SARS-Cov-2: From Lung to Brain

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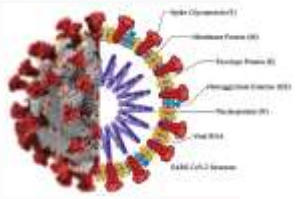
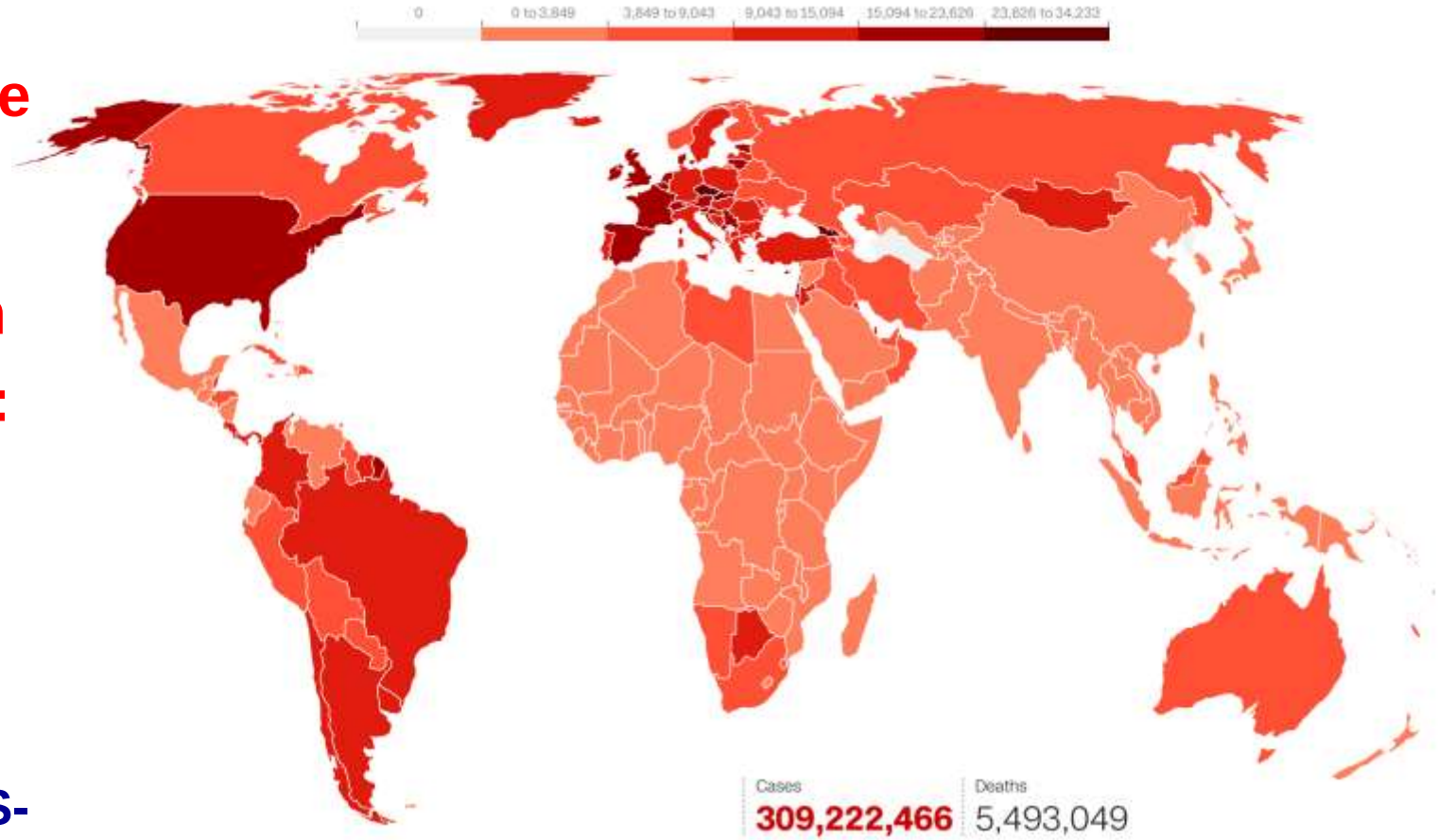


UCSD

Coronaviruses and the Brain

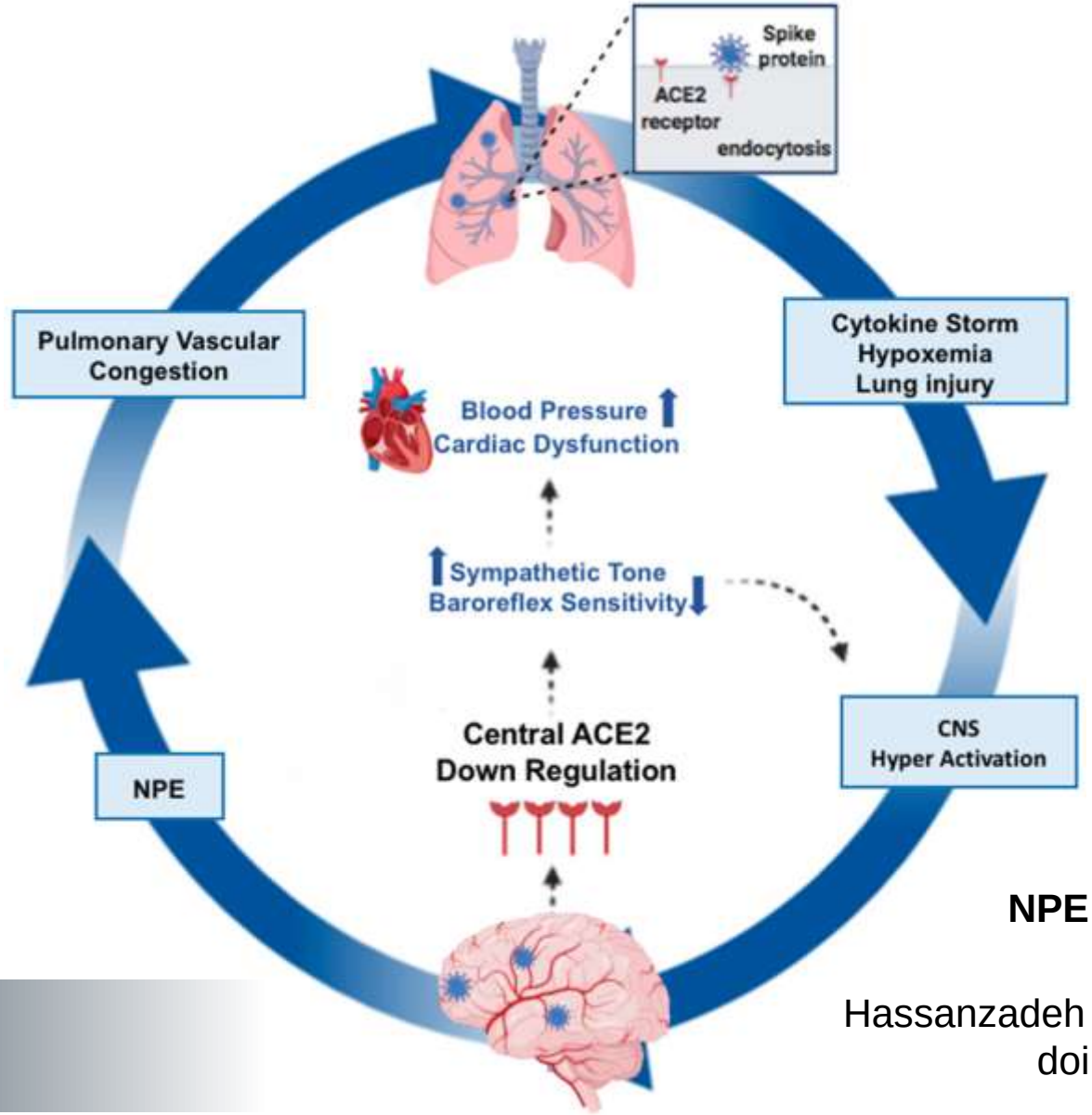
- **Coronaviruses typically cause disease of the respiratory tract, gastrointestinal tract, liver, and the nervous system**
- **<u>CoVs that can infect humans</u>: HCoV-OC43, HCoV–229E, HCoV-NL63, HCoV-HKU1, MERS-CoV, SARS-CoV-1, and SARS-CoV-2**
- **<u>Three HuCoVs before SARS-CoV-2 could infect neurons</u>: HCoV-OC43, HCoV-229E, and SARS-CoV-1**



As of 10 January 2022

Zubair et al, JAMA Neurol. doi:10.1001/jamaneurol.2020.2065
Glass et al, J Immunol. 2004. doi:10.4049/jimmunol.173.6.4030
Su et al, Trends Microbiol. 2016. doi:10.1016/j.tim.2016.03.003
Zhu et al, N Engl J Med. 2020. doi:10.1056/NEJMoa2001017
https://www.cnn.com/interactive/2020/health/coronavirus-maps-and-cases/

The Lungs and Brain Interact in Multiple Ways



NPE: Neurogenic Pulmonary Edema

Hassanzadeh et al, ACS Chem Neurosci 2020.
doi:20.1021/acschemneuro.0c00373

Neurologic Symptoms Are Common

Wuhan

Characteristic	No. (%)	COVID-19 Severity		
	Total (N = 214)	Severe (n = 88)	Nonsevere (n = 126)	*P* value[a]
Nervous system symptoms				
Any	78 (36.4)	40 (45.5)	38 (30.2)	.02
CNS	53 (24.8)	27 (30.7)	26 (20.6)	.09
Dizziness	36 (16.8)	17 (19.3)	19 (15.1)	.42
Headache	28 (13.1)	15 (17.0)	13 (10.3)	.15
Impaired consciousness	16 (7.5)	13 (14.8)	3 (2.4)	<.001
Acute cerebrovascular disease	6 (2.8)	5 (5.7)	1 (0.8)	.03
Ataxia	1 (0.5)	1 (1.1)	0	NA
Seizure	1 (0.5)	1 (1.1)	0	NA
PNS	19 (8.9)	7 (8.0)	12 (9.5)	.69
Impairment				
Taste	12 (5.6)	3 (3.4)	9 (7.1)	.24
Smell	11 (5.1)	3 (3.4)	8 (6.3)	.34
Vision	3 (1.4)	2 (2.3)	1 (0.8)	.37
Nerve pain	5 (2.3)	4 (4.5)	1 (0.8)	.07

- **Those with CNS symptoms had fewer platelets (p=0.005), lymphocytes (p=0.049), and higher blood urea nitrogen (p=0.04) and possibly creatinine (p=0.06)**

Mao et al, JAMA Neurol. doi:10.1001/jamaneurol.2020.1127

Bergamo

Neurological complications	*N* (%)			
	All patients (*N* = 137)	*N* of females (%)	Average age	Average *n* of comorbidities
Cerebrovascular diseases	53 (38.7%)	20 (37.7%)	68.6	3.1
Ischemic stroke	37 (27.0%)	15 (40.5%)	70.3	3
Haemorrhagic stroke	11 (8%)	4 (36.3%)	65.9	3.5
Transient ischemic attacks	4 (2.9%)	1 (25%)	63.5	3.4
Cerebral venous thrombosis	1 (0.7%)	0 (0%)	55	3
Peripheral neuropathies	31 (22.6%)	6 (19.3%)	56.3	2.1
Guillain–Barrè syndrome	17 (12.4%)	4 (23.5%)	55.6	2.2
Critical illness polyneuropathy	9 (6.6%)	1 (1.1%)	60.7	1.7
Others	5 (3.6%)	1 (20.0%)	54.2	3.6
Altered mental status	49 (35.8%)	17 (34.7%)	65.6	2.7
Encephalitis	5 (3.6%)	1 (40%)	66	2.4
Myelitis	2 (1.4%)	0 (0%)	64.5	3.5
Headache	3 (2.2%)	1 (33.3%)	61.5	0.7
Seizures	10 (7.3%)	3 (30.0%)	64.4	2.9
Syncope	3 (2.2%)	2 (66.7%)	72.6	3.7
Movement disorders	7 (5%)	3 (42.8%)	70.3	3.8
Other	5 (3.6%)	1 (20.0%)	61.2	4.6

