THE UNIVERSITY OF ALABAMA AT BIRMINGHAM
Heersink School of Medicine

Neuropsychiatric Effects of COVID

John E. Fanning, MD, FACP
Regional Chair of Internal Medicine
UAB School of Medicine - Huntsville

Objectives

1. Pathophysiology of Neuropsychiatric Effects of Acute COVID-19

2. Neuropsychiatric manifestations in
   - COVID-19
   - Post-acute COVID-19 syndrome (PACS) “Long COVID”

On Tuesday, January 28, 1986, at 11:39 AM EST, the Space Shuttle *Challenger* broke apart 73 seconds into its flight, killing all seven crew members aboard

The **fall of the Berlin Wall** on Thursday, November 9, 1989, during the Peaceful Revolution, was a pivotal event in world history.

The first impact was that of American Airlines Flight 11, which crashed into the North Tower of the World Trade Center complex in Lower Manhattan at 08:46. Sixteen minutes later, at 09:03, the World Trade Center's South Tower was hit by United Airlines Flight 175

On Wednesday, March 11, 2020, the WHO declared the SARS-CoV 2 outbreak to be a pandemic

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)
(COVID-19)

COVID-19 was initially thought to be primarily a respiratory disease, sometimes leading to viral pneumonia.

It is now recognized as a complex disorder affecting many body systems.

“He who knows syphilis knows medicine”

- Sir William Osler

Sir William Osler (1849 –1919)

Considered the “Father of Modern Medicine”

One of the "greatest diagnosticians ever to wield a stethoscope".

First Physician-in-Chief of the new Johns Hopkins Hospital 1889

Established the full-time, sleep-in residency system

Staff physicians lived in the administration building of the hospital.

Residency was open-ended, and long tenure was the rule.

Physicians spent as long as seven or eight years as residents, during which time they led a restricted, almost monastic life.

Sir William Osler

"Listen to your patient; he is telling you the diagnosis“

”Pneumonia is the friend of the aged."

"He who studies medicine without books sails an uncharted sea, but he who studies medicine without patients does not go to sea at all.“

"I desire no other epitaph than the statement that I taught medical students in the wards, as I regard this as by far the most useful and important work, I have been called upon to do."

SARS-CoV-2 (COVID-19)

WHO Data

As of 18 June 2023, over 768 million confirmed cases and over 6.9 million deaths have been reported globally.

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Research on coronavirus skyrocketed, even as partnerships shrank.

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Feb 23, 2021

More than 87,000 scientific papers on coronavirus since pandemic

Study finds "astonishing" growth even as partnerships shrink

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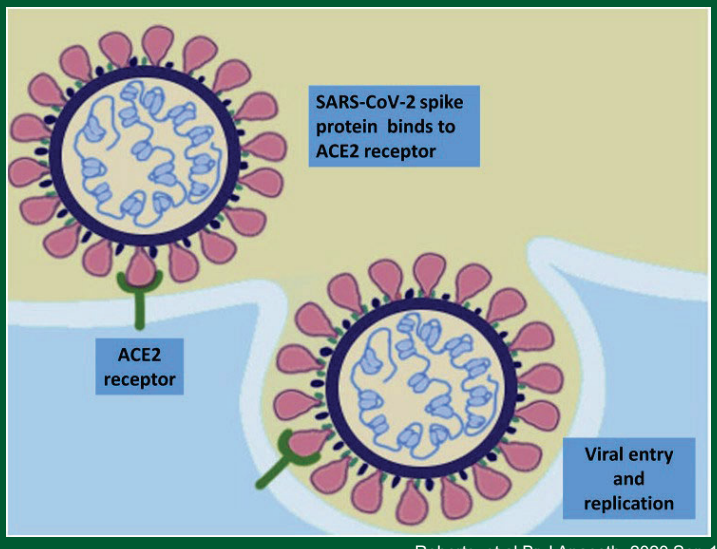
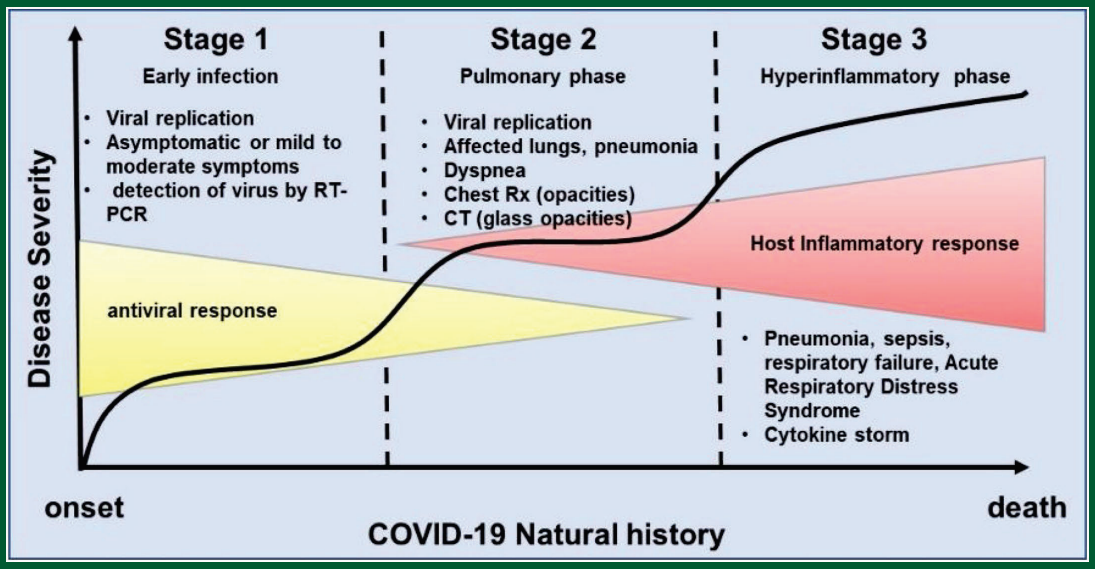
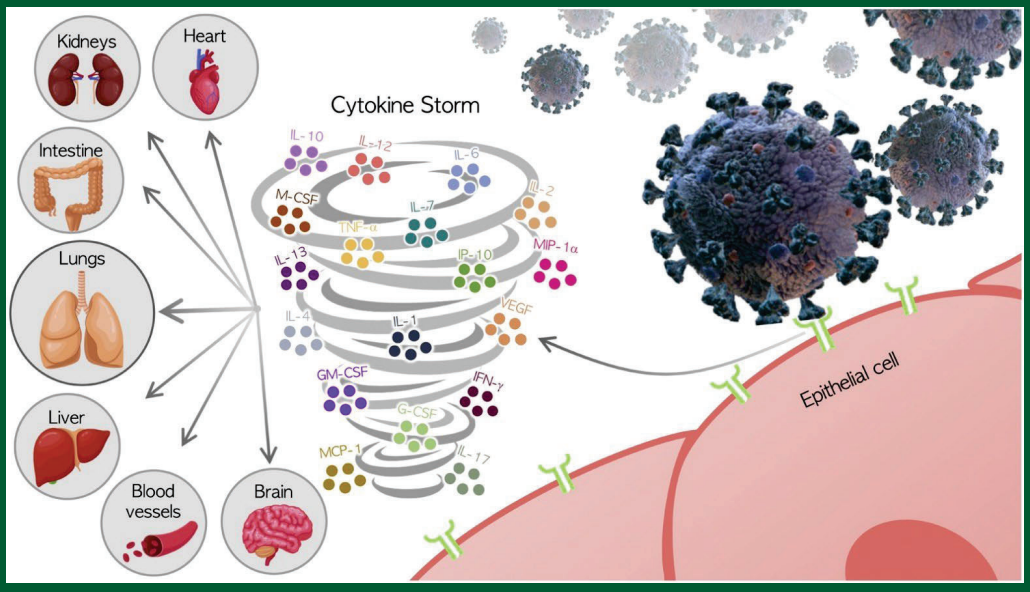
COVID-19



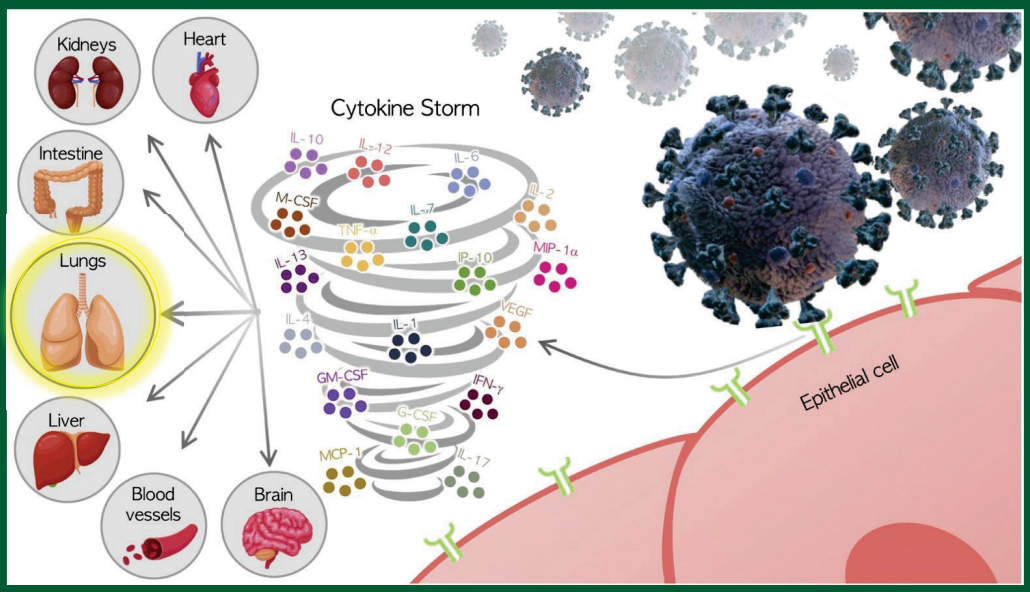
Roberts, et al Br J Anaesth. 2020 Sep;125(3):238-242.



dos Santos, et al Biomedicine & Pharmacotherapy, Volume 129, 2020,



Víctor J., et al, SARS-CoV-2 infection: The role of cytokines in COVID-19 disease, Cytokine & Growth Factor Reviews, Volume 54,2020



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“Happy Hypoxemia”

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NEJM 2020: 1099 hospitalized COVID-19 patients only 18.7% reported dyspnea despite low PaO2/FiO2

Guan, et al, Clinical characteristics of coronavirus disease 2019 in China. N Engl J Med 2020

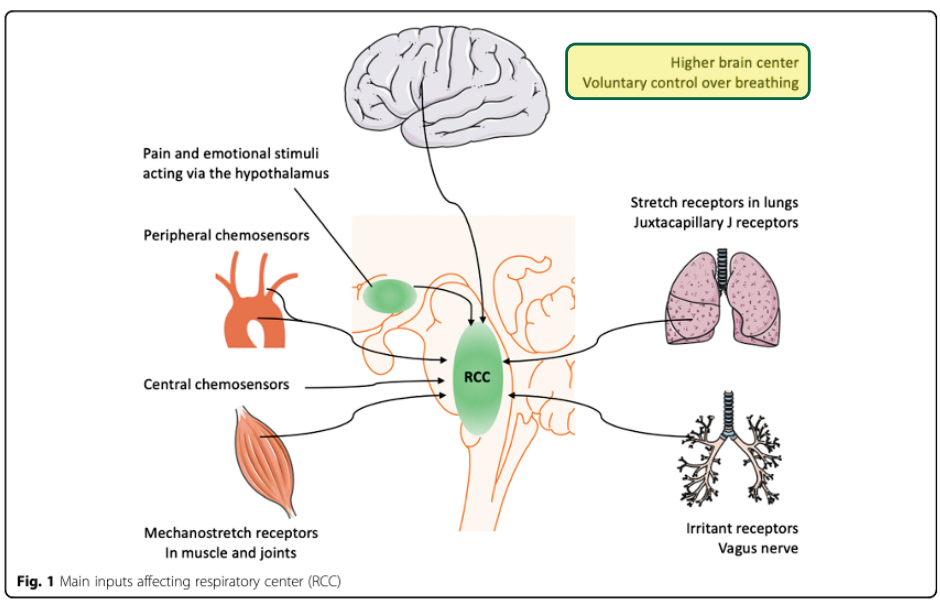
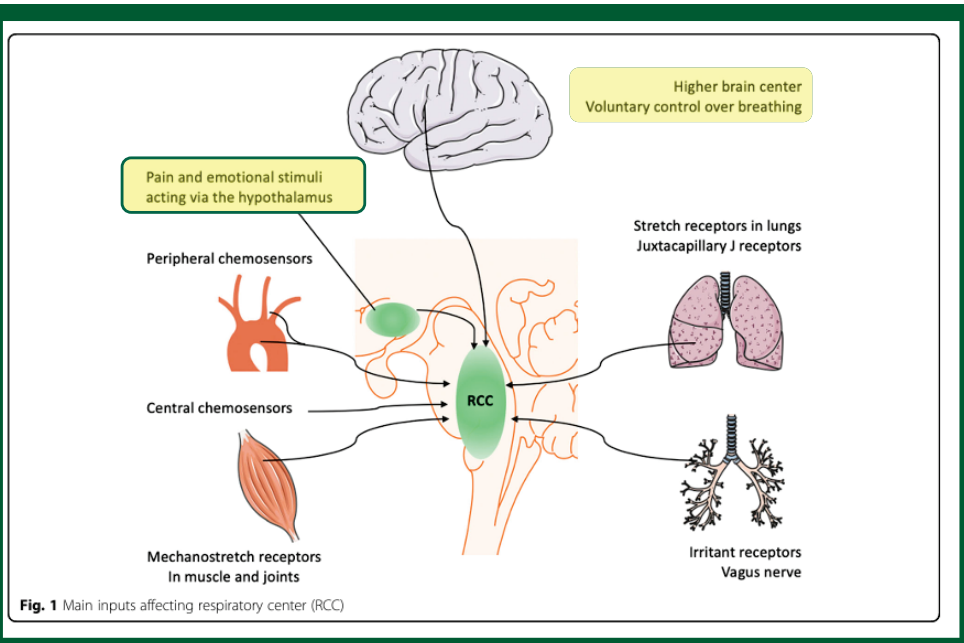


