Post-acute Sequelae of COVID-19 (PASC) and Sleep

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Accreditation Statement

This activity has been planned and implemented in accordance with the accreditation requirements and policies of the Accreditation Council for Continuing Medical Education (ACCME) through the joint providership of The American Academy of Sleep Medicine and the Michigan Academy of Sleep Medicine. The American Academy of Sleep Medicine is accredited by the ACCME to provide continuing medical education for physicians.

Conflict of Interest Disclosures for Speakers

- M. Safwan Badr, MD has no relevant financial relationships with ineligible companies to disclose.
- Member, ABIM Board of Directors
- Member, NSF Board of Directors

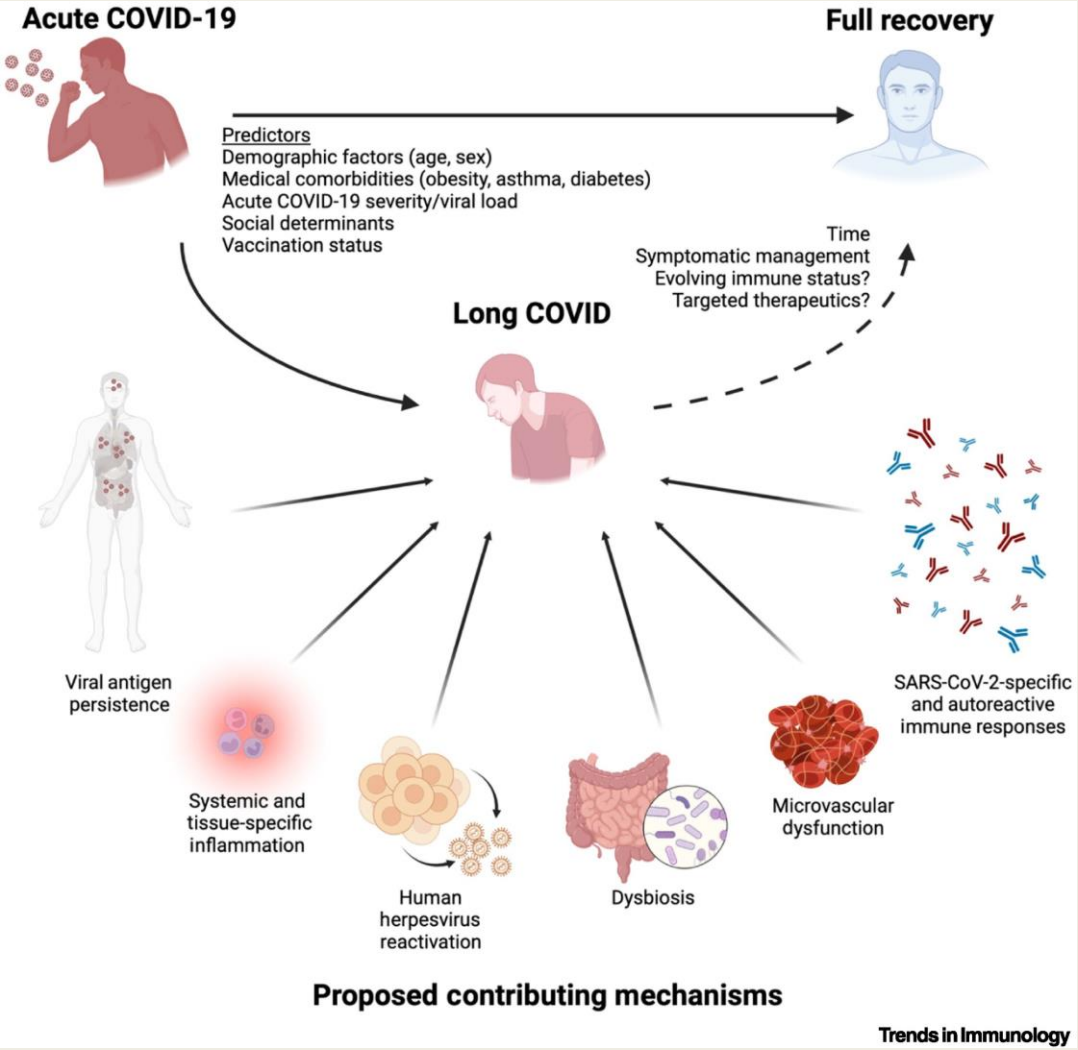
Objectives

- Describe the Post-Acute Sequalae COVID-19 (PASC)
- Describe major sleep disturbances of post-COVID
- Describe emerging studies and highlight limitations

Post-acute Sequelae of COVID-19 (PASC)

- A chronic condition
- Up to 80% of SARS-CoV-2-infected, hospitalized patients
- and in 40% to 70% of non-hospitalized patients
- Potentially debilitating impact
  - Dyspnea -exercise intolerance
  - Anxiety and Depression
  - Autonomic dysfunction
  - Cognitive impairment
  - Sleep disturbances.

Figure 1



Trends in Immunology 2022 43268-270DOI: (10.1016/j.it.2022.02.008)

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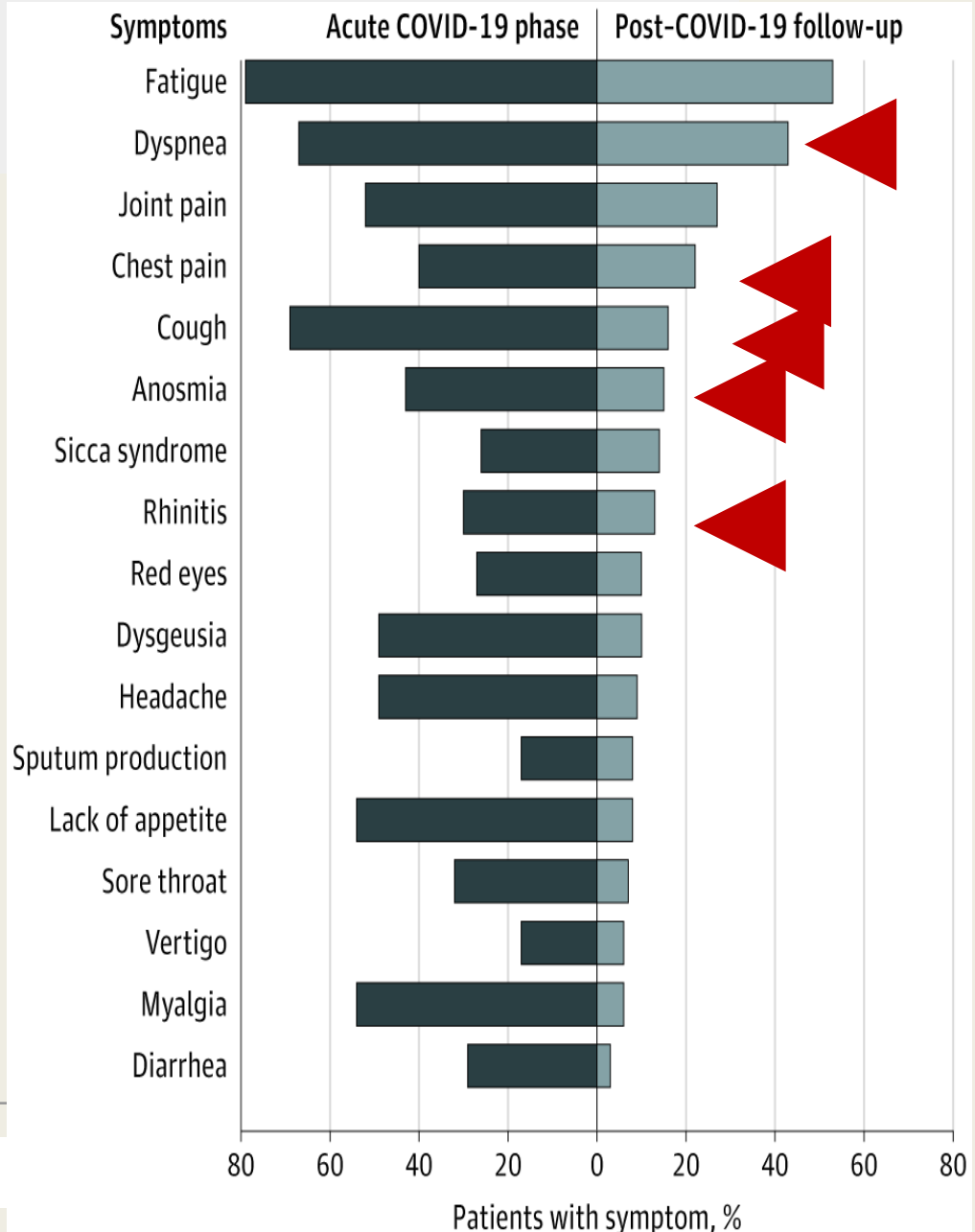
Persistent Symptoms in Patients After Acute COVID-19

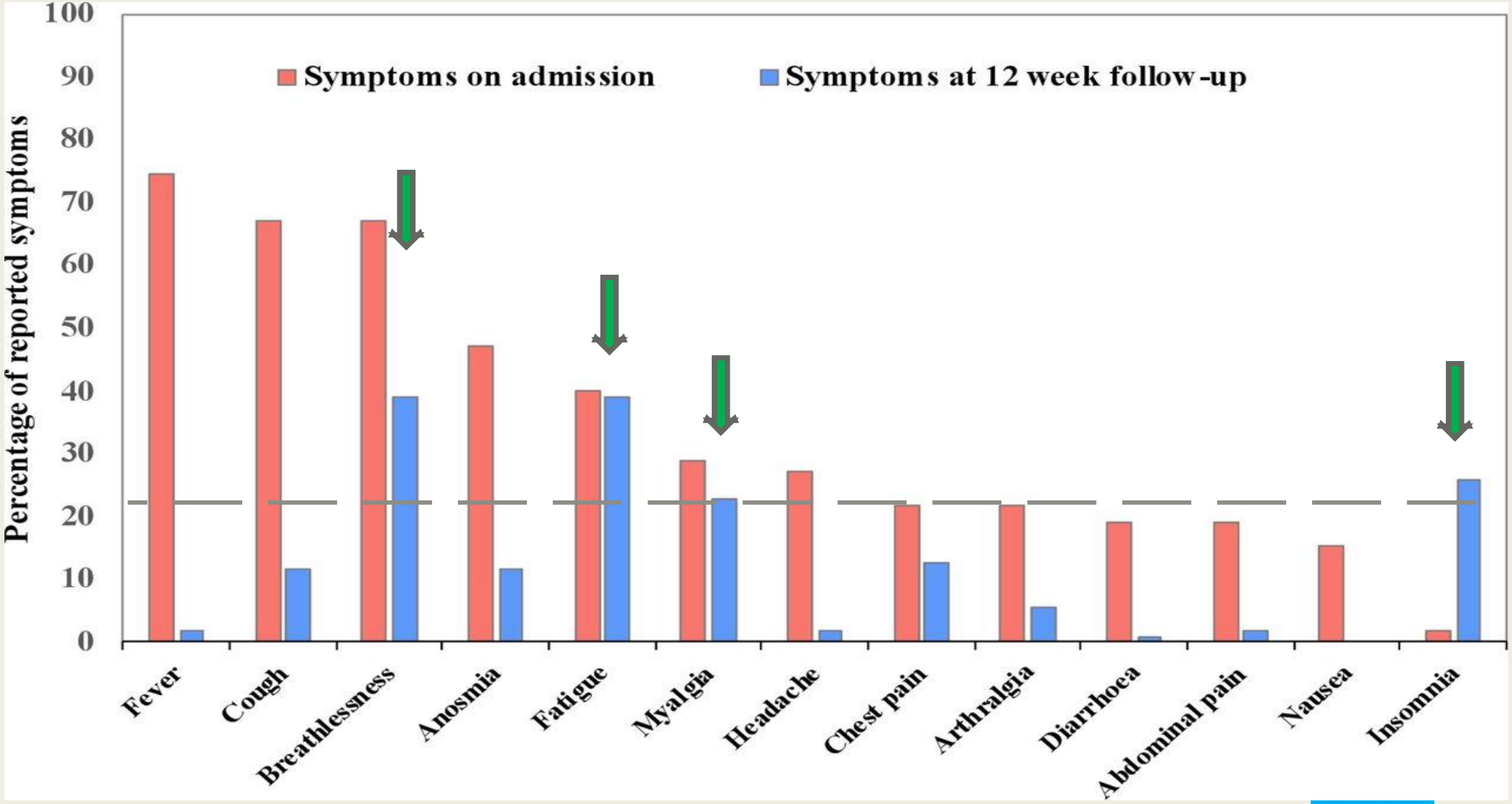
Post-acute Sequelae of COVID-19 (PASC)

- A syndrome characterized by the persistence of clinical symptoms beyond four weeks from the onset of acute symptoms.
- Persistent dyspnea is the second most common
  - Apparent organ damage
  - Non apparent organ damage



JAMA. 2020;324(6):603-605. doi:10.1001/jama.2020.12603

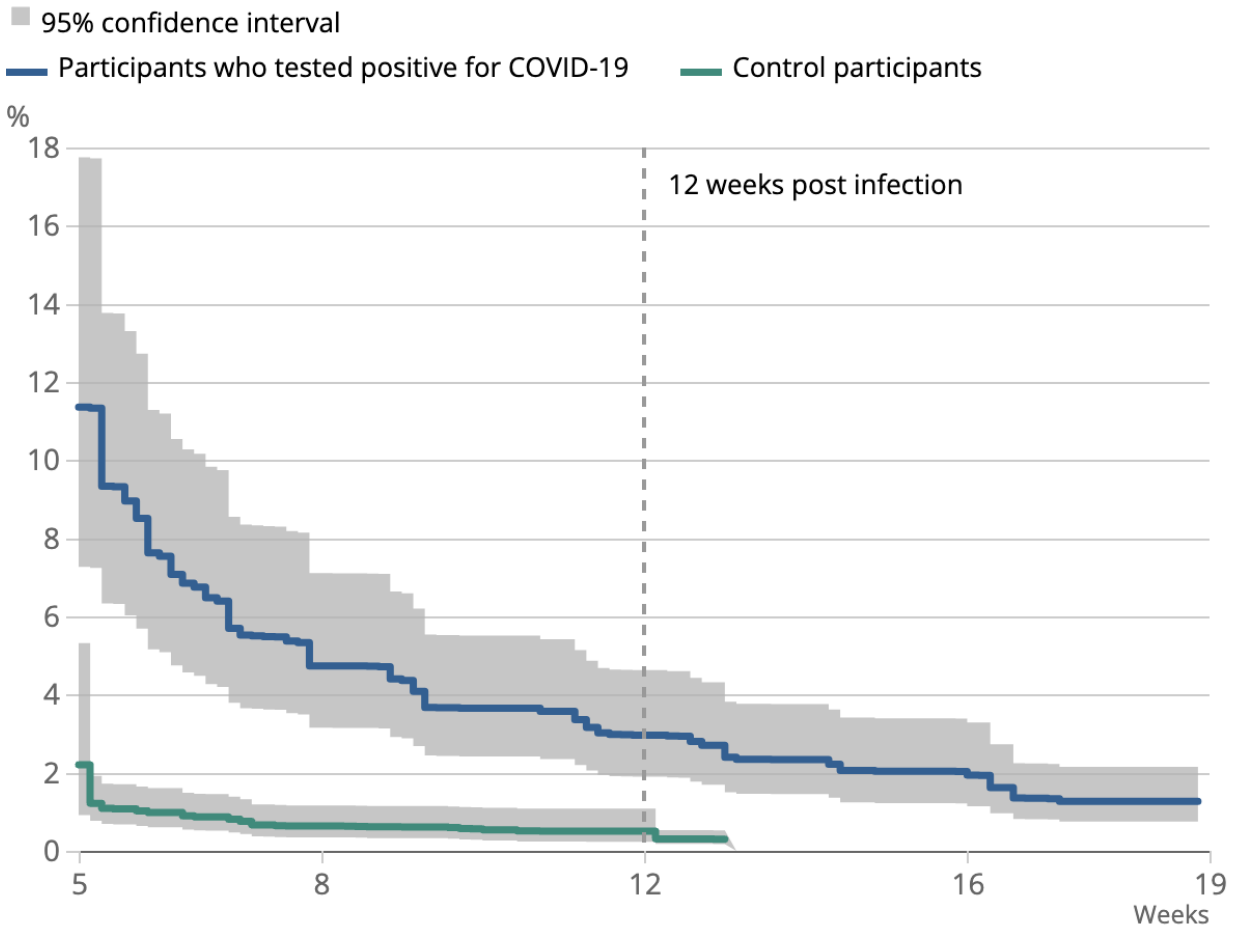
Frequency of symptoms reported at a 12-week follow-up compared with hospital admission.