- **137 of 1,760 (7.8%) COVID-19 patients had neurologic manifestations**
  - Presenting symptom in 39 (2.2%)
  - Presented after COVID-19 in 98 (5.6%)

Rifino et al, J Neurol. 2020 doi:10.1007/s00415-020-10251-5

Neurological Complications are Common

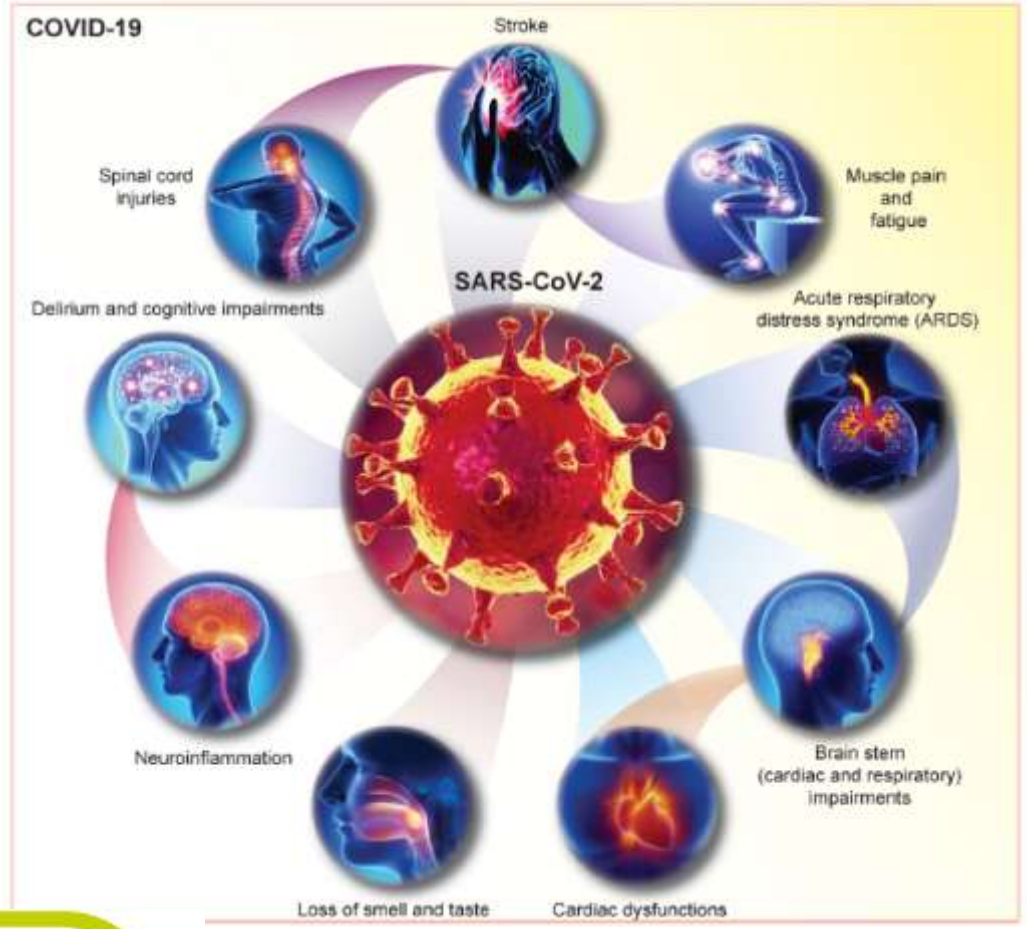
Clinical feature or diagnosis	Mao et al.[7]	Romero-Sánchez et al.[8]	Pinna et al.[9]	Karadaş et al.[10]	Xiong et al.[11]	Helms et al.[12]	Benussi et al.[13]	Paterson et al.[14]	Chen et al.[15]
COVID-19 (total number of patients)	214	841	650	239	917	58	56	43	274
COVID-19 with neurological manifestations (number (%) of patients)	78 (36.4)	483 (57.4)	50 (7.7)	83 (34.7)	39 (4.2)	49 (84.4)	56 (100)[b]	43 (100)[b]	78 (28.4)
CNS manifestations[a]									
Overall	53 (67.9)	NR	NR	NR	NR	NR	NR	35 (81.4)	NR
Dizziness	36 (46.1)	51 (10.5)	NR	16 (19.2)	NR	NR	NR	NR	21 (7.6)
Headache	28 (35.9)	119 (24.6)	12 (24)	64 (77.1)	2 (5.1)	NR	NR	NR	31 (11.3)
Impaired consciousness	16 (20.5)	165 (34.1)	30 (60)	23 (27.7)	25 (64.1)	NR	NR	7 (16.2)	26 (9.5)
Acute stroke	6 (7.7)	14 (2.9)	20 (40)	9 (10.8)	10 (25.6)	NR	43 (76.8)	8 (18.6)	NR
Ataxia	1 (1.3)	NR	1 (2)	NR	NR	NR	NR	NR	NR
Seizures	1 (1.3)	6 (1.2)	13 (26)	NR	0 (0.0)	NR	4 (7.1)	NR	NR
Agitation	NR	NR	NR	NR	NR	40 (6.9)	NR	NR	NR
Confusion	NR	69 (14.2)	NR	NR	NR	26 (65.0)	NR	10 (23.2)	NR
Corticospinal tract signs	NR	NR	NR	NR	NR	39 (67.2)	NR	5 (11.6)	NR
Dysexecutive syndrome	NR	NR	NR	NR	NR	14 (35.8)	NR	NR	NR
Other	NR	NR	NR	NR	NR	NR	9 (16.1)	3 (6.9)	NR
Neuropsychiatric symptoms	NR	167 (34.5)	NR	NR	NR	NR	NR	NR	NR
Movement disorders	NR	6 (1.2)	NR	NR	2 (5.1)	NR	NR	NR	NR
Encephalitis	NR	1 (0.2)	NR	NR	0 (0.0)	NR	NR	12 (27.9)	NR
PNS manifestations[a]									
Overall	19 (24.3)	NR	NR	53 (22.1)	NR	NR	NR	8 (18.6)	NR
Anosmia	11 (14.1)	41 (8.5)	3 (6)	18 (21.7)	NR	NR	NR	NR	NR
Dysgeusia	12 (15.4)	52 (10.7)	5 (10)	16 (19.2)	NR	NR	NR	NR	NR
Dysautonomia	NR	21 (4.3)	6 (12)	NR	NR	NR	NR	NR	NR
AIDP	NR	1 (0.2)	0 (0)	1 (1.2)	NR	NR	NR	7 (16.2)	NR

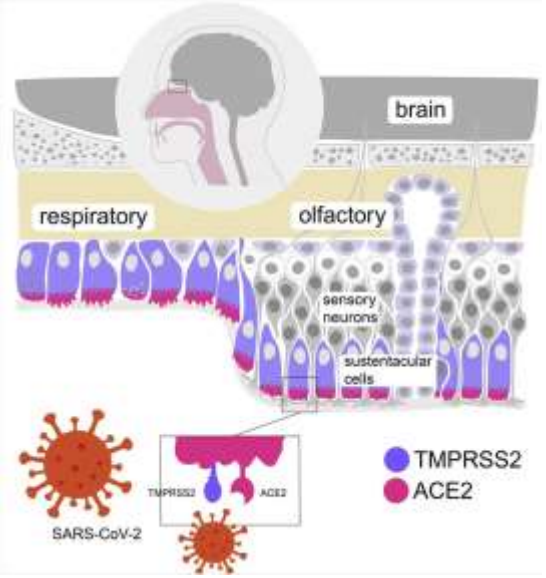
Overall:
959 of 3,292
29.1%

NR = Not reported

Pezzini & Padovani, Nat Rev Neurol. 2020, doi: 10.1038/s41582-020-0398-3

Neurological Complications of SARS-CoV-2 Infection

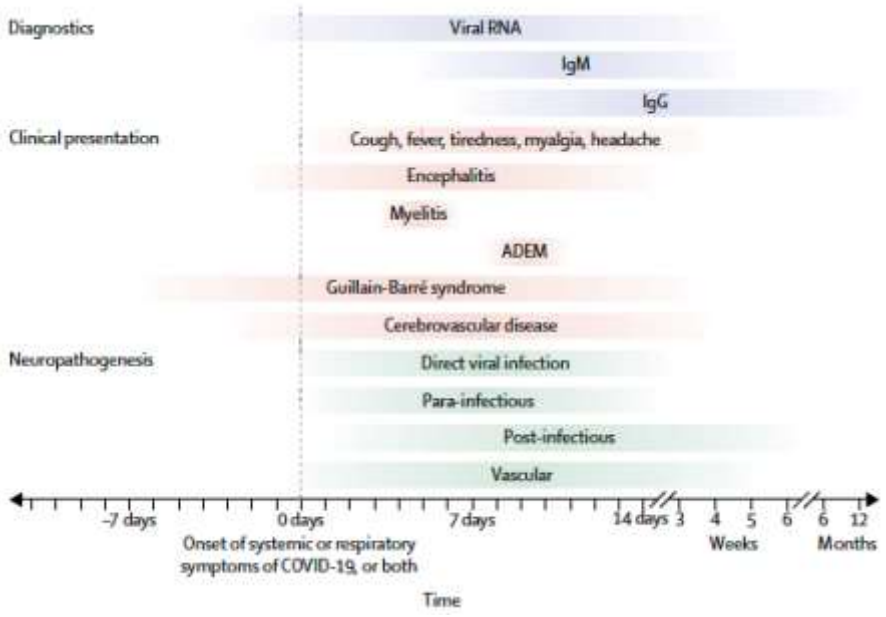


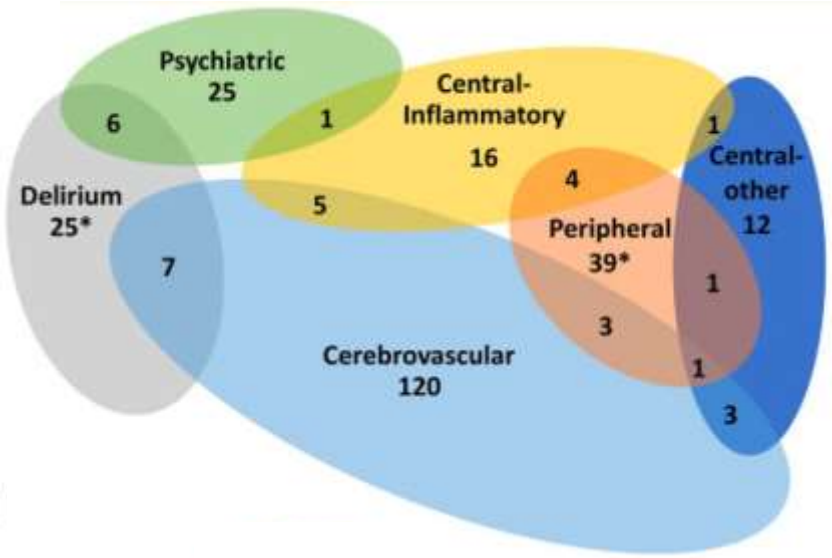


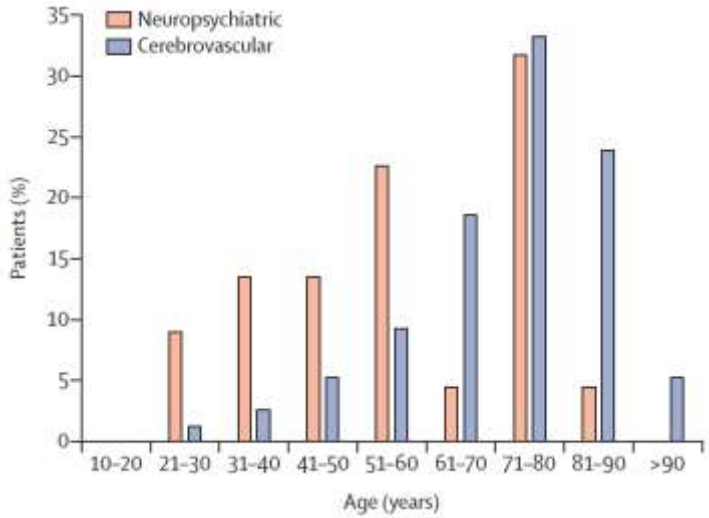
- **More common**
  - Anosmia/Hyposmia
  - Ageusia/Hypogeusia
  - Headache
- **Less common**
  - Delirium/impaired consciousness
  - Stroke (ischemic, hemorrhagic)
  - Seizure
  - Encephalomyelitis
  - Demyelinating polyneuropathy
  - Cranial neuropathy
  - Movement disorders
  - Vision and Hearing Decline