Fig. 1 Main inputs affecting respiratory center (RCC)

The pathophysiology of ‘happy’ hypoxemia in COVID-19 Dhont et al.Respiratory Research (2020) 21:198



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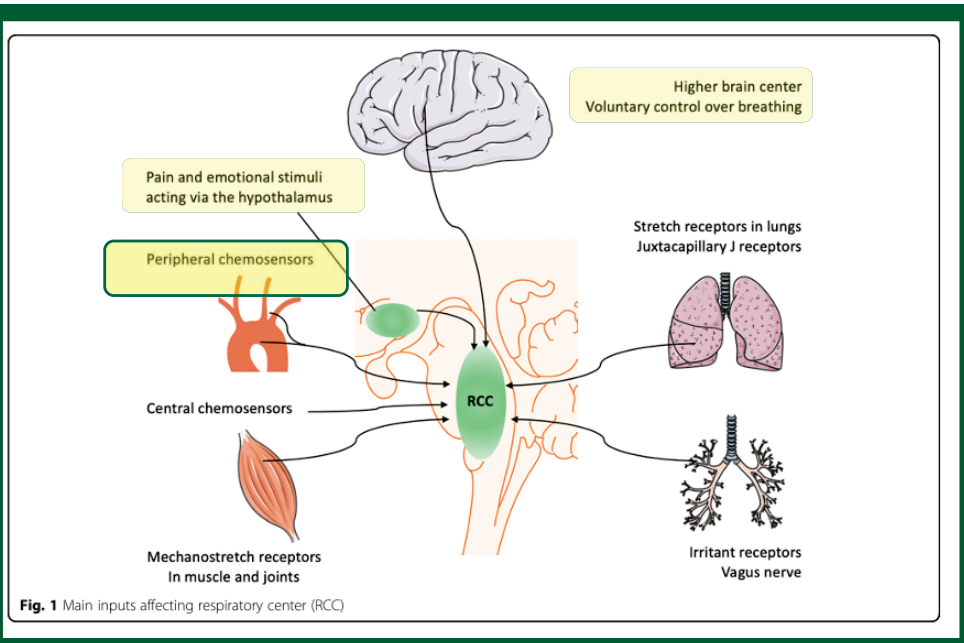

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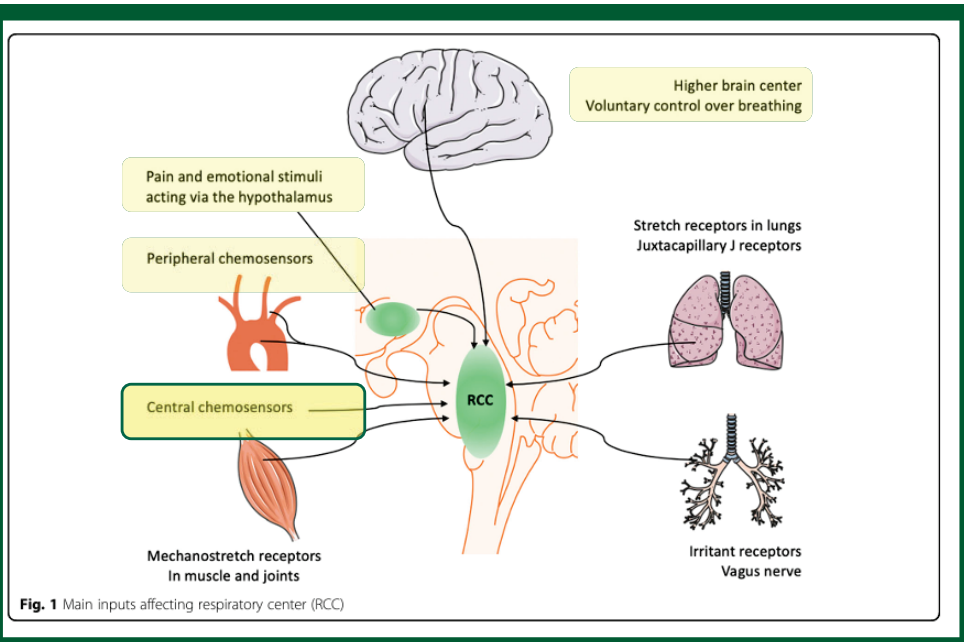

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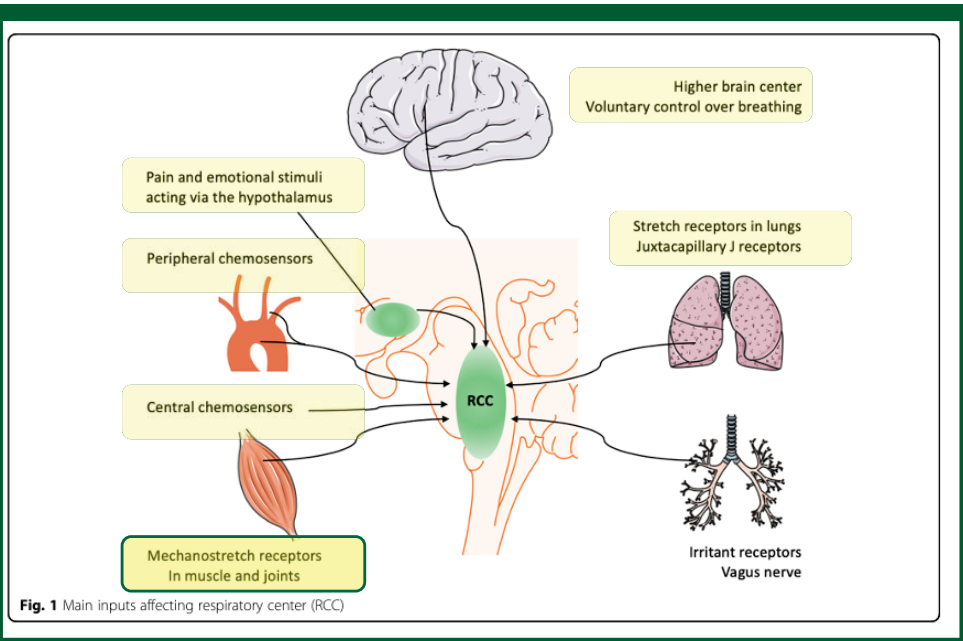

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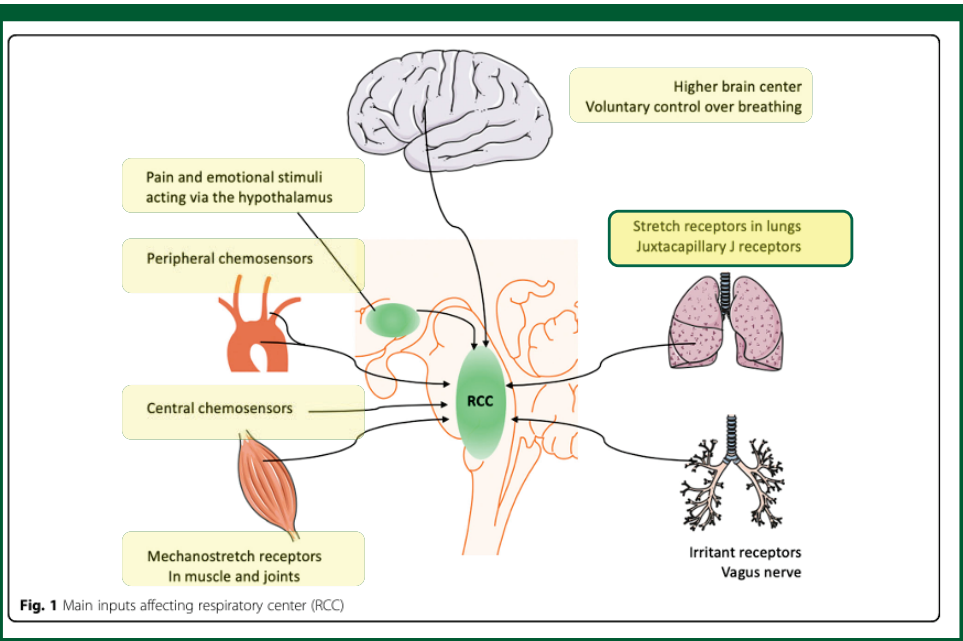

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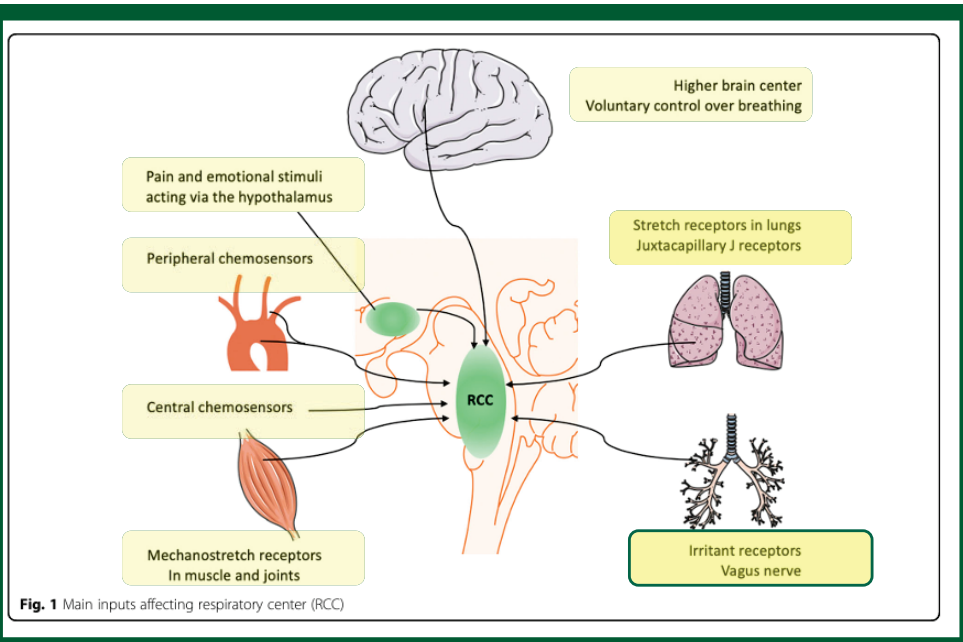

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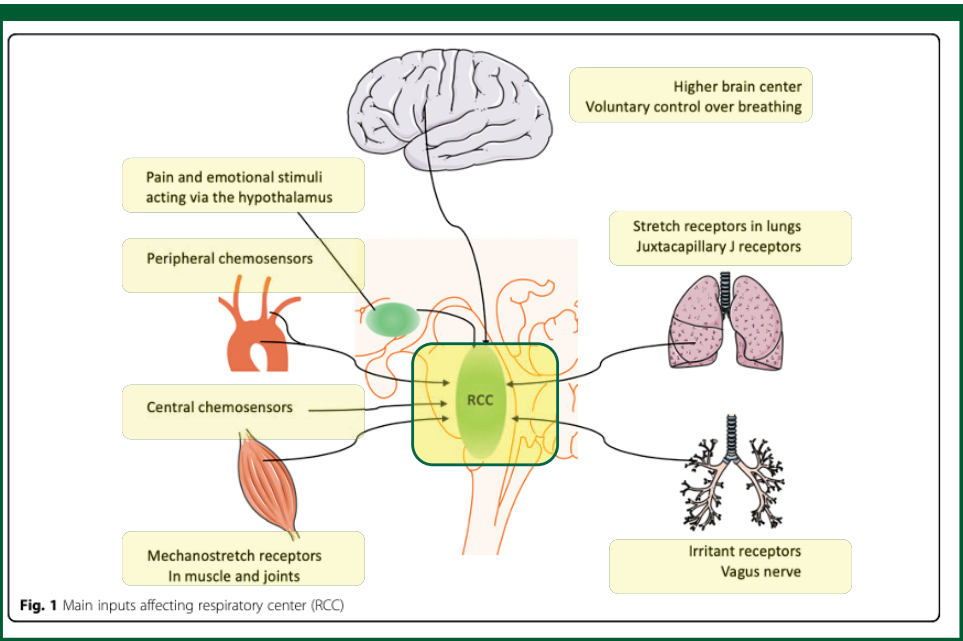

