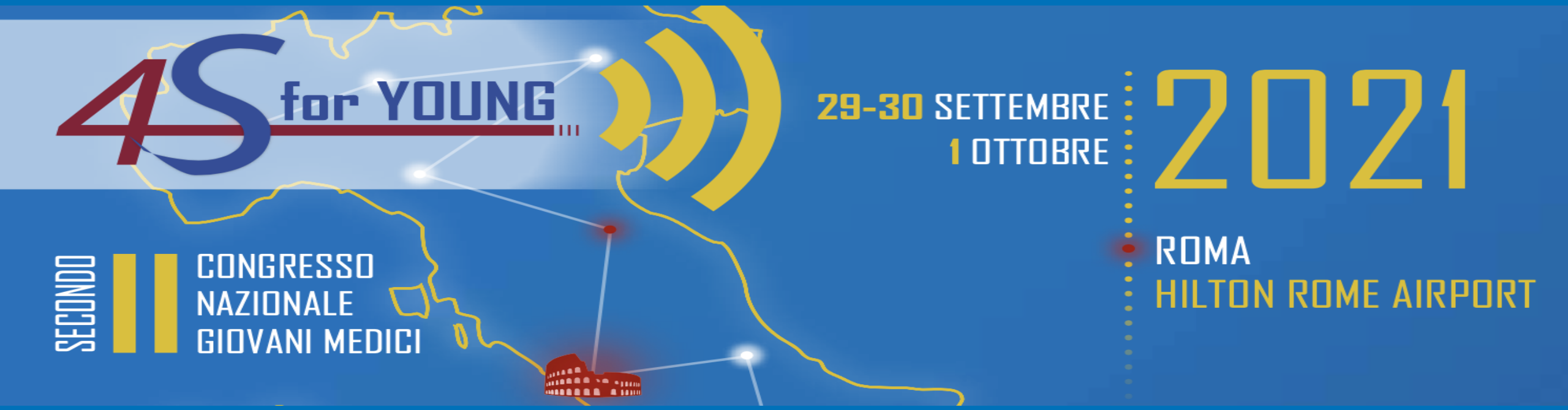

LONG COVID

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S.C. Malattie Infettive, Ospedale Maggiore di Trieste – ASUGI
30.09.2021

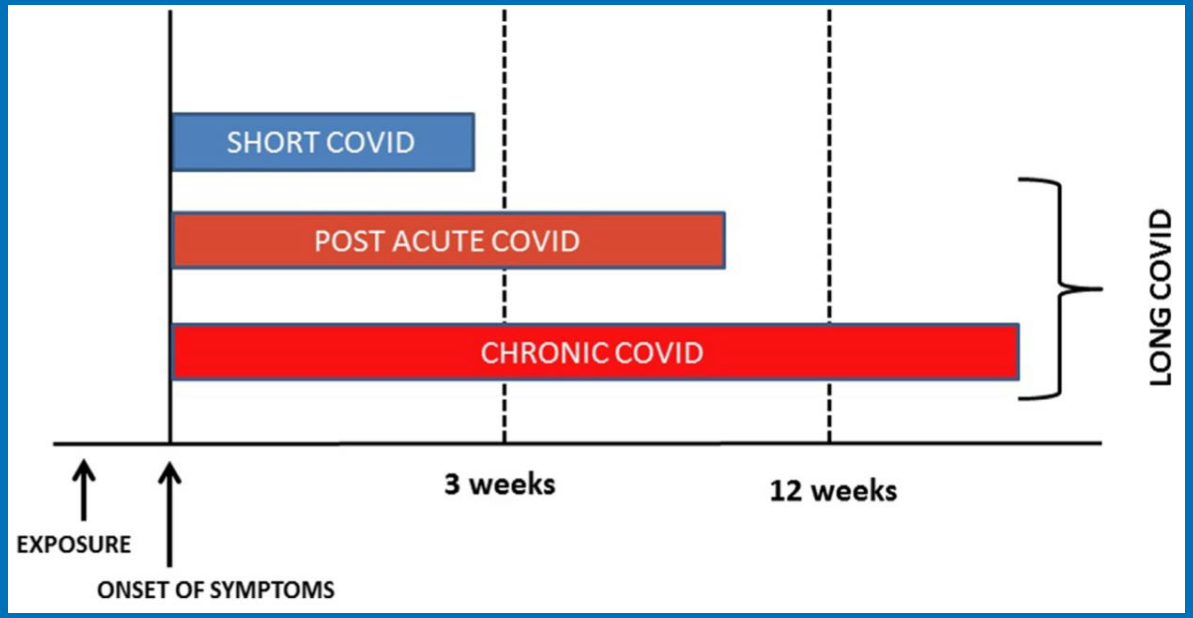
ASUGI
Azienda Sanitaria Universitaria Giuliano Isontina
REGIONE AUTONOMA FRIULI VENEZIA GIULIA

Definizione di LONG COVID

wide range of health consequences that are present four or more weeks after infection with SARS-CoV-2

- **Malattia COVID-19 sintomatica persistente** segni e sintomi attribuibili al COVID-19 di durata compresa tra 4 e 12 settimane dopo l'evento acuto

- **Sindrome post-COVID-19** segni e sintomi che si sono sviluppati durante o dopo un'infezione compatibile con il COVID-19, presenti per più di 12 settimane dopo l'evento acuto e non spiegabili con diagnosi alternative



- Diabetes & Metabolic Syndrome: Clinical Research & Reviews 15 (2021) 869e875
- Rapporto ISS COVID-19 n. 15/2021

Epidemiologia

- the accurate reporting of long covid is complicated
- various incidence rates: 76% of people at 6 months (Huang et al. 2021)
  32.6% at 60 days (Chopra V et al. 2021)
  87% at 60 days (Carfi, Bernabei & Landi 2021)

Il più ampio degli studi, svolto nel Regno Unito dall'*Office for National Statistics* su un campione di oltre 20.000 persone, ha mostrato una prevalenza di sintomi del 13% oltre le 12 settimane post-infezione, con una prevalenza otto volte superiore a quella di un gruppo di controllo, un rischio maggiore nelle donne rispetto agli uomini (14,7% *vs.* 12,7%) e prevalenza più alta nel gruppo di età 25-34 (18,2%) (41).

In un altro studio svolto nel Regno Unito su oltre 4.000 soggetti (COVID *Symptom Study*), la prevalenza è risultata più bassa, pari al 13% a 4 settimane, del 4,5% oltre le 8 settimane e del 2,3% oltre le 12 settimane. Long-COVID si manifestava con astenia, cefalea, dispnea e anosmia, e il rischio aumentava per i soggetti con un alto indice di massa corporea e per il genere femminile (47). In uno studio osservazionale svolto su pazienti dimessi da 38 ospedali statunitensi, la persistenza di sintomi a sessanta giorni interessava circa un terzo dei 488 soggetti che avevano risposto all'indagine, con dispnea come sintomo più frequente, seguito

Epidemiologia

- grande variabilità di sintomi e segni clinici
- singolarmente o in diverse combinazioni
- transitori o intermittenti
- cambiare nel tempo, oppure possono essere costanti
- più **grave** è stata la malattia acuta, maggiore rischia di essere l'**entità dei sintomi**
- anche persone che hanno avuto in fase acuta unicamente sintomi lievi

Anche in pediatria

- Young children are much less likely to develop severe illness, due to lower levels of expression of receptors
- multisystem inflammatory condition with some features of Kawasaki disease and toxic shock syndrome (Moreira, 2020)
- case series of five children, median age of 12 years, persisting symptoms for 6–8 months (Ludvigsson, 2020)
- **United Kingdom** study of 651 children admitted to hospital with COVID-19, median age was 4.6 years, 11% of children had a systematic mucocutaneous-enteric cluster of symptoms