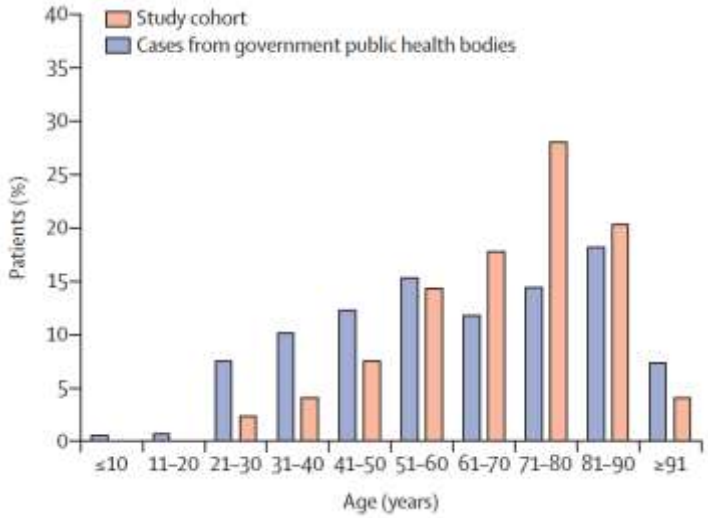
Zubair et al, JAMA Neurol. doi:10.1001/jamaneurol.2020.2065
Costello & Dalakas, Neurology 2020, doi: 10.1212/WNL.0000000000009921
Acharya et al, J Neuroimm Pharmacol 2020. doi: 10.1007/s11481-020-09924-9

Neurologic Complications of COVID-19 Overlap and Vary by Age





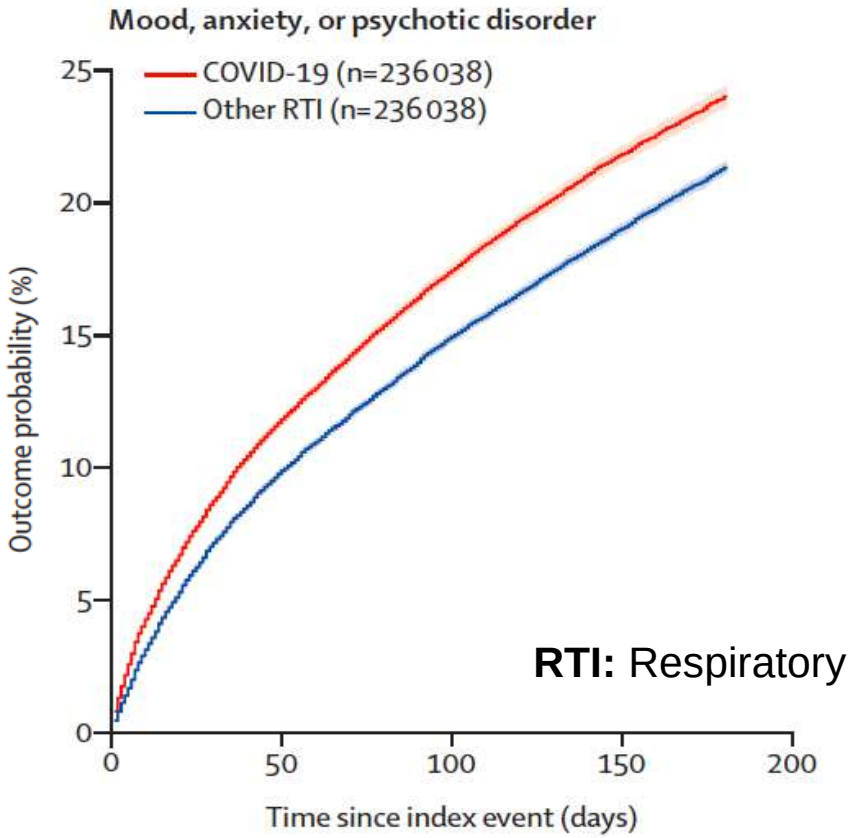




Ross Russell et al, Brain Communic. 2021. doi:10.1093/braincomms/fcab168
Ellul et al, Lancet Neurology. 2020. doi: 10.1016/S1474-4422(20)30221-0
Varatharaj et al, Lancet Psychiatry 2020. doi: 10.1016/S2215-0366(20)30287-X

Greater Incidence and Prevalence of Psychiatric Conditions with COVID-19

	COVID-19 vs other RTI (N=236 038)*	
	HR (95% CI)	p value
Encephalitis	1·41 (1·03–1·92)	0·028
Dementia	1·71 (1·50–1·95)	<0·0001
Mood, anxiety, or psychotic disorder (any)	1·20 (1·18–1·23)	<0·0001
Mood, anxiety, or psychotic disorder (first)	1·48 (1·42–1·55)	<0·0001
Mood disorder (any)	1·23 (1·20–1·26)	<0·0001
Mood disorder (first)	1·41 (1·33–1·50)	<0·0001
Anxiety disorder (any)	1·17 (1·15–1·20)	<0·0001
Anxiety disorder (first)	1·48 (1·42–1·55)	<0·0001
Psychotic disorder (any)	1·66 (1·53–1·81)	<0·0001
Psychotic disorder (first)	1·82 (1·53–2·16)	<0·0001
Substance use disorder (any)	1·09 (1·05–1·12)	<0·0001
Substance use disorder (first)	0·92 (0·86–0·99)	0·033
Insomnia (any)	1·15 (1·10–1·20)	<0·0001
Insomnia (first)	1·43 (1·34–1·54)	<0·0001



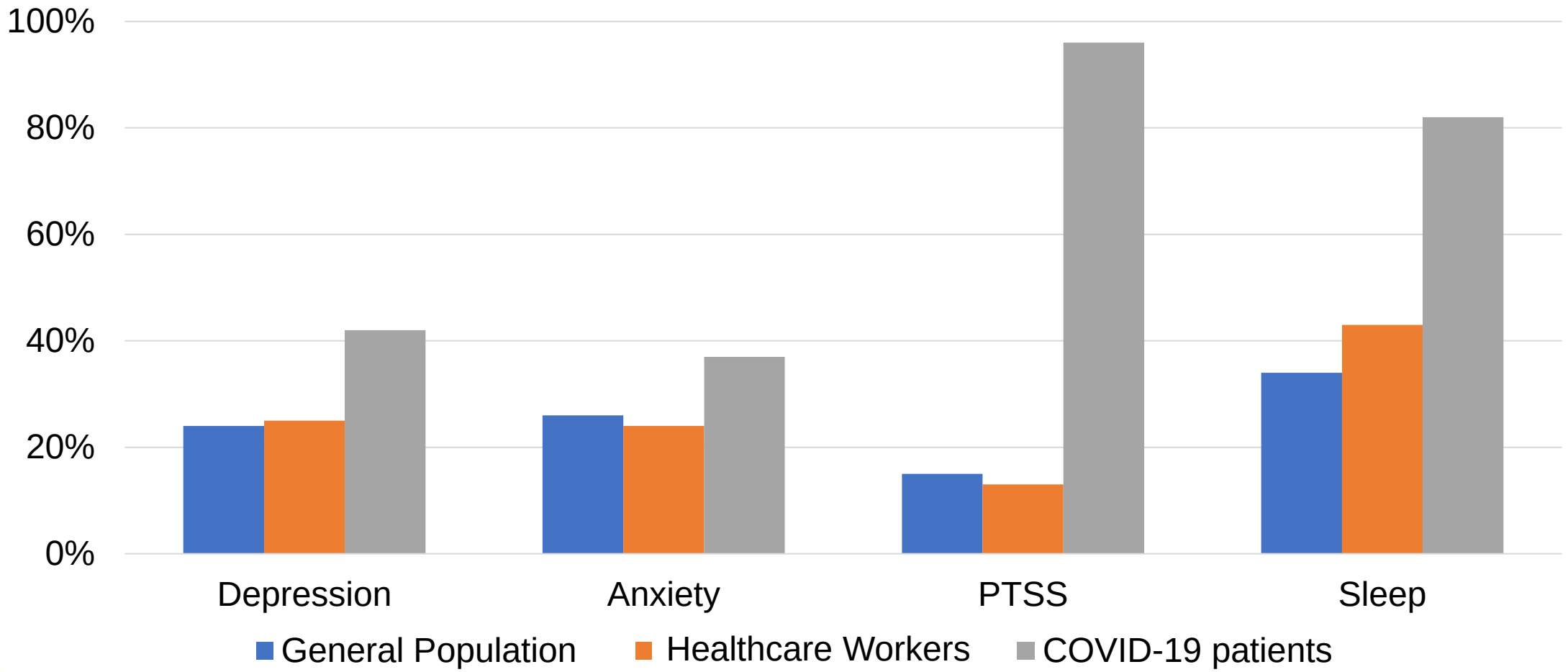
Number at risk	30	60	90	120	150	180
COVID-19	84 435	58 504	41 026	26 310	15 885	8741
Other RTI	122 790	103 824	89 662	75 998	63 173	51 033

RTI: Respiratory Tract Infection

Slide courtesy D. Grelotti, M.D.

Taquet et al, Lancet Psychiatry. 2021. DOI: /10.1016/ S2215-0366(21)00084-5

Pooled Estimates of Prevalence for Psychiatric Problems Stratified by SARS-CoV-2 Risk Population

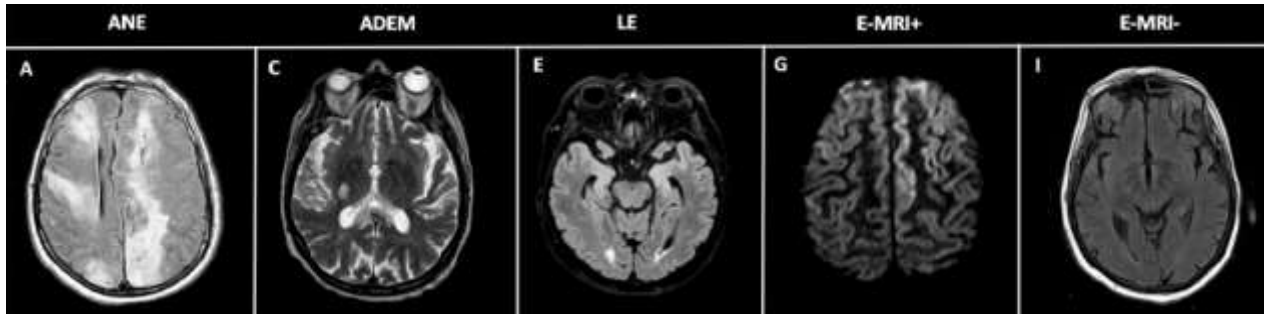


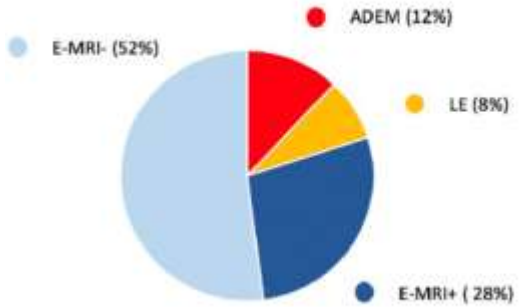
PTSS = Post-traumatic Stress Symptoms

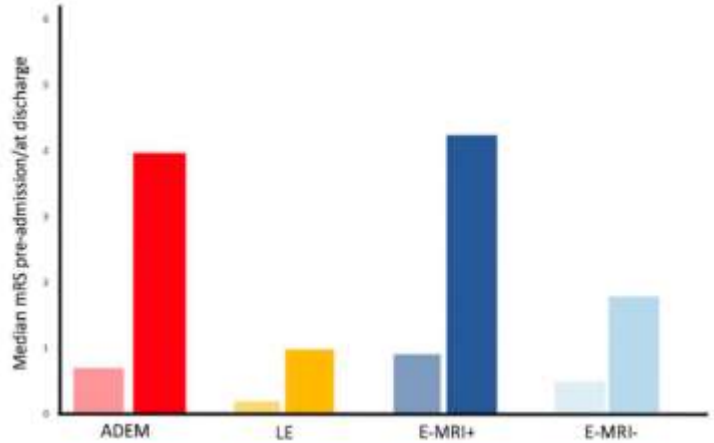
Krishnamoorthy et al. Psychiatry Research 2020 DOI: 10.1016/j.psychres.2020.113382

