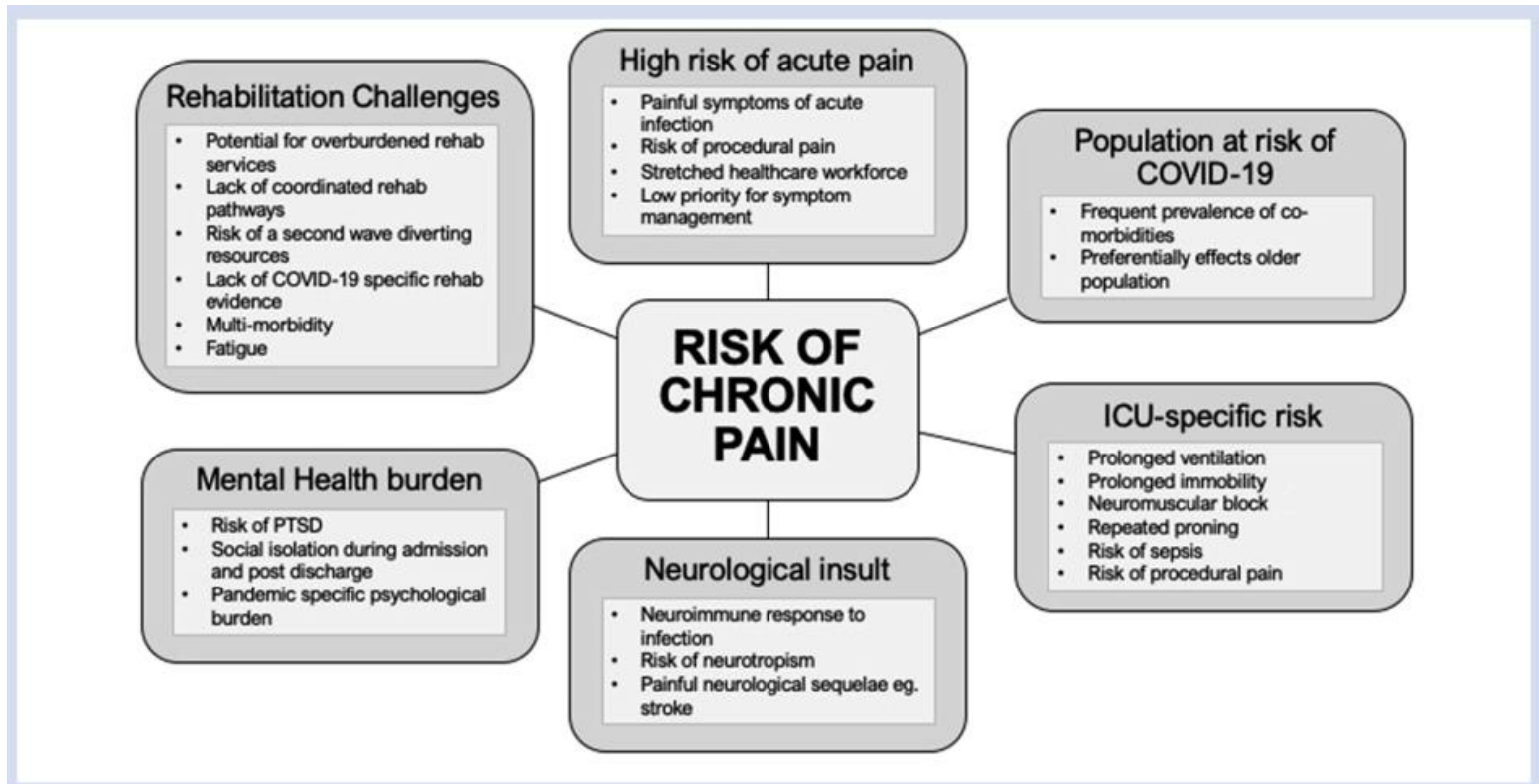
<sup>1</sup> Merad M et al. The immunology and immunopathology of COVID-19. *Science* 2022; 375:1122

<sup>2</sup> Fogarty H et al. Persistent endotheliopathy in the pathogenesis of long COVID syndrome. *J Thromb Haemost* 2021; 19:2546

<sup>3</sup> Pretorius E et al. Persistent clotting protein pathology in Long COVID/Post-Acute Sequelae of COVID-19 (PASC) is accompanied by increased levels of antiplasmin. *Cardiovasc Diabet* 2021; 20: 172

# Potential risk factors for development of chronic pain after COVID-19.

COVID-19, coronavirus disease 2019;  
PTSD, post-traumatic stress disorder.



**COVID-19 survivors are likely to have sustained a pro-longed period of immobilisation, sedation, and ventilation putting them at high risk of associated ICU-acquired weakness (ICUAW).**

**Commonly manifesting as any combination of critical illness myopathy (CIM), critical illness polyneuropathy (CIN), and muscle atrophy, known risk factors include the use of neuromuscular block and corticosteroids, the presence of sepsis and multi-organ dysfunction, and prolonged mechanical ventilation.**

*Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020; 8: 475e81*  
*De Jonghe B, Sharshar T, Lefaucheur J-P, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. JAMA 2002; 288: 2859e67*

Pain is a common symptom accompanying the coronavirus disease 2019 (COVID-19) caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2). **Nonspecific discomfort such as sore throat and body ache are frequent. Parainfectious pain such as headache, myalgia, or neuropathic pain has also been reported.** The latter seems to be associated with an autoimmune response or an affection of the peripheral neuromuscular system or the central nervous system because of the viral infection. **Furthermore, chronic pain can be a complication of intensive care unit treatment due to COVID-19 itself (such as intensive care–acquired weakness) or of secondary diseases associated with the SARS-CoV-2 infection, including Guillain–Barre´ syndrome, polyneuritis, critical illness polyneuropathy, or central pain following cerebrovascular events.** Data on long-lasting painful symptoms after clinically manifest COVID-19 and their consequences are lacking. **In addition, preexisting chronic pain may be exacerbated by limited and disrupted health care and the psychological burden of the COVID-19 pandemic. Medical providers should be vigilant on pain during and after COVID-19.**