David T Arnold et al. Thorax 2021;76:399-401

THORAX

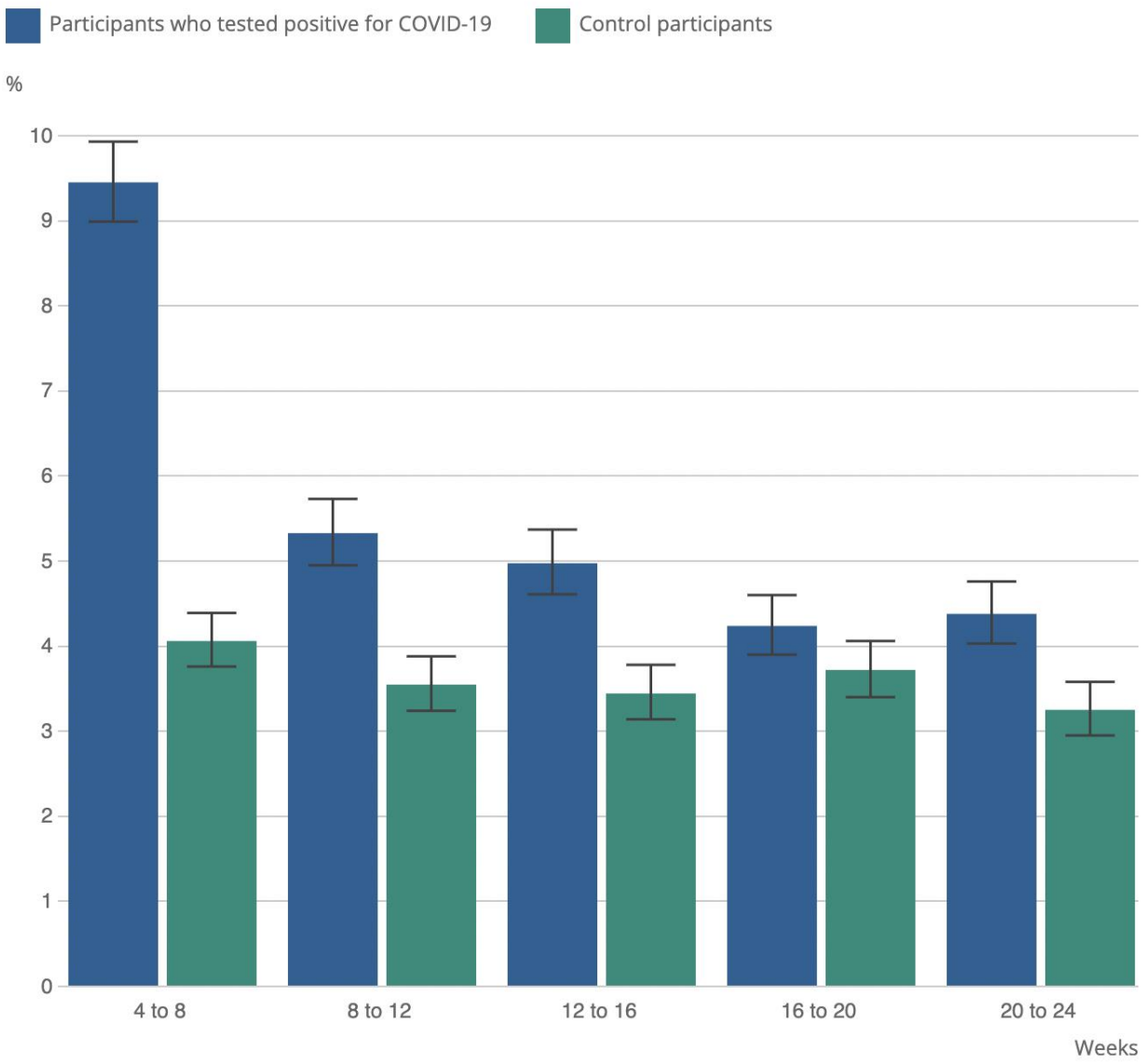
Estimated percentage of study participants reporting any of 12 symptoms with time from infection (participants with COVID-19) or time from equivalent date (control participants), UK: 26 April 2020 to 1 August 2021



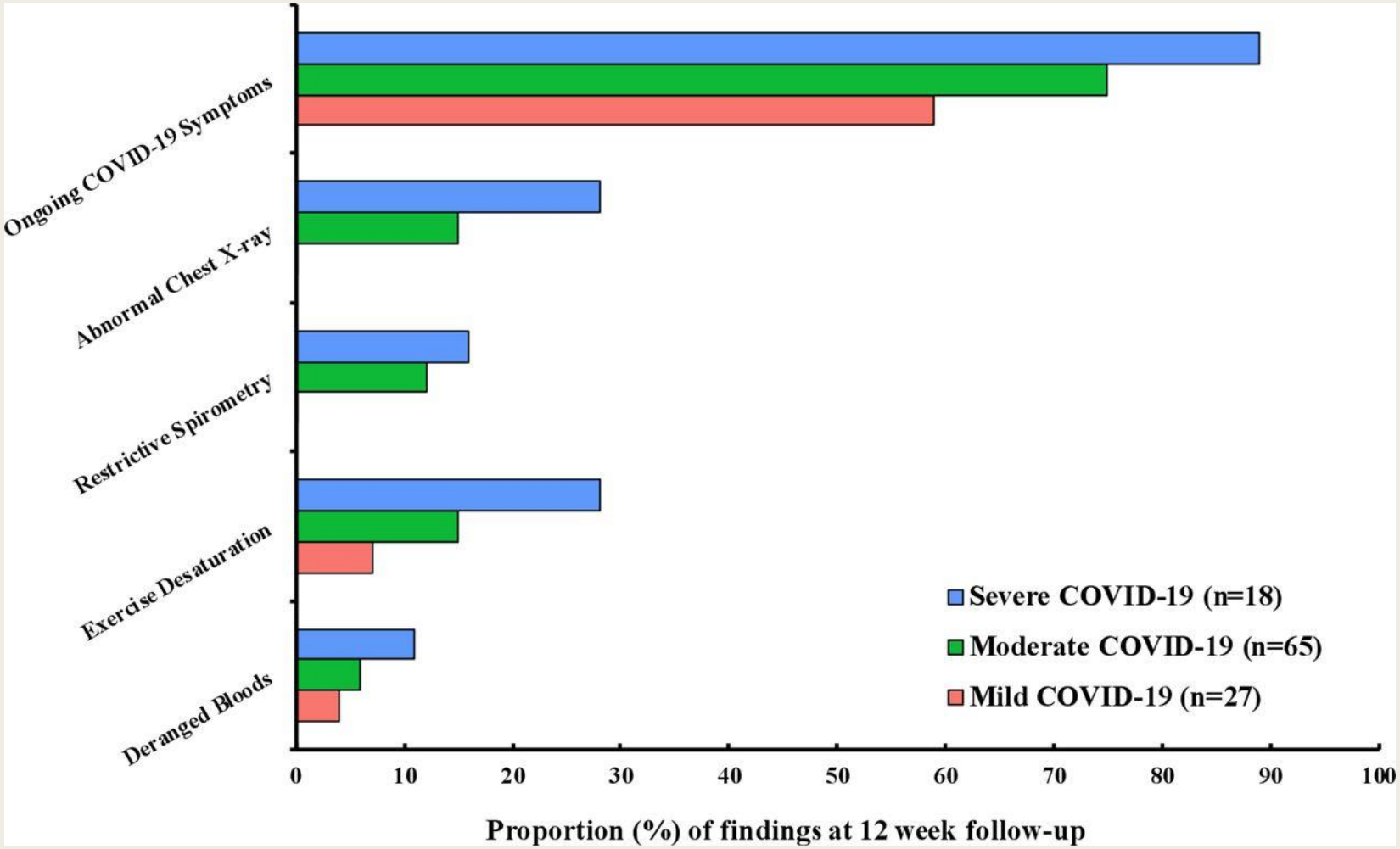
Source: Office for National Statistics - Coronavirus Infection Survey

Embed code

Percentage of study participants reporting any of 12 symptoms in four-week intervals from infection (participants with COVID-19) or from equivalent date (control participants), UK: 26 April 2020 to 1 August 2021



Summary of symptomatology and clinical results by disease severity.

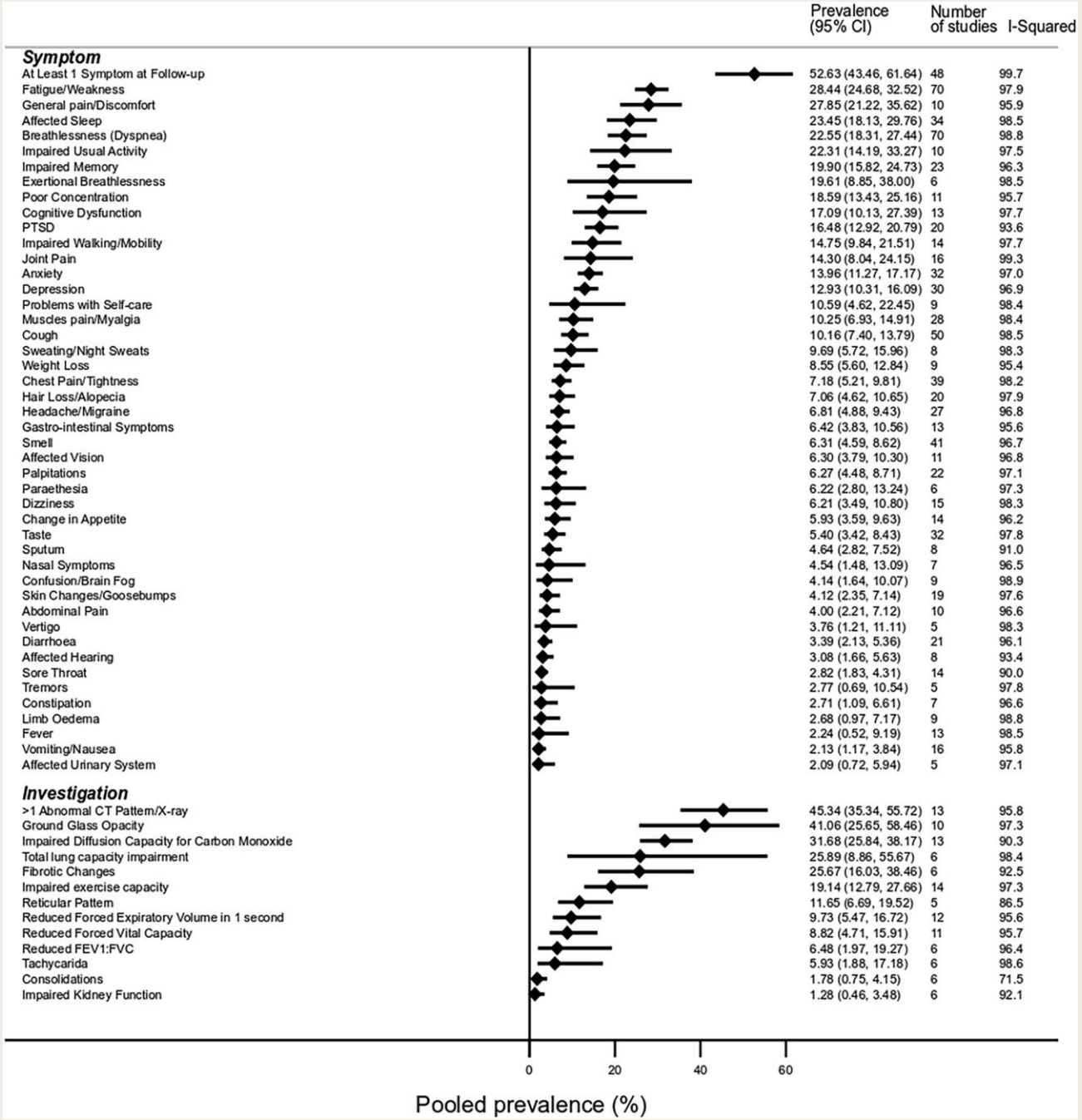


David T Arnold et al. Thorax 2021;76:399-401

THORAX

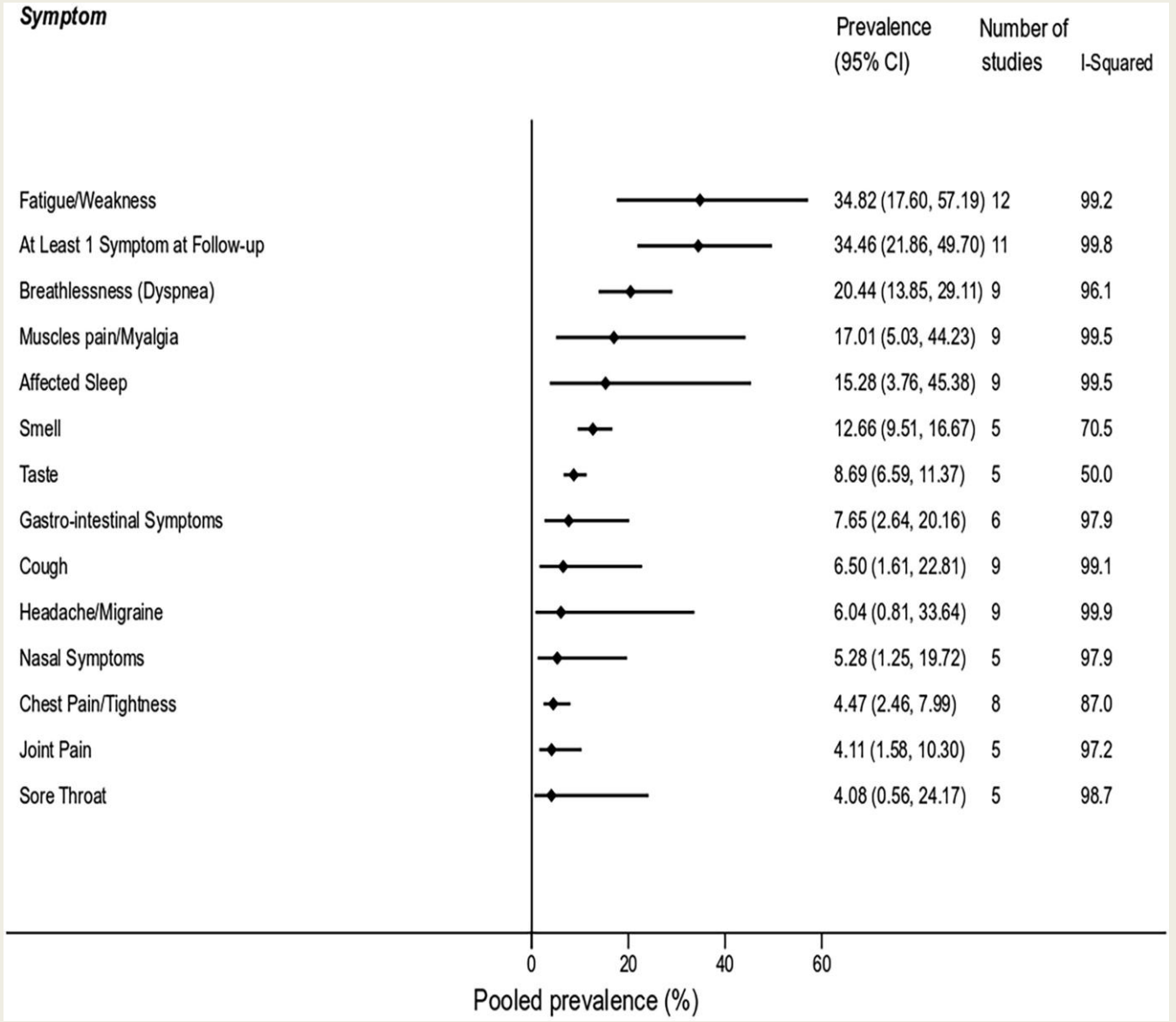
The prevalence and long-term health effects of Long Covid among hospitalised and non-hospitalised populations: a systematic review and meta-analysis *eClinicalMedicine* Volume 55 (January 2023) DOI: 10.1016/j.eclinm.2022.101762