Va sottolineato che tale sintomatologia potrebbe anche essere dovuta alle conseguenze indirette del COVID-19 nel lungo periodo, fra cui l'isolamento sociale e le ricadute socioeconomiche della pandemia sulle famiglie (43, 44). Infatti la salute dei bambini può risultare profondamente influenzata da modifiche delle

RISK FACTORS

March-June 2020 *MMWR Morb Mortal Wkly Rep* 2020;69:993-8. doi:10.15585

TABLE 1. Characteristics of symptomatic outpatients with SARS-CoV-2 real-time reverse transcription–polymerase chain reaction (RT-PCR)—positive test results (N = 270)* who reported returning to usual state of health or not returning to usual state of health at an interview conducted 14–21 days after testing — 14 academic health care systems,† United States, March–June 2020

Characteristic	Total	Returned to usual health, no. (row %)		P-value§
		Yes (n = 175)	No (n = 95)	
Sex				0.14
Women	**140**	85 (61)	55 (39)	
Men	**130**	90 (69)	40 (31)	
Age group (yrs)				0.010
18–34	**85**	63 (74)	22 (26)	
35–49	**96**	65 (68)	31 (32)	
≥50	**89**	47 (53)	42 (47)	

ONS (Office for National Statistics- UK) reported that:
the prevalence of any long covid symptoms is higher in women compared with men (23.6% versus 20.7%),
while the age group estimated to be most greatly affected by long covid symptoms is 35-49 years (26.8%), followed by 50-69 years (26.1%), and the ≥70 years group (18%)

RISK FACTORS

more severe acute phase may transform into the development of more severe symptoms of long covid *Int J Clin Pract* 2021;75:e13746

patients with more than five symptoms during the initial covid-19 infection and those that required hospital admission more likely to experience long covid symptoms. *Nat Med* 2021;27:626-31

pre-existence of asthma *Nat Med* 2021;27:626-31

March-June 2020 *MMWR Morb Mortal Wkly Rep* 2020;69:993-8. doi:10.15585

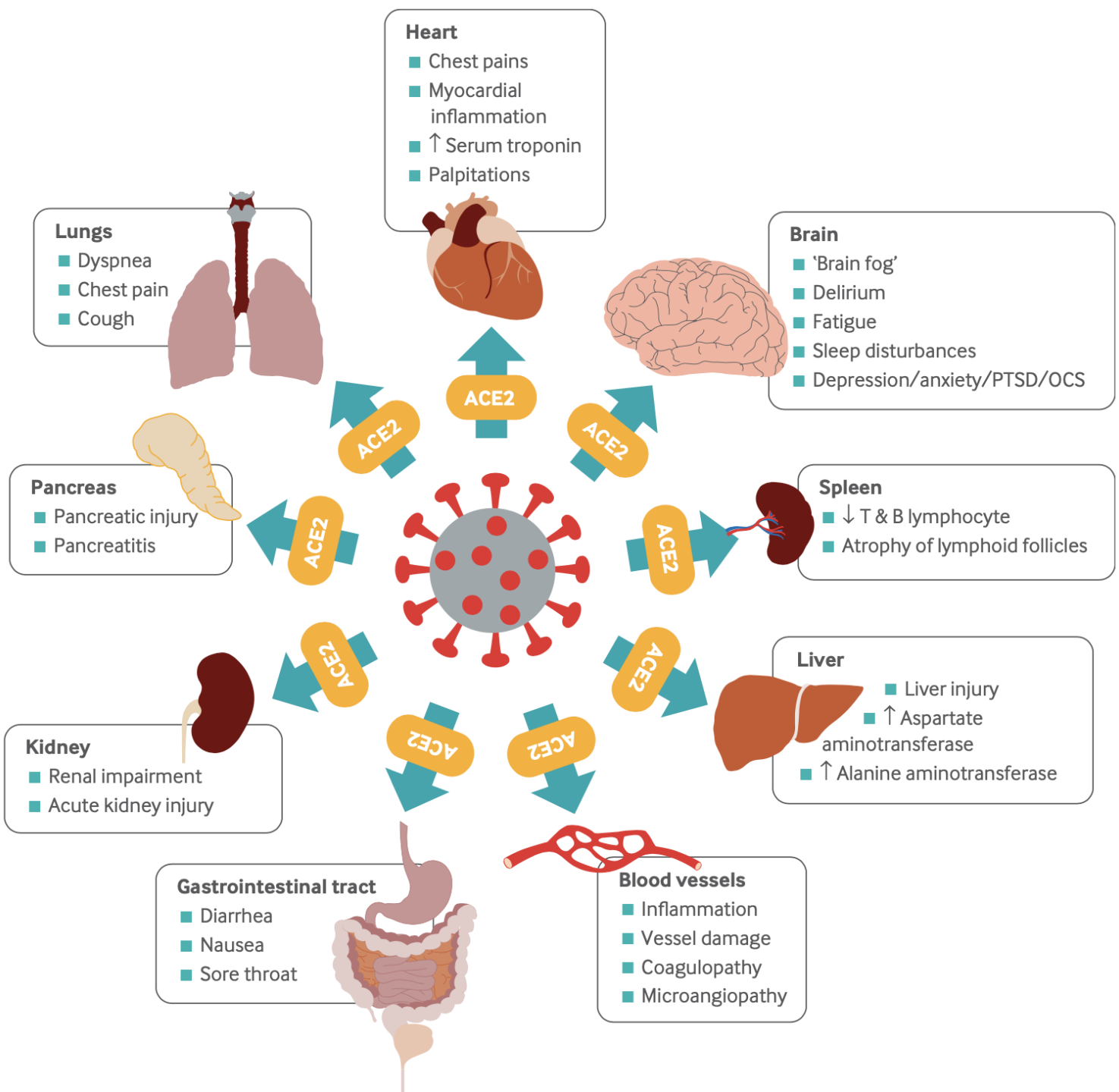
No. of medical conditions (7 missing)					0.003
0	**123**	87 (71)	36 (29)		
1	**57**	41 (72)	16 (28)		
2	**39**	21 (54)	18 (46)		
≥3	**44**	19 (43)	25 (57)		
Individual medical conditions (7 missing all)¶					
Hypertension	**64**	33 (52)	31 (48)	OR 1.3	0.018
Obesity (body mass index >30 kg/m^2)	**51**	23 (45)	28 (55)	OR 2.31	0.002
Psychiatric condition	**49**	23 (47)	26 (53)	OR 2.32	0.007
Asthma	**36**	23 (64)	13 (36)		0.99
Diabetes	**28**	16 (57)	12 (43)		0.43
Immunosuppressive condition	**15**	6 (40)	9 (60)	OR 2.33	0.047

Summary of selected studies on the prevalence of Long COVID in nonhospitalized patients

COUNTRY	STUDY	SAMPLE	NUMBER OF CASES INCLUDED	RESULTS
United Kingdom	Office for National Statistics (2020)	Population representative	8 193	• **21%** had symptoms **5 weeks** after infection • **10%** had symptoms **12 weeks** after infection
	Sudre et al. (2020)	COVID Symptom App users (out of which 14% were hospitalized)	4 182	• **13%** of cases had symptoms lasting **28 days** after symptom onset • **5%** of cases had symptoms for over **8 weeks** and **2%** for over **12 weeks** after symptom onset
	Townsend et al. (2020)	Hospital outpatients (out of which 56% were hospitalized)	127	• **52%** reported persistent fatigue at **10 weeks** after symptom onset
USA	Tenforde et al. (2020)	Hospital outpatients (out of which 7% were hospitalized)	292	• **35%** had symptoms after a median of **16 days** after testing positively for SARS-CoV-2 infection
Switzerland	Nehme et al. (2020)	Hospital outpatients	669	• About **33%** of cases had symptoms **30–45 days** after diagnosis
The Netherlands and Belgium	Goërtz et al. (2020)[b]	Facebook group for coronavirus patients with persistent complaints (out of which 5% were hospitalized)	2 113	• Over **99%** infected individuals did not fully recover within **12 weeks** after symptom onset