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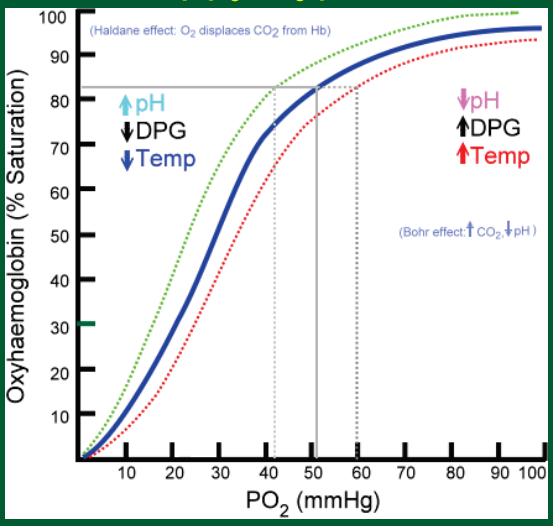

https://www.biosciencenotes.com/oxyhemoglobin-dissociation-curve/

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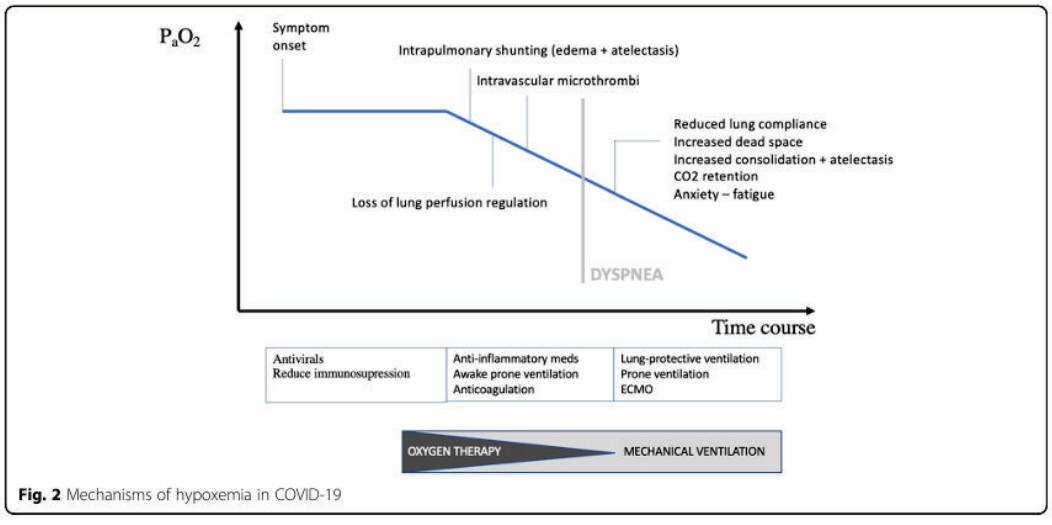
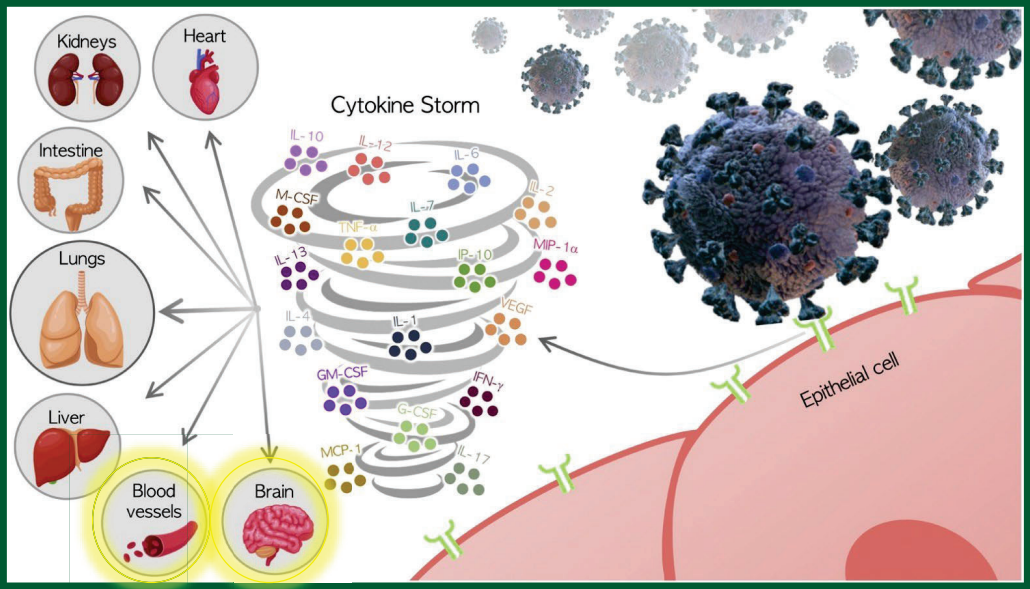


Fig. 2 Mechanisms of hypoxemia in COVID-19



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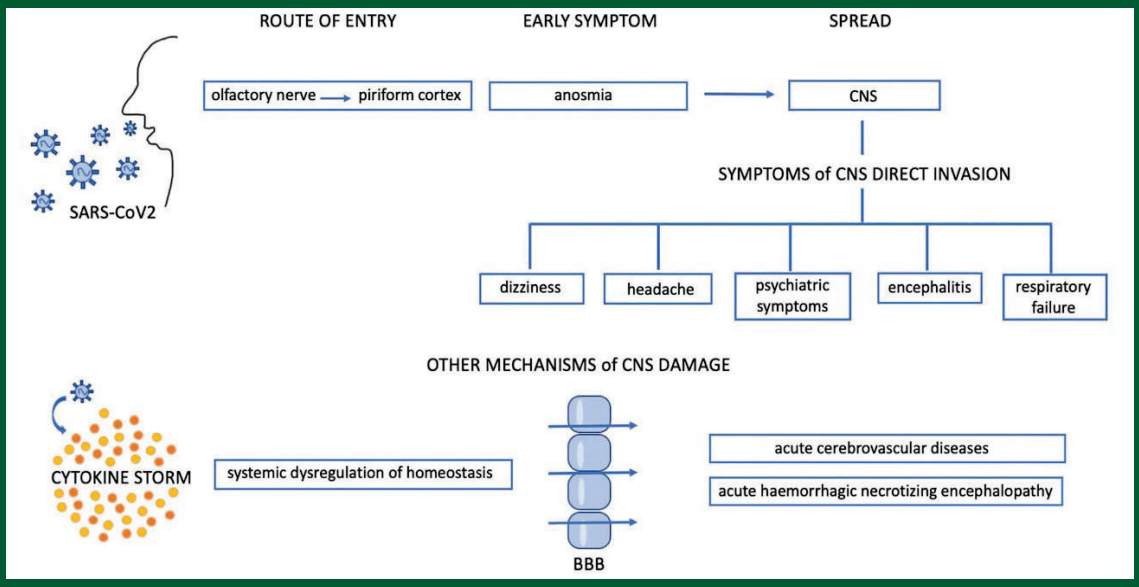

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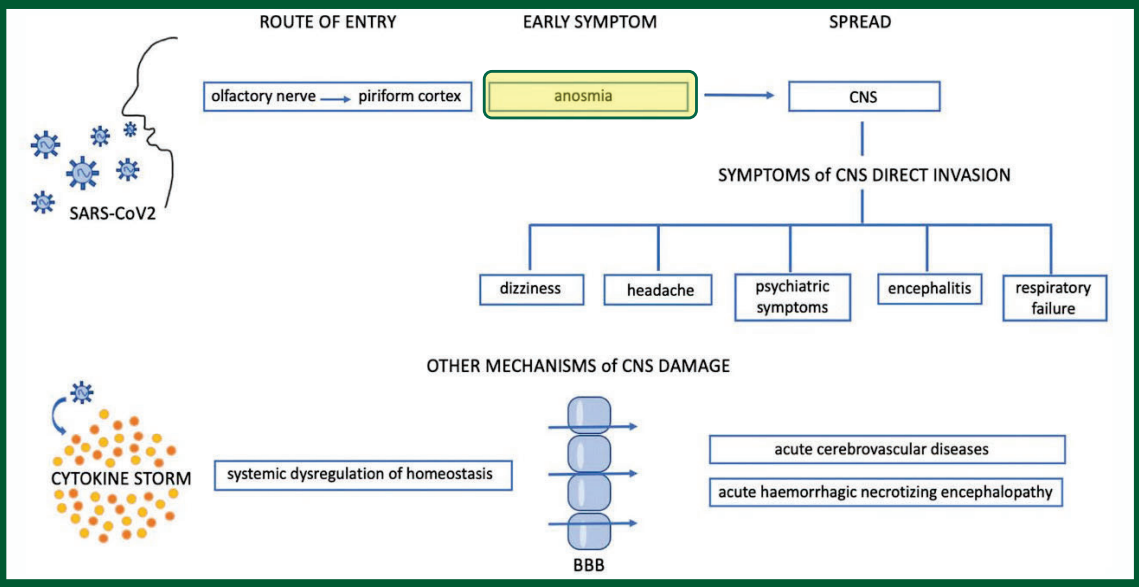

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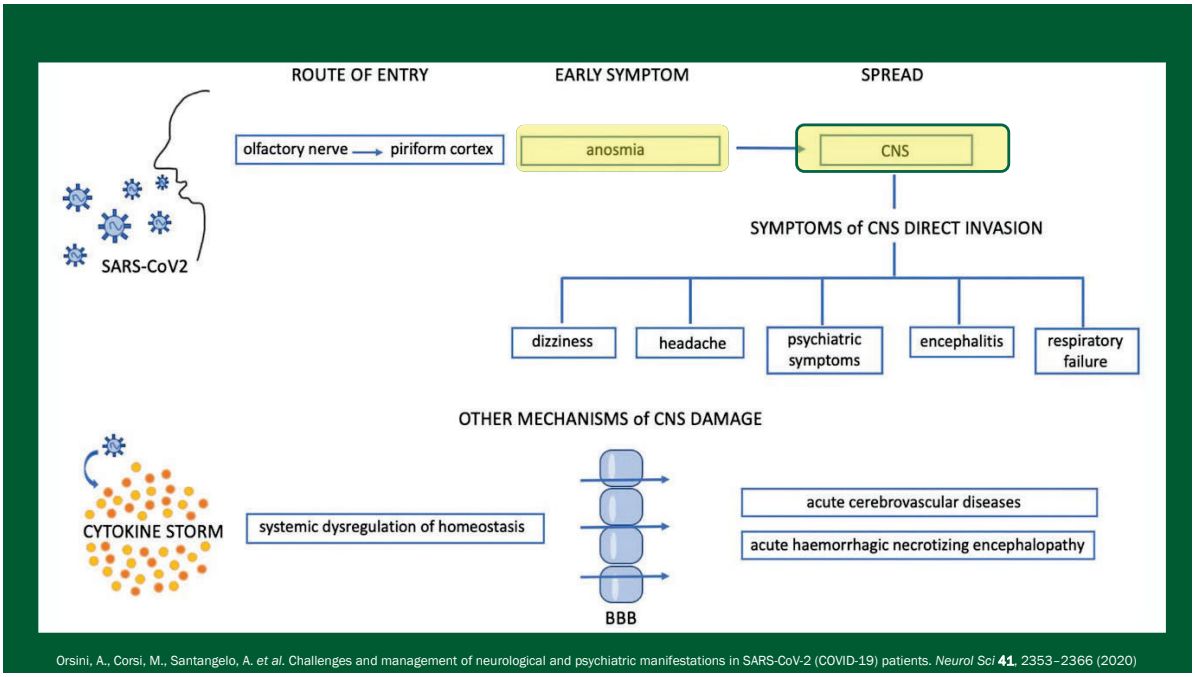

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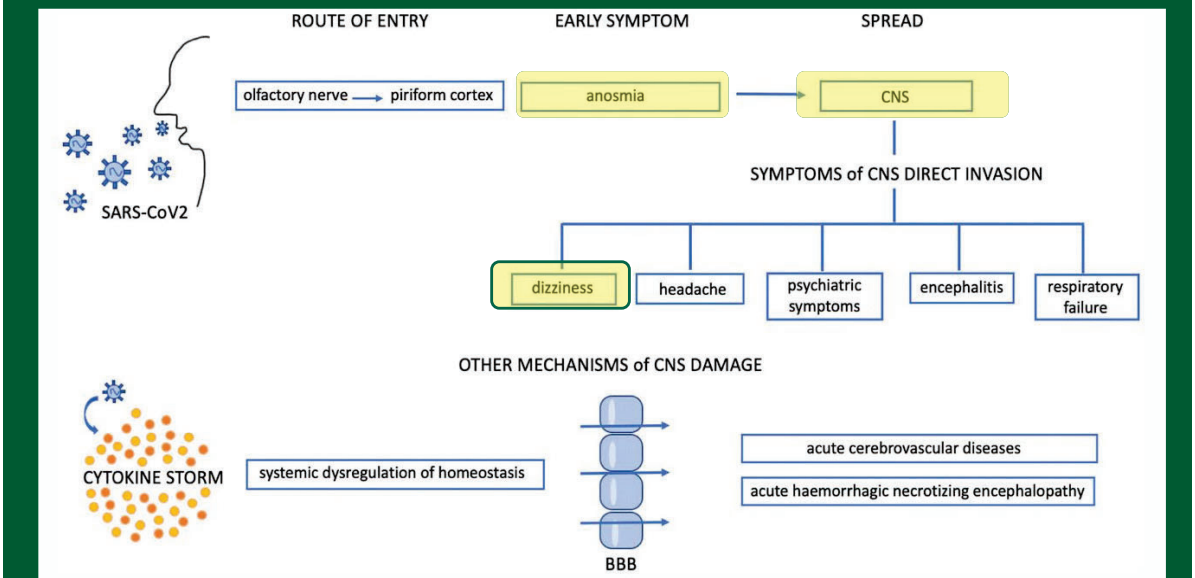