- 194 studies (n= 735,006 participants)
- More that 45% of COVID-19 survivors experience at least one symptoms
- Fatigue in hospitalized and non-hospitalized
- Radiologic abnormalities were common in hospitalized patients
- Heterogeneity of definitions is a challenge

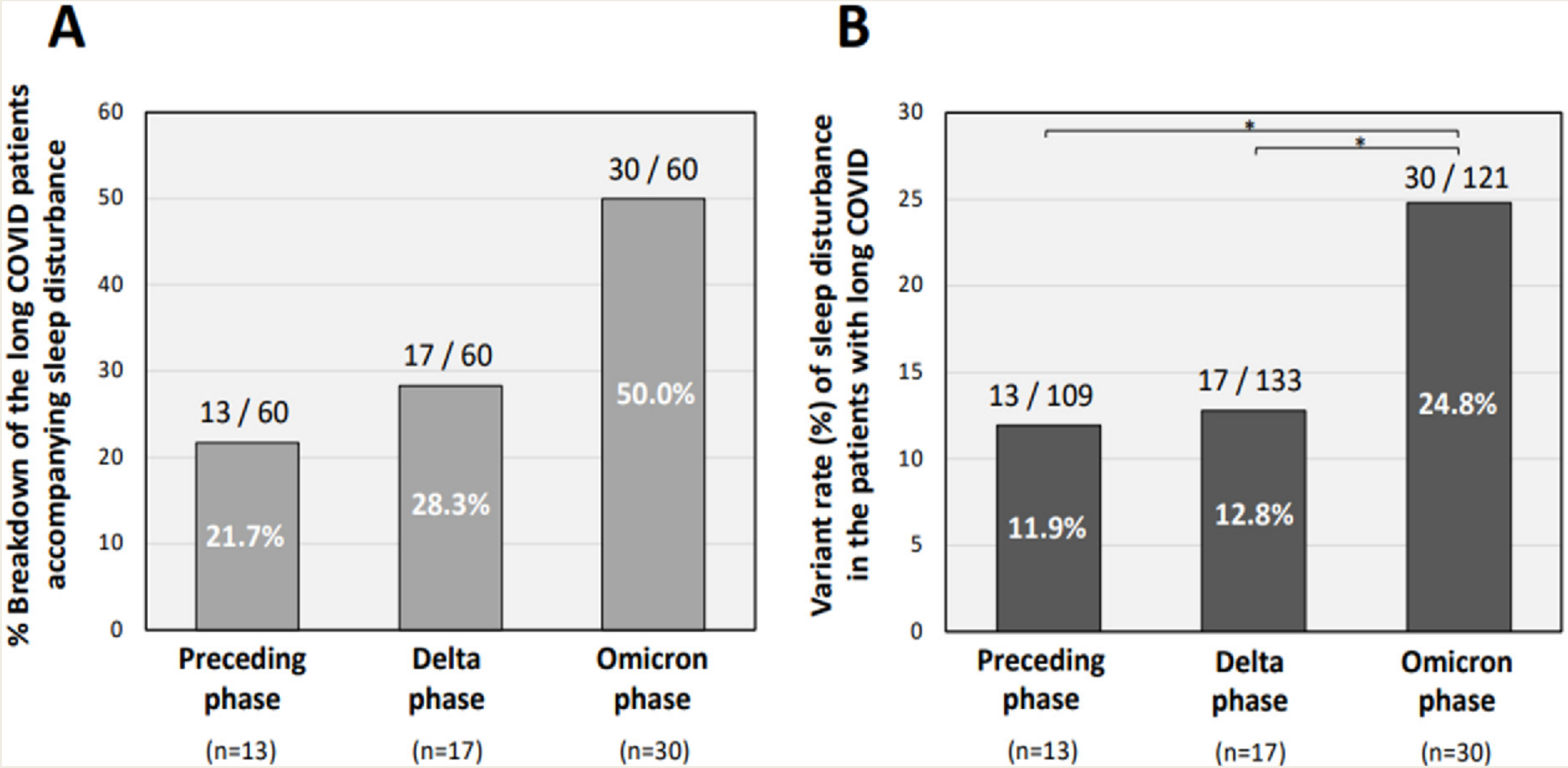


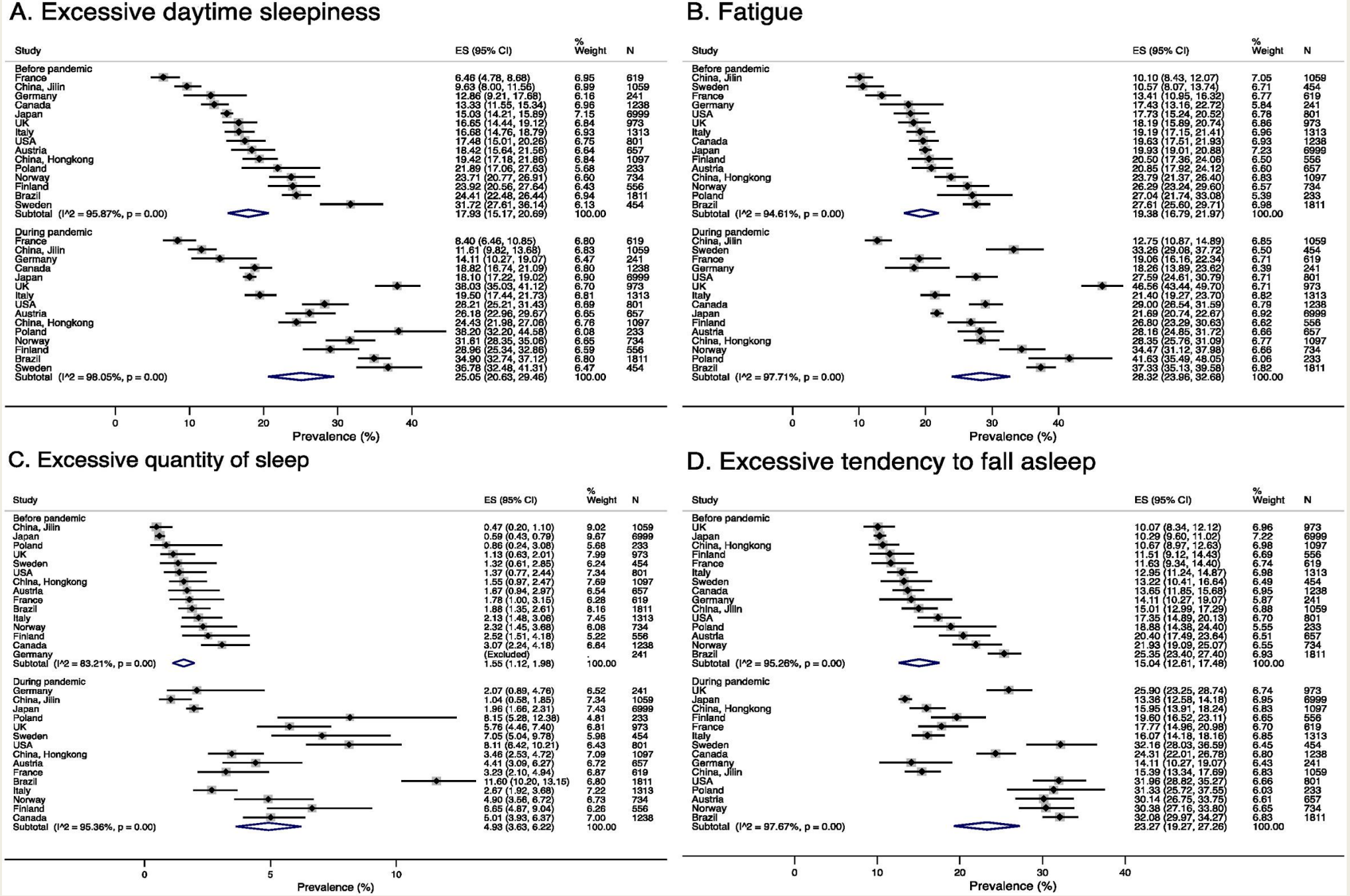
eClinicalMedicine 2023 55DOI: (10.1016/j.eclinm.2022.101762)

Fig. 3

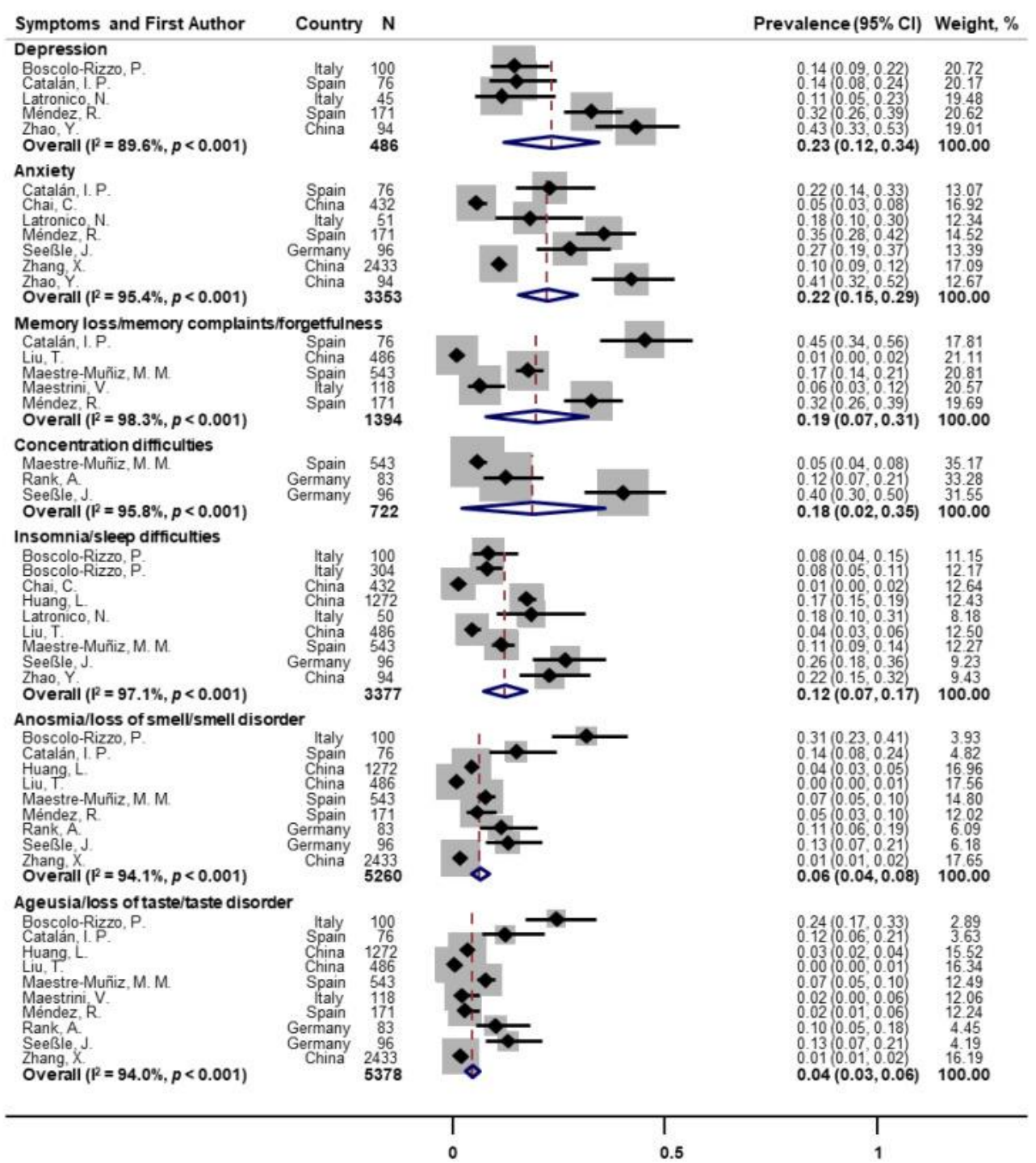


eClinicalMedicine 2023 55DOI: (10.1016/j.eclinm.2022.101762)


A
% Breakdown of the long COVID patients accompanying sleep disturbance
60
50
40
30
20
10
0
13 / 60
21.7%
17 / 60
28.3%
30 / 60
50.0%
Preceding phase
(n=13)
Delta phase
(n=17)
Omicron phase
(n=30)
B
Variant rate (%) of sleep disturbance in the patients with long COVID
30
25
20
15
10
5
0
*
*
13 / 109
11.9%
17 / 133
12.8%
30 / 121
24.8%
Preceding phase
(n=13)
Delta phase
(n=17)
Omicron phase
(n=30)