**Table 1**

**COVID-19-associated acute and subacute pain.**

Painful symptoms (synonyms)	German incidence in %	International incidence in %	Potential underlying causes/pathologies	References (examples)		
				Case reports*	Observational trials or retrospective records (n = total included patients)	Systematic reviews† (n = total included trials)
Sore throat and throat pain	4–8.5	5.1–44.4	Local infection of the upper respiratory tract	Bhatraju 2020 (n = 24) <sup>9</sup>	Dreher 2020 (n = 50), <sup>22</sup> Guan 2020 (n = 1099), <sup>32</sup> Gudbjardsson 2020 (n = 1321), <sup>33</sup> and Mao 2020 (n = 214) <sup>52</sup>	Li 2020 (n = 10), <sup>47</sup> Rodriguez-Morales 2020 (n = 19) <sup>63</sup>
Pharyngalgia	2	13.1–17.4	Local infection of the upper respiratory tract	n.f.	Dreher 2020 (n = 50), <sup>22</sup> Wang 2020 (n = 138)	Zhu 2020 (n = 38) <sup>92</sup>
Body ache	n.f.	7.7–28.8	Cytokine release during common cold	Aksan 2020 (n = 1) <sup>1</sup>	Guan 2020 (n = 1099), <sup>32</sup> Gudbjardsson 2020 (n = 1321) <sup>33</sup>	n.f.
Limb or joint pain and arthralgia	n.f.	2–14.9	Arthritis	n.f.	Yang 2020 (n = 52) <sup>88</sup>	n.f.
Chest pain, chest tightness, and angina	n.f.	2–35.7	Pneumonia, cough, lower respiratory tract sign, myocarditis, and thromboembolism	Greenan-Barrett (n = 4) <sup>30</sup>	Yang 2020 (n = 52) <sup>88</sup>	Zhu 2020 (n = 38) <sup>92</sup>



Abdominal pain	n.f.	2.2–4.7	Diarrhea, gastroenteritis and acute abdomen	Gahide 2020 (n = 3), <sup>28</sup> Saeed (n = 9) <sup>65</sup>	Mao 2020 (n = 214), <sup>52</sup> Wang 2020 (n = 138) <sup>82</sup>	Zhu 2020 (n = 38) <sup>92</sup>
Headache	2	2–71.1	Meningeal affection accompanying cerebrovascular events, encephalitis, meningitis, intracerebral hemorrhage, encephalopathy, cranial polyneuritis, inflammatory (activation of nociceptive sensory neurons by cytokines and chemokines), viral neuro-invasion, hypoxemia, and thrombosis secondary to COVID-19-induced hypercoagulable states	Bhatraju (n = 24), <sup>9</sup> Filatov 2020 (n = 1) <sup>26</sup>	Chen (n = 99), <sup>13</sup> Dreher 2020 (n = 50), <sup>22</sup> Guan 2020 (n = 1099), <sup>32</sup> Gudbjardsson 2020 (n = 1321), <sup>33</sup> Huang 2020 (n = 41), <sup>37</sup> Liu 2020 (n = 30), <sup>49</sup> Mao 2020 (n = 214), <sup>52</sup> Tian 2020 (n = 262), <sup>73</sup> Tostmann (n = 20), <sup>76</sup> Wang 2020 (n = 138), <sup>82</sup> Xu 2020 (n = 62), <sup>86</sup> and Yang 2020 (n = 52) <sup>88</sup>	Asadi-Pooya 2020 (n = 2), <sup>5</sup> Chen 2020 (n = 92), <sup>14</sup> Li 2020 (n = 10), <sup>47</sup> Rodriguez-Morales 2020 (n = 19), <sup>63</sup> Tsai 2020 (n = 79), <sup>79</sup> Tolebeyan 2020 (n = 20), <sup>74</sup> and Zhu 2020 (n = 38) <sup>92</sup>



Myalgia, muscle pain, skeletal muscle injury/pain, muscle ache, and muscle soreness	12	3.2–76.9	Myositis, ICU-acquired weakness, critical illness myopathy; generalized inflammation and cytokine response	n.f.	Dreher 2020 (n = 50), <sup>22</sup> Guan 2020 (n = 1099), <sup>32</sup> Huang 2020 (n = 41), <sup>37</sup> Mao 2020 (n = 214), <sup>52</sup> Wang 2020 (n = 138), <sup>82</sup> Xu 2020 (n = 62), <sup>86</sup> Yang (n = 52), <sup>88</sup> and Zhou 2020 (n = 191) <sup>90</sup>	Li 2020 (n = 10), <sup>47</sup> Rodriguez-Morales 2020 (n = 19), <sup>63</sup> Tsai 2020 (n = 79), <sup>79</sup> and Zhu 2020 (n = 38) <sup>92</sup>
Neuralgia, neuropathic pain, and nerve pain	n.f.	2.3	Guillain–Barré syndrome, Miller–Fisher syndrome, and critical illness polyneuropathy	Aksan 2020 (n = 1), <sup>1</sup> Alberti 2020 (n = 1), <sup>2</sup> Sedaghat 2020 (n = 1), <sup>69</sup> Toscano 2020 (n = 1), <sup>75</sup> and Zhao 2020 (n = 1) <sup>89</sup>	Mao 2020 (n = 214) <sup>52</sup>	n.f.

\* Incidences were only included if publications included at least 5 cases.

† Partially including duplicates to mentioned observational trials.

n.f., none found.