Summary of selected studies on the prevalence of Long COVID in hospitalized patients postdischarge

COUNTRY	STUDY	NUMBER OF CASES INCLUDED	RESULTS
Canada	Wong et al. (2020)	78	• **51%** had persistently reduced quality of life and **50%** had shortness of breath at **12 weeks** after symptom onset
France	Carvalho-Schneider et al. (2020)	130	• **40%** reported persistent fatigue and **30%** breathlessness at **60 days** after symptom onset
Italy	Carfì, Bernabei & Landi (2020)	143	• **87%** had symptoms, **55%** had three or more symptoms at **60 days** after discharge
United Kingdom	Cruz et al. (2020)	119	• **68%** reported persistent fatigue, **57%** sleep disturbance and **32%** breathlessness at **60 days** after discharge
	Arnold et al. (2020)	110	• **74%** had persistent symptoms, typically breathlessness and fatigue and **10%** had persistent anomalies on chest X-ray or respiratory function testing at **12 weeks** after discharge
USA	Donnelly et al. (2020)	2 179	• **19.9%** were readmitted, **9.1%** died and **27%** were readmitted or died within **60 days** after discharge
China	Huang et al. (2021)	1 733	• **76%** reported persistent symptoms, and **50%** had residual anomalies on chest imaging **6 months** after discharge



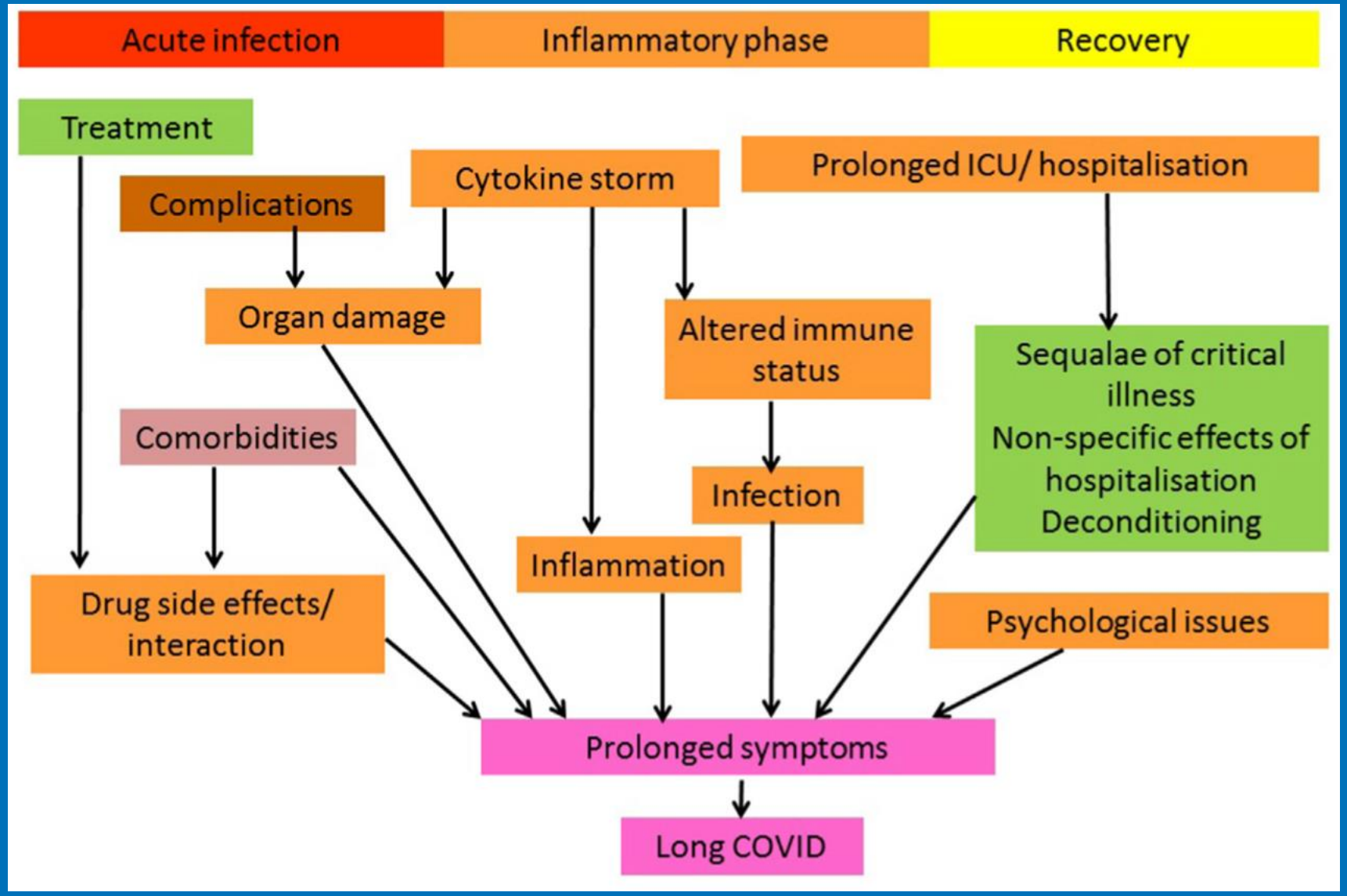
Fisiopatologia

The SARS-CoV-2 virus gains entry into the cells of multiple organs via the ACE2 receptor.

Once these cells have been invaded, the virus can cause a multitude of damage ultimately leading to numerous persistent symptoms.

BMJ 2021;374:n1648 | doi: 10.1136/bmj.n1648

The exact mechanism behind the persistence of symptoms has to be identified.



Manifestazioni generali

Manifestazioni	Caratteristiche
Generali	
	▪ Fatica persistente/Astenia ▪ Stanchezza eccessiva ▪ Febbre ▪ Debolezza muscolare ▪ Dolori diffusi ▪ Mialgie ▪ Artralgie ▪ Peggioramento dello stato di salute percepito ▪ Anoressia, riduzione dell'appetito ▪ Sarcopenia

	Total (n=1733)	OR or β (95% CI)	
		Scale 4 *vs* 3	Scale 5–6 *vs* 3
Symptoms			
Any one of the following symptoms	1265/1655 (76%)	OR 0·70 (0·52 to 0·96)*	OR 2·42 (1·15 to 5·08)*
Fatigue or muscle weakness	1038/1655 (63%)	OR 0·74 (0·58 to 0·96)*	OR 2·69 (1·46 to 4·96)*
Sleep difficulties	437/1655 (26%)	OR 0·92 (0·71 to 1·21)	OR 1·15 (0·68 to 1·94)
Hair loss	359/1655 (22%)	OR 0·99 (0·74 to 1·31)	OR 1·17 (0·67 to 2·04)
Smell disorder	176/1655 (11%)	OR 0·69 (0·48 to 1·00)	OR 0·90 (0·43 to 1·87)
Palpitations	154/1655 (9%)	OR 0·86 (0·58 to 1·28)	OR 1·31 (0·61 to 2·80)
Joint pain	154/1655 (9%)	OR 0·56 (0·38 to 0·83)*	OR 0·74 (0·36 to 1·50)
Decreased appetite	138/1655 (8%)	OR 0·84 (0·56 to 1·27)	OR 1·56 (0·71 to 3·43)
Taste disorder	120/1655 (7%)	OR 0·84 (0·54 to 1·30)	OR 0·80 (0·32 to 2·02)
Dizziness	101/1655 (6%)	OR 0·77 (0·48 to 1·22)	OR 0·95 (0·39 to 2·31)
Diarrhoea or vomiting	80/1655 (5%)	OR 0·71 (0·42 to 1·22)	OR 0·39 (0·11 to 1·42)
Chest pain	75/1655 (5%)	OR 0·94 (0·52 to 1·67)	OR 2·55 (0·99 to 6·62)
Sore throat or difficult to swallow	69/1655 (4%)	OR 0·91 (0·50 to 1·65)	OR 1·21 (0·40 to 3·73)
Skin rash	47/1655 (3%)	OR 0·64 (0·32 to 1·26)	OR 0·71 (0·18 to 2·87)
Myalgia	39/1655 (2%)	OR 0·80 (0·38 to 1·69)	OR 1·72 (0·47 to 6·27)
Headache	33/1655 (2%)	OR 0·76 (0·35 to 1·69)	OR 1·53 (0·36 to 6·52)
Low grade fever	2/1655 (<1%)	NA	NA