https://doi.org/10.1016/j.sleep.2023.04.024


Symptoms and First Author
Country
N
Prevalence (95% CI)
Weight, %
Depression
Boscolo-Rizzo, P. Italy 100 0.14 (0.09, 0.22) 20.72
Catalán, I. P. Spain 76 0.14 (0.08, 0.24) 20.17
Latronico, N. Italy 45 0.11 (0.05, 0.23) 19.48
Méndez, R. Spain 171 0.32 (0.26, 0.39) 20.62
Zhao, Y. China 94 0.43 (0.33, 0.53) 19.01
Overall (I² = 89.6%, p < 0.001) 486 0.23 (0.12, 0.34) 100.00
Anxiety
Catalán, I. P. Spain 76 0.22 (0.14, 0.33) 13.07
Chai, C. China 432 0.05 (0.03, 0.08) 16.92
Latronico, N. Italy 51 0.18 (0.10, 0.30) 12.34
Méndez, R. Spain 171 0.35 (0.28, 0.42) 14.52
Seeßle, J. Germany 96 0.27 (0.19, 0.37) 13.39
Zhang, X. China 2433 0.10 (0.09, 0.12) 17.09
Zhao, Y. China 94 0.41 (0.32, 0.52) 12.67
Overall (I² = 95.4%, p < 0.001) 3353 0.22 (0.15, 0.29) 100.00
Memory loss/memory complaints/forgetfulness
Catalán, I. P. Spain 76 0.45 (0.34, 0.56) 17.81
Liu, T. China 486 0.01 (0.00, 0.02) 21.11
Maestre-Muñiz, M. M. Spain 543 0.17 (0.14, 0.21) 20.81
Maestrini, V. Italy 118 0.06 (0.03, 0.12) 20.57
Méndez, R. Spain 171 0.32 (0.26, 0.39) 19.69
Overall (I² = 98.3%, p < 0.001) 1394 0.19 (0.07, 0.31) 100.00
Concentration difficulties
Maestre-Muñiz, M. M. Spain 543 0.05 (0.04, 0.08) 35.17
Rank, A. Germany 83 0.12 (0.07, 0.21) 33.28
Seeßle, J. Germany 96 0.40 (0.30, 0.50) 31.55
Overall (I² = 95.8%, p < 0.001) 722 0.18 (0.02, 0.35) 100.00
Insomnia/sleep difficulties
Boscolo-Rizzo, P. Italy 100 0.08 (0.04, 0.15) 11.15
Boscolo-Rizzo, P. Italy 304 0.08 (0.05, 0.11) 12.17
Chai, C. China 432 0.01 (0.00, 0.02) 12.64
Huang, L. China 1272 0.17 (0.15, 0.19) 12.43
Latronico, N. Italy 50 0.18 (0.10, 0.31) 8.18
Liu, T. China 486 0.04 (0.03, 0.06) 12.50
Maestre-Muñiz, M. M. Spain 543 0.11 (0.09, 0.14) 12.27
Seeßle, J. Germany 96 0.26 (0.18, 0.36) 9.23
Zhao, Y. China 94 0.22 (0.15, 0.32) 9.43
Overall (I² = 97.1%, p < 0.001) 3377 0.12 (0.07, 0.17) 100.00
Anosmia/loss of smell/smell disorder
Boscolo-Rizzo, P. Italy 100 0.31 (0.23, 0.41) 3.93
Catalán, I. P. Spain 76 0.14 (0.08, 0.24) 4.82
Huang, L. China 1272 0.04 (0.03, 0.05) 16.96
Liu, T. China 486 0.00 (0.00, 0.01) 17.56
Maestre-Muñiz, M. M. Spain 543 0.07 (0.05, 0.10) 14.80
Méndez, R. Spain 171 0.05 (0.03, 0.10) 12.02
Rank, A. Germany 83 0.11 (0.06, 0.19) 6.09
Seeßle, J. Germany 96 0.13 (0.07, 0.21) 6.18
Zhang, X. China 2433 0.01 (0.01, 0.02) 17.65
Overall (I² = 94.1%, p < 0.001) 5260 0.06 (0.04, 0.08) 100.00
Ageusia/loss of taste/taste disorder
Boscolo-Rizzo, P. Italy 100 0.24 (0.17, 0.33) 2.89
Catalán, I. P. Spain 76 0.12 (0.06, 0.21) 3.63
Huang, L. China 1272 0.03 (0.02, 0.04) 15.52
Liu, T. China 486 0.00 (0.00, 0.01) 16.34
Maestre-Muñiz, M. M. Spain 543 0.07 (0.05, 0.10) 12.49
Maestrini, V. Italy 118 0.02 (0.00, 0.06) 12.06
Méndez, R. Spain 171 0.02 (0.01, 0.06) 12.24
Rank, A. Germany 83 0.10 (0.05, 0.18) 4.45
Seeßle, J. Germany 96 0.13 (0.07, 0.21) 4.19
Zhang, X. China 2433 0.01 (0.01, 0.02) 16.19
Overall (I² = 94.0%, p < 0.001) 5378 0.04 (0.03, 0.06) 100.00
0
0.5
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Effects of sleep disturbance on dyspnoea and impaired lung function following hospital admission due to COVID-19 in the UK: a prospective multicentre cohort study

*Callum Jackson, Iain D Stewart, Tatiana Plekhanova, Peter S Cunningham, Andrew L Hazel, Bashar Al-Sheikly, Raminder Aul, Charlotte E Bolton, Trudie Chalder, James D Chalmers, Nazia Chaudhuri, Annemarie B Docherty, Gavin Donaldson, Charlotte L Edwardson, Omer Elneima, Neil J Greening, Neil A Hanley, Victoria C Harris, Ewen M Harrison, Ling-Pei Ho, Linzy Houchen-Wolloff, Luke S Howard, Caroline J Jolley, Mark G Jones, Olivia C Leavy, Keir E Lewis, Nazir I Lone, Michael Marks, Hamish J C McAuley, Melitta A McNarry, Brijesh V Patel, Karen Piper-Hanley, Krisnah Poinasamy, Betty Raman, Matthew Richardson, Pilar Rivera-Ortega, Sarah L Rowland-Jones, Alex V Rowlands, Ruth M Saunders, Janet T Scott, Marco Sereno, Ajay M Shah, Aarti Shikotra, Amisha Singapuri, Stefan C Stanel, Mathew Thorpe, Daniel G Wootton, Thomas Yates, R Gisli Jenkins, Sally J Singh, William D-C Man, Christopher E Brightling, Louise V Wain, Joanna C Porter, A A Roger Thompson, Alex Horsley, Philip L Molyneaux, Rachael A Evans, Samuel E Jones, Martin K Rutter, John F Blaikley, on behalf of the PHOSP-COVID Study Collaborative Group**

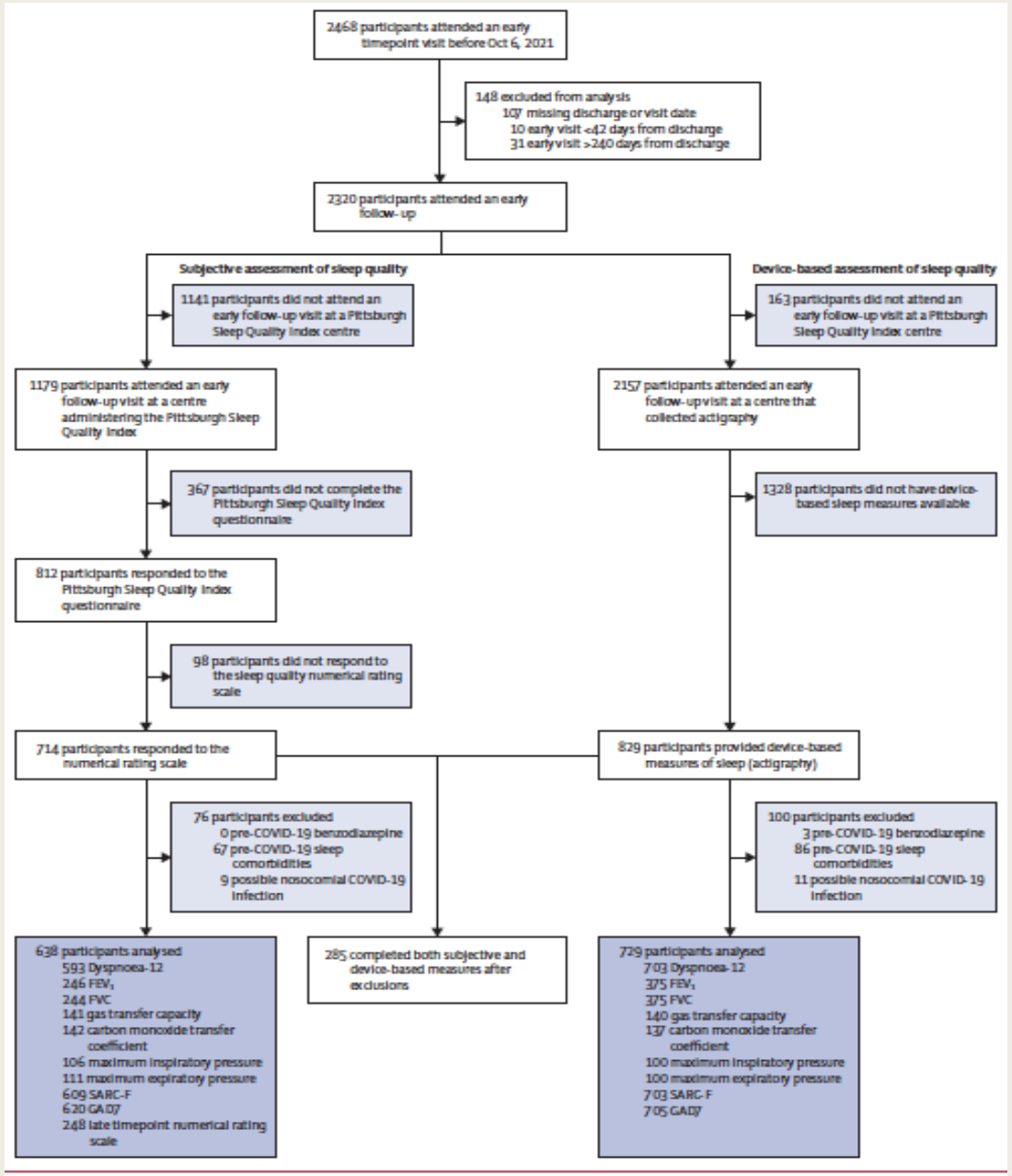
Summary

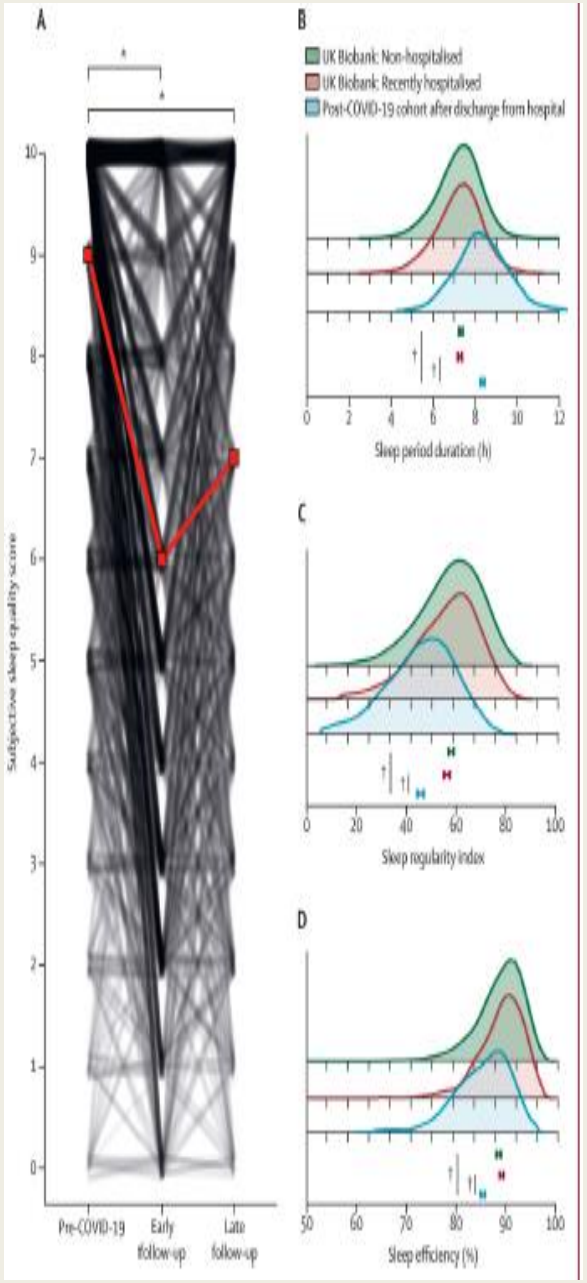
Background Sleep disturbance is common following hospital admission both for COVID-19 and other causes. The clinical associations of this for recovery after hospital admission are poorly understood despite sleep disturbance contributing to morbidity in other scenarios. We aimed to investigate the prevalence and nature of sleep disturbance after discharge following hospital admission for COVID-19 and to assess whether this was associated with dyspnoea.

Methods CircCOVID was a prospective multicentre cohort substudy designed to investigate the effects of circadian disruption and sleep disturbance on recovery after COVID-19 in a cohort of participants aged 18 years or older, admitted to hospital for COVID-19 in the UK, and discharged between March, 2020, and October, 2021. Participants were recruited from the Post-hospitalisation COVID-19 study (PHOSP-COVID). Follow-up data were collected at two timepoints: an early time point 2–7 months after hospital discharge and a later time point 10–14 months after hospital discharge. Sleep quality was assessed subjectively using the Pittsburgh Sleep Quality Index questionnaire and a numerical rating scale. Sleep quality was also assessed with an accelerometer worn on the wrist (actigraphy) for 14 days. Participants were also clinically phenotyped, including assessment of symptoms (ie, anxiety [Generalised Anxiety Disorder 7-item scale questionnaire], muscle function [SARC-F questionnaire], dyspnoea [Dyspnoea-12 questionnaire] and measurement of lung function), at the early timepoint after discharge. Actigraphy results were also compared to a matched UK Biobank cohort (non-hospitalised individuals and recently hospitalised individuals). Multivariable linear regression was used to define associations of sleep disturbance with the primary outcome of breathlessness and the other clinical symptoms. PHOSP-COVID is registered on the ISRCTN Registry (ISRCTN10980107).

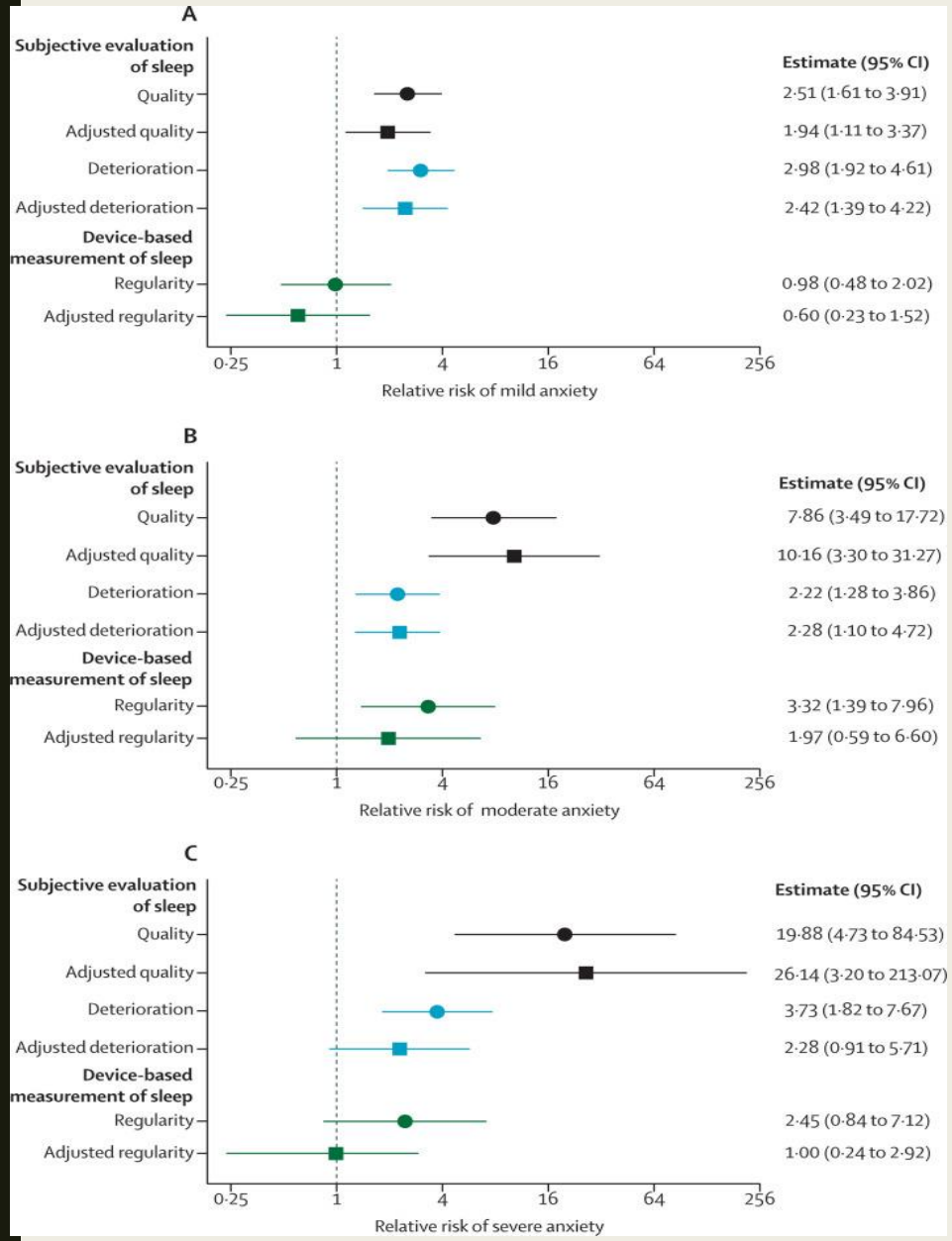
Findings 2320 of 2468 participants in the PHOSP-COVID study attended an early timepoint research visit a median of 5 months (IQR 4–6) following discharge from 83 hospitals in the UK. Data for sleep quality were assessed by subjective measures (the Pittsburgh Sleep Quality Index questionnaire and the numerical rating scale) for 638 participants at the early time point. Sleep quality was also assessed using device-based measures (actigraphy) a median of 7 months (IQR 5–8 months) after discharge from hospital for 729 participants. After discharge from hospital, the majority (396 [62%] of 638) of participants who had been admitted to hospital for COVID-19 reported poor sleep quality in response to the Pittsburgh Sleep Quality Index questionnaire. A comparable proportion (338 [53%] of 638) of participants felt their sleep quality had deteriorated following discharge after COVID-19 admission, as assessed by the numerical rating scale. Device-based measurements were compared to an age-matched, sex-matched, BMI-matched, and time from discharge-matched UK Biobank cohort who had recently been admitted to hospital. Compared to the recently hospitalised matched UK Biobank cohort, participants in our study slept on average 65 min (95% CI 59 to 71) longer, had a lower sleep regularity index (–19%; 95% CI –20 to –16), and a lower sleep efficiency (3·83 percentage points; 95% CI 3·40 to 4·26). Similar results were obtained when comparisons were made with the non-hospitalised UK Biobank cohort. Overall sleep quality (unadjusted effect estimate 3·94; 95% CI 2·78 to 5·10), deterioration in sleep quality following hospital admission (3·00; 1·82 to 4·28), and sleep regularity (4·38; 2·10 to 6·65) were associated with higher dyspnoea scores. Poor sleep quality, deterioration in sleep quality, and sleep regularity were also associated with impaired lung function, as assessed by forced vital capacity. Depending on the sleep metric, anxiety mediated 18–39% of the effect of sleep disturbance on dyspnoea, while muscle weakness mediated 27–41% of this effect.