ENCOVID Encephalitis Case Series

- **25 COVID-19 patients with encephalitis**
  - 68% had hyperproteinorrachia or pleocytosis
- **SARS-CoV-2 RNA not detected in CSF**
- **Four principal categories**
  - ADEM (n=3), limbic encephalitis (n=2), encephalitis with MRI alterations (n=7), and encephalitis with normal imaging (n=13)
- **ADEM and LE** had delayed onset vs. others (p=0.001) and were associated with more severe COVID-19
- **Patients with MRI alterations had worse response to therapy and neurologic disability than others**





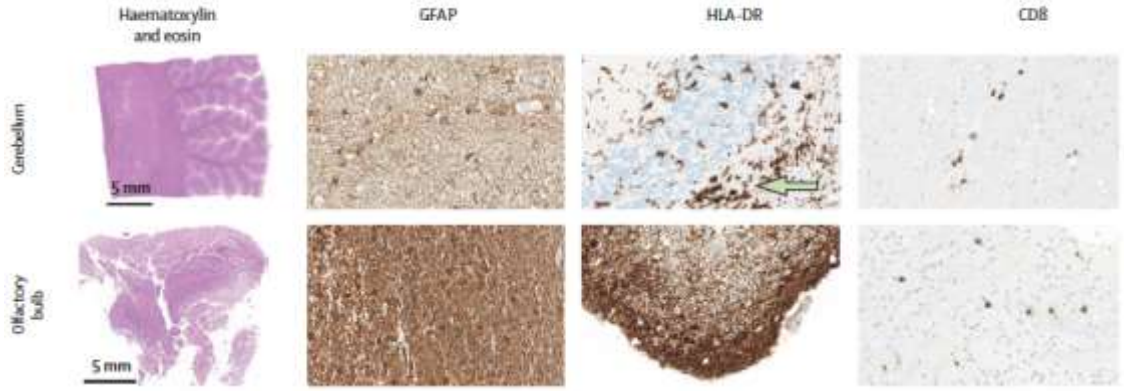


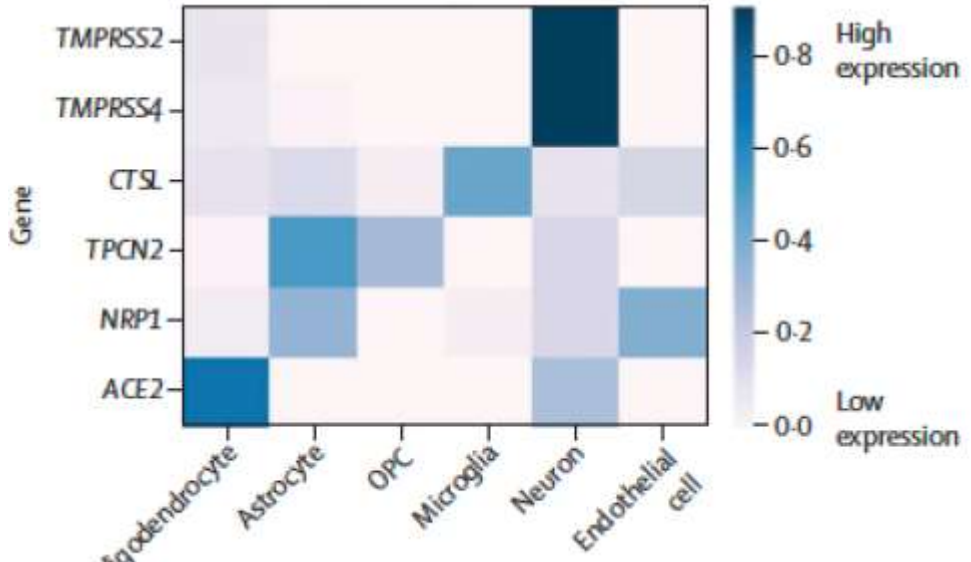
ADEM, acute disseminated encephalomyelitis;
ANE, acute necrotizing encephalitis;
E-MRI-, encephalitis with negative MRI;
E-MRI+, encephalitis with MRI alterations;
LE, Limbic encephalitis;
mRS, modified Rankin scale.

Pilotto et al, J Infect Dis 2020. doi:10.1093/infdis/jiaa609

Post-Mortem Case Series from Germany

- 43 patients, median age 76 years
- Territorial ischemic lesions in 14%
- 86% had astrogliosis in all assessed regions
- Microglial activation and infiltration by cytotoxic T cells was greatest in brainstem and cerebellum
- 79% had meningeal cytotoxic T cell infiltration
- SARS-CoV-2 detected in the brains of 21 (53%) of 40