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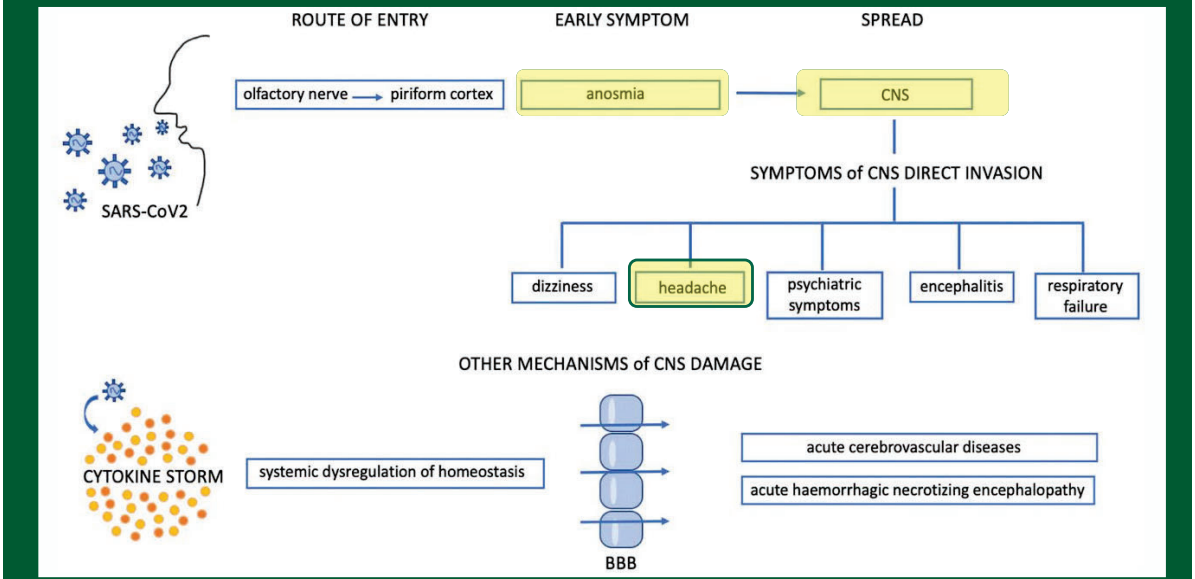

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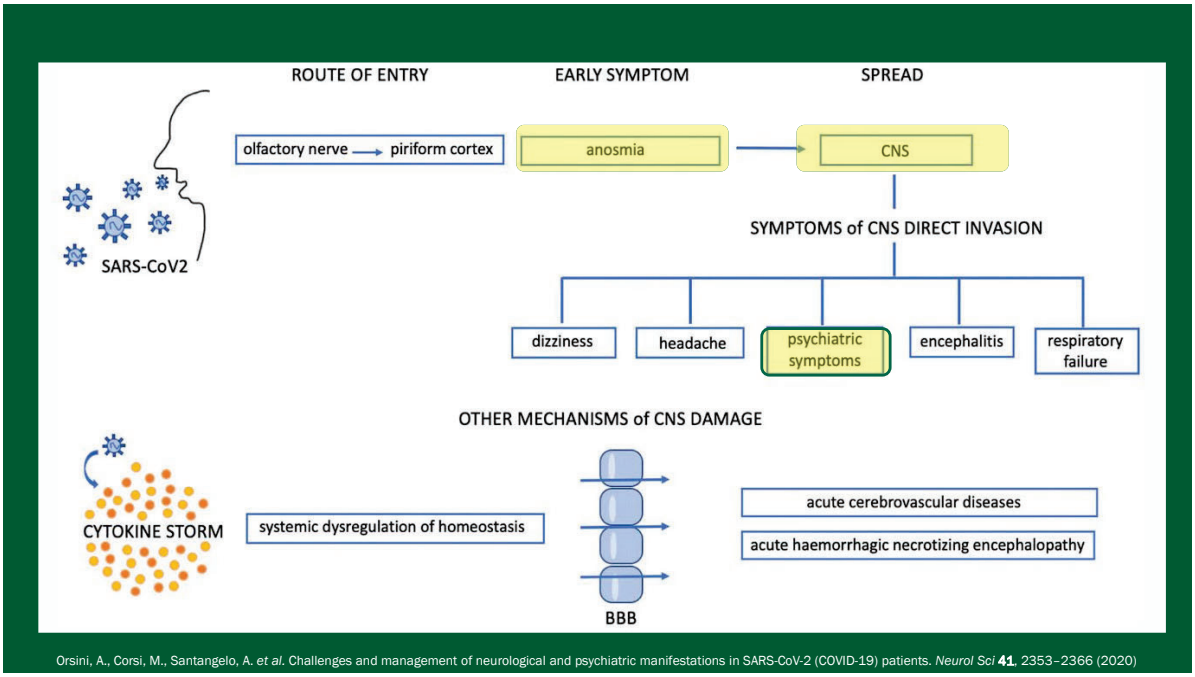

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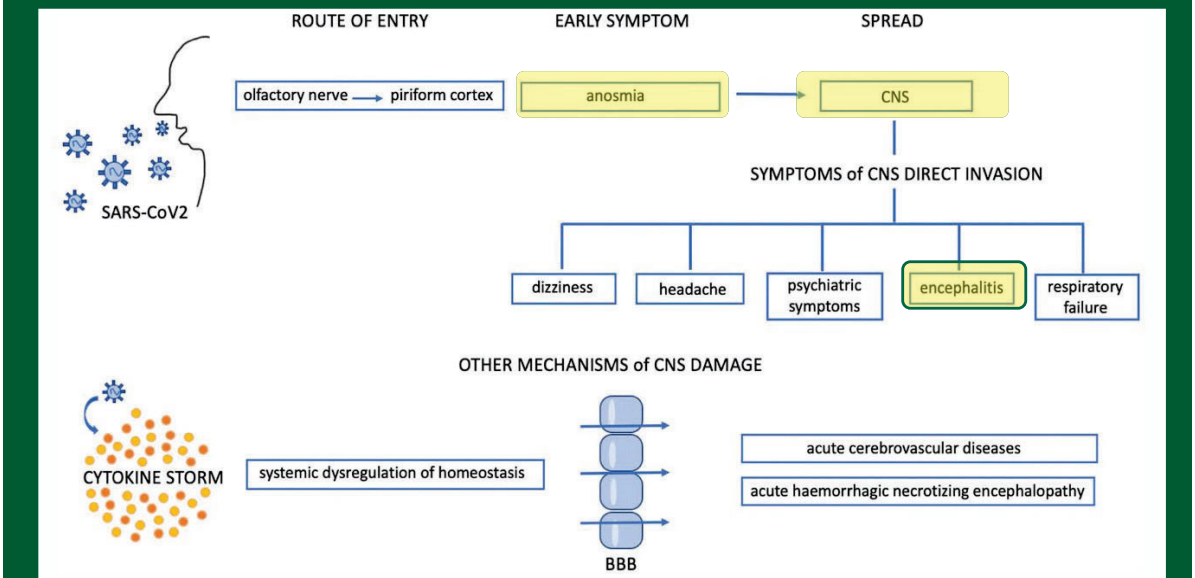

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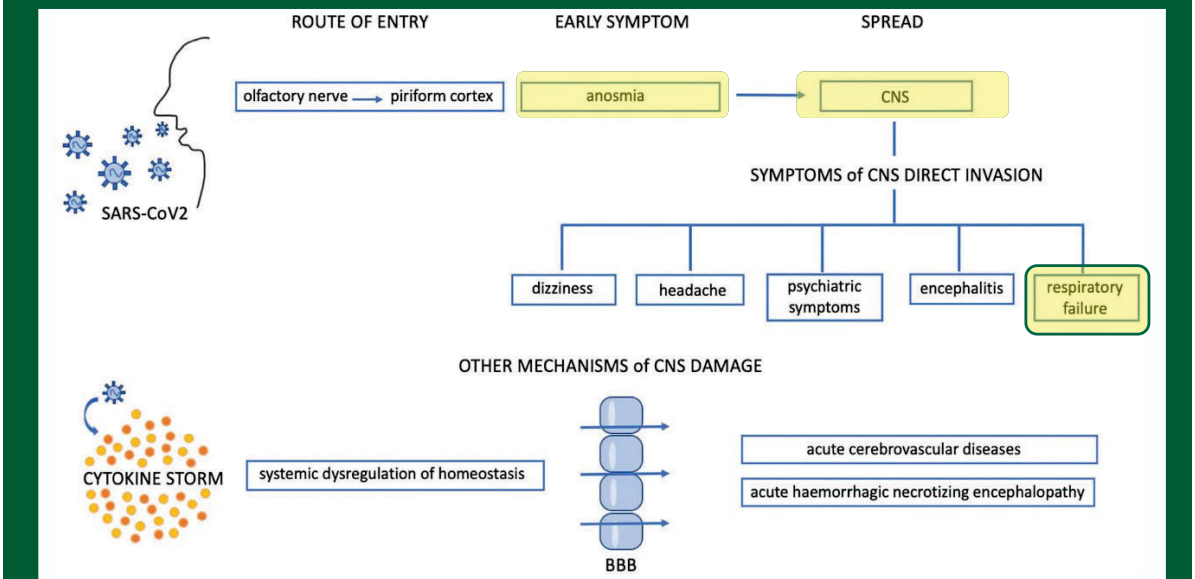

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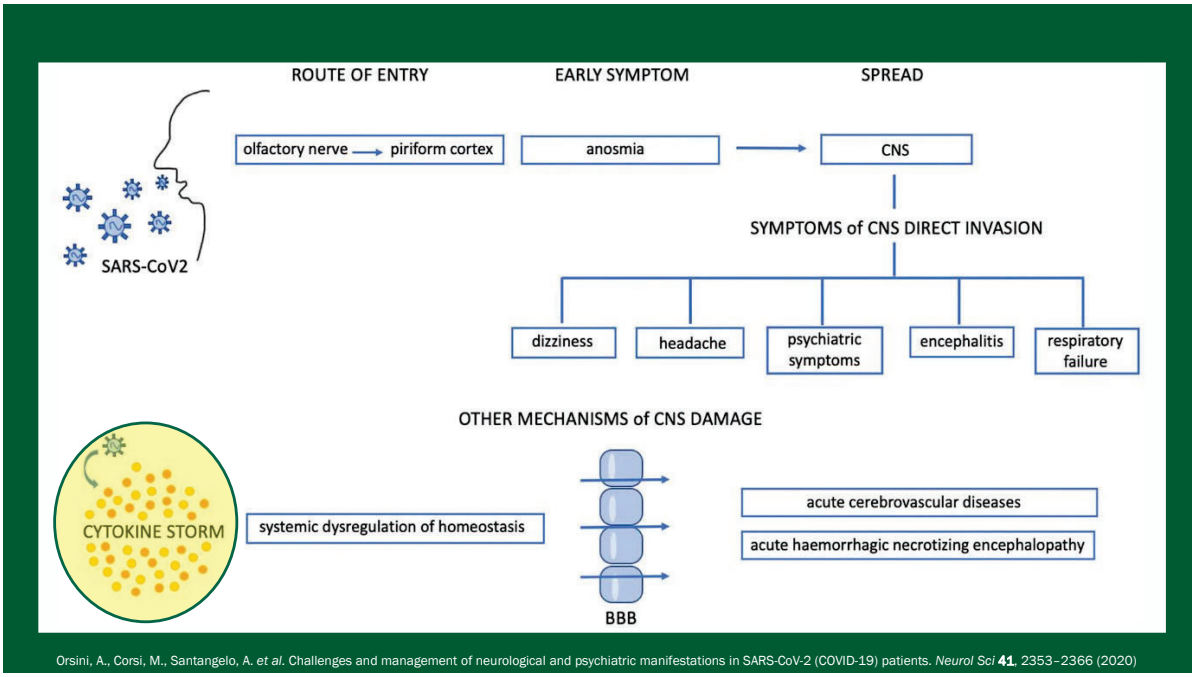

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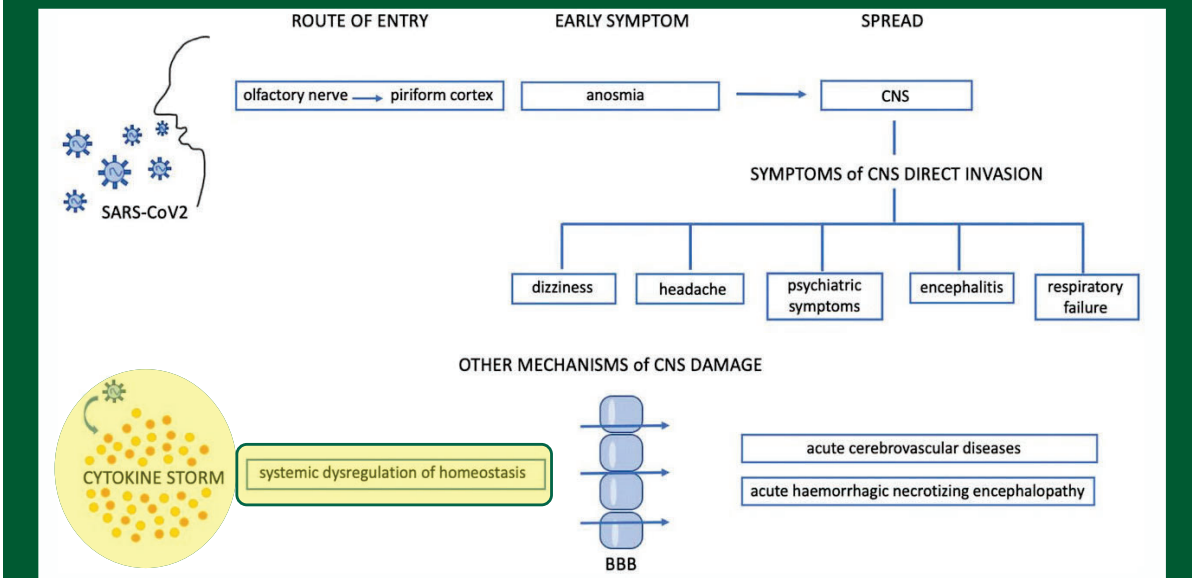