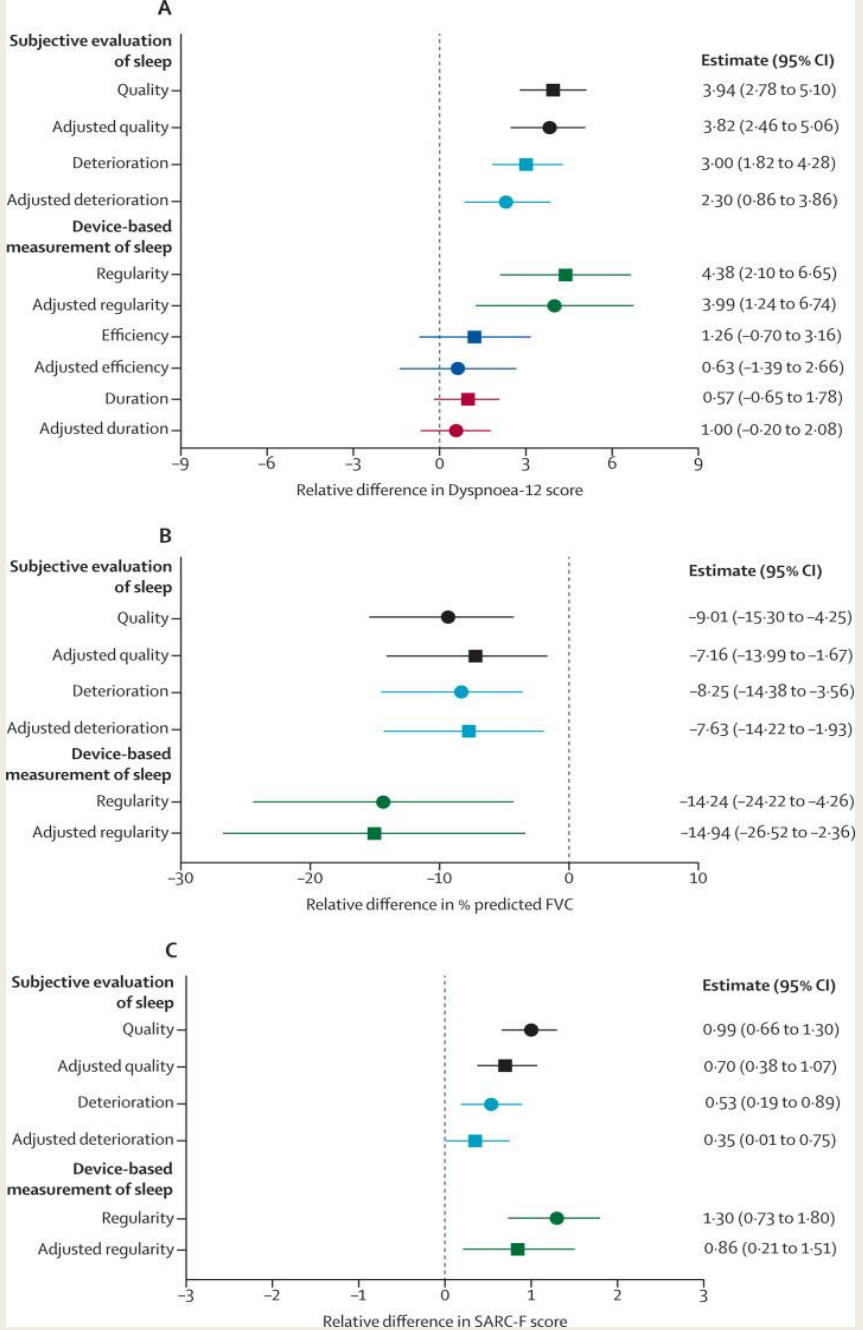
www.thelancet.com/respiratory Published online April 15, 2023 https://doi.org/10.1016/S2213-2600(23)00124-8





"Effects of sleep disturbance on dyspnoea and impaired lung function following hospital admission due to COVID-19 in the UK: a prospective multicentre cohort study" in *Lancet Respir Med*. 37072018.





"Effects of sleep disturbance on dyspnoea and impaired lung function following hospital admission due to COVID-19 in the UK: a prospective multicentre cohort study" in *Lancet Respir Med*. 37072018.

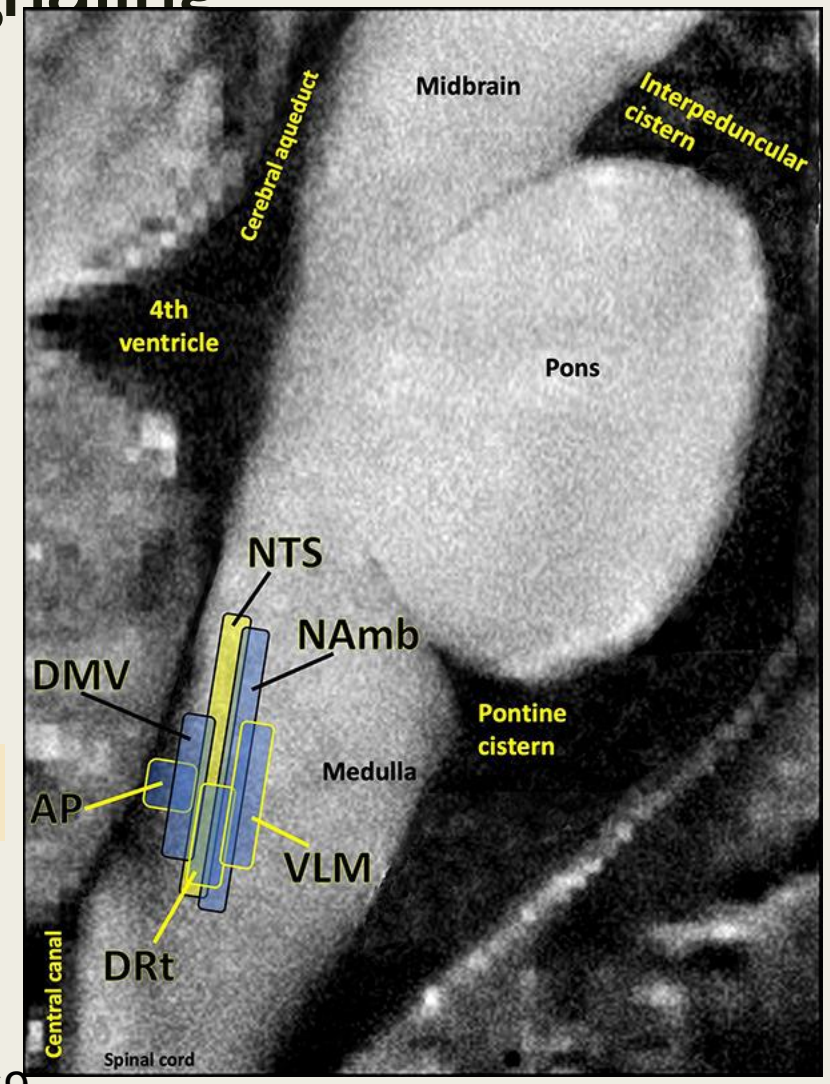
Myalgia- Encephalomyelitis/chronic Fatigue Syndrome (ME/CFS)

- Some PASC patients meet the diagnostic criteria for (ME/CFS)
- Neuroinflammation-linked condition
  - *Fatigue*
  - *Musculoskeletal pain*
  - *Post-exertional malaise*
- Most cases of ME/CFS begin with a viral infection, or exposure to pathogens over time.

SARS-CoV-2 and/or Related Inflammatory Insults May Disrupt Brainstem Signaling

- Similar to myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS)
- Dysautonomia, diffuse pain, sleep problems, flu-like symptoms, trouble concentrating, and nausea.
- Dysfunctional brainstem signaling may be an important driver of PASC symptoms that overlap with those of ME/CFS.

Are there residual derangements in ventilatory control?

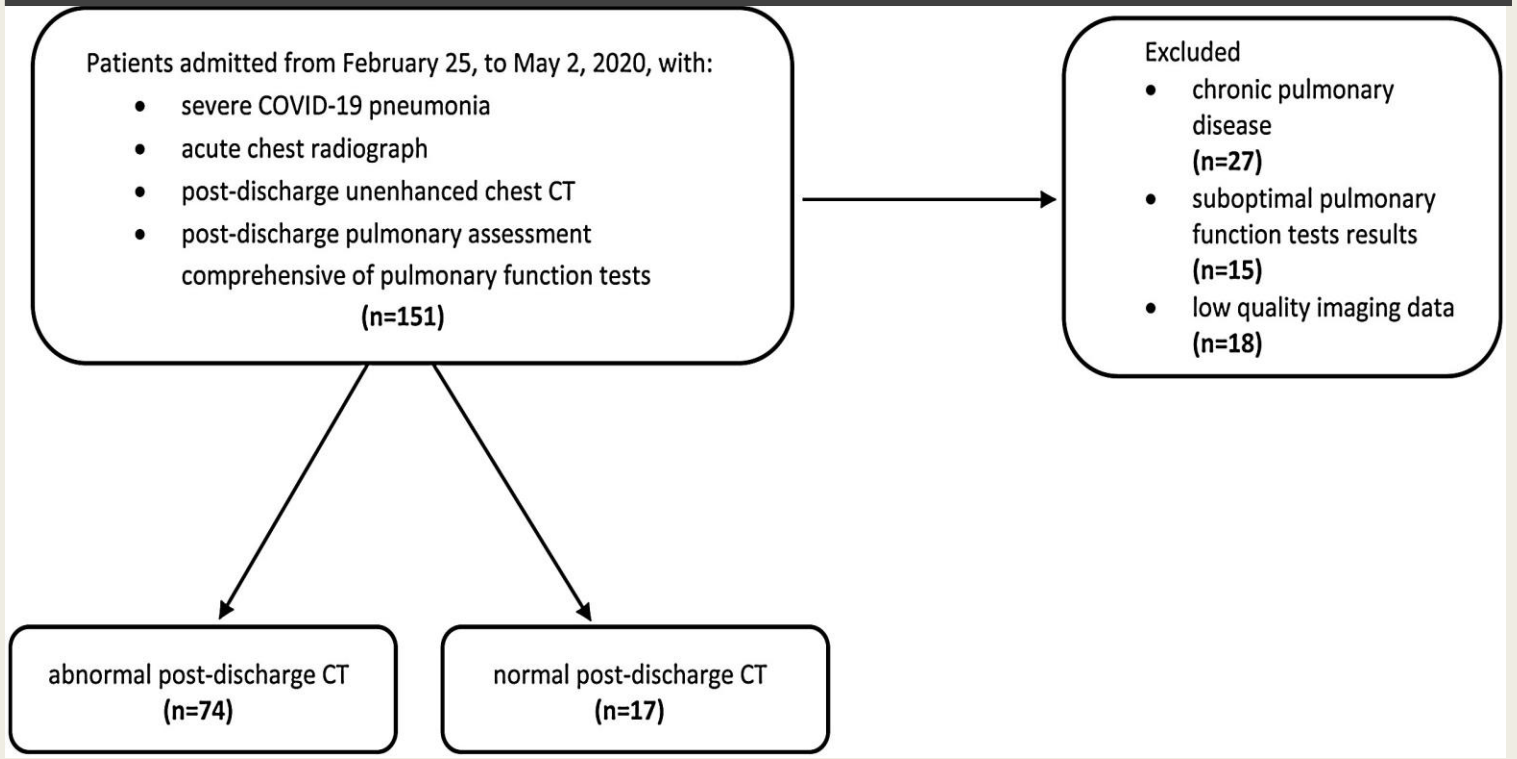


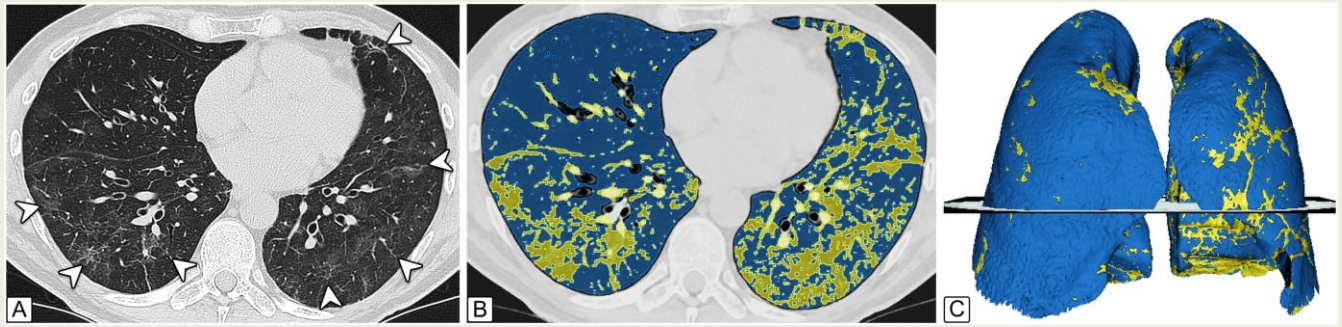
Proal AD, VanElzakker, MB. Front Microbiol. 2021; 12: 698169.