### 2.1. The nature of neurological complications

**Viral infections may have a direct impact on the peripheral nervous system or central nervous system (CNS) or induce postviral immune syndrome. The most common peripheral lesions responsible for neuropathic pain include acute or chronic polyneuropathy, acute polyradiculoneuritis (Guillain–Barre´ syndrome), chronic inflammatory demyelinating polyneuropathy, or ganglionopathy. Guillain–Barre´ syndrome and chronic inflammatory demyelinating polyneuropathy in particular have been associated with a large number of viral agents including coronaviruses, Epstein–Barr virus, HIV, hepatitis virus, cytomegalovirus, influenza A virus, and Zika.<sup>53</sup> Central nervous system lesions responsible for neuropathic pain after viral infections include transverse myelitis, encephalomyelitis, and stroke.**

## 5. Implications for therapeutic management

Neuropathic pain should be distinguished from other causes of COVID-19–induced pain because it is more difficult to treat.

**Although conventional analgesics are not effective and not recommended, a number of patients with neuropathic pain, particularly elderly patients, receive or self-administer these medications for their pain particularly nonsteroidal anti-inflammatory agents.** Multiple concerns have been raised about the use of nonsteroidal anti-inflammatory agents in patients infected with SARS Co-2, but recent large-scale surveys seem to indicate that their use is not associated with significant increase in mortality, hospitalization, or ICU admission.

*Lund LC, Kristensen KB, Reilev M, Christensen S, Thomsen RW, Christiansen CF, Støvring H, Johansen NB, Brun NC, Hallas J, Pottegård A. Adverse outcomes and mortality in users of non-steroidal anti-inflammatory drugs who tested positive for SARS-CoV-2: a Danish nationwide cohort study. PLoS Med 2020;17:e1003308.*

*Meisinger C, Bongaerts BWC, Heier M, Amann U, Kowall B, Herder C, Ruckert-Eheberg IM, Rathmann W, Ziegler D. Neuropathic pain is not adequately treated in the older general population: results from the KORA F4 survey. Pharmacoepidemiol Drug Saf 2018;27:806–14.*

*Moisset X, Moisset X, Bouhassira D, Avez Couturier J, Alchaar H, Conradi S, Delmotte MH, Lanteri-Minet M, Lefaucheur JP, Mick G, Piano V, Pickering G, Piquet E, Regis C, Salvat E, Attal N. Pharmacological and non-pharmacological treatments for neuropathic pain: systematic review and French recommendations. Rev Neurol (Paris) 2020;176:325–52, Vg.*

*Finnerup NB, Attal N, Haroutounian S, Finnerup NB, Attal N, Haroutounian S, McNicol E, Baron R, Dworkin RH, Gilron I, Haanpaää M, Hansson P, Jensen TS, Kamerman PR, Lund K, Moore A, Raja SN, Rice AS, Rowbotham M, Sena E, Siddall P, Smith BH, Wallace M. Pharmacotherapy for neuropathic pain in adults: a systematic review and meta-analysis. Lancet Neurol 2015;14:162–73.*

*Attal N., Martinez V., Bouhassira D.; Potential for increased prevalence of neuropathic pain after the COVID-19 pandemic. Pain Reports 6(2021) e884.*

**The mainstay of therapy for neuropathic pain is represented by gabapentinoids (gabapentin and pregabalin), antidepressants (serotonin and noradrenalin reuptake inhibitor antidepressants or tricyclic antidepressants), tramadol, and topical agents (lidocaine plasters, capsaicin high concentration patches or botulinum toxin A for peripheral neuropathic pain), while strong opioids may be considered in refractory cases.** However, these drugs have an overall modest therapeutic efficacy. Nonpharmacological treatments including invasive or noninvasive neurostimulation techniques (transcutaneous electrical nerve stimulation, repetitive transcranial magnetic stimulation, spinal cord stimulation, etc) may also be proposed, although robust evidence for their efficacy still needs adequate large-scale controlled trials. The reported female patient affected with COVID-19 who reported intense burning pain responded to gabapentin.

*Aksan F, Nelson EA, Swedish KA. A COVID-19 patient with intense burning pain. J Neurovirol 2020;26:800–1.*

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# Neurological Manifestations in COVID-19 Patients

nonspecific	CNS manifestations	PNS manifestations
Headache	Altered mental status	Olfactory dysfunction
Fatigue	Encephalitis	Gustatory dysfunction
Myalgia	Encephalopathy	Neuralgia
Dizziness	Hypoxic ischemia	Arthralgia
Nausea	Agitation	Dysautonomia
Vomiting	Confusion	Guillain–Barre syndrome
Malaise	Bradypsychia	Paraesthesia
	Acute confusional syndrome	Facial palsy
	Anxiety	Peripheral neuropathy
	Depression	Focal neurologic deficits
	Psychosis	Vision impairment
	Movement disorders	AIDP
	Shock	Hyper
	Orthostatic hypertension	Rhabdomyolysis
	Balance disorder	Myopathy
	Delirium	
	Tremors	
	Myelitis	
	Syncope	
	Ataxia	
	Seizure	
	Cerebrovascular disease	
	Sleep disorders	
	Cranial neuropathy	
	Cerebral venous sinus thrombosis	
	Posterior reversible encephalopathy syndrome (PRES)	

## Meta-Analysis, Summary Estimate of Pooled Prevalence, and Heterogeneity of Each Neurological Manifestation

event	studies (N)	summary estimate (%)	95% CI	I <sub>2</sub> (inconsistency)
Malaise	12	38.3	[24.7, 52.9]	97.2
Fatigue	147	33.6	[29.5, 37.8]	99.3
Gustatory dysfunction	74	27.2	[22.3, 32.3]	99.5
Olfactory dysfunction	89	26.4	[21.8, 31.3]	99.5
Encephalopathy	12	23.5	[14.3, 34.1]	98.1
Myalgia	154	21.4	[18.8, 24.1]	99.1
Arthralgia	34	19.9	[15.3, 25.0]	98.8
Altered mental status	30	17.1	[12.3, 22.5]	98.6
Sleep disorder	5	14.9	[1.9, 36.8]	98.5
Headache	176	14.6	[12.2, 17.2]	99.4
Confusion	13	14.2	[6.9, 23.5]	98.5
Cerebrovascular disease	28	9.9	[6.8, 13.4]	98.7
Nausea	100	9.8	[8.1, 11.7]	98.2
Guillain–Barre syndrome	7	6.9	[2.3, 13.7]	97.9
Vomiting	104	6.7	[5.5, 8.0]	97.8
Dizziness	50	6.7	[4.7, 9.1]	98.0
Movement disorders	9	5.2	[1.7, 10.4]	98.6
Seizure	24	4.05	[2.5, 5.8]	97.7
Neuralgia	7	2.4	[0.8, 4.7]	90.3
Encephalitis	8	0.6	[0.2, 1.3]	92.5