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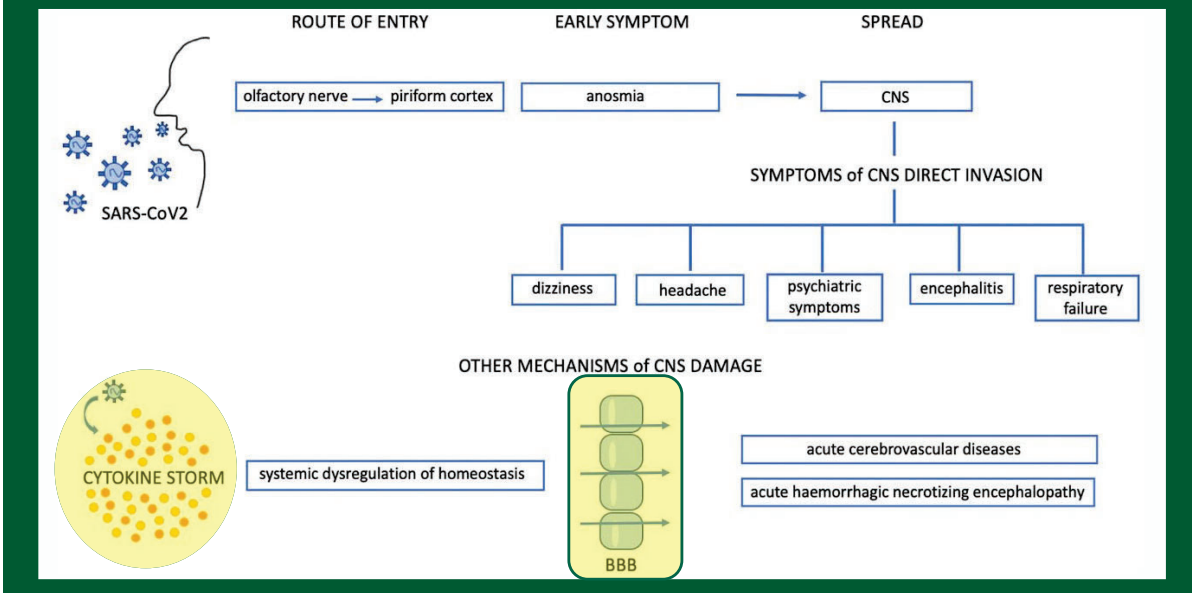

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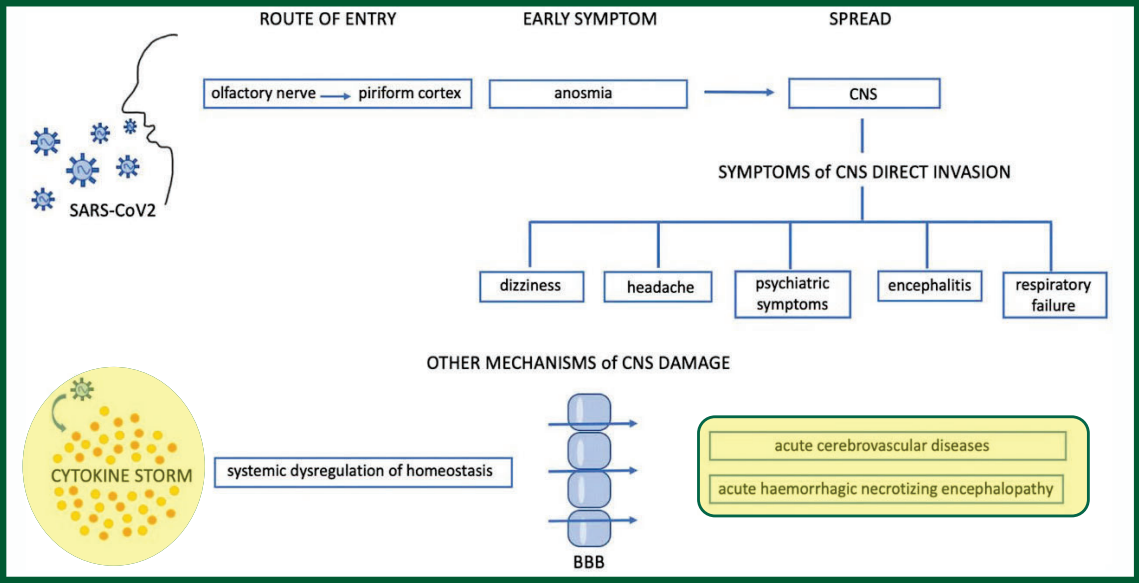

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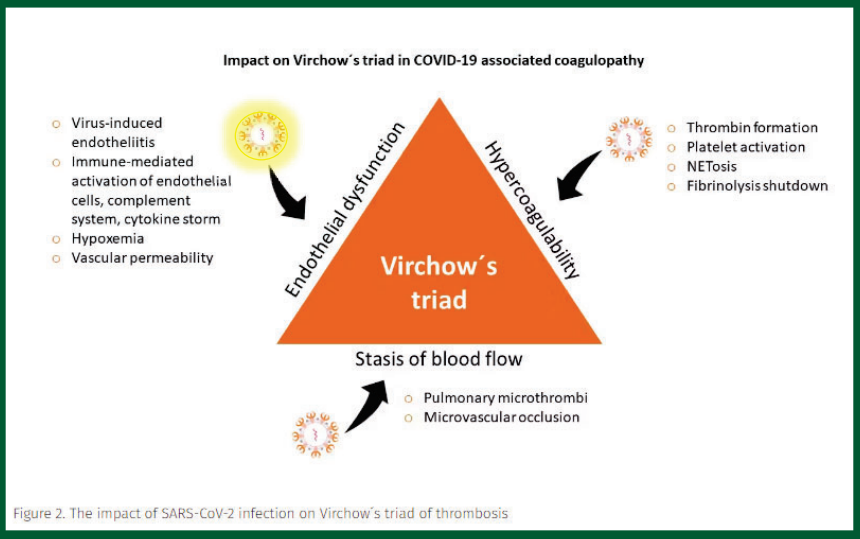
COVID Coagulopathy

From benign skin lesions on the feet (e.g., COVID toe), to life-threatening thrombotic events, the SARS-CoV-2 virus has high prevalence of deadly blood clots.

Early studies have shown that approximately 25-70 percent — of critically ill patients have a confirmed venous thromboembolism (VTE)

Approximately 70 percent of COVID-19 patients who died met criteria for disseminated intravascular coagulation (DIC)

Dahler, et al. **Pathophysiology of COVID-19-associated coagulopathy and its impact on laboratory measures of coagulation Molecular mlo-online.com**



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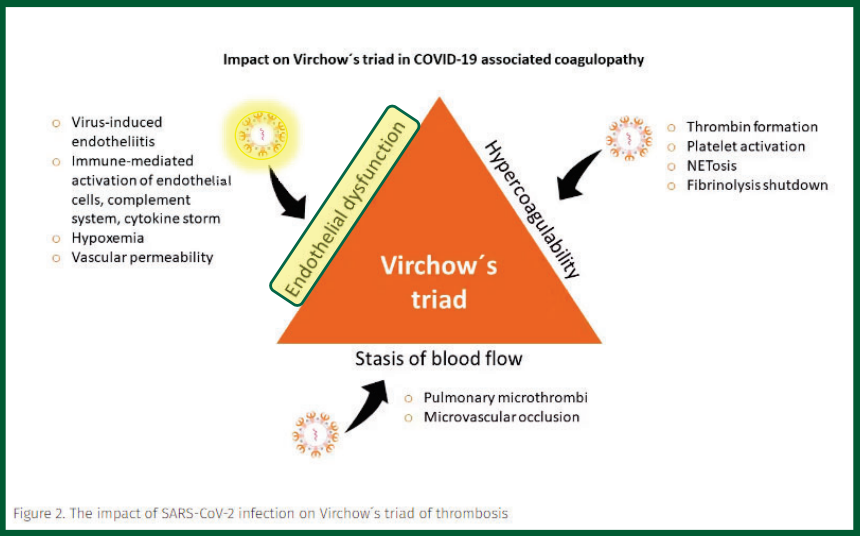
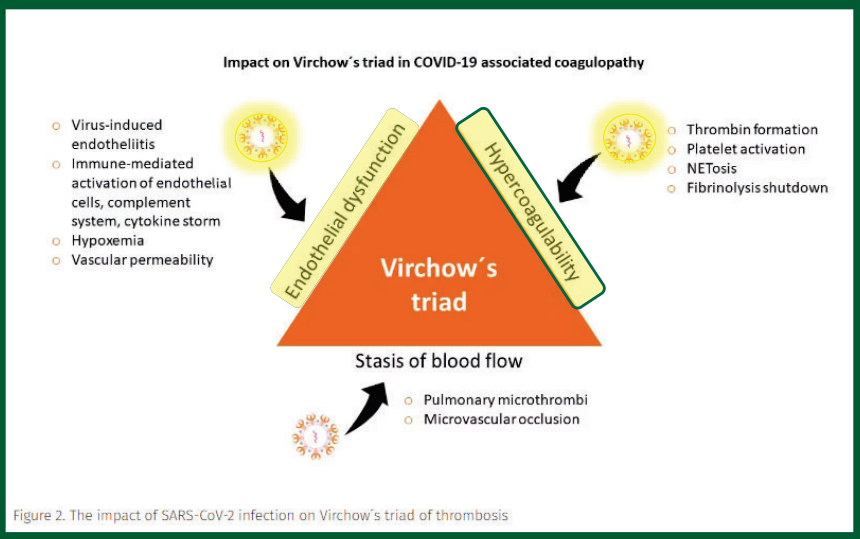


Figure 2. The impact of SARS-CoV-2 infection on Virchow´s triad of thrombosis



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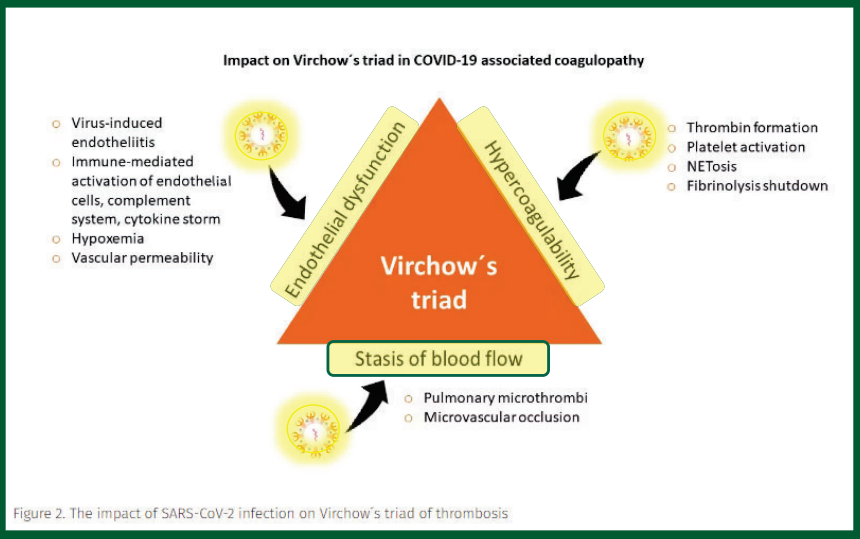

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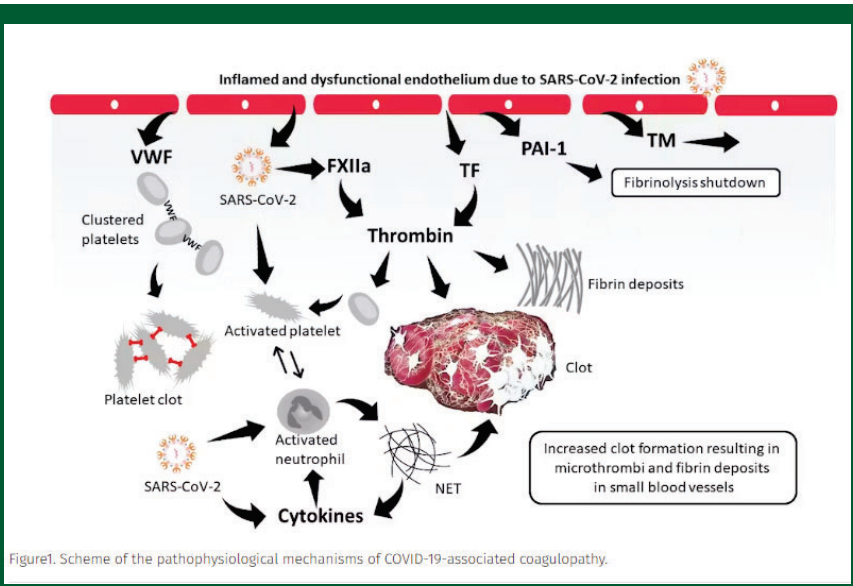

Figure1. Scheme of the pathophysiological mechanisms of COVID-19-associated coagulopathy.