Respiratory Manifestations of Long COVID

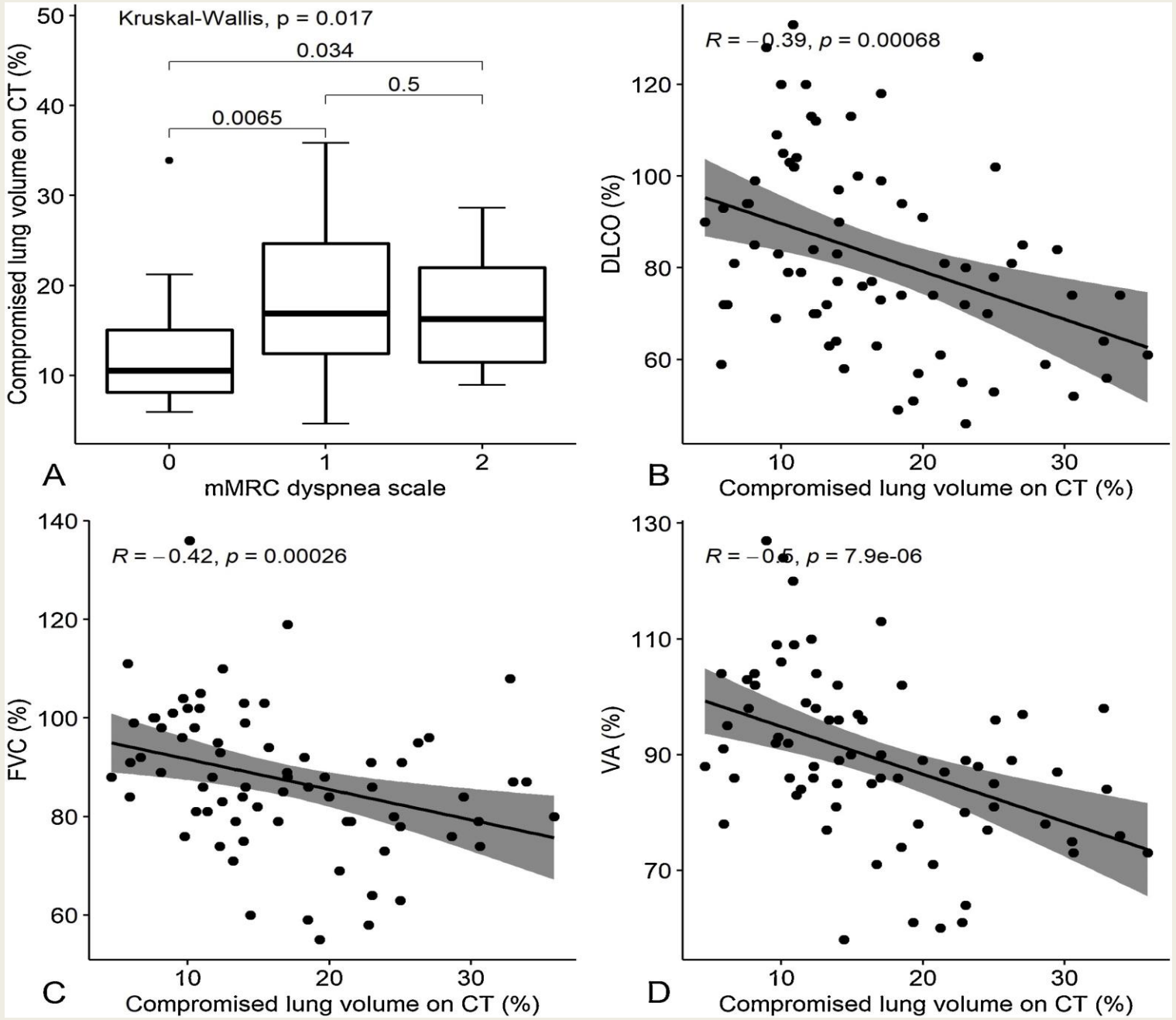
- Breathlessness
- Changes on imaging can persist in large numbers of patients beyond 12 weeks.
- Similar course to those observed in SARS-CoV-1 : 4.6% still had visible lesions on their lungs, and 38% had reduced diffusion capacity after 15 years following acute infection.
- >40% of COVID-19 patients report breathlessness, and >50% fatigue even 2 months after hospitalization
- 52% of home isolated young adults experienced Long COVID symptoms at 6 months following COVID-19 infection

Residual symptoms with apparent organ involvement

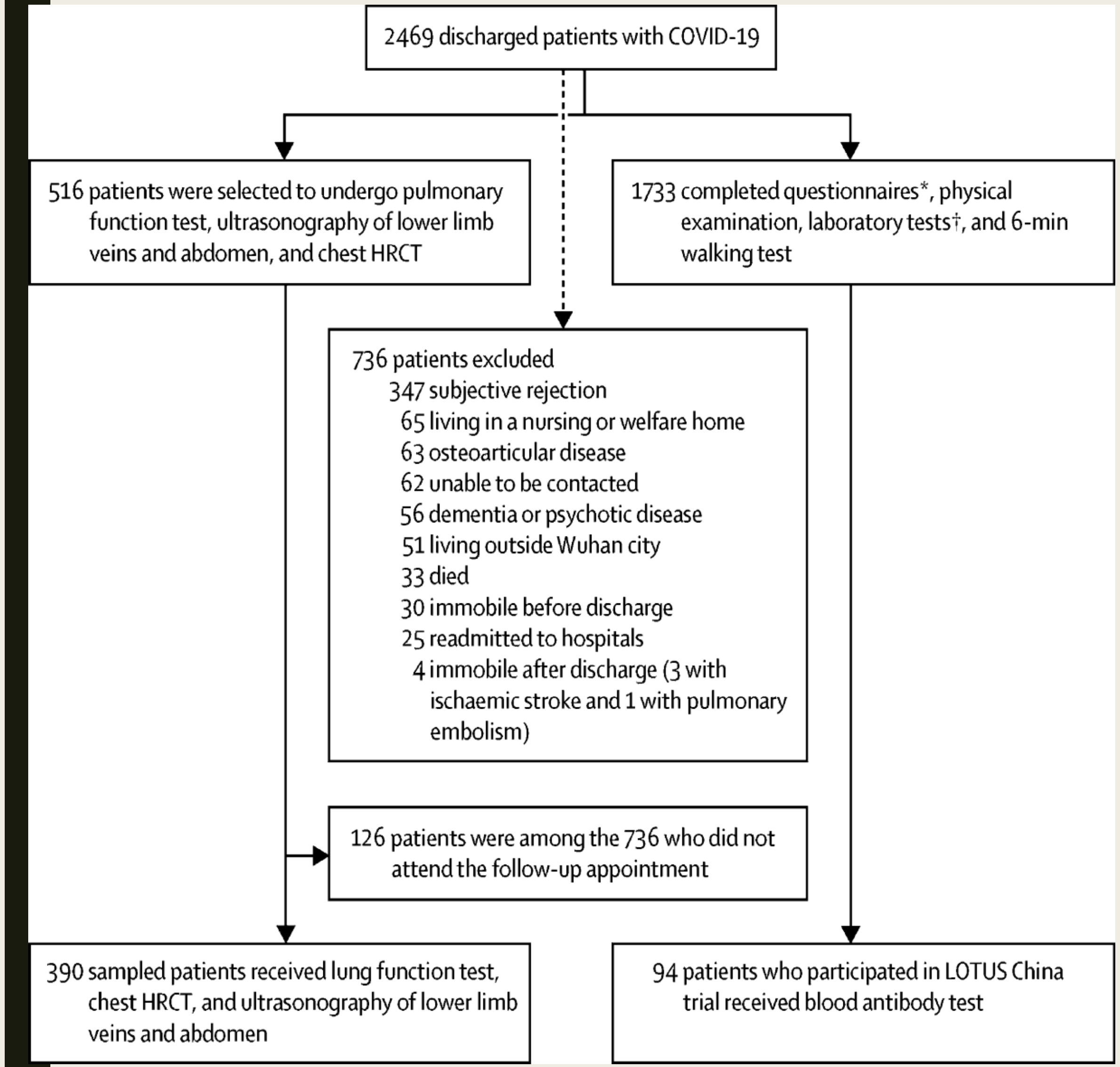




European Journal of Radiology 2021 138DOI: (10.1016/j.ejrad.2021.109676)



European Journal of Radiology 2021 138DOI: (10.1016/j.ejrad.2021.109676)



6-month consequences of COVID-19 in patients discharged from hospital: a cohort study

Chaolin Huang*, Lixue Huang*, Yeming Wang*, Xia Li*, Lili Ren*, Xiaoying Gu*, Liang Kang*, Li Guo*, Min Liu*, Xing Zhou, Jianfeng Luo, Zhenghui Huang, Shengjin Tu, Yue Zhao, Li Chen, Decui Xu, Yanping Li, Caihong Li, Lu Peng, Yong Li, Wuxiang Xie, Dan Cui, Lianhan Shang, Guohui Fan, Jiuyang Xu, Geng Wang, Ying Wang, Jingchuan Zhong, Chen Wang, Jianwei Wang†, Dingyu Zhang†, Bin Cao†

Lancet 2021; 397: 220–32

Published Online January 8, 2021 https://doi.org/10.1016/S0140-6736(20)32656-8

See Comment page 173

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Summary

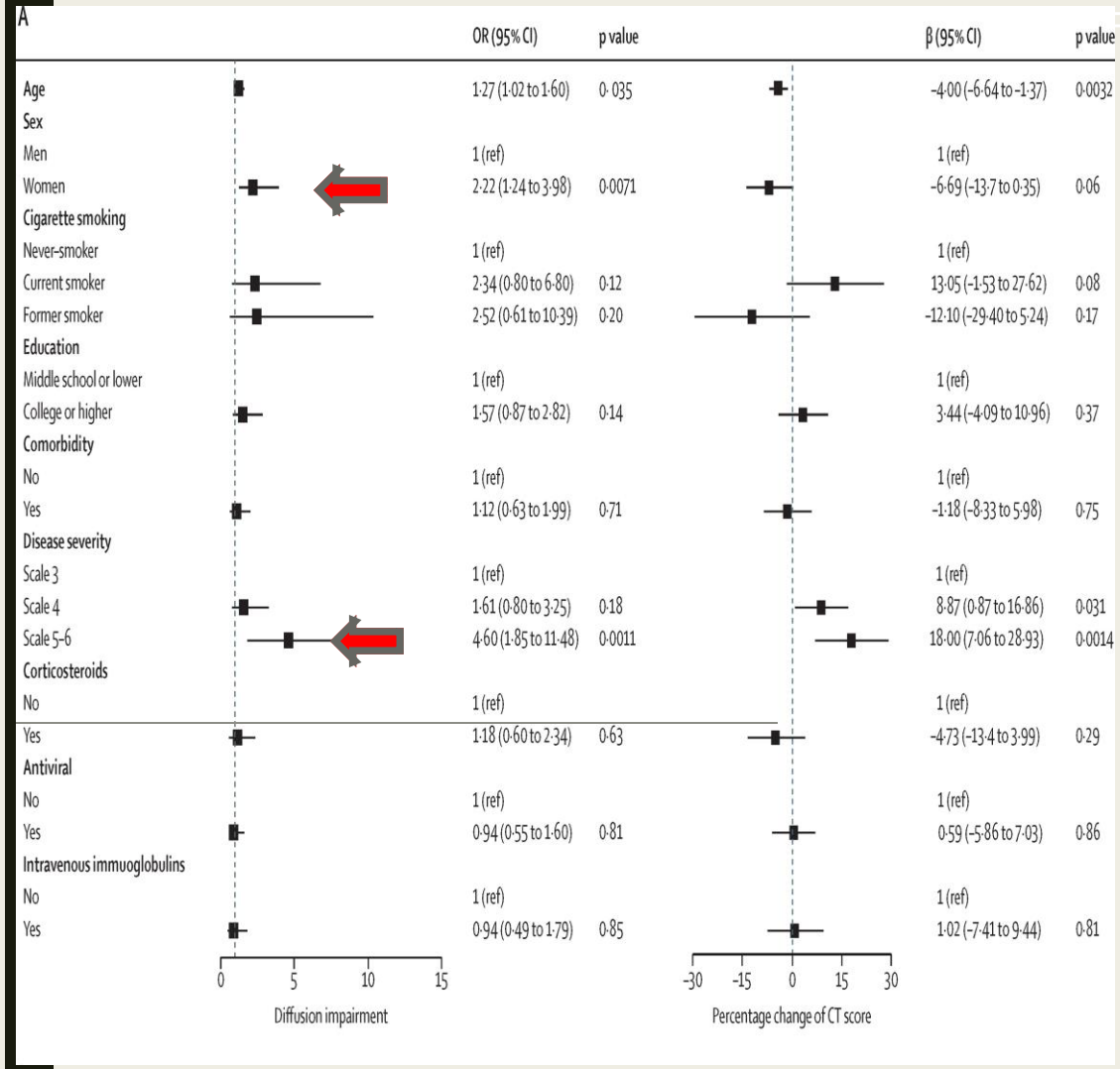
Background The long-term health consequences of COVID-19 remain largely unclear. The aim of this study was to describe the long-term health consequences of patients with COVID-19 who have been discharged from hospital and investigate the associated risk factors, in particular disease severity.

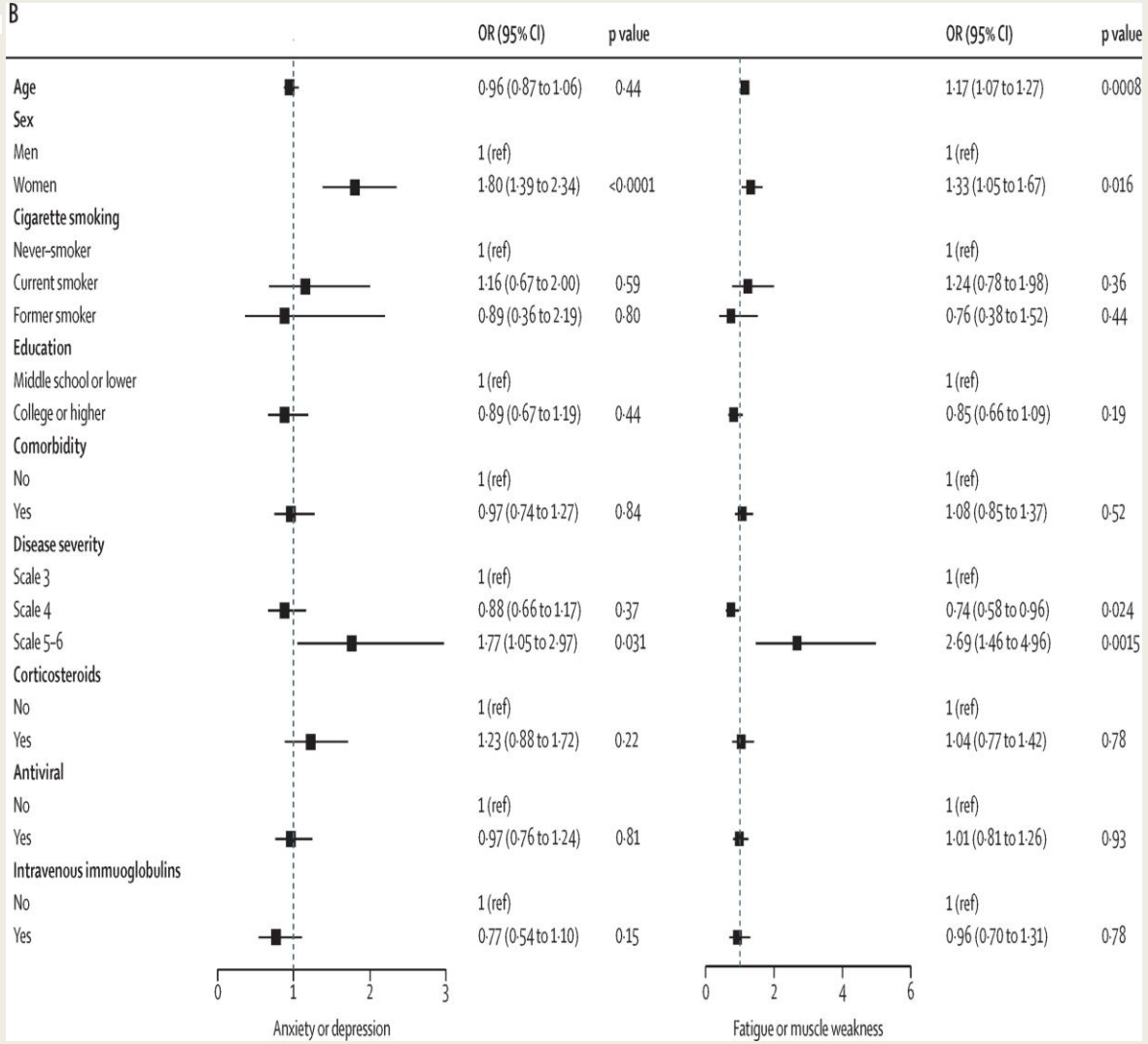
Methods We did an ambidirectional cohort study of patients with confirmed COVID-19 who had been discharged from Jin Yin-tan Hospital (Wuhan, China) between Jan 7, 2020, and May 29, 2020. Patients who died before follow-up, patients for whom follow-up would be difficult because of psychotic disorders, dementia, or re-admission to hospital, those who were unable to move freely due to concomitant osteoarthropathy or immobile before or after discharge due to diseases such as stroke or pulmonary embolism, those who declined to participate, those who could not be contacted, and those living outside of Wuhan or in nursing or welfare homes were all excluded. All patients were interviewed with a series of questionnaires for evaluation of symptoms and health-related quality of life, underwent physical examinations and a 6-min walking test, and received blood tests. A stratified sampling procedure was used to sample patients according to their highest seven-category scale during their hospital stay as 3, 4, and 5–6, to receive pulmonary function test, high resolution CT of the chest, and ultrasonography. Enrolled patients who had participated in the Lopinavir Trial for Suppression of SARS-CoV-2 in China received severe acute respiratory syndrome coronavirus 2 antibody tests. Multivariable adjusted linear or logistic regression models were used to evaluate the association between disease severity and long-term health consequences.