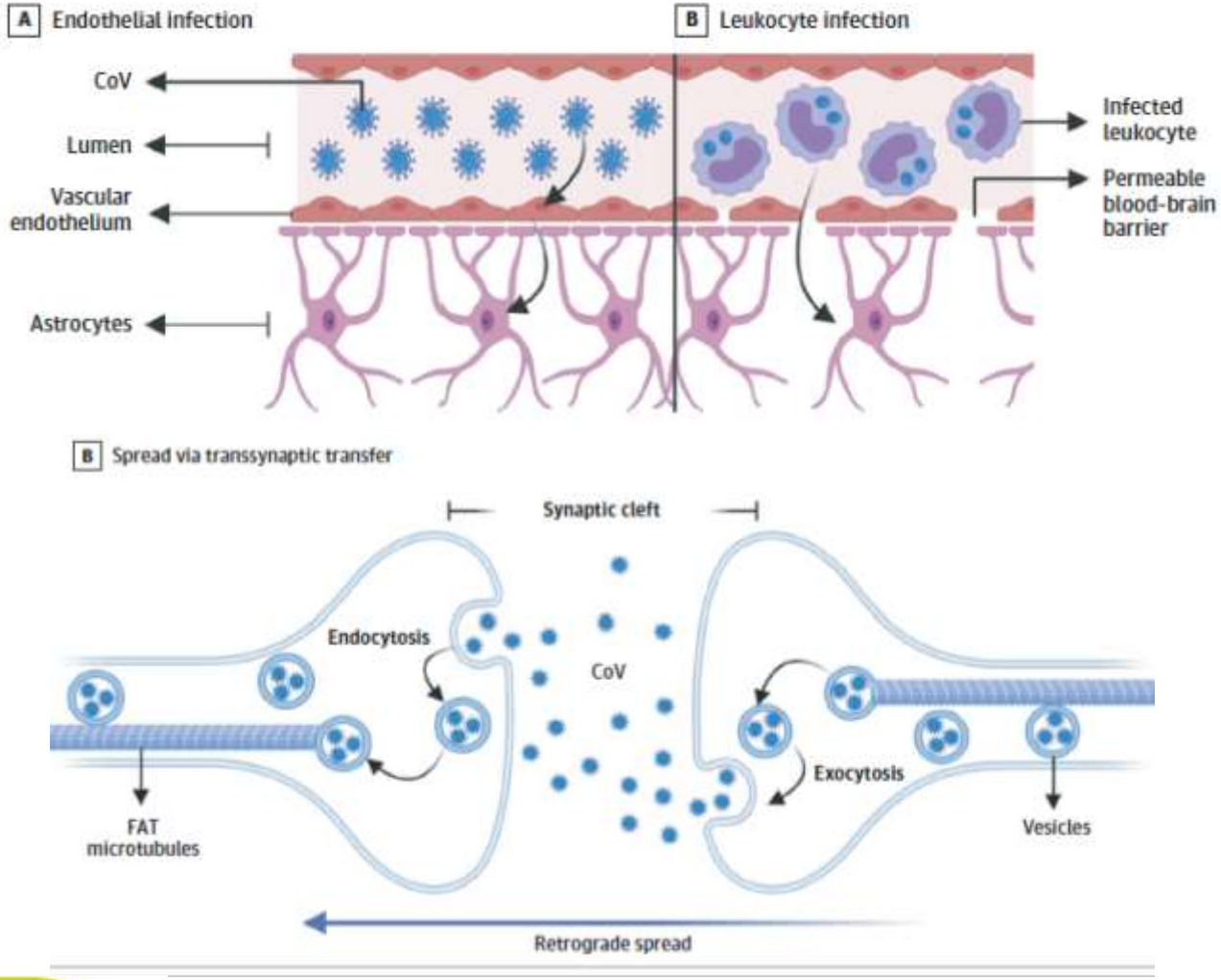


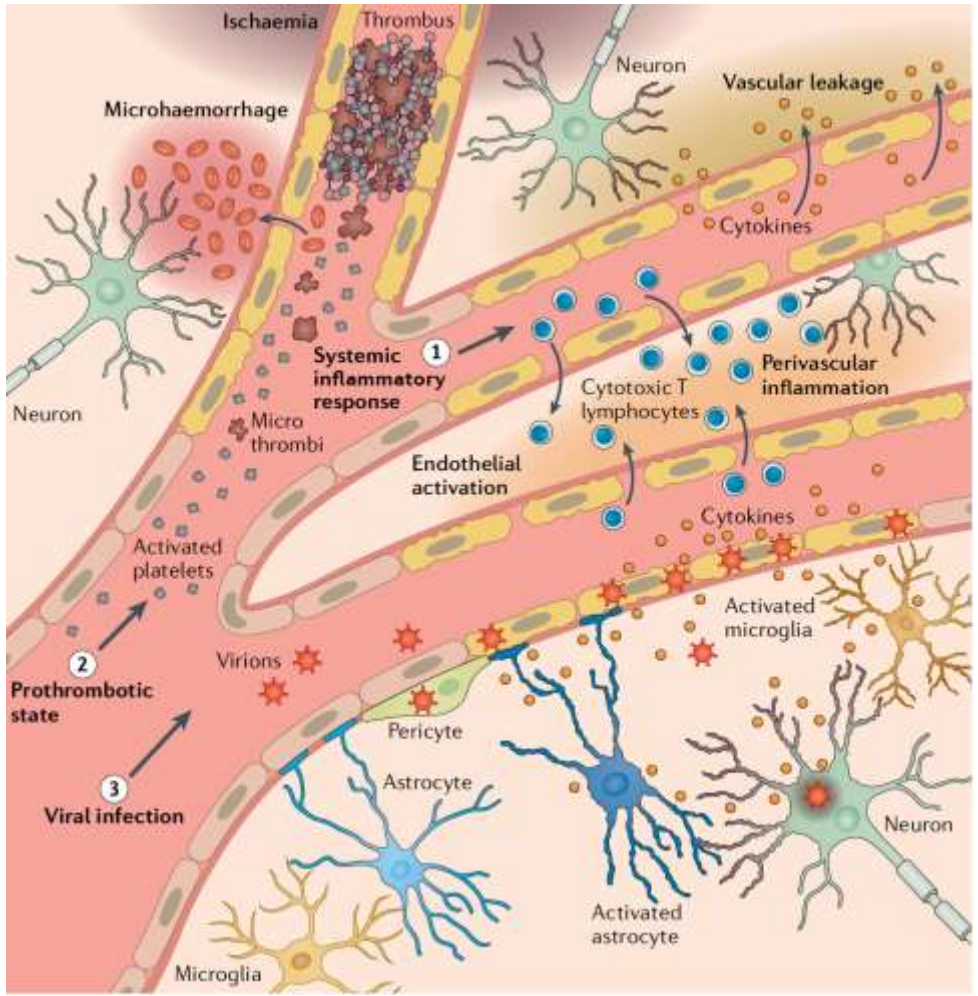


TMPRSS = Transmembrane Protease Serine

Matschke et al, Lancet Neurol. 2020. doi: 10.1016/ S1474-4422(20)30371-9

Pathogenesis of Neurological Complications



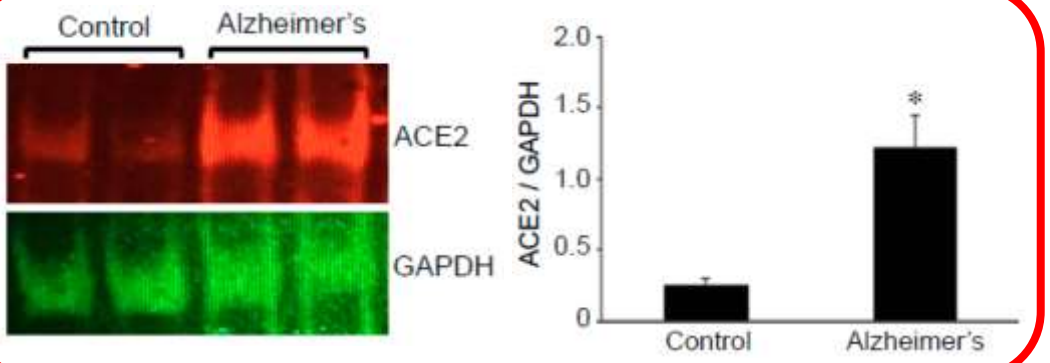


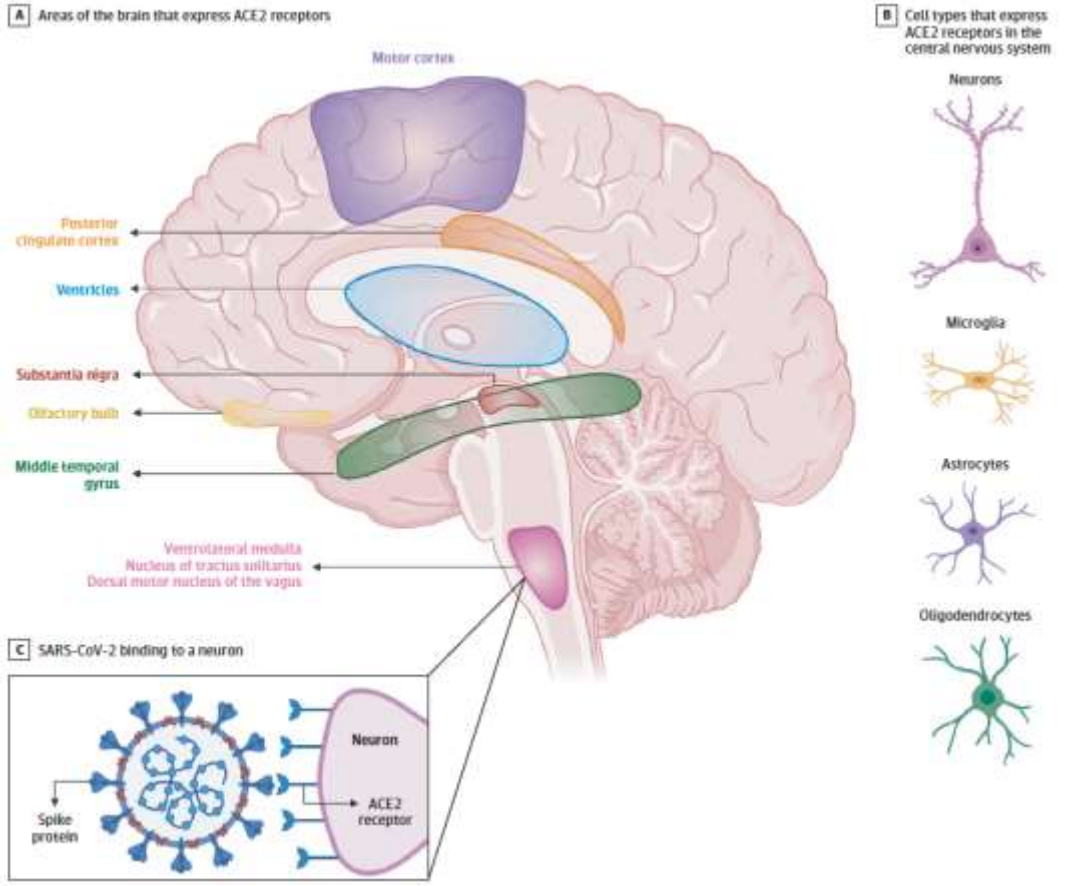
Zubair et al, JAMA Neurol. doi:10.1001/jamaneurol.2020.2065
Solomon T. Nat Rev Neurol. doi: 10.1038/s41582-020-00453- w

ACE2 Expression Increases with Aging-Related Diseases, Possibly Including Alzheimer's Disease

Comorbidities/Risk Factors	Conclusion	References
Cardiovascular Disease	Increased myocardial *ACE2* expression (pericytes).	[16,47,69–71]
Respiratory Conditions: COPD and Lung Cancer	Increased airway/lung tissue *ACE2* expression.	[59,72–79]
Obesity	Expression levels of *ACE2* in adipose tissue higher than those in the lung.	[7,33,80–82]
Diabetes	Increased pancreatic islets *ACE2* expression.	[83,84]
Asthma (type 2) #	IL-13 down-regulates *ACE2* expression in the nasal and airway epithelial cells.	[85–87]
Male gender	Androgens regulate the transcription of the *ACE2* gene, up-regulating its expression at the cell surface.	[88–92]
Age	*ACE2* expression seems to increase with age in the respiratory epithelium.	[92–94]
RAAS Inhibitors	Not associated with increased risk in COVID-19 patients.	[95–98]

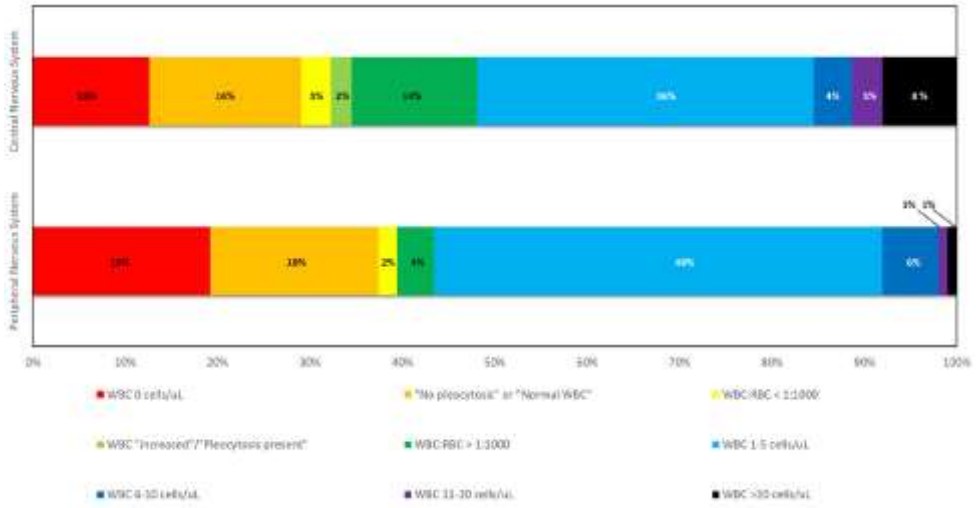
not a comorbidity with higher risk in COVID-19, as it could be expected.





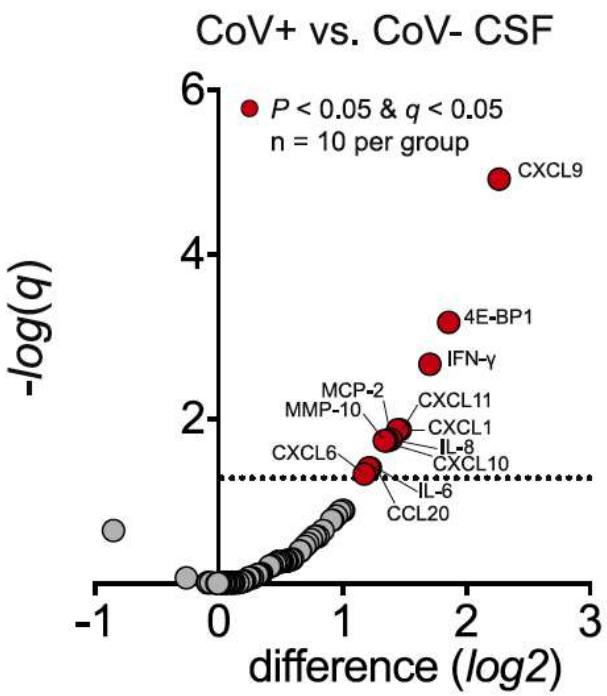
Zubair et al, JAMA Neurol. doi:10.1001/jamaneurol.2020.2065
Rodrigues & Costa de Oliveira, Microorganisms. doi: 10.3390/microorganisms9081692
Ding et al, Intl J Molecul Sci. doi: 10.3390/ijms22041687

CSF Findings with COVID-19

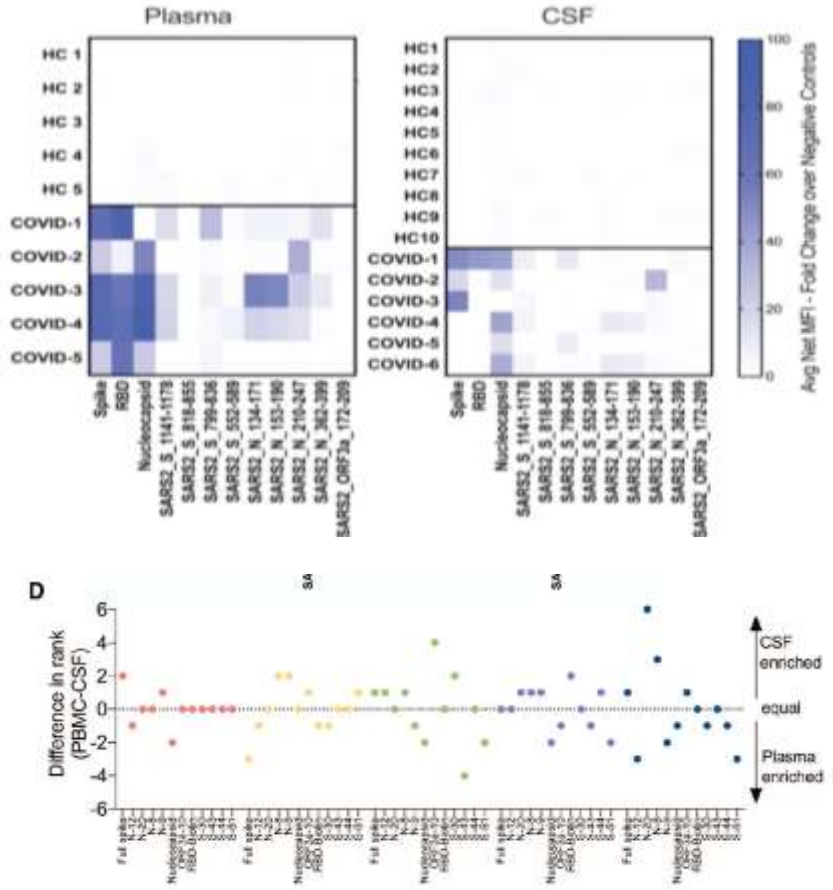


- **430 people with COVID-19, neurological symptoms, CSF collected**
- **6% had detectable SARS-CoV-2 RNA**
- **12% had SARS-CoV-2 antibody**
- **2% had oligoclonal bands in CSF**
- **5% had autoimmune antibodies**