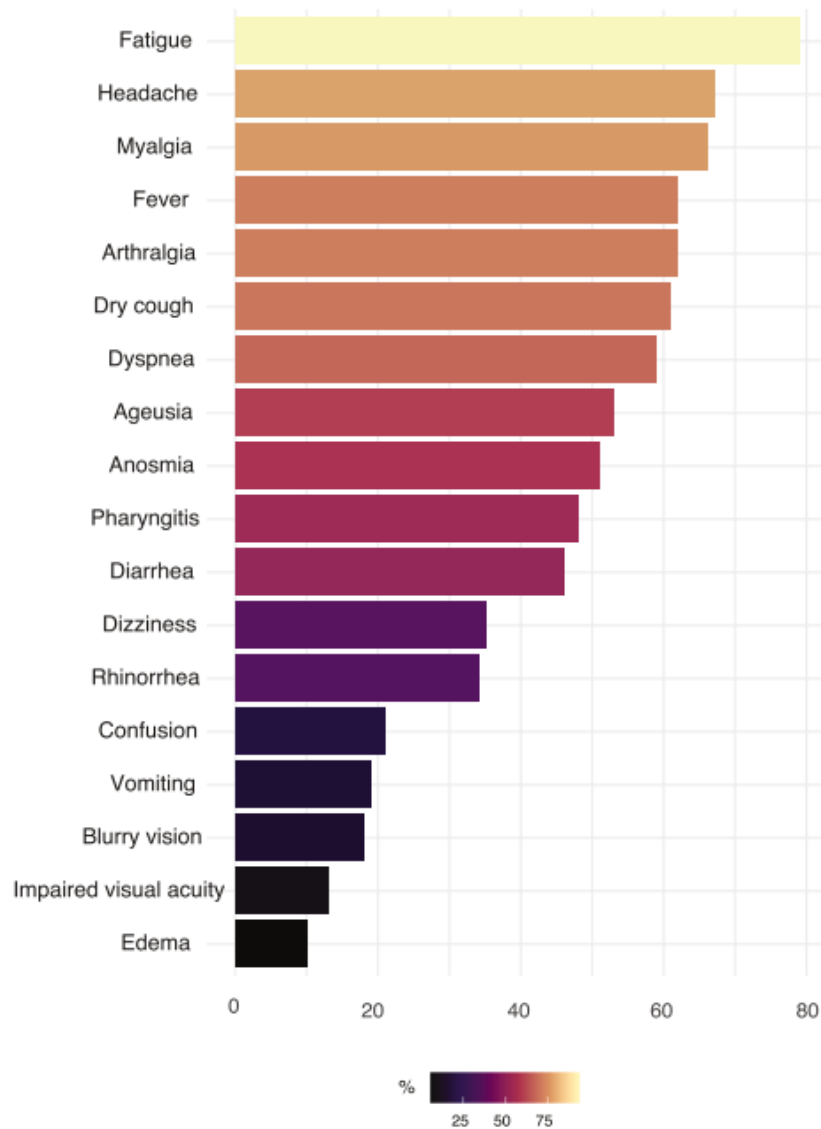
## CONCLUSION

**Our study demonstrates that neurological manifestations are significantly reported in COVID-19 patients. The most common neurological manifestations in COVID-19 patients were headache, fatigue, olfactory dysfunction, gustatory dysfunction, vomiting, nausea, dizziness, myalgia, seizure, cerebrovascular diseases, sleep disorders, altered mental status, neuralgia, arthralgia, encephalopathy, encephalitis, malaise, confusion, movement disorders, and Guillain–Barre syndrome depending upon the individual, which indicates the involvement of CNS as well as PNS.**

**A total of 40 articles (11,196 patients) were included in the meta-analysis. Fatigue/ muscle weakness, dyspnea, pain and discomfort, anxiety/depression and impaired concentration were presented in more than 20% of patients reported. In conclusion, PCS is mainly characterized by musculoskeletal, pulmonary, digestive and neurological involvement including depression. PCS is independent of severity of acute illness and humoral response.** Long-term antibody responses to SARS-CoV-2 infection and a high inter-individual variability were confirmed. Future studies should evaluate the mechanisms by which SARS-CoV-2 may cause PCS and the best therapeutic options