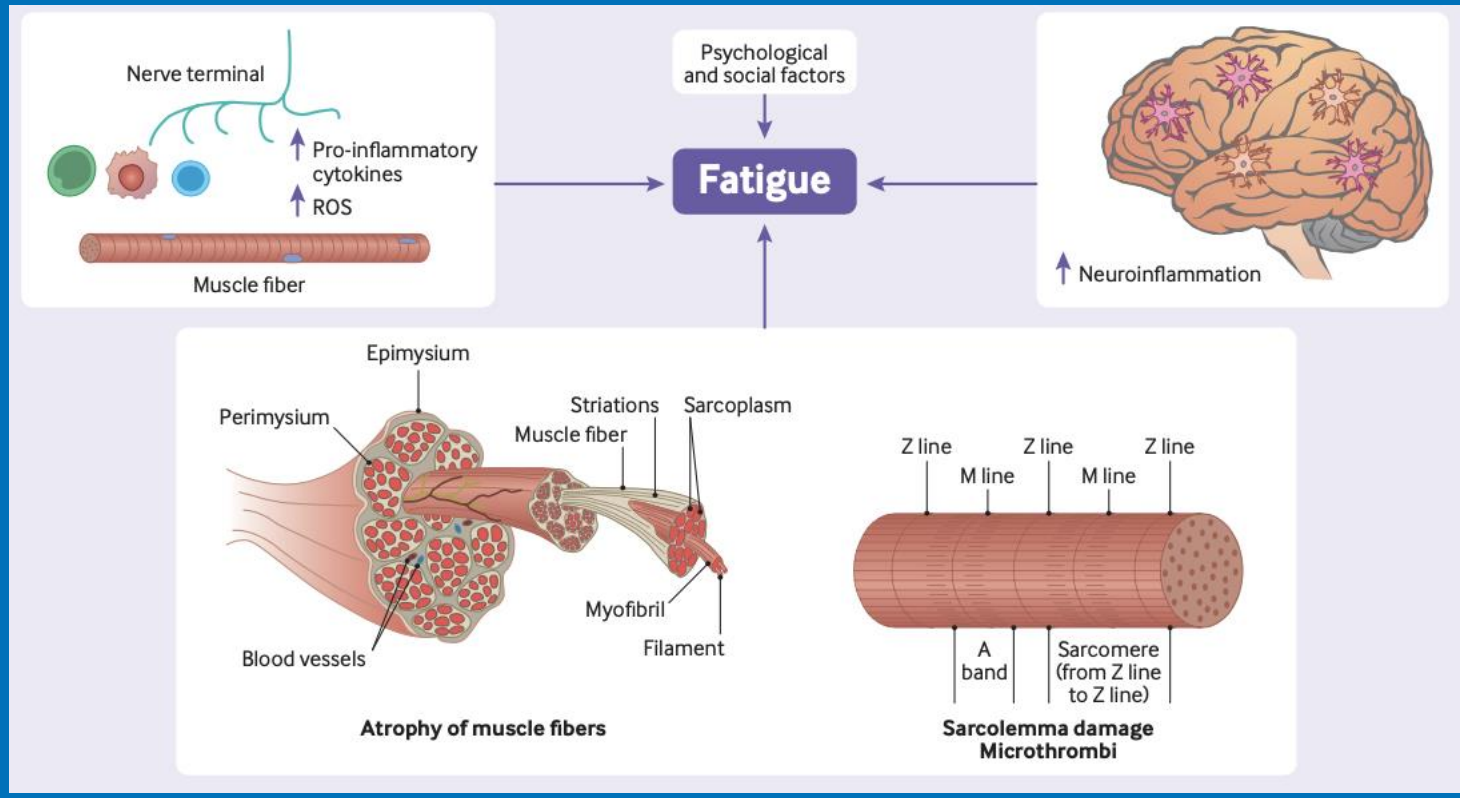
6-month consequences of COVID-19 in patients discharged from hospital: a cohort study Lancet. 2021 Jan 16;397(10270):220-232

FATIGUE

- Fatigue is more profound than being overtired; it is unrelenting exhaustion and a constant state of weariness that reduces a person's energy, motivation, and concentration.

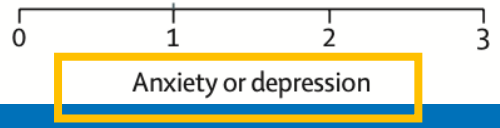
- may be the result of miscommunication in the inflammatory response pathways
- range of central, peripheral, and psychological factors

- ONS- five week prevalence of fatigue 11.9%
- regardless of severity of the acute stage
- Huang et al. (2021)
  1038/1655 (63%)
  OR 2.69 (1.96 to 4.96)

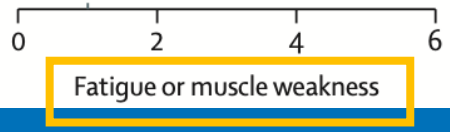


B

	OR (95% CI)	p value	OR (95% CI)	p value
Age	0·96 (0·87 to 1·06)	0·44	1·17 (1·07 to 1·27)	0·0008
Sex				
Men	1 (ref)		1 (ref)	
Women	1·80 (1·39 to 2·34)	<0·0001	1·33 (1·05 to 1·67)	0·016
Cigarette smoking				
Never–smoker	1 (ref)		1 (ref)	
Current smoker	1·16 (0·67 to 2·00)	0·59	1·24 (0·78 to 1·98)	0·36
Former smoker	0·89 (0·36 to 2·19)	0·80	0·76 (0·38 to 1·52)	0·44
Education				
Middle school or lower	1 (ref)		1 (ref)	
College or higher	0·89 (0·67 to 1·19)	0·44	0·85 (0·66 to 1·09)	0·19
Comorbidity				
No	1 (ref)		1 (ref)	
Yes	0·97 (0·74 to 1·27)	0·84	1·08 (0·85 to 1·37)	0·52
Disease severity				
Scale 3	1 (ref)		1 (ref)	
Scale 4	0·88 (0·66 to 1·17)	0·37	0·74 (0·58 to 0·96)	0·024
Scale 5–6	1·77 (1·05 to 2·97)	0·031	2·69 (1·46 to 4·96)	0·0015
Corticosteroids				
No	1 (ref)		1 (ref)	
Yes	1·23 (0·88 to 1·72)	0·22	1·04 (0·77 to 1·42)	0·78
Antiviral				
No	1 (ref)		1 (ref)	
Yes	0·97 (0·76 to 1·24)	0·81	1·01 (0·81 to 1·26)	0·93
Intravenous immuoglobulins				
No	1 (ref)		1 (ref)	
Yes	0·77 (0·54 to 1·10)	0·15	0·96 (0·70 to 1·31)	0·78