Lewis et al, J Neurol Sci, 2021 421: 117316



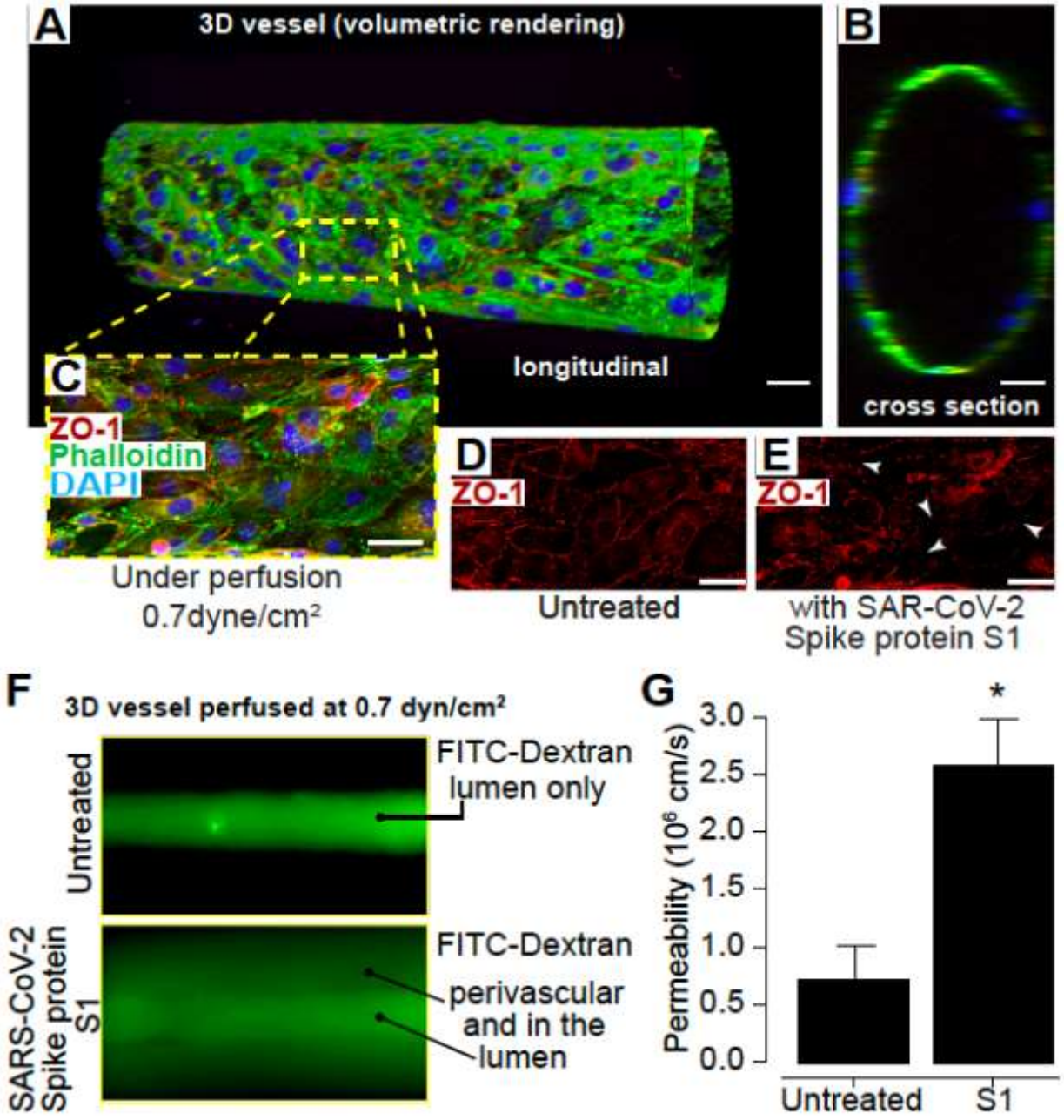
Remsik et al, Cancer Cell. doi: 10.1016/j.ccell.2021.01.007



Song et al, Cell Reports Med. doi: 10.1016/j.xcrm.2021.100288

SARS-CoV-2 S Protein Alters BBB Integrity

- SARS-CoV-2 spike proteins were used in model systems that have the essential features of the BBB
- S1 subunit promoted loss of barrier integrity in an advanced 3D microfluid model of the human BBB
- SARS-CoV-2 spike proteins triggered a pro-inflammatory response in brain endothelial cells that contributed to altered BBB function



Buzhdygan et al, Neurobiol Dis. 2020. PMID 33053430

Long-Term Consequences of COVID-19

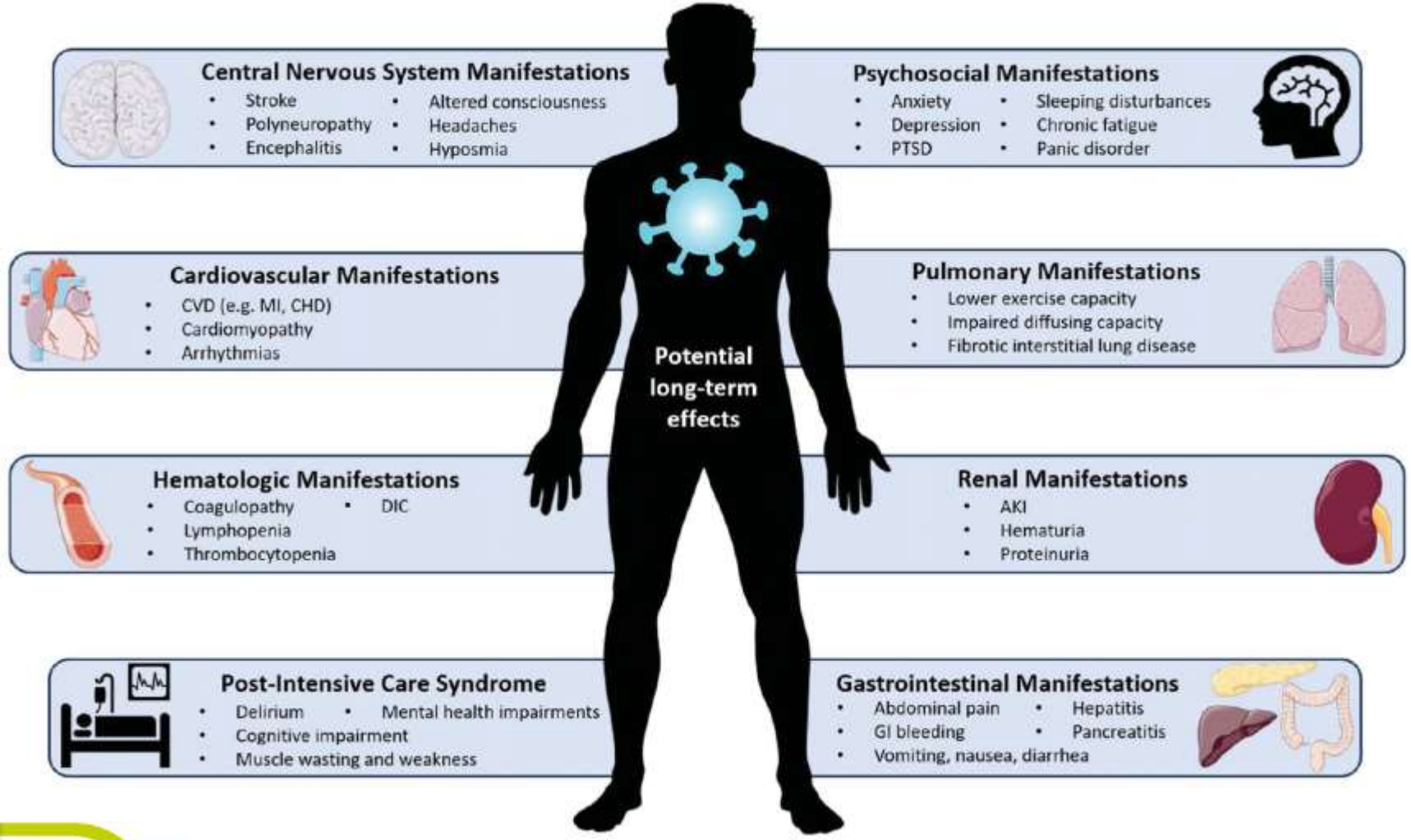
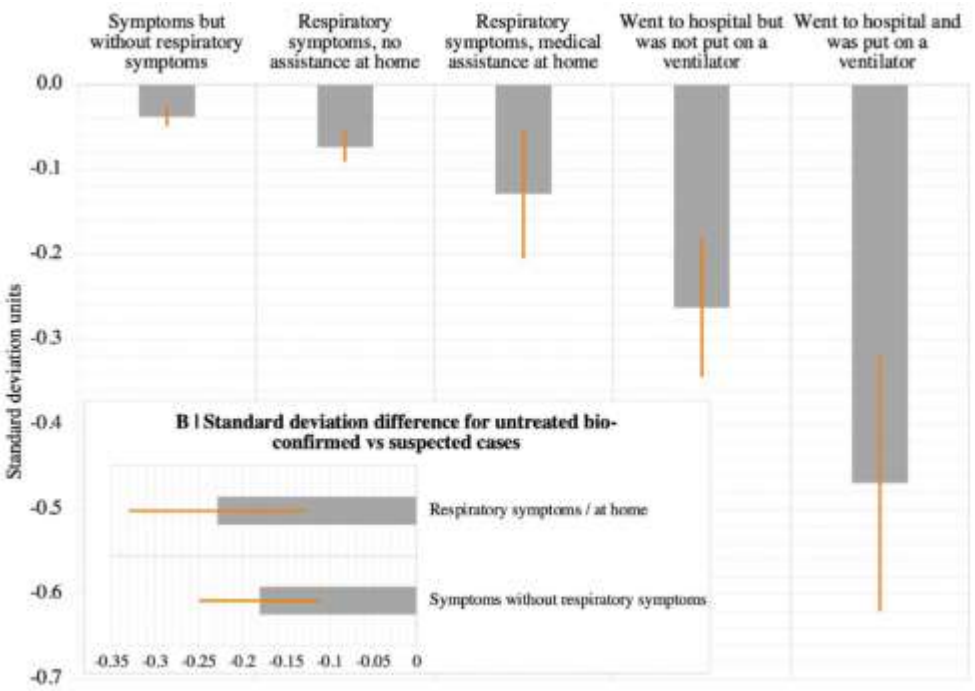


Table 2 Possible etiopathogenesis of Long-Haul COVID

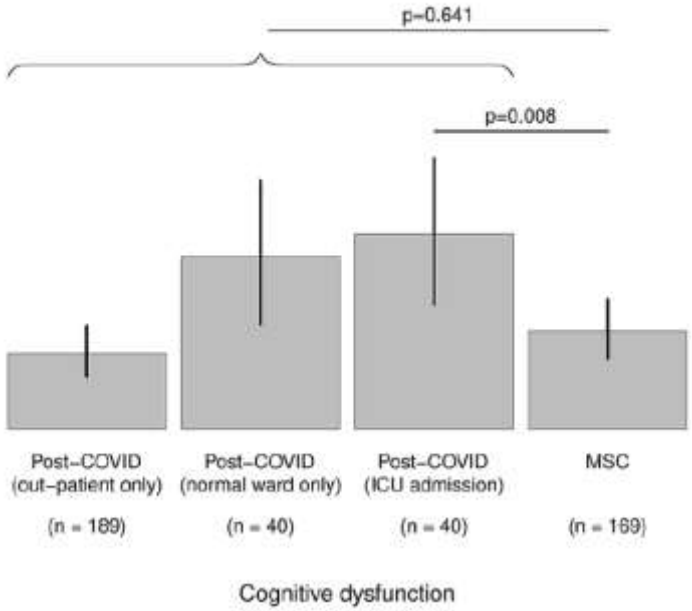
1. Unmasking of underlying comorbidities
2. Residual damage from acute infection
3. Persistent or restricted viral replication
4. Persistent immune activation
5. Unknown cause

Higgins et al, Crit Rev Clin Lab Sci. 2021. PMID 33347790
Nath A. Neurology 2020;95:559-560. PMID 32788251