Findings In total, 1733 of 2469 discharged patients with COVID-19 were enrolled after 736 were excluded. Patients had a median age of 57·0 (IQR 47·0–65·0) years and 897 (52%) were men. The follow-up study was done from June 16, to Sept 3, 2020, and the median follow-up time after symptom onset was 186·0 (175·0–199·0) days. Fatigue or muscle weakness (63%, 1038 of 1655) and sleep difficulties (26%, 437 of 1655) were the most common symptoms. Anxiety or depression was reported among 23% (367 of 1617) of patients. The proportions of median 6-min walking distance less than the lower limit of the normal range were 24% for those at severity scale 3, 22% for severity scale 4, and 29% for severity scale 5–6. The corresponding proportions of patients with diffusion impairment were 22% for severity scale 3, 29% for scale 4, and 56% for scale 5–6, and median CT scores were 3·0 (IQR 2·0–5·0) for severity scale 3, 4·0 (3·0–5·0) for scale 4, and 5·0 (4·0–6·0) for scale 5–6. After multivariable adjustment, patients showed an odds ratio (OR) 1·61 (95% CI 0·80–3·25) for scale 4 versus scale 3 and 4·60 (1·85–11·48) for scale 5–6 versus scale 3 for diffusion impairment; OR 0·88 (0·66–1·17) for scale 4 versus scale 3 and OR 1·77 (1·05–2·97) for scale 5–6 versus scale 3 for anxiety or depression, and OR 0·74 (0·58–0·96) for scale 4 versus scale 3 and 2·69 (1·46–4·96) for scale 5–6 versus scale 3 for fatigue or muscle weakness. Of 94 patients with blood antibodies tested at follow-up, the seropositivity (96·2% vs 58·5%) and median titres (19·0 vs 10·0) of the neutralising antibodies were significantly lower compared with at the acute phase. 107 of 822 participants without acute kidney injury and with estimated glomerular filtration rate (eGFR) 90 mL/min per 1·73 m^2 or more at acute phase had eGFR less than 90 mL/min per 1·73 m^2 at follow-up.

Interpretation At 6 months after acute infection, COVID-19 survivors were mainly troubled with fatigue or muscle weakness, sleep difficulties, and anxiety or depression. Patients who were more severely ill during their hospital stay had more severe impaired pulmonary diffusion capacities and abnormal chest imaging manifestations, and are the main target population for intervention of long-term recovery.

Funding National Natural Science Foundation of China, Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences, National Key Research and Development Program of China, Major Projects of National Science and Technology on New Drug Creation and Development of Pulmonary Tuberculosis, and Peking Union Medical College Foundation.





Sex appears to be associated with post long-term sequelae

Determinants of long-term outcome remain unclear.

The Lancet 2021 397220-232DOI: (10.1016/S0140-6736(20)32656-8)

6-month consequences of COVID-19 in patients discharged from hospital: a cohort study

- Fatigue or muscle weakness, sleep difficulties, and anxiety or depression were common, even at 6 months after symptom onset.
- Consistent with previous SARS long term follow-up studies.
- Being a woman and severity of illness were risk factors for persistent anxiety and depression
- Persistent diffusion abnormalities were common
- The disease severity in the acute phase was found to be associated with pulmonary diffusion abnormality and percentage change of CT score in the multivariable analysis.

From: **Respiratory and Psychophysical Sequelae Among Patients With COVID-19 Four Months After Hospital Discharge**

JAMA Netw Open. 2021;4(1):e2036142. doi:10.1001/jamanetworkopen.2020.36142

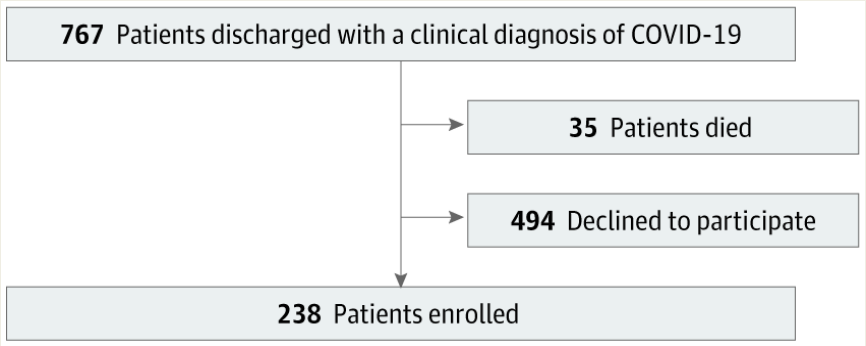


Figure Legend:

Flowchart of the Study PopulationCOVID-19 indicate coronavirus disease 2019.

From: **Respiratory and Psychophysical Sequelae Among Patients With COVID-19 Four Months After Hospital Discharge**

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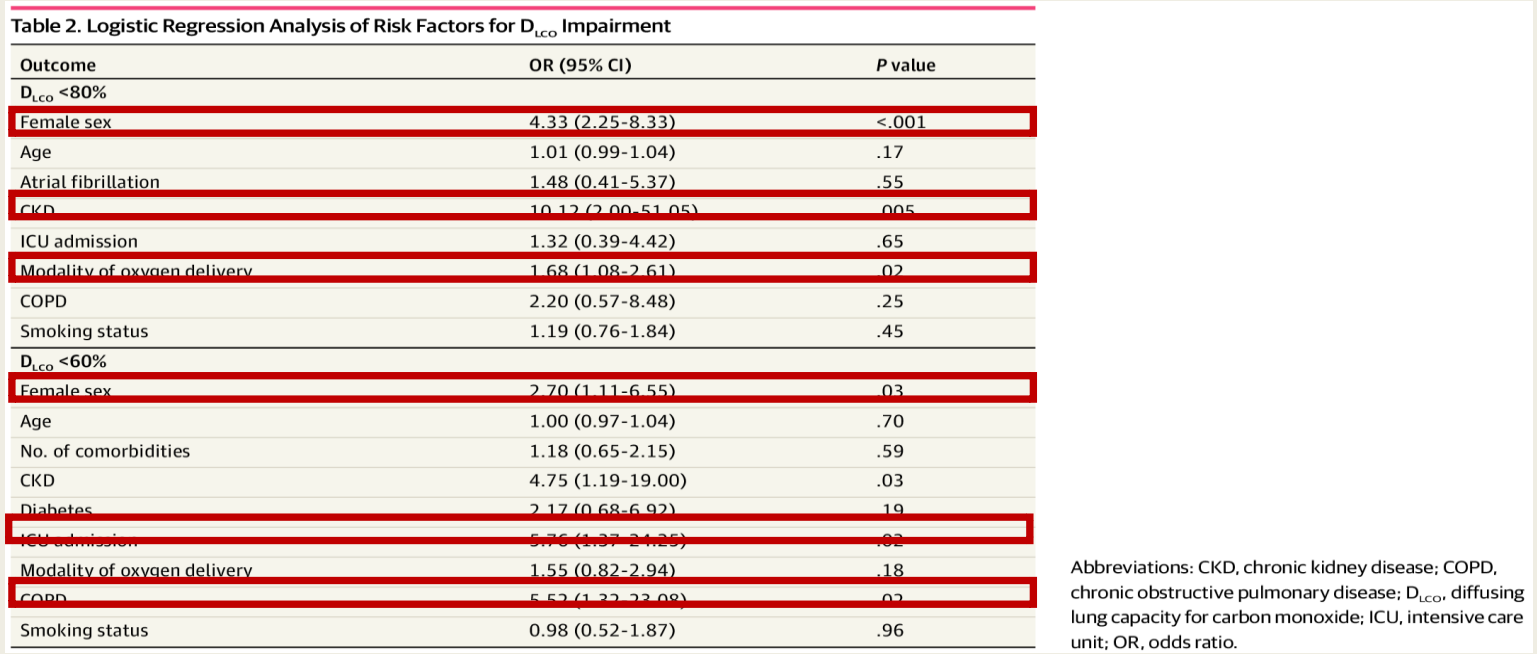

Table 2. Logistic Regression Analysis of Risk Factors for D_{LCO} Impairment

Outcome	OR (95% CI)	*P* value
D_{LCO} <80%		
Female sex	4.33 (2.25-8.33)	<.001
Age	1.01 (0.99-1.04)	.17
Atrial fibrillation	1.48 (0.41-5.37)	.55
CKD	10.12 (2.00-51.05)	.005
ICU admission	1.32 (0.39-4.42)	.65
Modality of oxygen delivery	1.68 (1.08-2.61)	.02
COPD	2.20 (0.57-8.48)	.25
Smoking status	1.19 (0.76-1.84)	.45
D_{LCO} <60%		
Female sex	2.70 (1.11-6.55)	.03
Age	1.00 (0.97-1.04)	.70
No. of comorbidities	1.18 (0.65-2.15)	.59
CKD	4.75 (1.19-19.00)	.03
Diabetes	2.17 (0.68-6.92)	.19
ICU admission	5.76 (1.37-24.25)	.02
Modality of oxygen delivery	1.55 (0.82-2.94)	.18
COPD	5.52 (1.32-23.08)	.02
Smoking status	0.98 (0.52-1.87)	.96

Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; D_{LCO}, diffusing lung capacity for carbon monoxide; ICU, intensive care unit; OR, odds ratio.

Table Title:

Logistic Regression Analysis of Risk Factors for D_{lco} ImpairmentAbbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; D_{lco}, diffusing lung capacity for carbon monoxide; ICU, intensive care unit; OR, odds ratio.

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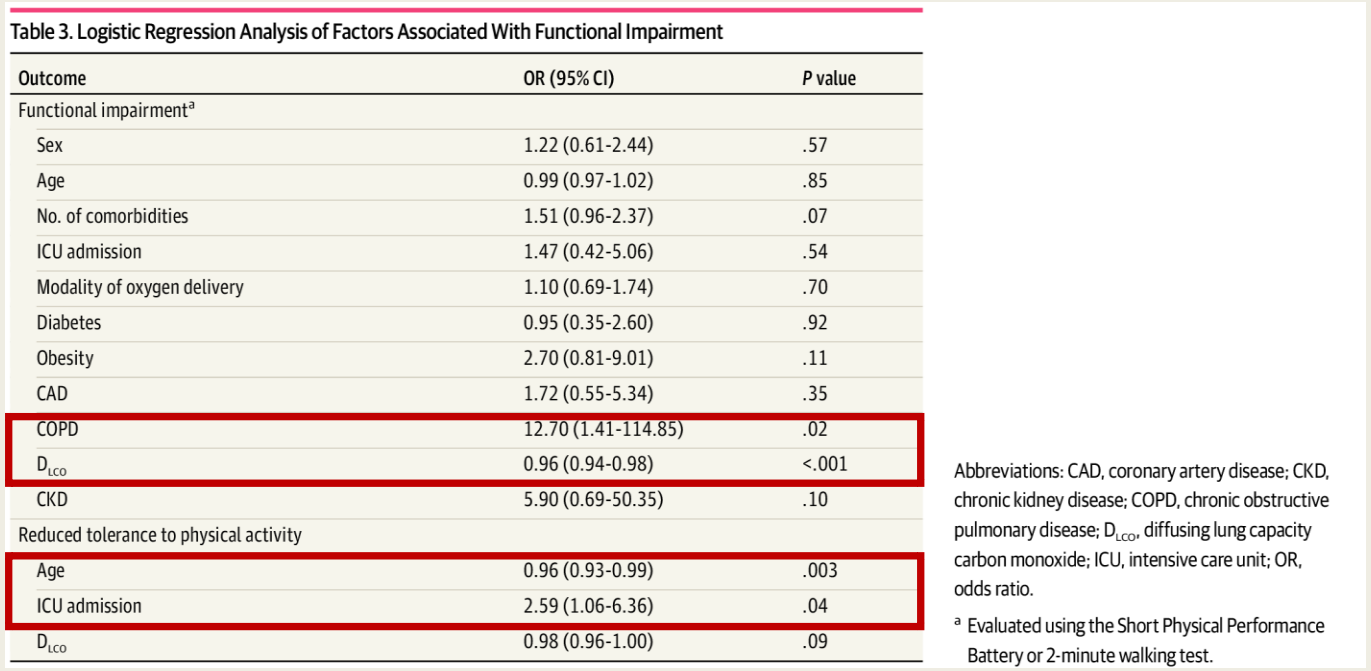

Table 3. Logistic Regression Analysis of Factors Associated With Functional Impairment

Outcome	OR (95% CI)	*P* value
Functional impairment[a]		
Sex	1.22 (0.61-2.44)	.57
Age	0.99 (0.97-1.02)	.85
No. of comorbidities	1.51 (0.96-2.37)	.07
ICU admission	1.47 (0.42-5.06)	.54
Modality of oxygen delivery	1.10 (0.69-1.74)	.70
Diabetes	0.95 (0.35-2.60)	.92
Obesity	2.70 (0.81-9.01)	.11
CAD	1.72 (0.55-5.34)	.35
COPD	12.70 (1.41-114.85)	.02
D_{LCO}	0.96 (0.94-0.98)	<.001
CKD	5.90 (0.69-50.35)	.10
Reduced tolerance to physical activity		
Age	0.96 (0.93-0.99)	.003
ICU admission	2.59 (1.06-6.36)	.04
D_{LCO}	0.98 (0.96-1.00)	.09

Abbreviations: CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; D_{LCO}, diffusing lung capacity carbon monoxide; ICU, intensive care unit; OR, odds ratio.

[a] Evaluated using the Short Physical Performance Battery or 2-minute walking test.

Table Title:

Logistic Regression Analysis of Factors Associated With Functional ImpairmentAbbreviations: CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; D_{lco}, diffusing lung capacity carbon monoxide; ICU, intensive care unit; OR, odds ratio.

[a] Evaluated using the Short Physical Performance Battery or 2-minute walking test.

Recovery Time course

- **Fatigue, weakness, and poor endurance** –three months or longer, particularly among ICU survivors
- **Dyspnea** –resolving slowly in most patients over two to three months, sometimes longer (eg, up to 12 months)
- **Chronic cough** –two to three weeks following initial symptoms – resolution in 3 months
- **Chest discomfort** –persists in 12 to 22 percent of patients 2-3 months
- **Altered taste and smell** –Complete or near-complete recovery at one month following acute illness,
- **Neurocognitive symptoms** –persist for six weeks or more in COVID-19 patients after discharge from the hospital
- **Psychological** – Observational studies report that psychological symptoms (eg, anxiety, depression, PTSD) are common after acute COVID-19 infection, with anxiety being the most common. In general, psychological symptoms improve over time but may persist for more than six months for a subset of survivors.