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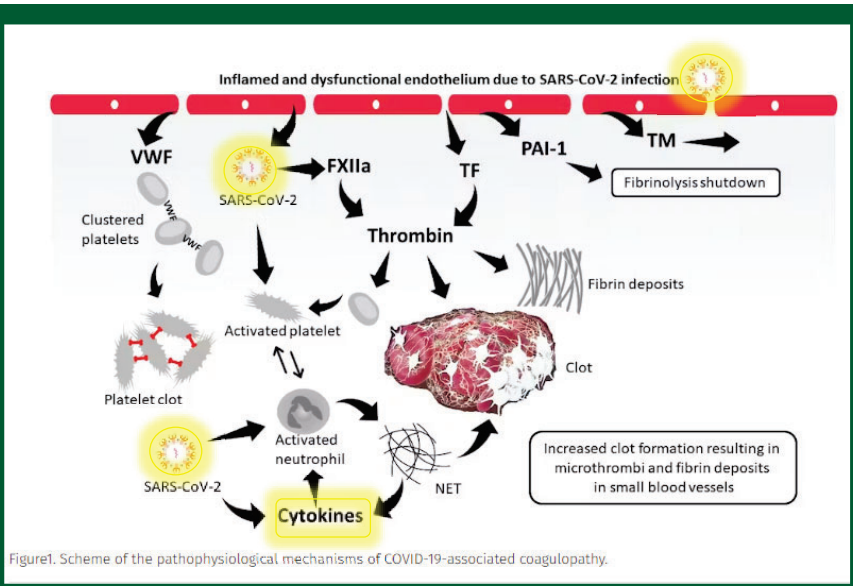

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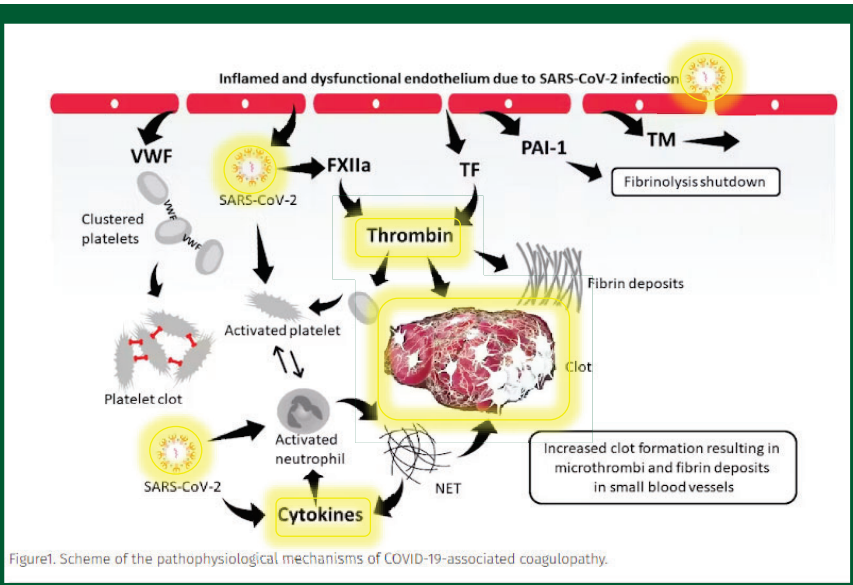

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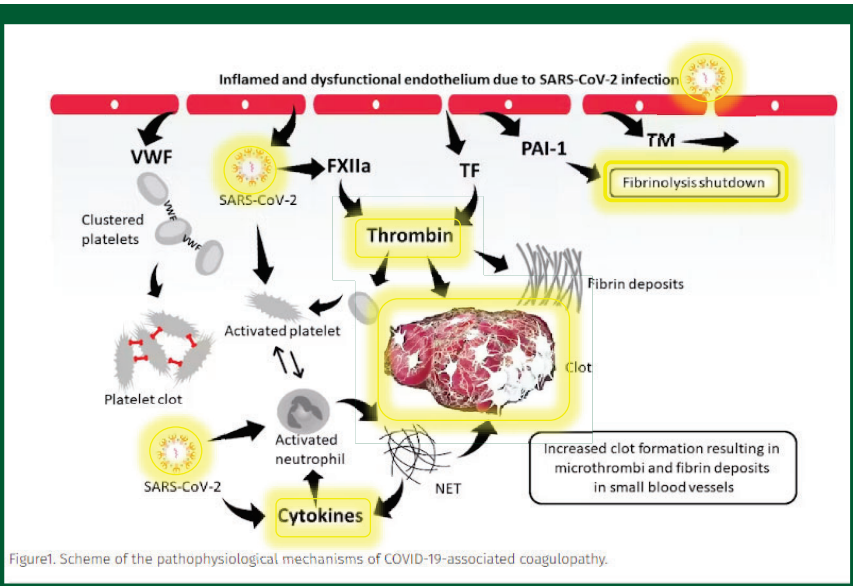

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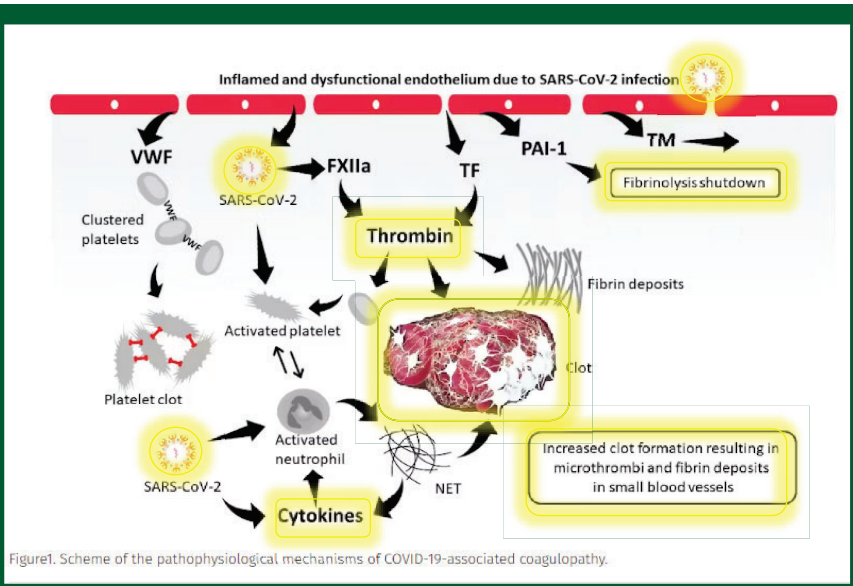

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Laboratory Coagulation Parameter	Change in COVID-19	Indication
D-dimer	↑↑	Increased clot formation
Prothrombin time	↑	Unbalanced extrinsic coagulation
Fibrinogen	↑ (acute phase) ↓ (DIC phase)	Inflammation DIC
Platelet count	↓/↑	Increased platelet consumption
Von Willebrand Factor (VWF)	↑↑	Endothelial dysfunction and platelet activation
Coagulation Factor VIII	↑↑	Thrombotic risk
Plasminogen Activator Inhibitor-1 (PAI-1)	↑↑	Endothelial dysfunction/fibrinolysis shutdown
Prothrombin fragment 1+2	↑↑	Increased clot formation
Soluble thrombomodulin	↑↑	Endothelial dysfunction/decreased anticoagulant activity of endothelium

Table 1. Significantly altered laboratory parameters of coagulation and their indication in COVID-19

Dahler, et al. **Pathophysiology of COVID-19-associated coagulopathy and its impact on laboratory measures of coagulation Molecular mlo-online.com**

COVID-19 Acute Neurological Complications

- Encephalopathy
- Encephalitis
- Acute Demyelinating Encephalomyelitis
- Stroke
- Guillain-Barré syndrome

Brown , et al. Pathophysiology, diagnosis, and management of neuroinflammation in covid-19 *BMJ* 2023

GCS-Neuro-COVID Study

28 centers, 13 countries,
Documented Neurological Manifestations

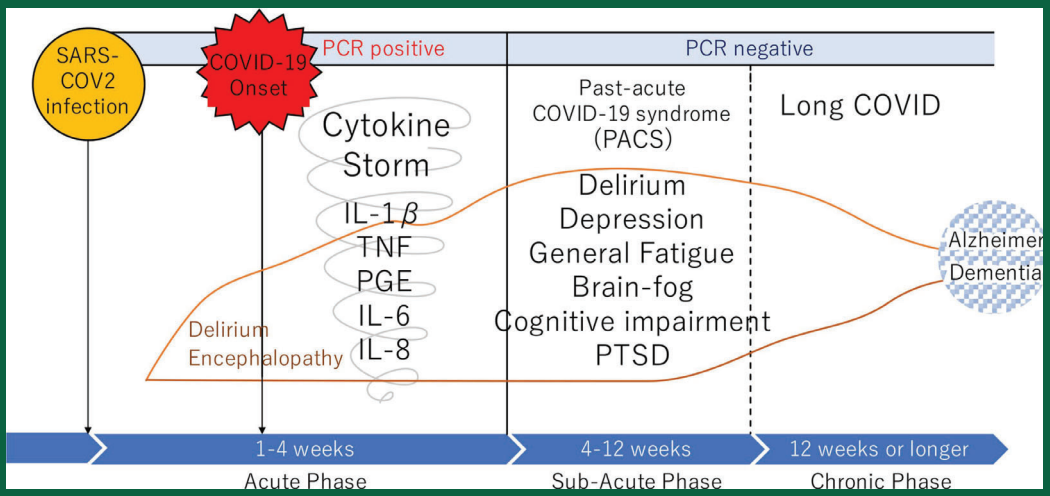
- **Headache (37%)**
- **Anosmia or ageusia (26%)**
- **Acute encephalopathy (49%)**
- **Coma (17%)**
- **Stroke (6%)**
- **Meningitis/encephalitis (0.5%)**

GCS-Neuro-COVID Consortium and the ENERGY Consortium. JAMA Netw Open2021

...COVID-19 delirium is associated with autoimmune encephalitis, post-ARDS brain dysfunction caused by systemic hyperinflammation and neuroinflammation associated with COVID-19 ...multiple strokes caused by abnormal blood clotting, microthrombosis, and extensive cerebral infarction

COVID-19 patients who left the ICU after intubation showed cognitive decline at the rate of 46.6% at approximately 6 months (as compared to 31.8% in non-COVID patients) and 53.1% at approximately 1 year

Kyohei, et al COVID-19 delirium and encephalopathy: Pathophysiology assumed in the first 3 years of the ongoing pandemic, Brain Disorders, Volume 10, 2023,



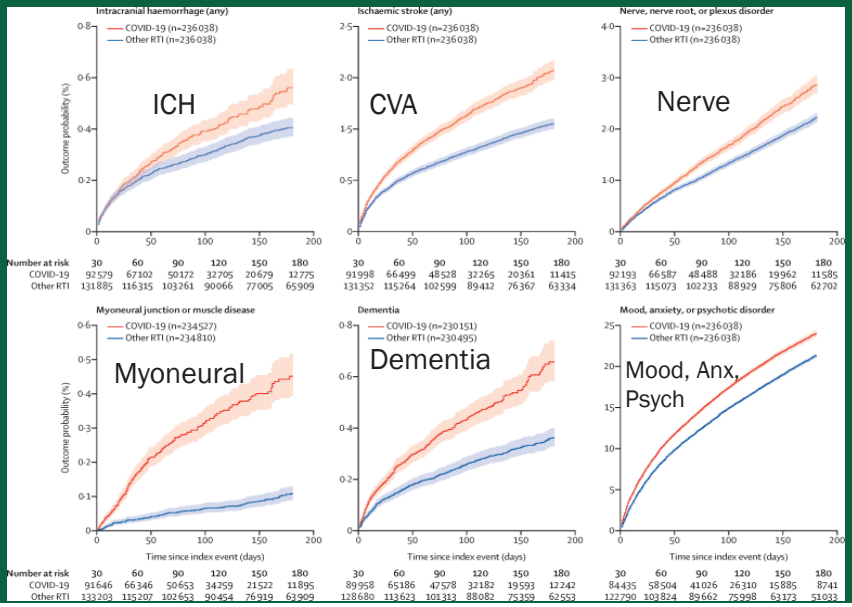
Kyohei, et al COVID-19 delirium and encephalopathy: Pathophysiology assumed in the first 3 years of the ongoing pandemic, Brain Disorders, Volume 10, 2023,

The Lancet 2021

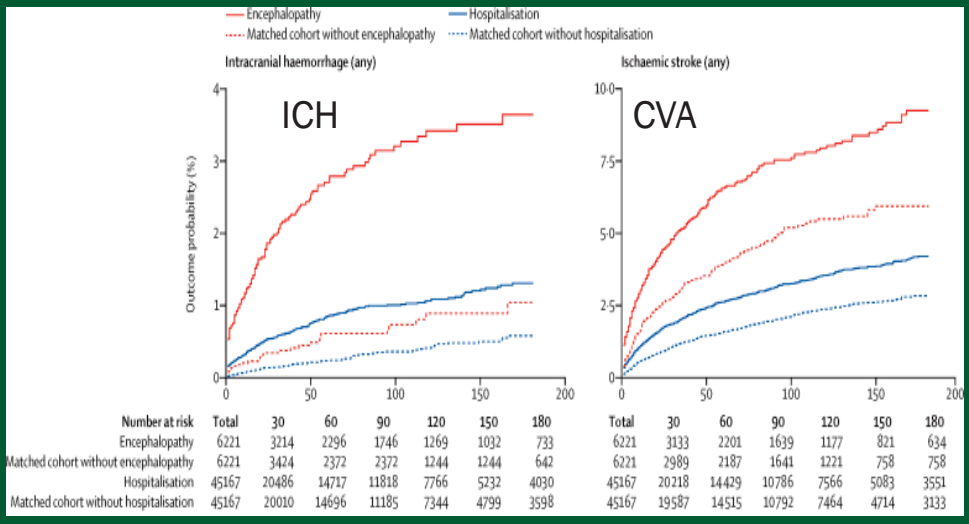
6-month neurological and psychiatric outcomes in 236,379 survivors of COVID-19: a retrospective cohort study using electronic health records