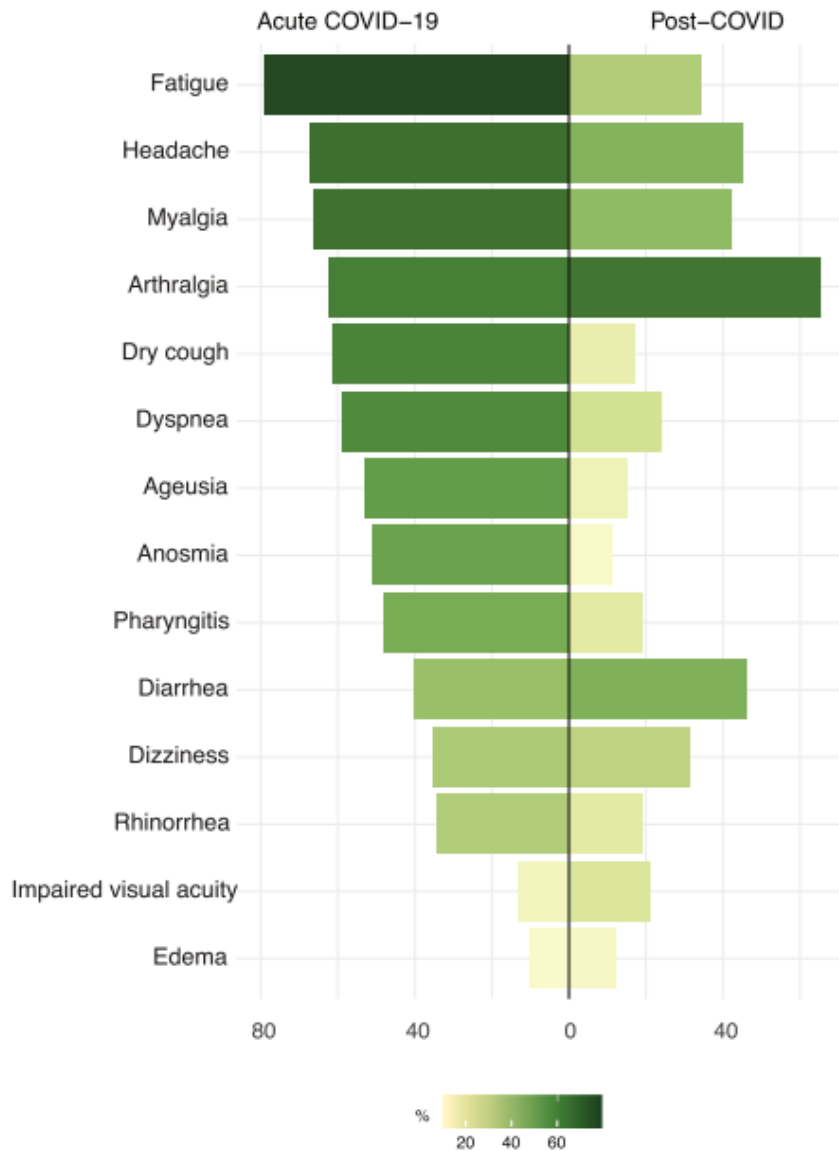


A



Acute and post-COVID symptoms.  
A. Frequency bar plot for clinical manifestations on acute COVID-19.

D



D. Mirrored bar plot for symptoms on acute COVID-19 and post COVID syndrome

**Background:** The COVID-19 pandemic has forced sweeping social and behavioral changes that have adversely affected the general population. Many changes, such as business closures, working from home, increased psychological distress, and delayed access to health care, could have unique adverse effects on patients diagnosed with chronic pain (CP). The present study sought to examine perceived changes in the CP experience brought about by the COVID-19 pandemic.

**Design:** Participants included 487 self-reported patients with musculoskeletal, neuropathic, or postsurgical pain recruited using CloudResearch. A 53-item survey was created to assess changes in perceived pain, mood, control over pain, physical activity, employment, and medical access since the onset of the pandemic.

## Small Fiber Neuropathie

- Neuropathie der A $\delta$ -Fasern und unmyelinisierten C-Fasern
- Betrifft sensorische und/oder autonome Fasern
- Bei Long Covid beschrieben<sup>1,2</sup>
- Diagnostik z.B. per Hautbiopsie in Kombination mit Klinik
- Kann prinzipiell Dysautonomie und häufige neuropathische Schmerzen<sup>3</sup> erklären

<sup>1</sup> Novak P et al. Multisystem Involvement in Post-acute Sequelae of COVID-19 (PASC). *Ann Neurol* 2021; [doi.org/10.1002/ana.26286](https://doi.org/10.1002/ana.26286)

<sup>2</sup> Oaklander AL et al. Peripheral Neuropathy Evaluations of Patients With Prolonged Long COVID. *Neurol Neuroimmunol Neuroinflamm* 2022; 9:e1146

<sup>3</sup> Odozor C et al. Post-acute sensory neurological sequelae in patients with severe acute respiratory syndrome coronavirus 2 infection: the COVID-PN observational cohort study. *Pain* 2022; doi: 10.1097/j.pain.0000000000002639

## Therapie bei Neuroinflammation

### Low Dose Naltrexon (off-label)<sup>1</sup>

- Moduliert Mikroglia<sup>2</sup>
- Hat oft positiven Effekt bei ME-myalgische Encephalomyelitis/CFS<sup>3</sup>
- Dosierung:
  - Beginn mit 0,5mg abends
  - Steigerung um 0,5mg alle 7-14 Tage
  - Merkbarer Effekt meist bei 1,5-2,5mg
  - Max. 5mg/d
- Nebenwirkungen hauptsächlich schlechterer Schlaf, gastrointestinal

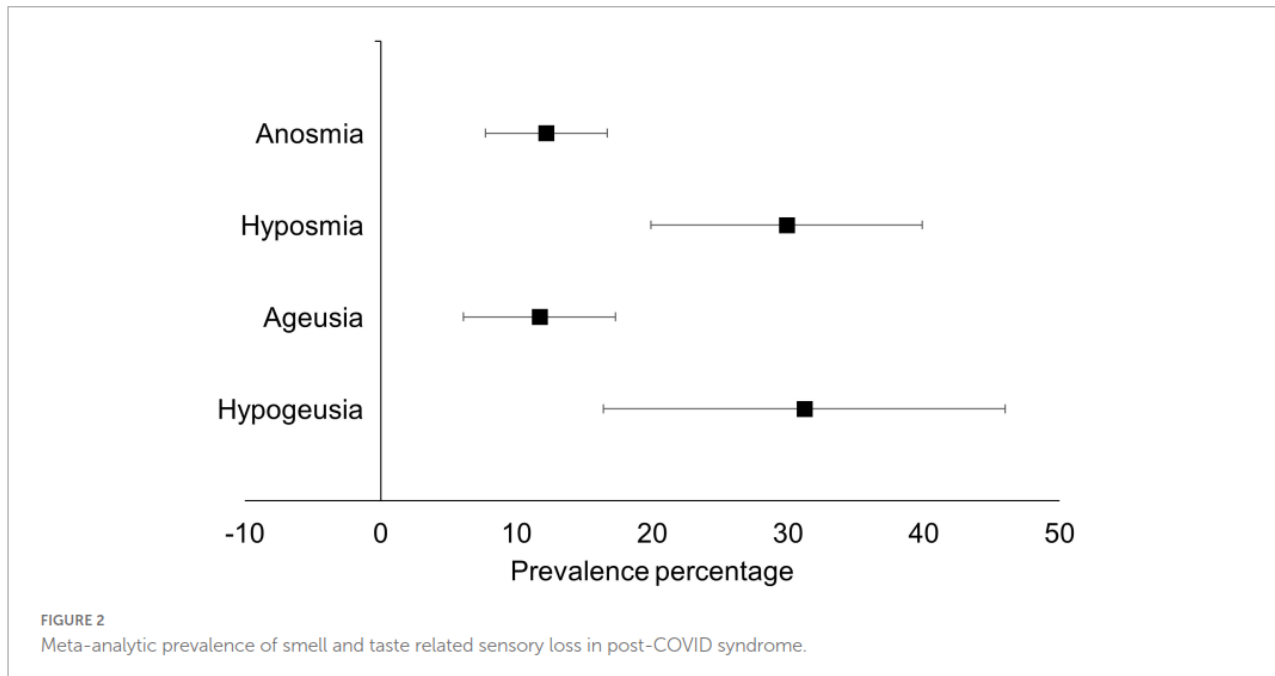
<sup>1</sup> Toljan K, Vrooman B. Low-Dose Naltrexone (LDN)—Review of Therapeutic Utilization. *Med Sci* 2018; 6:82