Persistent Post–COVID-19 Interstitial Lung Disease

An Observational Study of Corticosteroid Treatment

Katherine Jane Myall[1], Bhashkar Mukherjee[1], Ana Margarida Castanheira[1], Jodie L. Lam[1], Giulia Benedetti[2], Sze Mun Mak[2], Rebecca Preston[2], Muhunthan Thillai[3], Amy Dewar[1], Philip L. Molyneaux[4,5], and Alex G. West[1]

[1]Department of Respiratory Medicine and [2]Department of Radiology, Guy's and St. Thomas' NHS Foundation Trust, London, United Kingdom; [3]Department of Interstitial Lung Disease, Royal Papworth Hospital NHS Foundation Trust, Cambridge, United Kingdom; [4]National Heart and Lung Institute, Imperial College London, London, United Kingdom; and [5]Royal Brompton Hospital, London, United Kingdom

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Abstract

Rationale: The natural history of recovery from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remains unknown. Because fibrosis with persistent physiological deficit is a previously described feature of patients recovering from similar coronaviruses, treatment represents an early opportunity to modify the disease course, potentially preventing irreversible impairment.

Objectives: Determine the incidence of and describe the progression of persistent inflammatory interstitial lung disease (ILD) following SARS-CoV-2 when treated with prednisolone.

Methods: A structured assessment protocol screened for sequelae of SARS-CoV-2 pneumonitis. Eight hundred thirty-seven patients were assessed by telephone 4 weeks after discharge. Those with ongoing symptoms had outpatient assessment at 6 weeks. Thirty patients diagnosed with persistent interstitial lung changes at a multidisciplinary team meeting were reviewed in the interstitial lung disease service and offered treatment. These patients had persistent, nonimproving symptoms.

Results: At 4 weeks after discharge, 39% of patients reported ongoing symptoms (325/837) and were assessed. Interstitial lung disease, predominantly organizing pneumonia, with significant functional deficit was observed in 35/837 survivors (4.8%). Thirty of these patients received steroid treatment, resulting in a mean relative increase in transfer factor following treatment of 31.6% (standard deviation [SD] $\pm$27.6, $P < 0.001$), and forced vital capacity of 9.6% (SD $\pm$ 13.0, $P = 0.014$), with significant symptomatic and radiological improvement.

Conclusions: Following SARS-CoV-2 pneumonitis, a cohort of patients are left with both radiological inflammatory lung disease and persistent physiological and functional deficit. Early treatment with corticosteroids was well tolerated and associated with rapid and significant improvement. These preliminary data should inform further study into the natural history and potential treatment for patients with persistent inflammatory ILD following SARS-CoV-2 infection.

Keywords: COVID-19; interstitial lung disease; organizing pneumonia; fibrosis

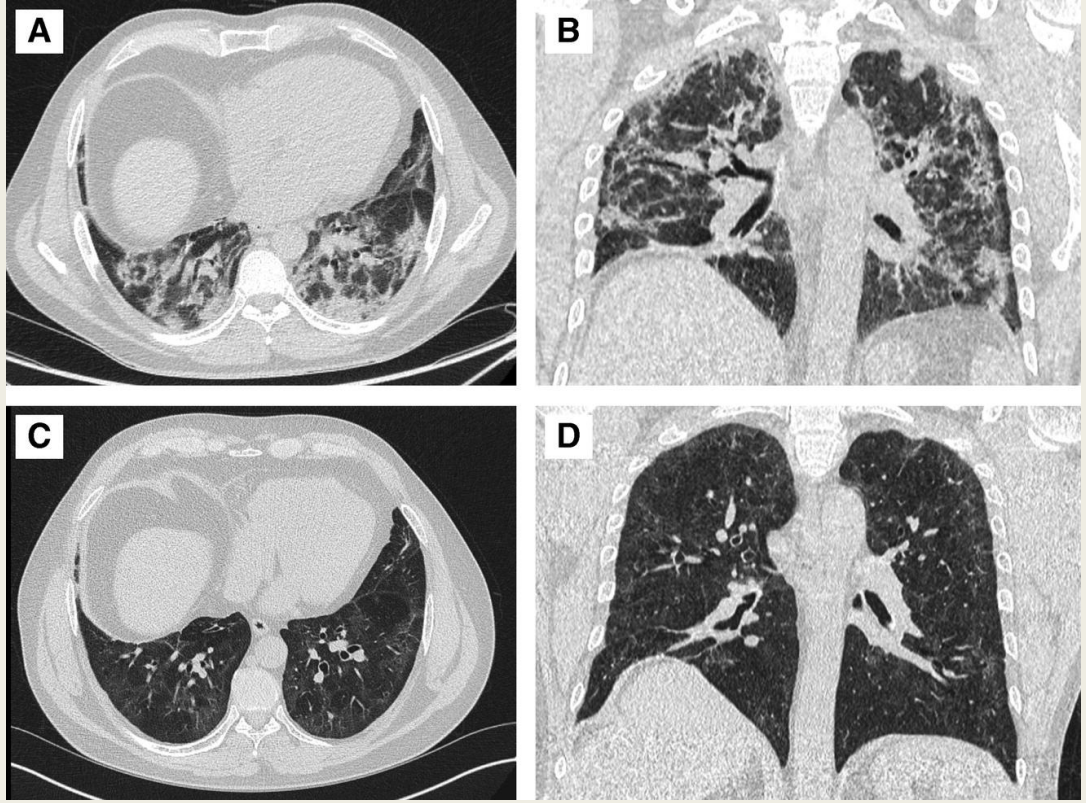

Figure 4. Axial image and coronal reconstruction from computed tomographic (CT) imaging of the thorax acquired immediately before discharge in a previously fit and well 57-year-old man (*A* and *B*) shows a radiological pattern of organizing pneumonia disease with predominant peribronchial and perilobular dense consolidation mild traction bronchiectasis of the airways. At this stage, the patient could only walk 30 yards. Follow-up CT imaging of the thorax acquired after 3 weeks of oral prednisolone (*C* and *D*) shows resolution of consolidation with residual ground glass and fine subpleural reticulation. The airways still have a slightly nontapering appearance. The patient was now able to run for 30 minutes a day.

Annals ATS, 2021
https://www.atsjournals.org/doi/abs/10.1513/AnnalsATS.202008-1002OC

Published in: Katherine Jane Myall; Bhashkar Mukherjee; Ana Margarida Castanheira; Jodie L. Lam; Giulia Benedetti; Sze Mun Mak; Rebecca Preston; Muhunthan Thillai; Amy Dewar; Philip L. Molyneaux; Alex G. West; *Annals ATS* 18799-806.
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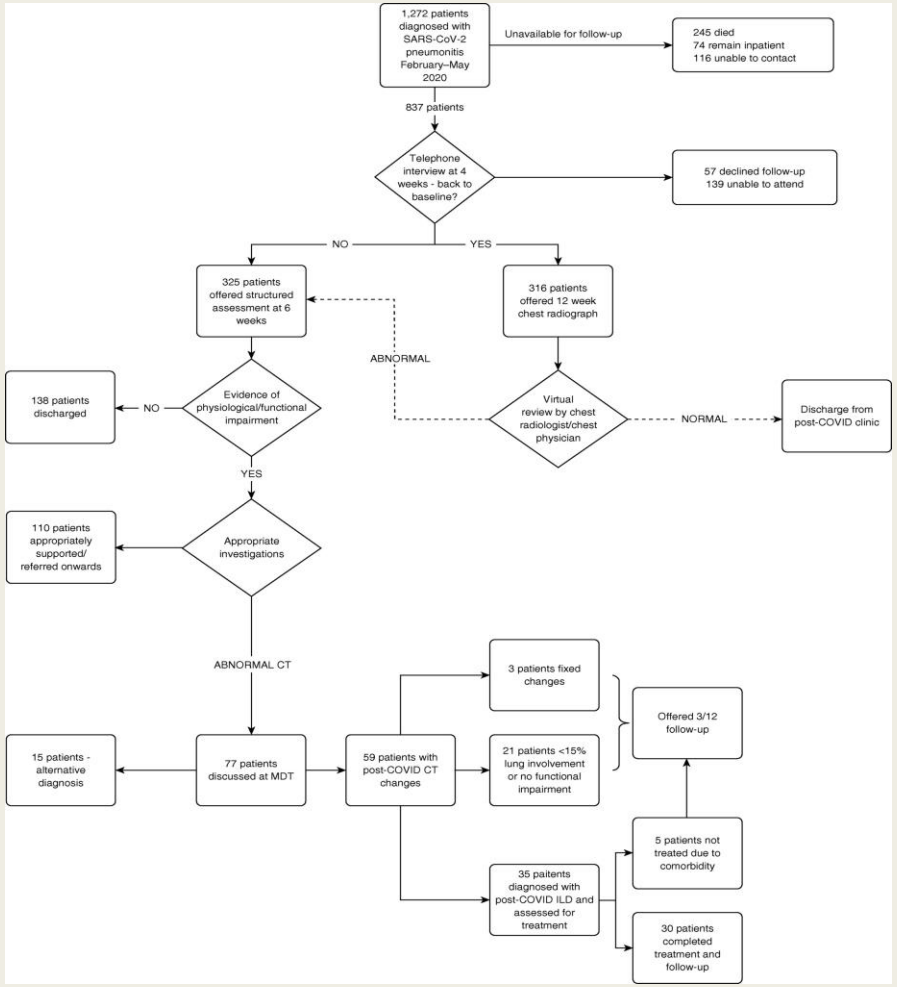

Flowchart of the study population recruited between February and May 2020. COVID = coronavirus disease; CT = computed tomography; ILD = interstitial lung disease; MDT = multidisciplinary team meeting; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

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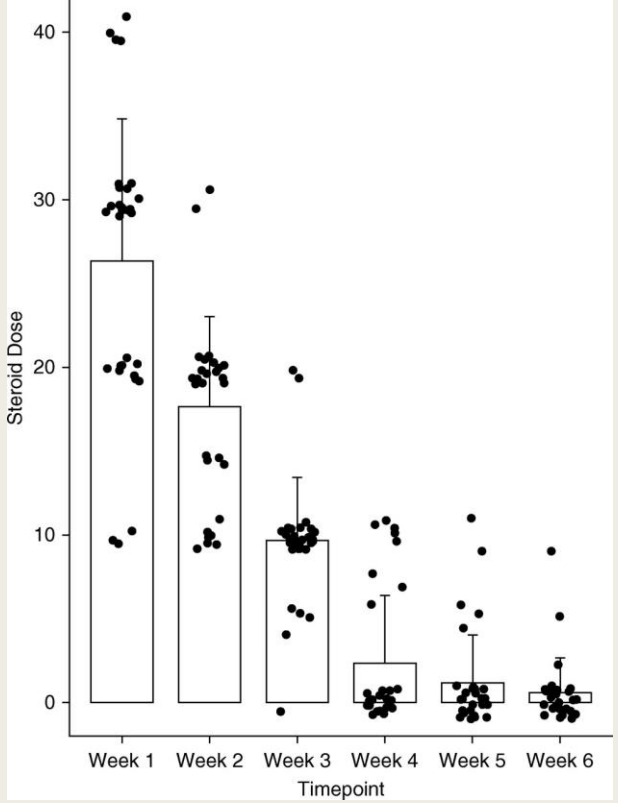

Figure 2. Steroid dosing by week. Data are presented as median and interquartile range.

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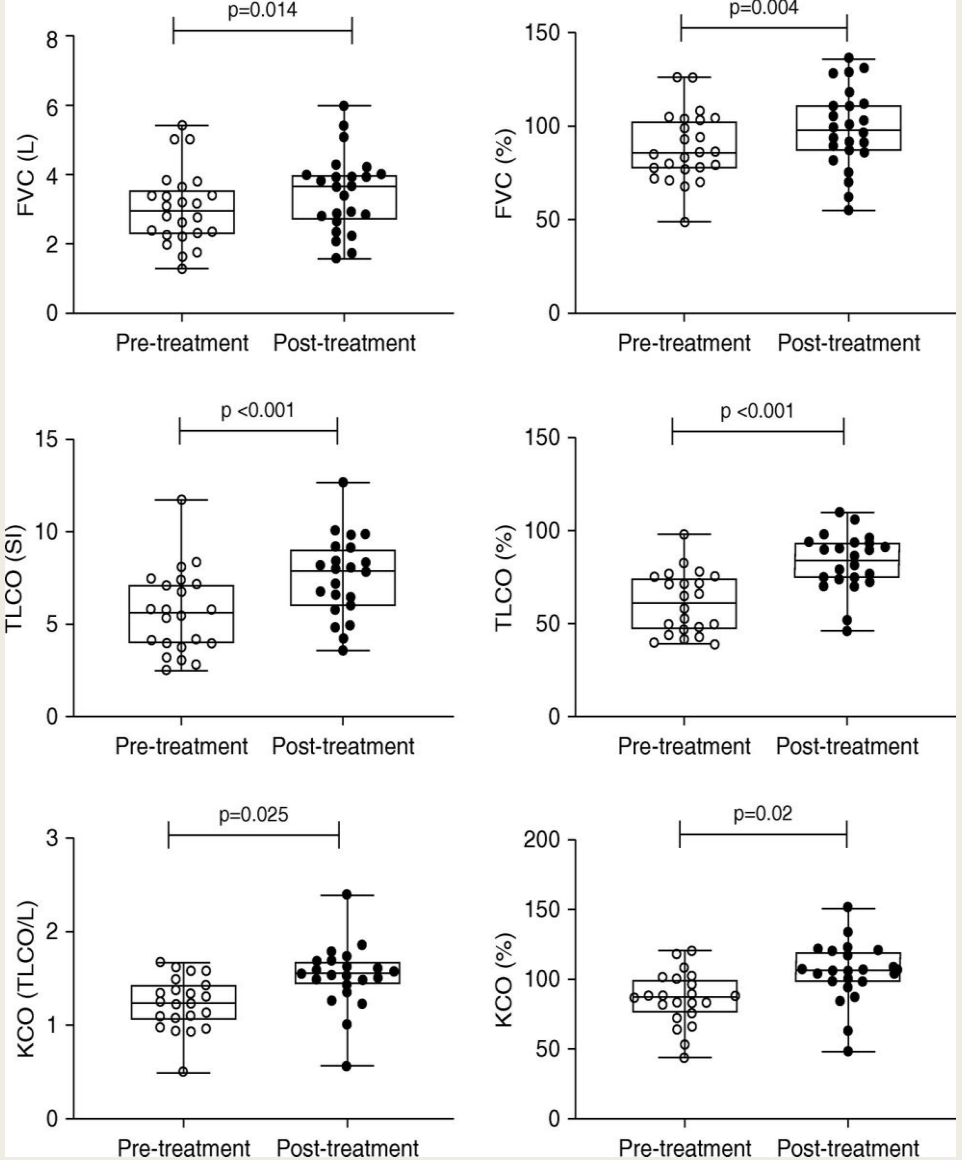

Figure 3. Change in lung function after treatment with oral prednisolone in patients with interstitial lung disease after infection with SARS-CoV-2. FVC = forced vital capacity; KCO = transfer coefficient; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SI = International System of Units; transfer; TlCO = transfer factor of the lung for carbon monoxide.

Annals ATS, 2021
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Where facts are few, experts are many

Limitations and Opportunities

- What are the determinants of PASC?
- What is the effect of age, race, or sex?
- Social determinants of Health and SES
- Natural history of the condition
- Need a comparison group.

Future Directions

- Prospective cohort studies of COVID-19 survivors, including asymptomatic and those with PASC. What is the proportion of the population who develop PASC?
- Underlying biological cause of these prolonged symptoms?
- Underlying cause of vulnerability
- Etiology of unexplained prolonged dyspnea?
- Interaction with underlying health status,
- Physiologic studies addressing ventilatory control, sleep, PLMS
- Dedicated clinics with registries.