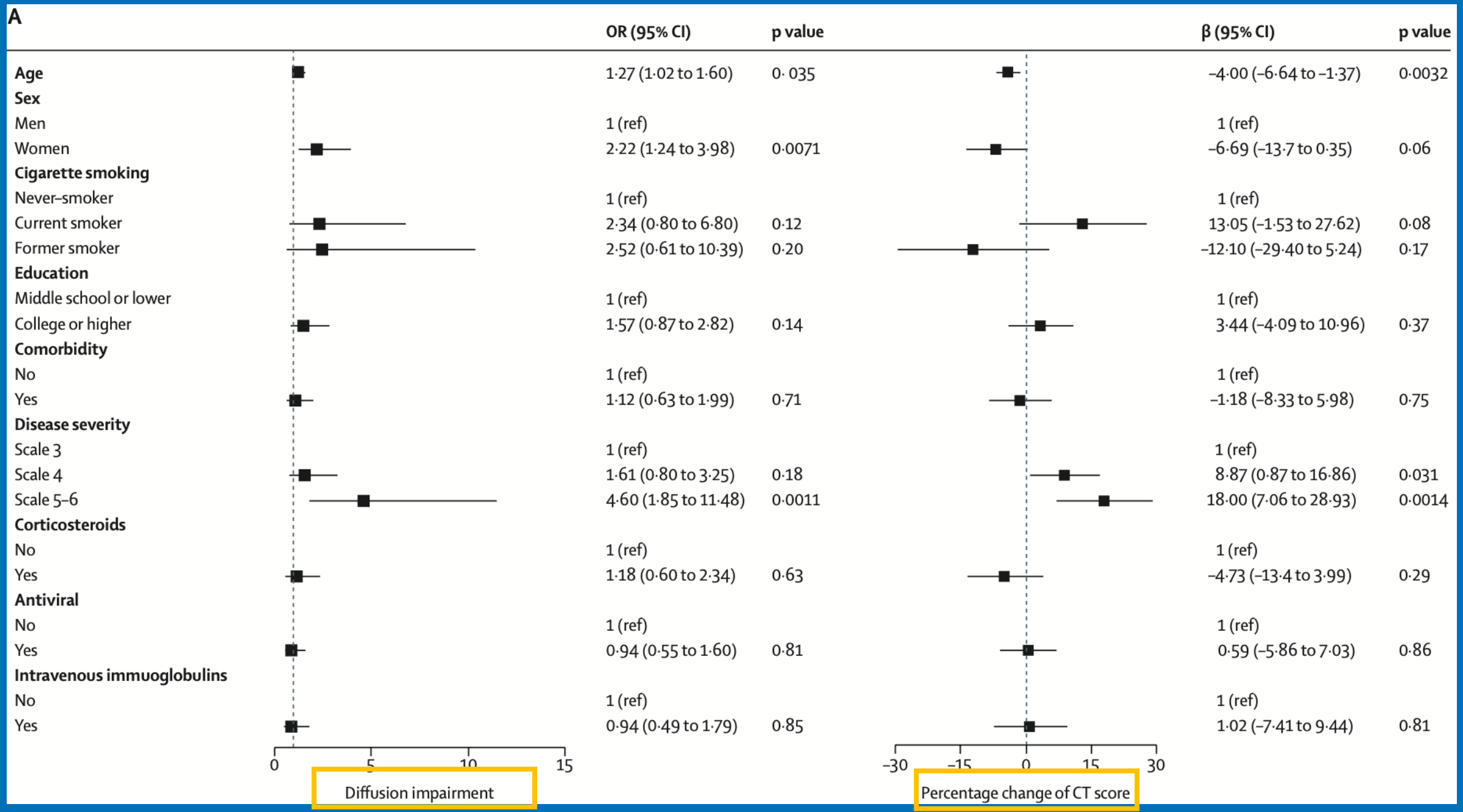


Anxiety or depression



Fatigue or muscle weakness

6-month consequences of COVID-19 in patients discharged from hospital: a cohort study Lancet. 2021 Jan 16;397(10270):220-232



6-month consequences of COVID-19 in patients discharged from hospital: a cohort study Lancet. 2021 Jan 16;397(10270):220-232

Manifestazioni organo-specifiche

Rapporto ISS COVID-19 n. 15/2021

- POLMONARI Dispnea/Affanno, Tosse persistente

- CARDIOVASCOLARI Senso di oppressione toracica, Dolore toracico, Palpitazioni, Tachicardia, Aritmie, Variazione della pressione arteriosa

- NEUROLOGICHE

Manifestazioni del sistema nervoso centrale: Cefalea (spesso refrattaria agli antidolorifici), Deterioramento cognitivo (annebbiamento cerebrale o *brain fog*), Difficoltà di concentrazione e attenzione, Problemi di memoria, Difficoltà nelle funzioni esecutive, Vertigini, Disturbi del sonno, Disautonomia (ipotensione ortostatica)

*Manifestazioni del sistema nervoso periferico: F*ormicolio e intorpidimento (neuropatie periferiche), Perdita di gusto e olfatto

Manifestazioni neurologiche rare (complicanze della fase acuta dell'infezione COVID-19 che potrebbero comportare un danno neurologico permanente): Eventi cerebrovascolari acuti (ictus ischemico/ emorragico), Crisi epilettiche, Meningite/encefalite, Mielopatia/mielite, Sindrome di Guillain-Barré, di Miller Fisher, polinevriti craniche, malattia demielinizzante del sistema nervoso centrale

- PSICHIATRICHE/PSICOLOGICHE Depressione, Ansia, Sindrome da stress post-traumatico (PTSD), Sintomi ossessivo-compulsivi, Delirium (negli anziani), Psicosi

Manifestazioni organo-specifiche

- **GASTROINTESTINALI** Dolori addominali, Nausea, Vomito, Diarrea, Dispepsia, Eruttazione, Reflusso gastroesofageo, Distensione addominale