Taquet M, et al. Lancet Psychiatry. 2021 May;8(5):416-427

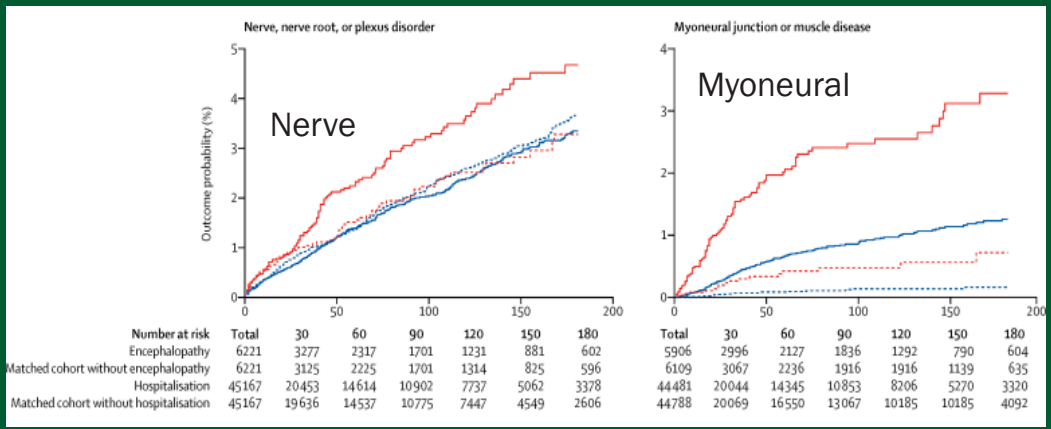
Incidence of Major Outcomes after COVID-19 vs Respiratory Infections



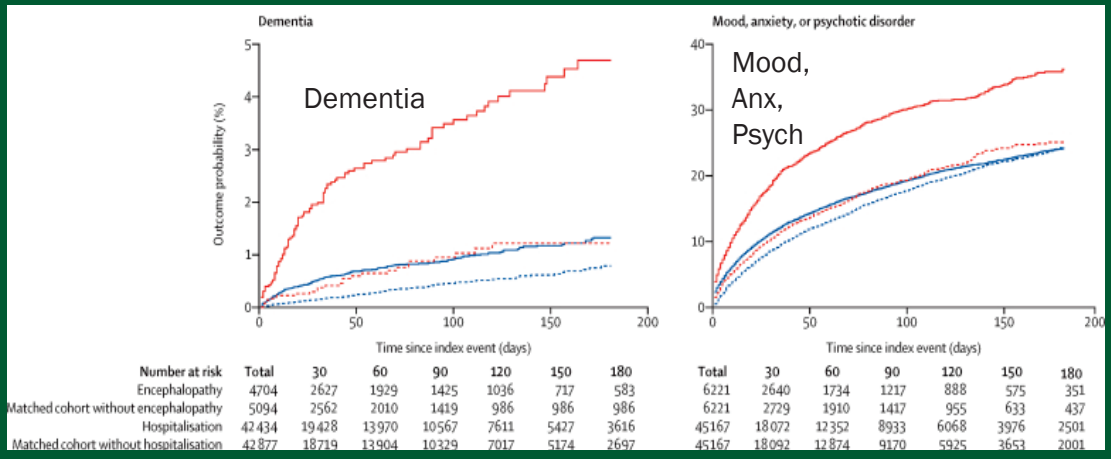
Incidence of major outcomes after COVID-19
Hospitalisation vs No Hospitalisation
Encephalopathy vs No Encephalopathy



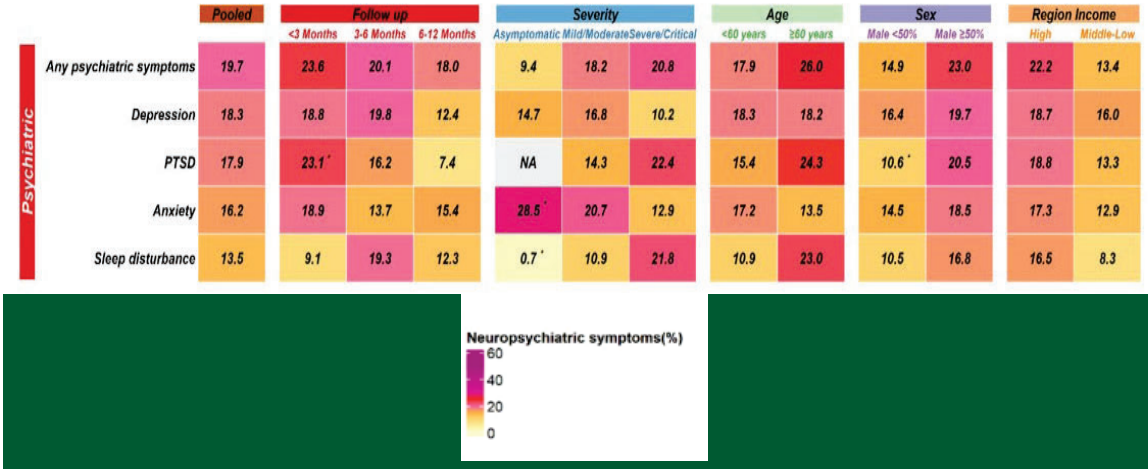
Number at risk	Total	30	60	90	120	150	180	Total	30	60	90	120	150	180
Encephalopathy	6221	3214	2296	1746	1269	1032	733	6221	3133	2201	1639	1177	821	634
Matched cohort without encephalopathy	6221	3424	2372	2372	1244	1244	642	6221	2989	2187	1641	1221	758	758
Hospitalisation	45167	20486	14717	11818	7766	5232	4030	45167	20218	14429	10786	7566	5083	3551
Matched cohort without hospitalisation	45167	20010	14696	11185	7344	4799	3598	45167	19587	14515	10792	7464	4714	3133



Number at risk	Total	30	60	90	120	150	180	Total	30	60	90	120	150	180
Encephalopathy	6221	3277	2317	1701	1231	881	602	5906	2996	2127	1836	1292	790	604
Matched cohort without encephalopathy	6221	3125	2225	1701	1314	825	596	6109	3067	2236	1916	1916	1139	635
Hospitalisation	45167	20453	14614	10902	7737	5062	3378	44481	20044	14345	10853	8206	5270	3320
Matched cohort without hospitalisation	45167	19636	14537	10775	7447	4549	2606	44788	20069	16550	13067	10185	10185	4092

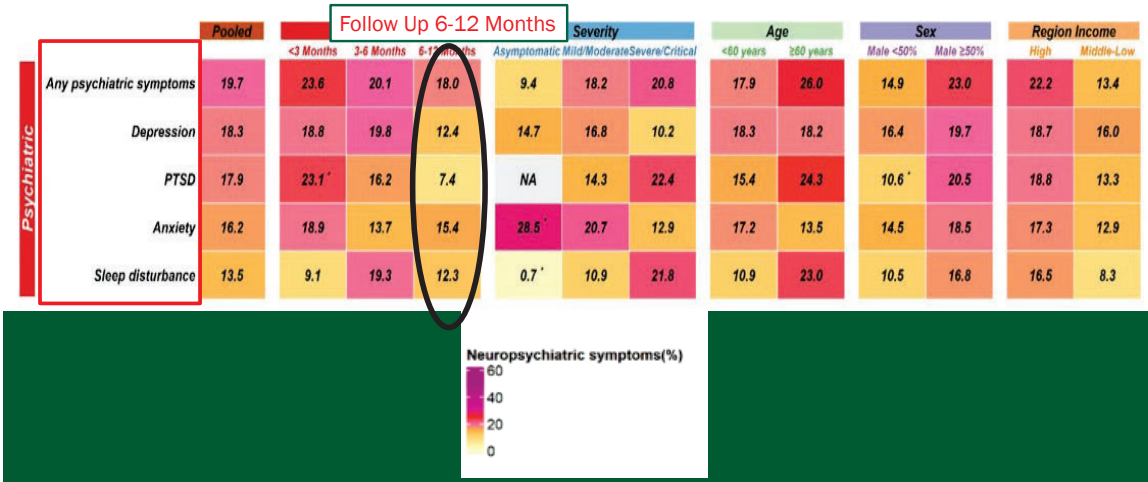


A systematic review and meta-analysis of long term physical and mental sequelae of COVID-19 pandemic



Zeng, N, et al *Mol Psychiatry* **28**, 423–433 (2023).

A systematic review and meta-analysis of long term physical and mental sequelae of COVID-19 pandemic



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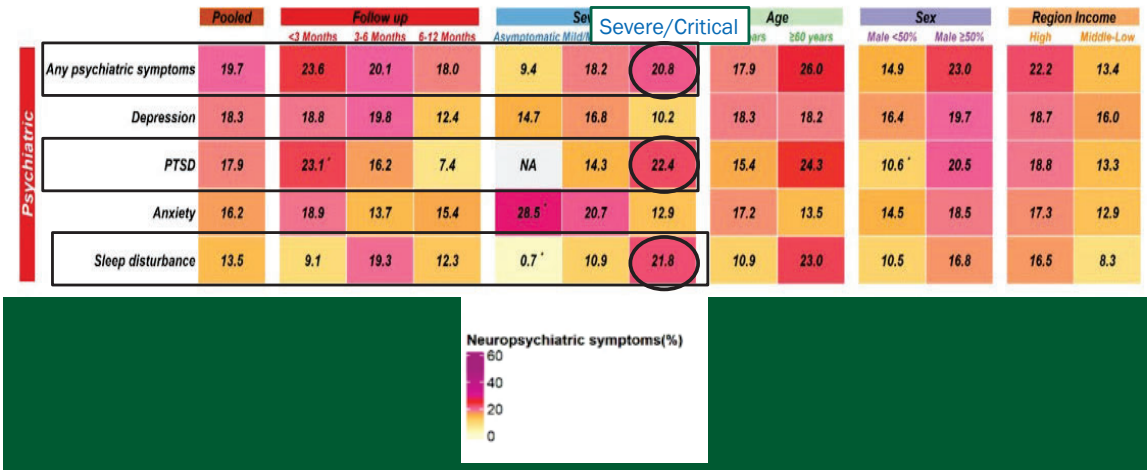

Zeng, N, et al *Mol Psychiatry* **28**, 423–433 (2023).

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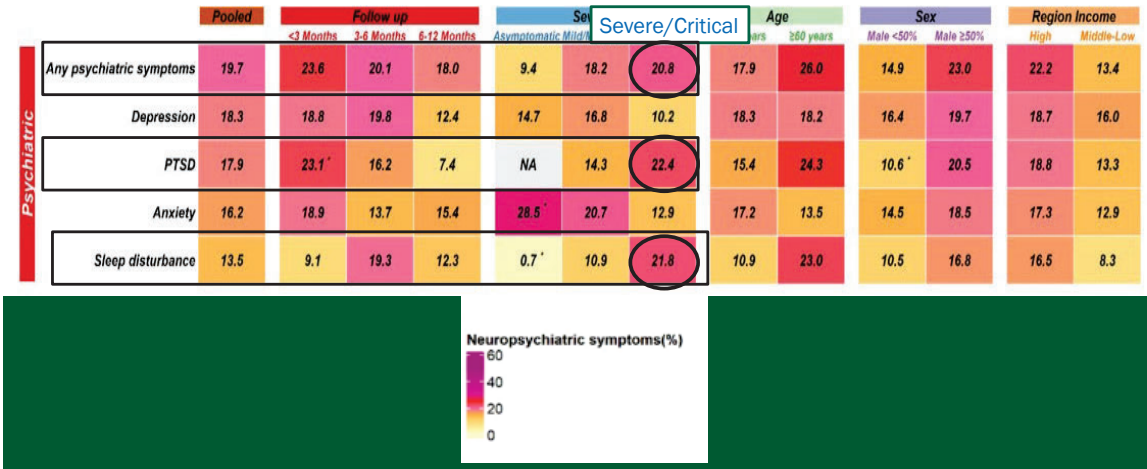