<sup>2</sup> Younger J et al. The use of low-dose naltrexone (LDN) as a novel anti-inflammatory treatment for chronic pain. *Clin Rheumatol* 2014; 33:451

<sup>3</sup> Bolton MJ et al. Low-dose naltrexone as a treatment for chronic fatigue syndrome. *BMJ Case Rep* 2020; 13: e232502

TABLE 2 Meta-analysis results.

Impairment type	N studies (k outcomes)	Prevalence (95% CI)	I <sup>2</sup>	Eggers bias P-value
Anosmia (complete loss of smell)	11 (12)	12.2 (7.7–16.6)	94.4%	0.343
Hyposmia (reduced sense of smell)	8 (8)	29.9 (19.9–40)	93.4%	0.081
Ageusia (complete loss of taste)	4 (5)	11.7 (6.1–17.3)	89.0%	0.781
Hypogeusia (reduced sense of taste)	5 (5)	31.2 (16.4–46.1)	96.8%	0.453



## Conclusion

While anosmia and ageusia appear to be present in around 12% of people 12 weeks post COVID-19, the prevalence of hyposmia and hypogeusia appears to be much higher, with prevalence rates being 30% and 31% respectively.

Considering that changes in taste, smell, vision, and hearing are associated with decreases in quality of life and also reduced overall well-being, future research is required to ascertain the mechanisms behind this phenomenon and the creation of therapeutic interventions.



**Parosmia Prevalence in COVID-19** Chemosensory deficits are found in approximately 60% of COVID-19 patients by self-report, where assessment using objective psychophysical testing suggests even higher rates of olfactory disruption. Approximately 7.0% to 27.7% of COVID-positive patients experience parosmia within the first 15 days of diagnosis or symptom onset. In a study of patients 4 to 6 weeks after symptom onset, 29.7% had parosmia. But studies of acutely ill individuals likely underestimate the eventual toll of parosmia because the onset is often months after recovery from active infection. **At 6-month follow-up, parosmia was present in 43.1% of subjects who reported smell loss at the beginning of the COVID-19 pandemic.** In a survey that followed-up COVID-19 infection by a median of 200 days, 47% of 1468 participants reported parosmia (vs. 10% immediately following infection). In an online observational study of 3111 respondents with COVID-19-related Olfactory dysfunction , 55.8% reported parosmia, which was significantly correlated with the presence of persistent **Olfactory dysfunction** , as well as **age**. Due to its latent delayed onset and the recency of the COVID-19 pandemic, there will be increasingly greater prevalence and thus extensive opportunity for further investigation

## Conclusion

**Qualitative Olfactory dysfunction is a potentially debilitating condition that occurs in upwards of 40% of COVID-19 patients with persistent olfactory deficits.** Our current best treatment is Olfactory training. Parosmia may predict protracted quantitative Olfactory dysfunction in COVID-19 patients, and yet among postviral Olfactory dysfunction patients undergoing Olfactory training therapy, parosmia is associated with clinically relevant improvement in discrimination and identification capacity, but not threshold detection of odors. The high prevalence of Olfactory dysfunction following COVID-19 warrants further investigation into the pathogenesis and unique clinical manifestations of both qualitative and quantitative deficits, and into the development of targeted treatments for parosmia.