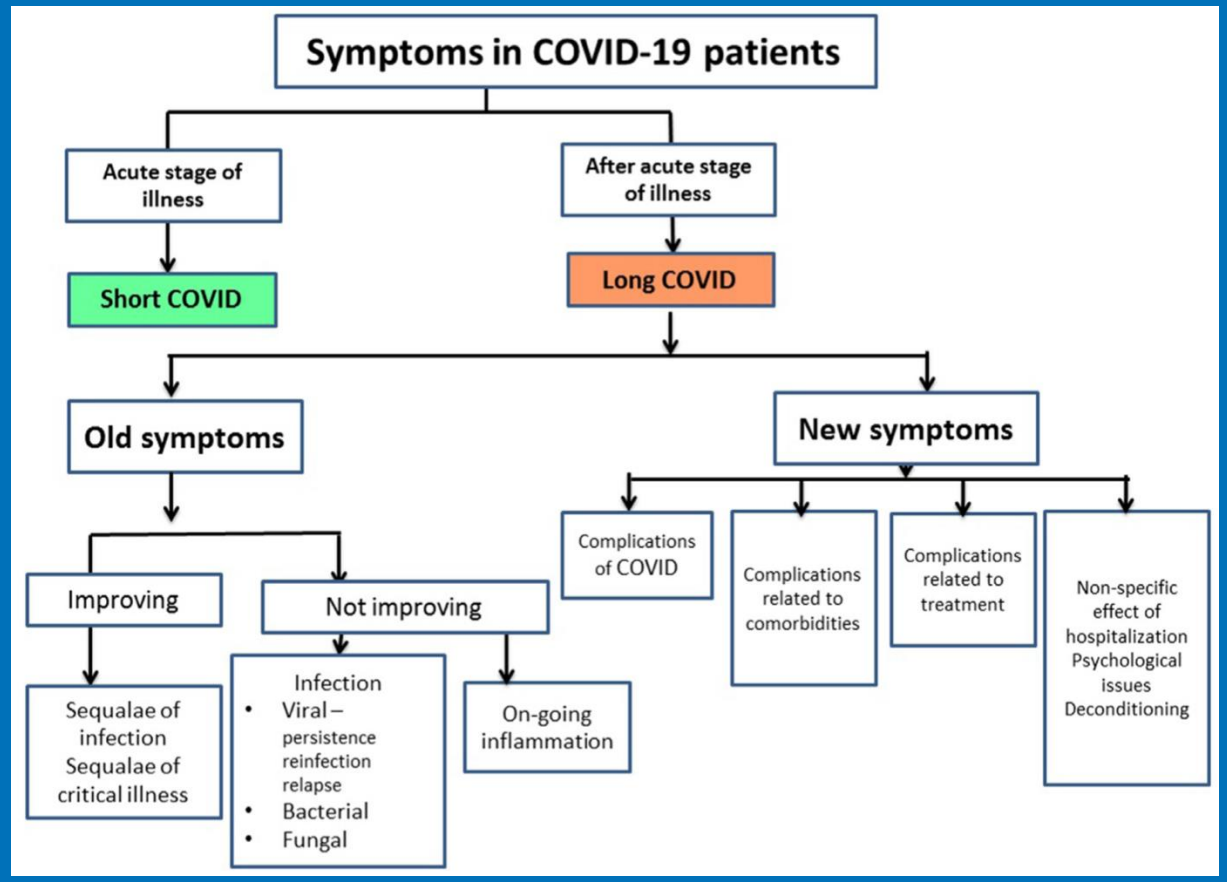
- **OTORINOLARINGOIATRICHE** Acufeni, Otalgia, Mal di gola (faringodinia), Difficoltà a deglutire (disfagia), Disfonia

- **DERMATOLOGICHE** Eritema pernio, Eruzioni papulo-squamose, Rash morbilliformi, Eruzioni orticaroidi, Alopecia

- **EMATOLOGICHE** Tromboembolismo
- RENALI Ematuria e proteinuria (nefropatia)
- ENDOCRINE Diabete mellito di nuova insorgenza e tiroidite subacuta

La diagnosi di Long-COVID è prettamente clinica

- storia di COVID-19 + mancato recupero completo con lo sviluppo di alcuni dei sintomi
- distinto dalla sindrome post-terapia intensiva (Post-Intensive Care Syndrome, PICS)
- e dalla sindrome da fatica cronica
- incertezza nella diagnosi e una ampia variabilità nell'identificazione



Diabetes & Metabolic Syndrome: Clinical Research & Reviews 15 (2021) 869e875

Gestione

- **Identificazione del paziente con Long-COVID**
- **Valutazione multidimensionale**
- **Approccio multidisciplinare**
- **Assistenza nelle cure primarie**
  Stratificazione per classi di rischio di sviluppare Long-COVID
  Valutazione dei pazienti con sintomi sospetti di Long-COVID
  Pianificazione del percorso assistenziale
- **Coinvolgimento del paziente e autogestione (*self-management*)**

Riferimenti

- **Indicazioni *ad interim* sui principi di gestione del Long-COVID -** Rapporto ISS COVID-19 n. 15/2021
- **WHO -**https://apps.who.int/iris/bitstream/handle/10665/339629/Policy-brief-39-1997-8073-eng.pdf
- CDC- Evaluating and Caring for Patients with Post-COVID Conditions: Interim Guidance, Updated June 14, 2021
- NICE - COVID-19 rapid guideline: managing the long-term effects of COVID-19 NICE guideline [NG188] Published: 18 December 2020
- NIH RECOVER initiative

Post-acute effects of SARS-CoV-2 infection in individuals not requiring hospital admission: a Danish population-based cohort study

Lars Christian Lund, Jesper Hallas, Henrik Nielsen, Anders Koch, Stine Hasling Mogensen, Nikolai Constantin Brun, Christian Fynbo Christiansen, Reimar Wernich Thomsen, Anton Pottegård

Background **Individuals admitted to hospital for COVID-19 might have persisting symptoms (so-called long COVID) and delayed complications after discharge. However, little is known regarding the risk for those not admitted to hospital. We therefore examined prescription drug and health-care use after SARS-CoV-2 infection not requiring hospital admission.**

- Symptom persistence vary widely—eg, dyspnoea has been reported in 10–20% and up to 75% of patients
- Based on selected patient samples
- Did not have a control group

AIM

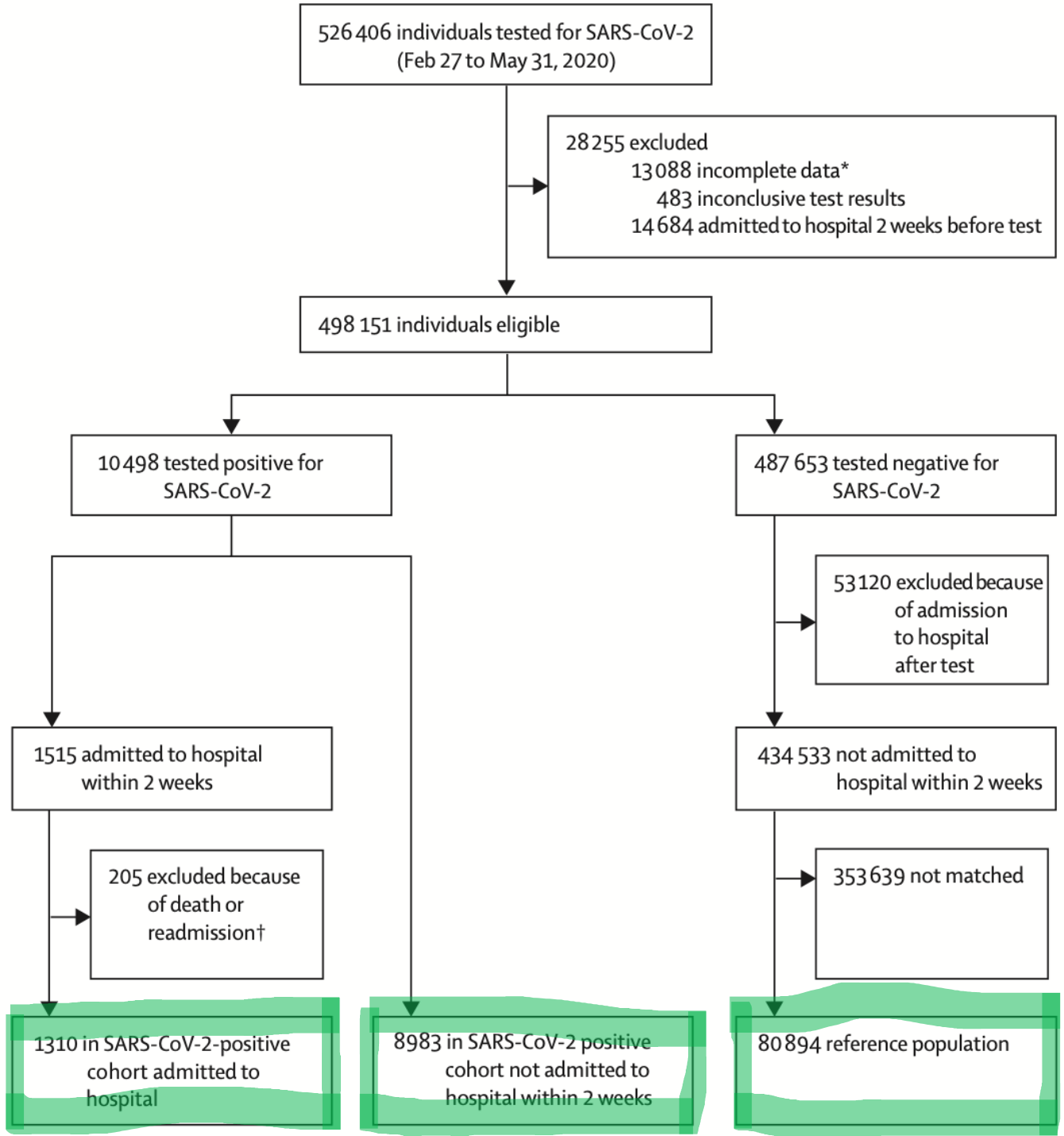
- occurrence of post-acute effects 2 weeks to 6 months after SARS-CoV-2 infection not requiring hospital admission
- initiation of specific drugs, hospital diagnoses, and overall frequency of health-care encounters