Post-Acute Cognitive and Imaging Effects of COVID-19

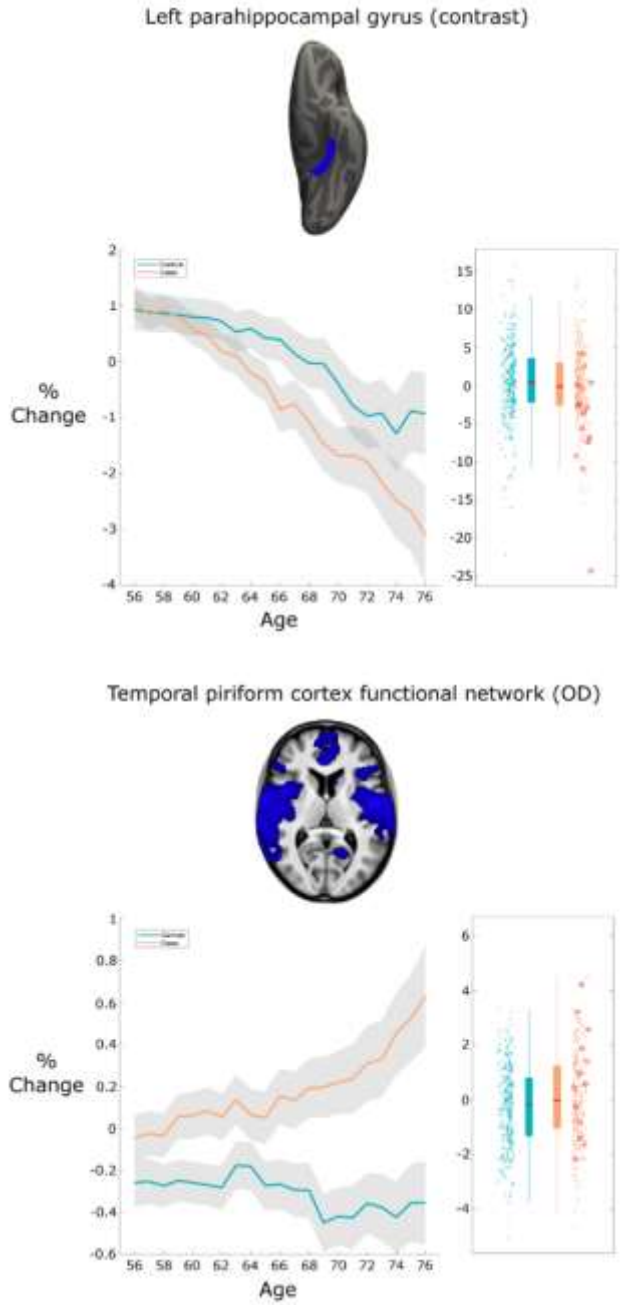


Hampshire A et al, EClinicalMedicine. 2021. PMID 34316551



MSC: Mid-German Sepsis Cohort

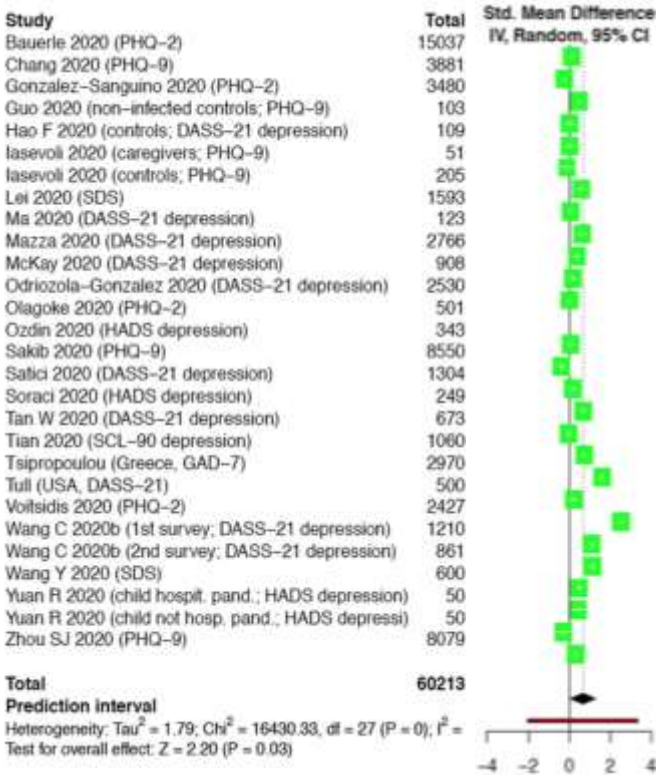
Stallmach A et al, Infection. 2022. PMID 34997542



Douaud G et al. medRxiv 2021. PMID 34189535

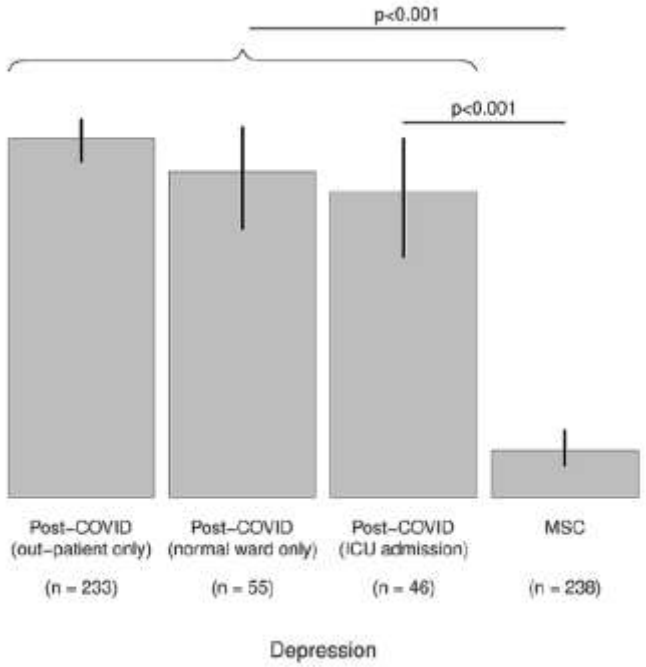
Mental Health Symptoms Can Also Persist and Are Influenced by Risk & Protective Factors

Change in Depressive Symptoms In the General Population from Before to After COVID-19



Standardized Mean Difference=0.67

Kunzler et al. Globalization and Health. doi: 10.1186/s12992-021-00670-y



MSC: Mid-German Sepsis Cohort

Stallmach A et al, Infection. 2022. PMID 34997542

Wide Range of Mental Health Symptoms Among COVID-19 Patients

Condition	Studies	Lowest	Highest
Anxiety Symptoms	6	19.5%	80.2%
Depressive Symptoms	8	27.8%	55.3%
Post-Traumatic Stress	2	31.0%	43.4%
Sleep Symptoms	2	27.6%	66.3%
Stress	1	17.0%	-
Psychological Distress	1	13.1%	-

Risk Factors	Protective Factors
Inflammation biomarkers	Higher lymphocyte ratio
Physical symptoms	Concomitant medical diseases
	Higher education
	Better socioeconomic status

Chau et al. BMC Public Health 2021. PMID 33827499

Severity of COVID-19 Among PWH

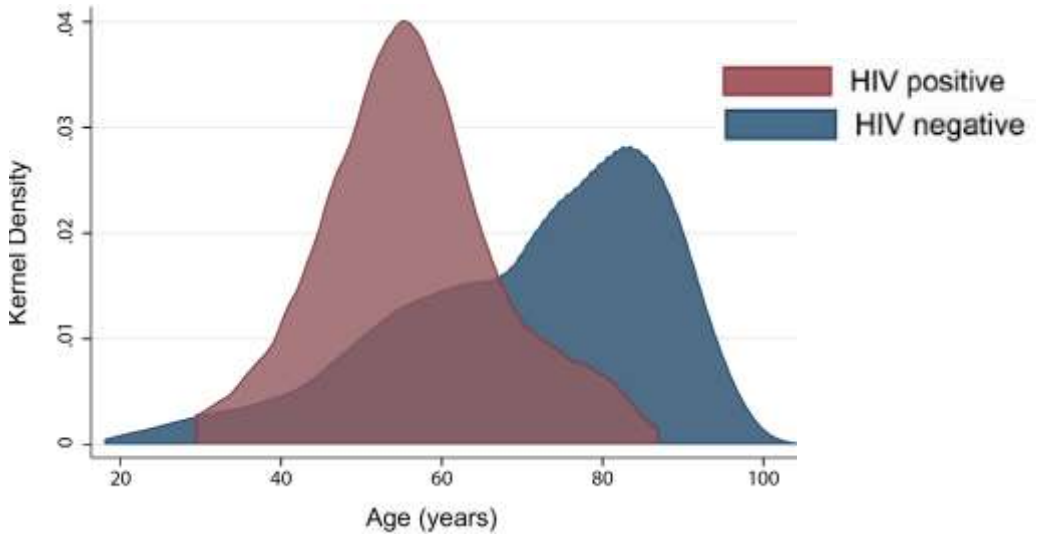
- Reviewed 25 published reports of COVID-19 in PWH
  - Mean age 52.7 years
  - 98% on ART
- Comorbidities
  - Hypertension (39.3%)
  - COPD (18.0%)
  - Diabetes (17.2%)
- 33.5% had severe or critical disease
- Among those who died
  - 90.5% were older than 50
  - 85.7% were men
  - 64.3% had multimorbidity

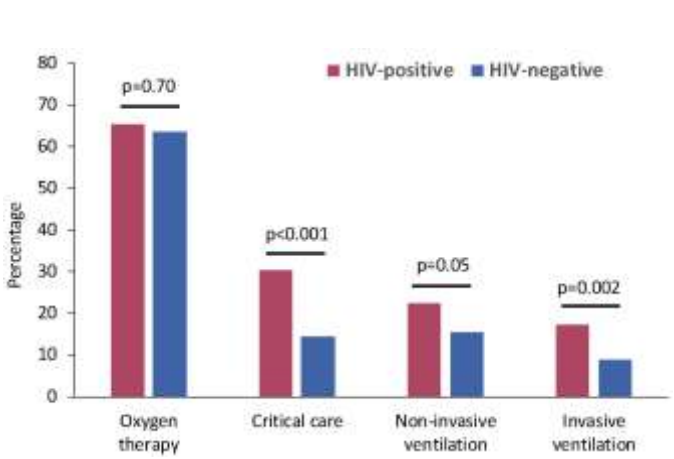
First author (Reference)	Setting	Publication date	Study type	Data type[a]	Sample size	Case definition	Quality assessment
Zhu [22]	Wuhan, China	12/03/20	Case report	Individual	1	Confirmed	5/8
Guo [23]	Wuhan, China	03/04/20	Cross-sectional	Aggregate	8	Confirmed	7/9
Zhao [24]	Shenzhen, China	10/04/20	Case report	Individual	1	Confirmed	6/8
Chen [25]	Guizhou, China	15/04/20	Case report	Individual	1	Confirmed	6/8
Su [26]	China	17/04/20	Case report	Individual	1	Confirmed	6/8
Schweitzer [27]	Italy	18/04/20	Case report	Individual	1	Confirmed	4/8
Blanco [28]	Barcelona, Spain	19/04/20	Case series	Individual	5	Confirmed	8/10
Riva [29]	Italy	24/04/20	Case series	Individual	3	Confirmed	4/10
Wang [30]	Wuhan, China	27/04/20	Case report	Individual	1	Confirmed	6/8
Altuntas Aydin [31]	Istanbul, Turkey	30/04/20	Case series	Individual	4	Confirmed	7/10
Haerter [32]	Germany	01/05/20	Case series	Individual	33	Confirmed	8/10
Karmen [33]	New York, USA	12/05/20	Retrospective cohort	Aggregate	21	Confirmed	8/11
Wu [34]	Wuhan, China	13/05/20	Case series	Individual	2	Confirmed	4/10
Gervasoni [35]	Italy	15/05/20	Cross-sectional	Aggregate	47	Confirmed/Probable	6/9
Benkovic [36]	New York, USA	20/05/20	Case series	Individual	4	Confirmed	4/10
Haddad [37]	Wynnewood, USA	20/05/20	Case report	Individual	1	Confirmed	7/8
Baluku [38]	Uganda	22/05/20	Case report	Individual	1	Confirmed	6/8
Patel [39]	USA	23/05/20	Case report	Individual	1	Confirmed	6/8
Iordanou [40]	Cyprus	25/05/20	Case report	Individual	1	Confirmed	7/8
Kumar [41]	Chicago, USA	27/05/20	Case report	Individual	1	Confirmed	7/8
Childs [42]	UK	28/05/20	Case series	Aggregate	18	Confirmed	4/10
Suwanwongse [43]	New York, USA	29/05/20	Case series	Individual	9	Confirmed	5/10
Ridgway [44]	Chicago, USA	30/05/20	Case series	Individual	5	Confirmed	7/10
Shalev [45]	New York, USA	31/05/20	Case series	Aggregate	31	Confirmed	8/10
Vizcarra [20]	Madrid, Spain	01/06/20	Prospective cohort	Aggregate	51	Confirmed, probable	9/11

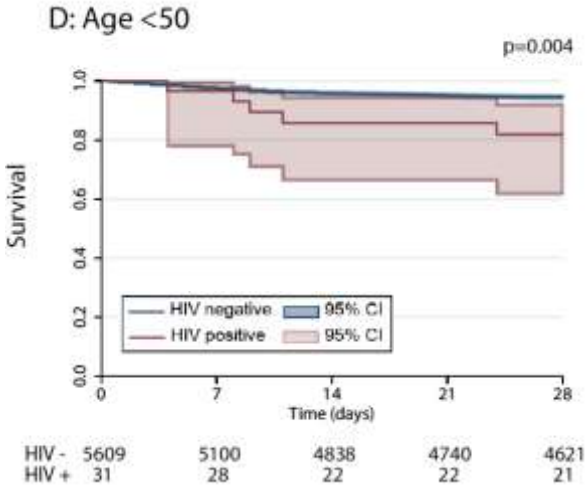
Mirzaei et al, AIDS & Behavior. 2020. doi: 10.1007/s10461-020-02983-2

Worse Mortality in PWH in the U.K.