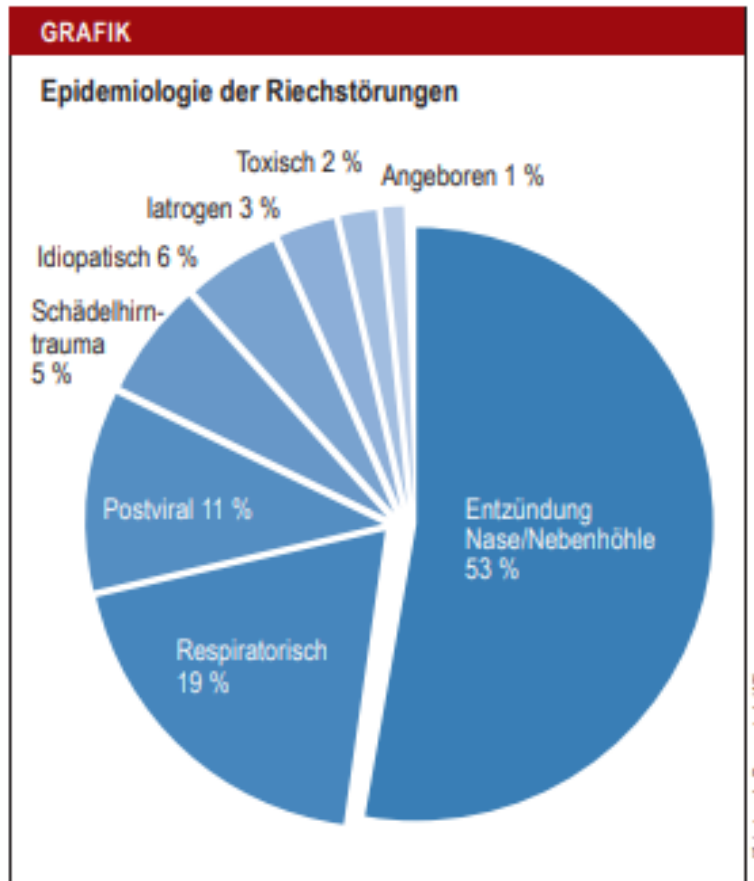
**Die Ergebnisse von 4 000 COVID-19-Patienten zeigen, dass die meisten von ihnen einen Verlust ihrer Riech- und Schmeckfähigkeit während der Erkrankung erlebten, viele auch den der Chemethesis..** Die Probanden beschrieben dabei einen massiven Rückgang der Empfindlichkeit ihres Geruchs- oder Geschmackssinns – von einer Skala von 0 bis 100 zum Teil um 90 Punkte, erklärt Ohla. Parosmien – wenn etwas als schlecht riechend empfunden wird, was vorher gut roch, oder umgekehrt – und Phantosmien – Geruchswahrnehmungen ohne Geruchsreiz – traten in der Umfrage bisher sehr selten auf, so Ohla. **Noch sei es zu früh, Aussagen darüber zu machen, ob die Sinnesstörungen so rasch und plötzlich auftreten wie in den bisherigen Berichten. Dies sei erkennbar anders als der postgrippale Geruchsverlust, der meist schleichend auftritt und wieder verschwinde. Inzwischen wurde Anosmie (auch ohne Rhinitis) als gelegentliches Symptom in die Hinweise vom Robert Koch-Institut aufgenommen.**

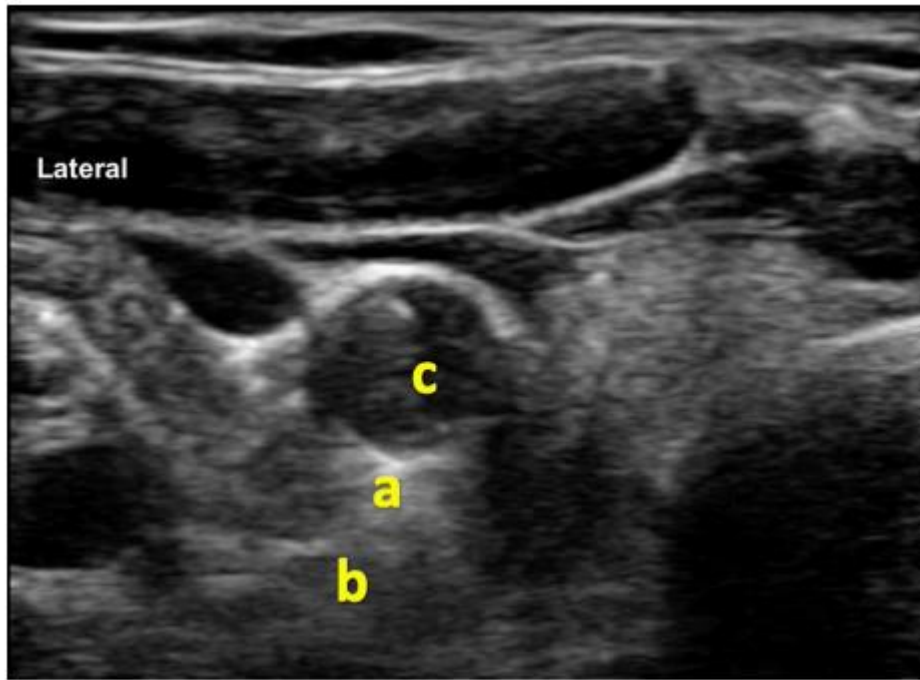
*Forschungszentrum Jülich: Geschmacks und Geruchsstörungen bei COVID-19. Pressemitteilung vom 9. April 2020.*

*<https://www.fz-juelich.de/SharedDocs/Pressemitteilungen/UK/DE/2020/2020-04-09-onlineumfrage-covid19.html> (last accessed on 30 April 2020). Link zur Umfrage: <https://gcchemosensr.org/surveys/>*

*Robert Koch-Institut: Hinweise zu Erkennung, Diagnostik und Therapie von Patienten mit COVID-19. Stand: 17. April 2020.*

*[https://www.rki.de/DE/Content/Kommissionen/Stakob/Stellungnahmen/Stellungnahme-Covid-19\\_Therapie\\_Diagnose.html](https://www.rki.de/DE/Content/Kommissionen/Stakob/Stellungnahmen/Stellungnahme-Covid-19_Therapie_Diagnose.html) (last accessed on 30 April 2020)*





Ultrasonographic image of the right side of the neck depicting stellate ganglion  
a: stellate ganglion above the longus colli muscle. Site for deposition of local anesthetic solution.  
b: longus colli muscle.  
c: right carotid artery

## Conclusions

The mechanistic factors related to the dramatic improvement of anosmia due to SGB are still debatable; however, SGB may be an effective treatment option for patients with olfactory and taste issues associated with post acute sequelae of SARS-CoV-2 infection(PASC). **At this point, the evidence for using SGB to alleviate anosmia and dysgeusia associated with Long COVID is anecdotal and limited to a few case reports. Collaborative multi-institutional research might be required to gather more evidence to support using SGB as a treatment modality for anosmia and dysgeusia due to Long COVID.**

## Results

Patient on LTOT had a higher risk ratio (RR) than control patients to visit an emergency department (RR 2.04, 95% CI 1.93 to 2.16) and be hospitalised (RR 2.91, 95% CI 2.69 to 3.15). Once admitted, LTOT patients were more likely to require intensive care (RR 3.65, 95% CI 3.10 to 4.29), mechanical ventilation (RR 3.47, 95% CI 2.89 to 4.15) and vasopressor support (RR 5.28, 95% CI 3.70 to 7.53) and die within 30 days (RR 1.96, 95% CI 1.67 to 2.30). The LTOT group also showed increased risk (RRs from 2.06 to 3.98, all significant to 95% CI) of more severe infection (eg, cough, dyspnoea, fever, hypoxaemia, thrombocytopenia and acute respiratory distress syndrome). Statistically significant differences in several laboratory results and other vital signs appeared clinically negligible.