Methods

- Danish population-based cohort study used the Danish national health registries and the Danish COVID-19 cohort.
- positive or negative RT-PCR test for SARS-CoV-2 in Denmark between Feb 27 and May 31, 2020
- NB. Danish testing strategy due to global shortage of reagents

Outcomes

- delayed acute complications, chronic disease, persisting symptoms, and prescription drug use
- overall event rates of general practitioner visits, hospital outpatient visits, emergency department visits, and hospital admissions per 1000 individuals between 6 months and 2 weeks before a SARS-CoV-2 test and 2 weeks to 6 months after the test

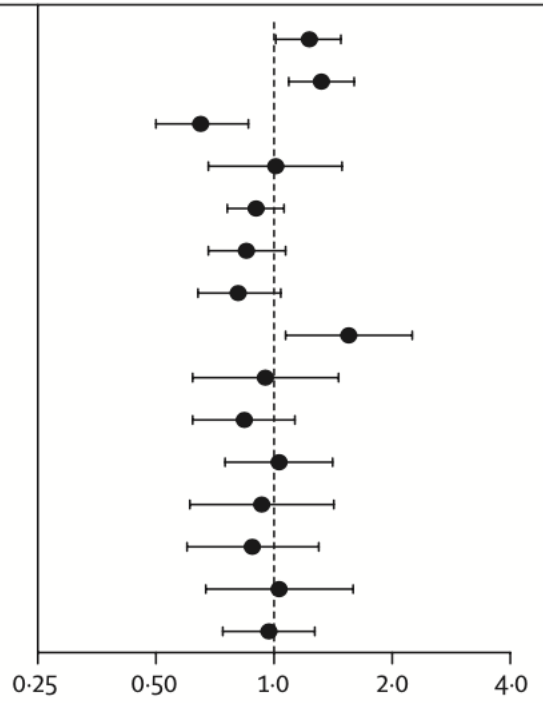


BASELINE CHARACTERISTICS

	SARS-CoV-2 positive (n=8983)	SARS-CoV-2 negative (n=80 894)	Standardised mean difference	SARS-CoV 2-negative, weighted (n=8977)*	Standardised mean difference, weighted
Demographics					
Age, median (IQR)	43 (30–56)	43 (29–56)	0·02	44 (30–56)	0·00
Age <18 years	584 (6·5%)	5662 (7·0%)	0·02	567 (6·3%)	0·01
Sex					
Female	5471 (60·9%)	51 631 (63·8%)	0·06	5479 (61·0%)	0·00
Male	3512 (39·1%)	29 263 (36·2%)	0·06	3498 (39·0%)	0·00
Tested before April 11, 2020	4342 (48·3%)	34 946 (43·2%)	0·10	4440 (49·5%)	0·02
Prescription drug use†					
Bronchodilating agents	757 (8·4%)	10 984 (13·6%)	0·17	1039 (11·6%)	0·10
Inhaled corticosteroids	531 (5·9%)	7160 (8·9%)	0·11	667 (7·4%)	0·06
Paracetamol	2257 (25·1%)	22 769 (28·1%)	0·07	2279 (25·4%)	0·01
NSAIDs	1485 (16·5%)	15 532 (19·2%)	0·07	1598 (17·8%)	0·03
Opioids and opioid-like drugs	591 (6·6%)	7340 (9·1%)	0·09	612 (6·8%)	0·01
Antidepressants	634 (7·1%)	8896 (11·0%)	0·14	798 (8·9%)	0·07
Benzodiazapines and Z-drugs	362 (4·0%)	4738 (5·9%)	0·08	419 (4·7%)	0·03
Antipsychotics	168 (1·9%)	2453 (3·0%)	0·08	163 (1·8%)	0·00
Platelet inhibitors	396 (4·4%)	4592 (5·7%)	0·06	425 (4·7%)	0·02
Anticoagulants	214 (2·4%)	2245 (2·8%)	0·02	209 (2·3%)	0·00
Loop diuretics	171 (1·9%)	2386 (2·9%)	0·07	180 (2·0%)	0·01
Lipid-lowering drugs	794 (8·8%)	7846 (9·7%)	0·03	790 (8·8%)	0·00
Lifestyle-related diagnoses					
Hospital diagnosis of obesity	682 (7·6%)	7745 (9·6%)	0·07	682 (7·6%)	0·00
Markers of smoking	246 (2·7%)	4548 (5·6%)	0·14	246 (2·7%)	0·00
Alcohol-related disorders	184 (2·0%)	3151 (3·9%)	0·11	184 (2·1%)	0·00
Mental health					
Depression	99 (1·1%)	1278 (1·6%)	0·04	78 (0·9%)	0·02
Anxiety disorders	197 (2·2%)	3240 (4·0%)	0·10	211 (2·3%)	0·01
Psychosis	39 (0·4%)	650 (0·8%)	0·05	35 (0·4%)	0·01
Frailty-related diagnoses					
Cancer	398 (4·4%)	4139 (5·1%)	0·03	399 (4·4%)	0·00
Dementia	69 (0·8%)	426 (0·5%)	0·03	71 (0·8%)	0·00
Chronic conditions					
Diabetes (type 1 or 2)‡	526 (5·9%)	4910 (6·1%)	0·01	529 (5·9%)	0·00
Hypertension†	2127 (23·7%)	21 808 (27·0%)	0·08	2132 (23·7%)	0·00
Cardiovascular disease	837 (9·3%)	9120 (11·3%)	0·06	839 (9·3%)	0·00
Peripheral vascular disease	44 (0·5%)	662 (0·8%)	0·04	56 (0·6%)	0·02
Pulmonary disease	788 (8·8%)	10 173 (12·6%)	0·12	788 (8·8%)	0·00
Kidney disease§	49 (0·5%)	555 (0·7%)	0·02	49 (0·5%)	0·00