- 122 of 47,592 (0.26%) COVID-19 hospitalizations had HIV
- PWH were younger and had fewer comorbidities but had more symptoms & higher CRP
- Overall 28-day mortality was similar in both groups
  - Younger than 60:
    PWH 21.3% vs. 9.6%; p<0.001
- Mortality higher among PWH after adjusting for age and other variables
  - Adjusted HR 1.69
  - 95% CI 1.15-2.48; p=0.008

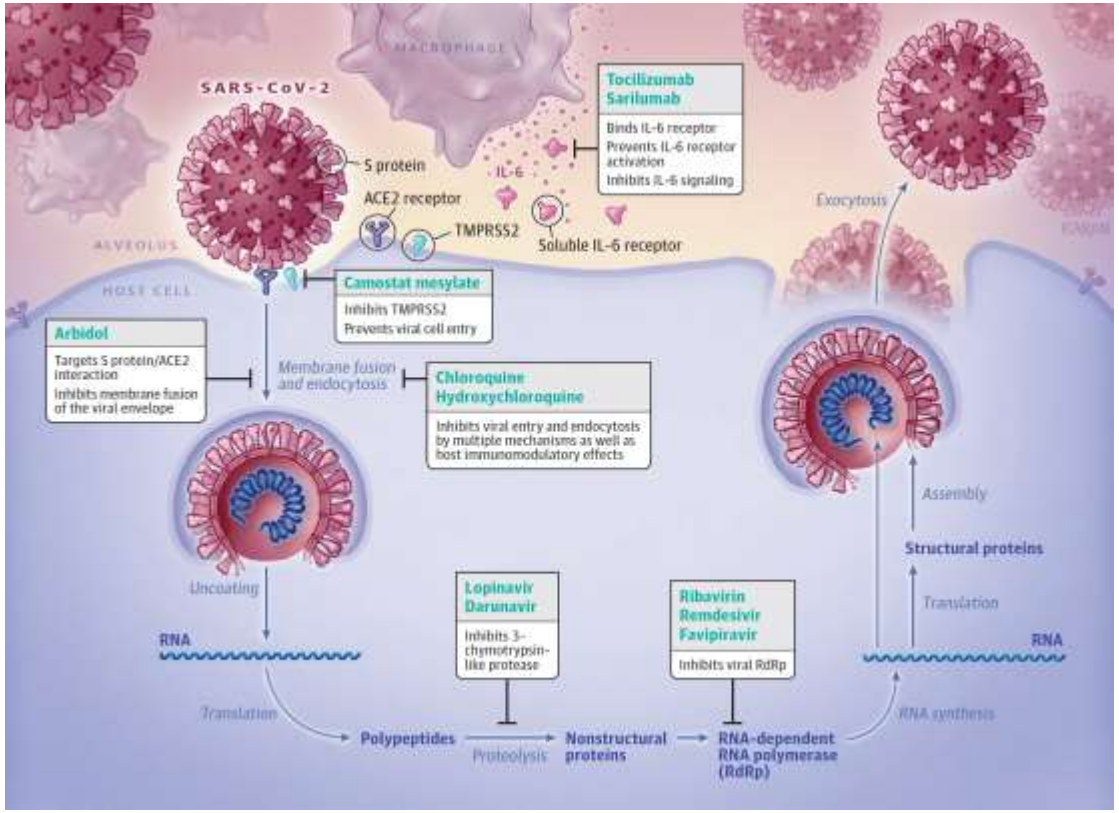






Geretti et al, Clin Infect Dis. 2020. doi: 10.1093/cid/ciaa1605

CNS Aspects of SARS-CoV-2 Therapies



Sanders et al, JAMA. 2020. doi: 10.1001/jama.2020.6019
Richardson et al, J Neurol. 2020. PMID 32361836
Humeniuk et al, Clin Pharmacokinet 2021. PMID 33782830
PubChem: https://pubchem.ncbi.nlm.nih.gov

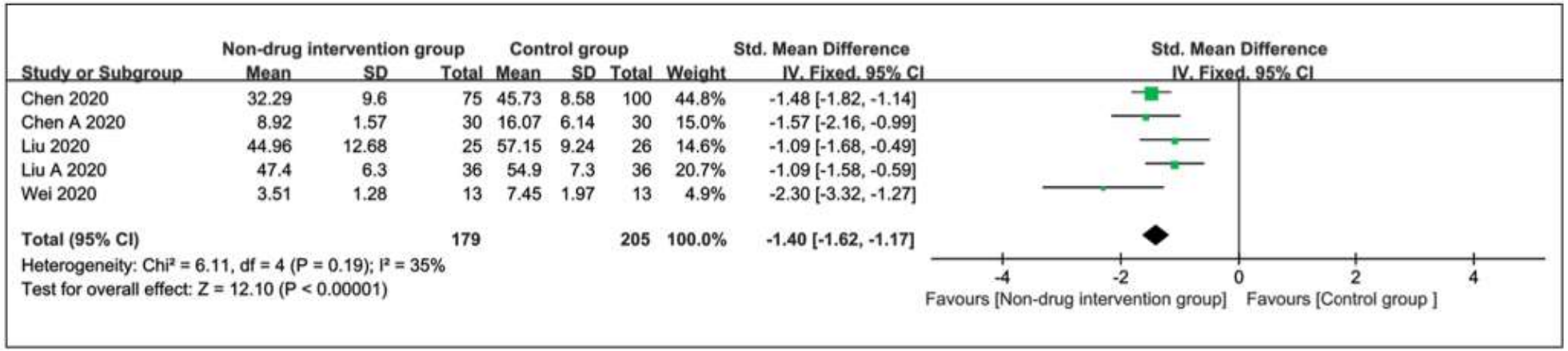
- **Dexamethasone**
  - Macaque data support **15% CSF distribution**
  - **Neuropsychiatric AEs** include depression, sleep disturbance, irritability, seizure, stroke, and others
  - 77% protein binding, MW 392.5, LogP 1.9, P-gp
- **Remdesivir**
  - Macaque data support **<5% brain distribution**
  - No human data on distribution into CSF
  - 88-93.6% protein binding, MW 602.6, LogP 1.9, P-gp
- **Baricitinib**
  - Rodent data support **~20% brain distribution**
  - No human data on distribution into CSF
  - 50% protein binding, MW 371.4, LogP -0.5, P-gp
- **Tocilizumab or Sarilumab**
  - Likely **poor distribution into the CNS** with normal BBB
  - **Neurologic AEs** include headache and dizziness; Rare cerebral microangiopathy (tocilizumab)

Non-Pharmacological Interventions Reduce Anxiety and Depressive Symptoms in SARS-CoV-2 Patients

Interventions

- Respiratory rehabilitation
- Progressive muscle relaxation
- Traditional medicine
- Breathing
- Mindfulness

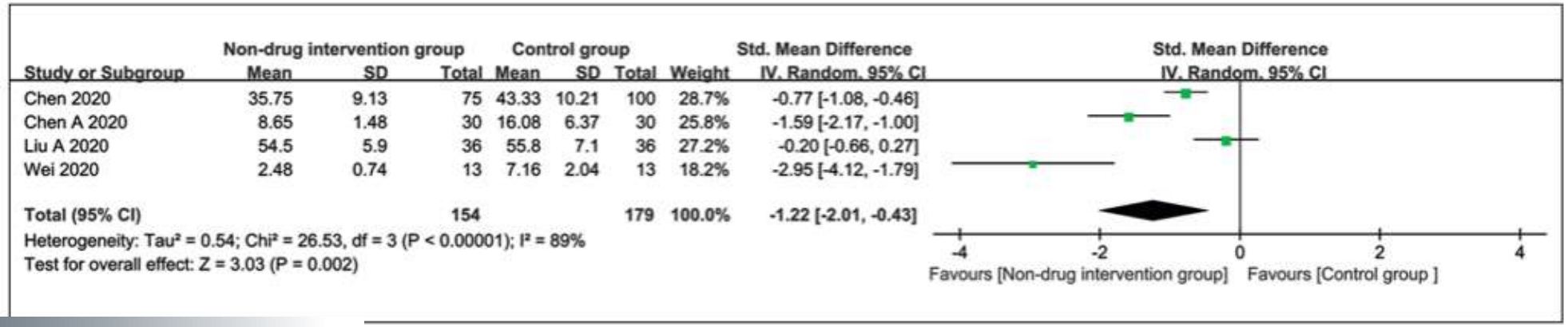
Anxiety symptoms



Study or Subgroup	Non-drug intervention group Mean	SD	Total	Control group Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
Chen 2020	32.29	9.6	75	45.73	8.58	100	44.8%	-1.48 [-1.82, -1.14]
Chen A 2020	8.92	1.57	30	16.07	6.14	30	15.0%	-1.57 [-2.16, -0.99]
Liu 2020	44.96	12.68	25	57.15	9.24	26	14.6%	-1.09 [-1.68, -0.49]
Liu A 2020	47.4	6.3	36	54.9	7.3	36	20.7%	-1.09 [-1.58, -0.59]
Wei 2020	3.51	1.28	13	7.45	1.97	13	4.9%	-2.30 [-3.32, -1.27]
Total (95% CI)			**179**			**205**	**100.0%**	**-1.40 [-1.62, -1.17]**

Heterogeneity: Chi² = 6.11, df = 4 (P = 0.19); I² = 35%
Test for overall effect: Z = 12.10 (P < 0.00001)

Depressive symptoms



Study or Subgroup	Non-drug intervention group Mean	SD	Total	Control group Mean	SD	Total	Weight	Std. Mean Difference IV, Random, 95% CI
Chen 2020	35.75	9.13	75	43.33	10.21	100	28.7%	-0.77 [-1.08, -0.46]
Chen A 2020	8.65	1.48	30	16.08	6.37	30	25.8%	-1.59 [-2.17, -1.00]
Liu A 2020	54.5	5.9	36	55.8	7.1	36	27.2%	-0.20 [-0.66, 0.27]
Wei 2020	2.48	0.74	13	7.16	2.04	13	18.2%	-2.95 [-4.12, -1.79]
Total (95% CI)			**154**			**179**	**100.0%**	**-1.22 [-2.01, -0.43]**

Heterogeneity: Tau² = 0.54; Chi² = 26.53, df = 3 (P < 0.00001); I² = 89%
Test for overall effect: Z = 3.03 (P = 0.002)

Ding et al. Eur Rev Med Pharm Sci 2021 doi: 10.26355/eurrev_202101_24679

Conclusions

- **Spectrum of neuropsychiatric complications occurs in COVID-19**
  - **The most severe are life-threatening but uncommon. If patients survive, they may have persistent sequelae.**
  - **Less severe complications are more common and their persistence is uncertain. Longer term follow-up is needed.**
- **Pathogenesis of many complications are likely due to robust immune and endothelial responses to SARS-CoV-2**
- **Disease severity and vulnerability to neuropsychiatric complications (both during infection and after recovery) likely vary by HIV and age.**
  - **Does SARS-CoV-2 accelerate brain aging?**
- **Resources are needed to protect PWH and older people for the direct and indirect effects of COVID-19.**

Filgueira et al, Cells. doi:10.3390/cells10071836

NIMH Neurologic and Psychiatric Effects of SARS-CoV-2 Meeting

https://www.nimh.nih.gov/news/events/2021/neurologic-and-psychiatric-effects-of-sars-cov-2-meeting

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