## Conclusion

**COVID-19 patients on LTOT were at higher risk of increased morbidity, mortality and healthcare utilisation. Interventions to reduce the need for LTOT and to increase compliance with COVID-19 protective measures may improve outcomes and reduce healthcare cost in this population. Prospective studies need to confirm and refine these findings.**

## Abstract

The risk of COVID-19 in those with chronic pain is unknown. We investigated whether self-reported chronic pain was associated with COVID-19 hospitalisation or mortality. UK Biobank recruited 502,624 participants aged 37 to 73 years between 2006 and 2010. Baseline exposure data, including chronic pain (.3 months, in at least 1 of 7 prespecified body sites) and chronic widespread pain (.3 months, all over body), were linked to COVID-19 hospitalisations or mortality. Univariable or multivariable Poisson regression analyses were performed on the association between chronic pain and COVID-19 hospitalisation and Cox regression analyses of the associations with COVID-19 mortality. Multivariable analyses adjusted incrementally for sociodemographic confounders, then lifestyle risk factors, and finally long-term condition count. Of 441,403 UK Biobank participants with complete data, 3180 (0.7%) were hospitalised for COVID-19 and 1040 (0.2%) died from COVID-19. Chronic pain was associated with hospital admission for COVID-19 even after adjustment for all covariates (incidence rate ratio 1.16; 95% confidence interval [CI] 1.08-1.24; P , 0.001), as was chronic widespread pain (incidence rate ratio 1.33; 95% CI 1.06-1.66; P 5 0.012). There was clear evidence of a doseresponse relationship with number of pain sites (fully adjusted global P-value , 0.001). After adjustment for all covariates, there was no association between chronic pain (HR 1.01; 95% CI 0.89-1.15; P 5 0.834) but attenuated association with chronic widespread pain (HR 1.50, 95% CI 1.04-2.16, P-value 5 0.032) and COVID-19 mortality. **Chronic pain is associated with higher risk of hospitalisation for COVID-19, but the association with mortality is unclear. Future research is required to investigate these findings further and determine whether pain is associated with long COVID.**



Prevalence, intensity and associated disability of spontaneously reported new onset persistent symptoms related to coronavirus disease 2019 (COVID-19) in 162 survivors at one year after hospital discharge (order according to frequency)

Symptom	Prevalence N (%)	Intensity (1 = slight ... 4 = severe) Mean (SD)	Disability (0 = none; 4 = very severe) Mean (SD)
Fatigue	40 (24.7)	2.3 (0.9)	2.3 (0.9)
Cognitive dysfunction	24 (14.8)	2.4 (1.4)	2.2 (1.2)
Shortness of breath	14 (8.6)	1.9 (0.6)	1.6 (1.1)
Pain in muscles and joints	11 (6.8)	2.3 (0.8)	2.0 (1.1)
Headache	10 (6.2)	2.4 (0.7)	1.3 (1.2)
Cough	3 (1.8)	2.3 (0.6)	1.3 (1.2)
Altered smell/taste	3 (1.8)	1.7 (1.2)	0.3 (0.6)
Posttraumatic stress symptoms	2 (1.2)	3.0 (1.0)	3.0 (1.0)
Sleep problems	2 (1.2)	3.0	1.5 (1.5)
Anxiety	1 (0.6)	3.0	3.0
Depression	1 (0.6)	3.0	3.0
Disturbance of sensitivity in one leg	1 (0.6)	1.0	1.0
Loss of appetite and weight	1 (0.6)	2.0	2.0
Nausea	1 (0.6)	3.0	1.0
Pain in hands and feet	1 (0.6)	3.0	3.0
Pruritus	1 (0.6)	2.0	2.0
Thoracic burning	1 (0.6)	2.0	2.0
Vertigo	1 (0.6)	1.0	2.0
Weakness of forefoot	1 (0.6)	1.0	1.0
<i>SD</i> standard deviation			

## Conclusions for clinical practice

- The consequences of COVID-19 can be diverse and prolonged. Our results suggest that most patients will experience a self-limited acute infection with full recovery, but every third patient develops symptoms that persist for at least 1 year. For some COVID-19 survivors, persisting symptoms are sufficiently severe to preclude return to employment.
- **New-onset headache and pain in muscles and joints are frequently associated with each other and with physical fatigue and cognitive disturbances.**
- **The severity of acute COVID-19 might increase the risk of post-COVID-19 conditions.**
- Some post-COVID-19 symptoms such as shortness of breath can be explained by persistent structural changes of the pulmonary systems.
- The most frequently reported PCS, namely fatigue and cognitive disturbances, are common symptoms in the general population and should not be solely attributed to infection by SARS-CoV-2 virus.
- Acute COVID-19 can worsen pre-existing diseases, e.g., chronic obstructive pulmonary disease (COPD), dementia or FMS.
- **Pain medicine physicians should be involved in the management of chronic pain (headache, musculoskeletal system) and mental health care specialist in the management of fatigue and cognitive problems after COVID-19.**

Dr. Rudolf Likar  
Dr. Georg Pinter Dr. Herbert Janig  
Thomas Frühwald Dr. Karl Cernic



**ES LEBE DER TOD**

**Tabuthema Sterben**

ueberreuter



# Danke für Ihre Aufmerksamkeit