Results

	SARS-CoV-2-positive cohort (n/N)	SARS-CoV-2-negative cohort (n/N)	Propensity score-weighted risk ratio (95% CI)
Bronchodilating agents	121/6782 (1·78)	814/55 482 (1·47)	1·23 (1·01 to 1·48)
Short-acting β2-agonists	117/6935 (1·69)	743/57 206 (1·30)	1·32 (1·09 to 1·60)
Inhaled corticosteroids	57/7696 (0·74)	733/64 870 (1·13)	0·65 (0·50 to 0·86)
Cough preparations	28/7456 (0·38)	262/64 857 (0·40)	1·01 (0·68 to 1·49)
Paracetamol	153/4781 (3·20)	1422/39 052 (3·64)	0·90 (0·76 to 1·06)
NSAIDs	83/3234 (2·57)	745/24 688 (3·02)	0·85 (0·68 to 1·07)
Opioids and opioid-like drugs	72/6316 (1·14)	721/51 042 (1·41)	0·81 (0·64 to 1·04)
Triptans	33/8292 (0·40)	198/72 828 (0·27)	1·55 (1·07 to 2·25)
Glucose-lowering drugs	23/8457 (0·27)	254/75 984 (0·33)	0·95 (0·62 to 1·46)
Antidepressants	47/7324 (0·64)	478/58 620 (0·82)	0·84 (0·62 to 1·13)
Benzodiazapines and Z–drugs	42/7364 (0·57)	368/61 354 (0·60)	1·03 (0·75 to 1·41)
Antipsychotics	24/8527 (0·28)	271/74 255 (0·36)	0·93 (0·61 to 1·42)
Platelet inhibitors	28/8229 (0·34)	284/72 700 (0·39)	0·88 (0·60 to 1·30)
Anticoagulants	23/8659 (0·27)	209/77 469 (0·27)	1·03 (0·67 to 1·59)
Antihypertensives	58/6856 (0·85)	525/59 086 (0·89)	0·97 (0·74 to 1·27)

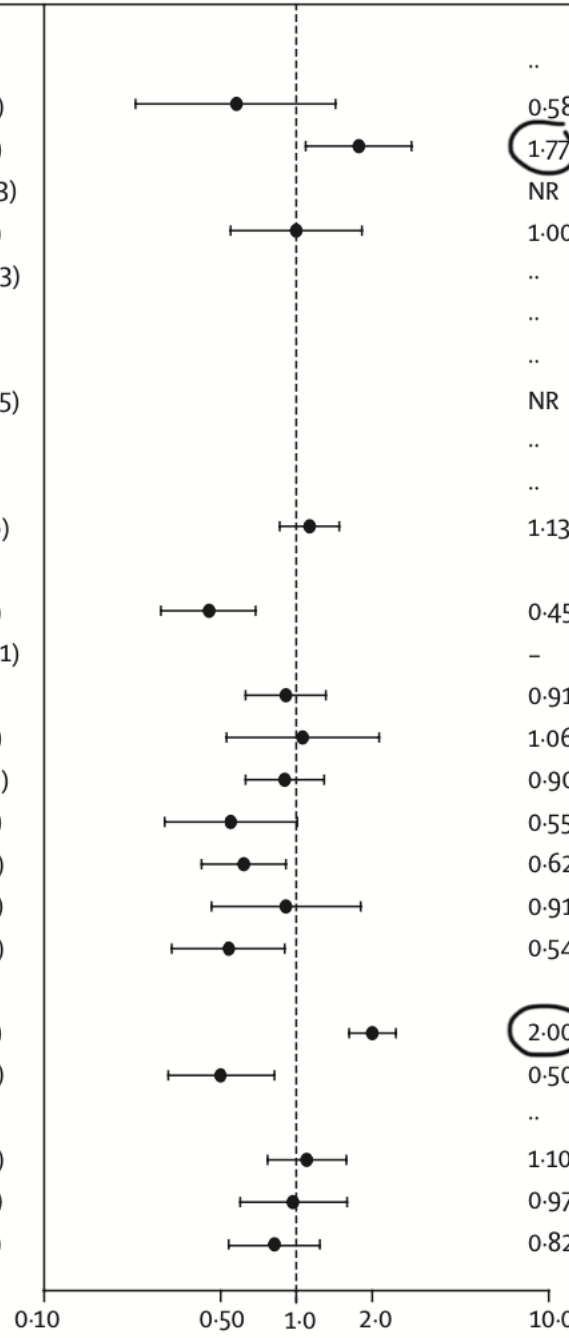


- 2757/8983 SARS-CoV-2-positive (30·7%) initiated new drug treatments during follow-up compared with 28 525/ 80 894 SARS-CoV-2-negative (35·3%)
- increased risk of initiating bronchodilating agents
- and triptans

risks of receiving any new hospital diagnosis during follow-up were 26·3% (2362 of 8983) among SARS-CoV-2- positive individuals and 28·8% (23 314 of 80 894) among SARS-CoV-2-negative

increased risk of receiving a first diagnosis of dyspnoea and venous thromboembolism

	SARS-CoV-2-positive cohort (n/N)	SARS-CoV-2-negative cohort (n/N)	Propensity score-weighted risk ratio (95% CI)
Delayed acute complications			
Myocarditis	0/NR (0)	n<5	..
Heart failure	5/8908 (0·06)	86/79893 (0·1)	0·58 (0·23 to 1·43)
Venous thromboembolism	20/8785 (0·2)	110/78872 (0·1)	1·77 (1·09 to 2·86)
Peripheral vascular disease	n<5	22/80232 (0·03)	NR
Ischaemic stroke or transient ischaemic attack	12/8748 (0·1)	117/78411 (0·2)	1·00 (0·55 to 1·82)
Cerebral haemorrhage	0/8947 (0)	22/80462 (0·03)	..
Guillian–Barré syndrome	0/8976 (0)	n<5	..
Encephalitis	0/8975 (0)	n<5	..
Psychosis	n<5	43/80244 (0·05)	NR
Kawasakis disease	0/NR (0)	0/80882 (0)	..
PIMS	0/8976 (0)	n<5	..
Acute kidney injury	58/8983 (0·7)	492/80894 (0·6)	1·13 (0·86 to 1·48)
Chronic disease			
Pulmonary disease	22/8195 (0·3)	441/70721 (0·6)	0·45 (0·29 to 0·69)
Interstitial pulmonary fibrosis	0/8977 (0)	11/80800 (0·01)	–
Cardiovascular disease	32/8146 (0·4)	328/71774 (0·5)	0·91 (0·63 to 1·31)
Diabetes mellitus	9/8691 (0·1)	81/77928 (0·1)	1·06 (0·53 to 2·13)
Neurological disease	33/8028 (0·4)	343/69664 (0·5)	0·90 (0·63 to 1·29)
Neuropathies	11/8537 (0·1)	188/75365 (0·3)	0·55 (0·30 to 1·01)
Psychiatric illness	27/8586 (0·3)	429/74641 (0·6)	0·62 (0·42 to 0·91)
Depression	9/8884 (0·1)	107/79616 (0·1)	0·91 (0·46 to 1·80)
Anxiety disorders	15/8786 (0·2)	293/77654 (0·4)	0·54 (0·32 to 0·90)
Persisting symptoms			
Dyspnoea	103/8676 (1·2)	499/76728 (0·7)	2·00 (1·62 to 2·48)
Cough	17/8677 (0·2)	300/77596 (0·4)	0·50 (0·31 to 0·82)
Anosmia	n<5	0/80865 (0)	..
Headache	33/8400 (0·4)	299/73799 (0·4)	1·10 (0·77 to 1·58)
Fatigue-related disorders	18/8809 (0·2)	175/78543 (0·2)	0·97 (0·60 to 1·59)
Non-specific pain	24/8438 (0·3)	301/74235 (0·4)	0·82 (0·54 to 1·24)



Results

By the end of follow-up, 6557 (73·0%) of 8983 non- hospitalised individuals with SARS-CoV-2 infection and 62 391 (77·1%) of 80 894 SARS-CoV-2-negative individuals had visited their general practitioner, were seen at a hospital outpatient clinic, or were admitted to hospital

Comparing overall health-care use between SARS- CoV-2-positive and SARS-CoV-2-negative individuals, we observed increased PERR-adjusted rate ratios for general practitioner visits (1·18 [95% CI 1·15–1·22]) and outpatient clinic visits (1·10 [1·05–1·16]) among SARS-CoV-2-positive individuals.

PERR prior event rate ratio

Grazie per l'attenzione