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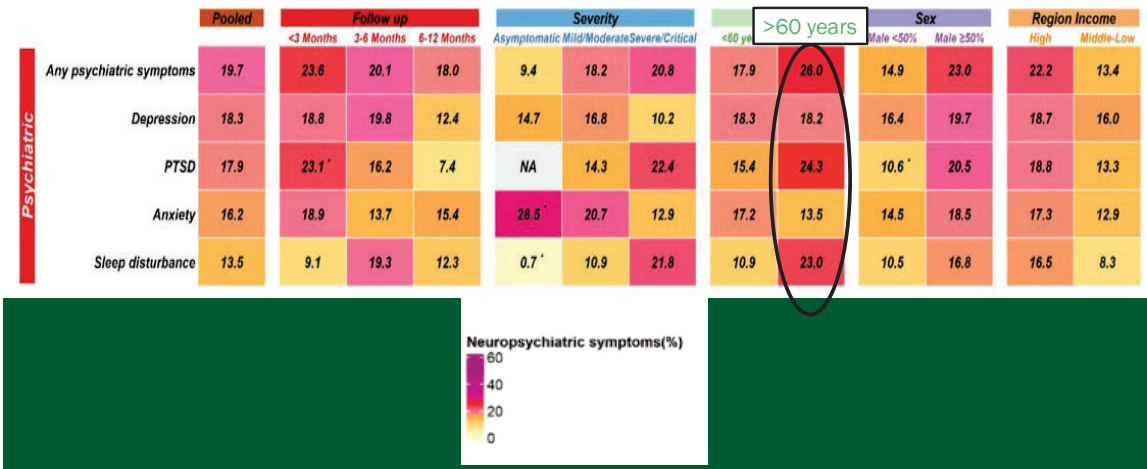

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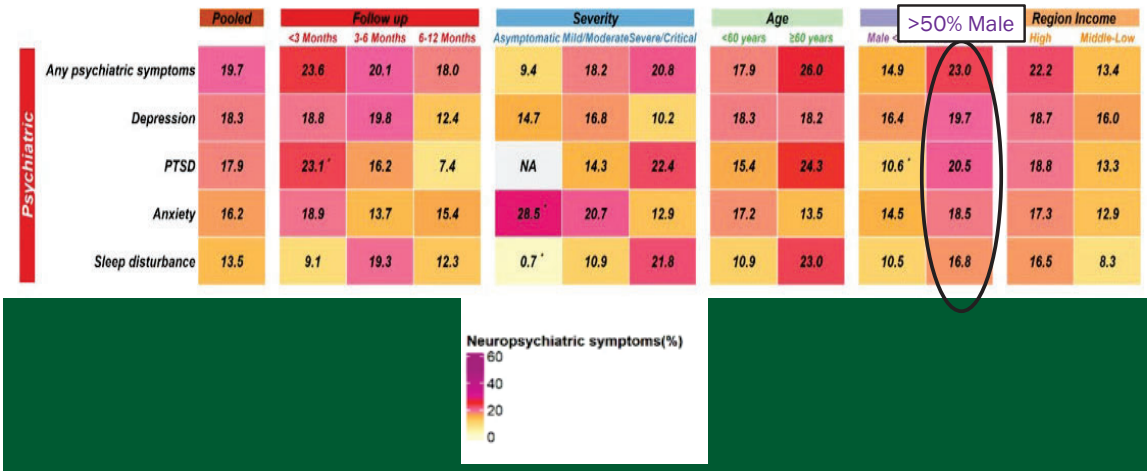
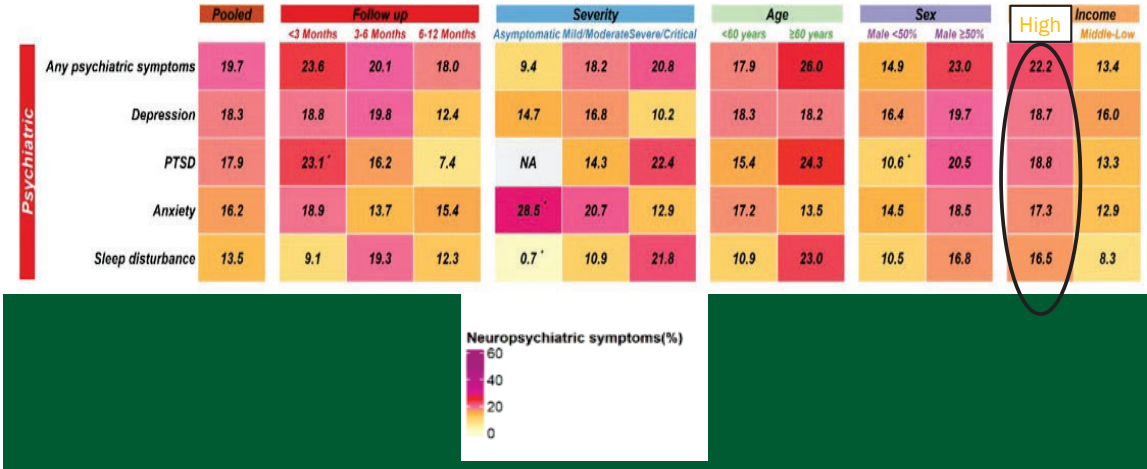


Zeng, N, et al *Mol Psychiatry* **28**, 423–433 (2023).

A systematic review and meta-analysis of long term physical and mental sequelae of COVID-19 pandemic



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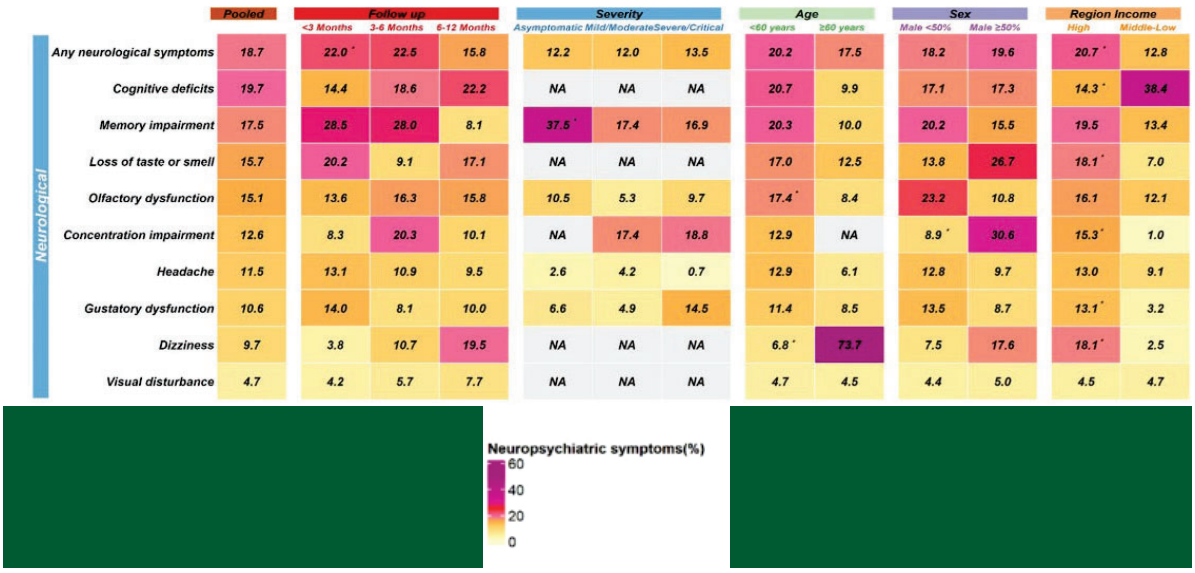

Follow Up 6-12 Months

	Pooled	<3 Months	3-6 Months	6-12 Months	Severity: Asymptomatic	Severity: Mild/Moderate	Severity: Severe/Critical	Age: <60 years	Age: ≥60 years	Sex: Male <50%	Sex: Male ≥50%	Region Income: High	Region Income: Middle-Low
Neurological: Any neurological symptoms	18.7	22.0 *	22.5	15.8	12.2	12.0	13.5	20.2	17.5	18.2	19.6	20.7 *	12.8
Neurological: Cognitive deficits	19.7	14.4	18.6	22.2	NA	NA	NA	20.7	9.9	17.1	17.3	14.3 *	38.4
Neurological: Memory impairment	17.5	28.5	28.0	8.1	37.5 *	17.4	16.9	20.3	10.0	20.2	15.5	19.5	13.4
Neurological: Loss of taste or smell	15.7	20.2	9.1	17.1	NA	NA	NA	17.0	12.5	13.8	26.7	18.1 *	7.0
Neurological: Olfactory dysfunction	15.1	13.6	16.3	15.8	10.5	5.3	9.7	17.4 *	8.4	23.2	10.8	16.1	12.1
Neurological: Concentration impairment	12.6	8.3	20.3	10.1	NA	17.4	18.8	12.9	NA	8.9 *	30.6	15.3 *	1.0
Neurological: Headache	11.5	13.1	10.9	9.5	2.6	4.2	0.7	12.9	6.1	12.8	9.7	13.0	9.1
Neurological: Gustatory dysfunction	10.6	14.0	8.1	10.0	6.6	4.9	14.5	11.4	8.5	13.5	8.7	13.1 *	3.2
Neurological: Dizziness	9.7	3.8	10.7	19.5	NA	NA	NA	6.8 *	73.7	7.5	17.6	18.1 *	2.5
Neurological: Visual disturbance	4.7	4.2	5.7	7.7	NA	NA	NA	4.7	4.5	4.4	5.0	4.5	4.7

Neuropsychiatric symptoms(%)
60
40
20
0

Follow Up 6-12 Months

	Pooled	<3 Months	3-6 Months	6-12 Months	Severity: Asymptomatic	Severity: Mild/Moderate	Severity: Severe/Critical	Age: <60 years	Age: ≥60 years	Sex: Male <50%	Sex: Male ≥50%	Region Income: High	Region Income: Middle-Low
Neurological: Any neurological symptoms	18.7	22.0 *	22.5	15.8	12.2	12.0	13.5	20.2	17.5	18.2	19.6	20.7 *	12.8
Neurological: Cognitive deficits	19.7	14.4	18.6	22.2	NA	NA	NA	20.7	9.9	17.1	17.3	14.3 *	38.4
Neurological: Memory impairment	17.5	28.5	28.0	8.1	37.5 *	17.4	16.9	20.3	10.0	20.2	15.5	19.5	13.4
Neurological: Loss of taste or smell	15.7	20.2	9.1	17.1	NA	NA	NA	17.0	12.5	13.8	26.7	18.1 *	7.0
Neurological: Olfactory dysfunction	15.1	13.6	16.3	15.8	10.5	5.3	9.7	17.4 *	8.4	23.2	10.8	16.1	12.1
Neurological: Concentration impairment	12.6	8.3	20.3	10.1	NA	17.4	18.8	12.9	NA	8.9 *	30.6	15.3 *	1.0
Neurological: Headache	11.5	13.1	10.9	9.5	2.6	4.2	0.7	12.9	6.1	12.8	9.7	13.0	9.1
Neurological: Gustatory dysfunction	10.6	14.0	8.1	10.0	6.6	4.9	14.5	11.4	8.5	13.5	8.7	13.1 *	3.2
Neurological: Dizziness	9.7	3.8	10.7	19.5	NA	NA	NA	6.8 *	73.7	7.5	17.6	18.1 *	2.5
Neurological: Visual disturbance	4.7	4.2	5.7	7.7	NA	NA	NA	4.7	4.5	4.4	5.0	4.5	4.7

Neuropsychiatric symptoms(%)
60
40
20
0

Follow Up 6-12 Months

>60 years

	Pooled	<3 Months	3-6 Months	6-12 Months	Severity: Asymptomatic	Severity: Mild/Moderate	Severity: Severe/Critical	Age: <60 years	Age: ≥60 years	Sex: Male <50%	Sex: Male ≥50%	Region Income: High	Region Income: Middle-Low
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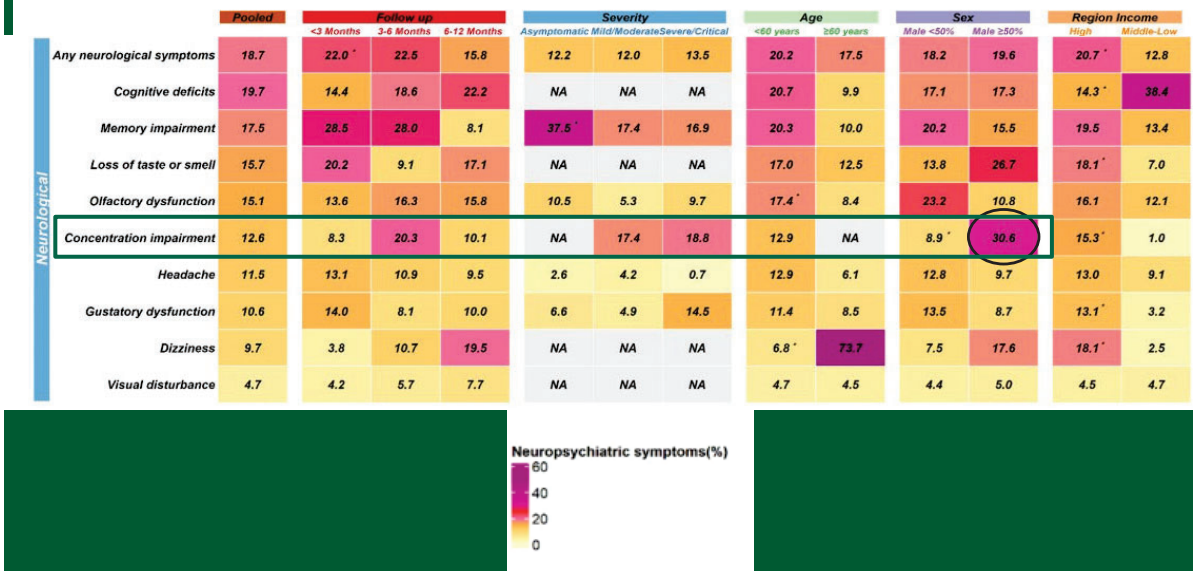
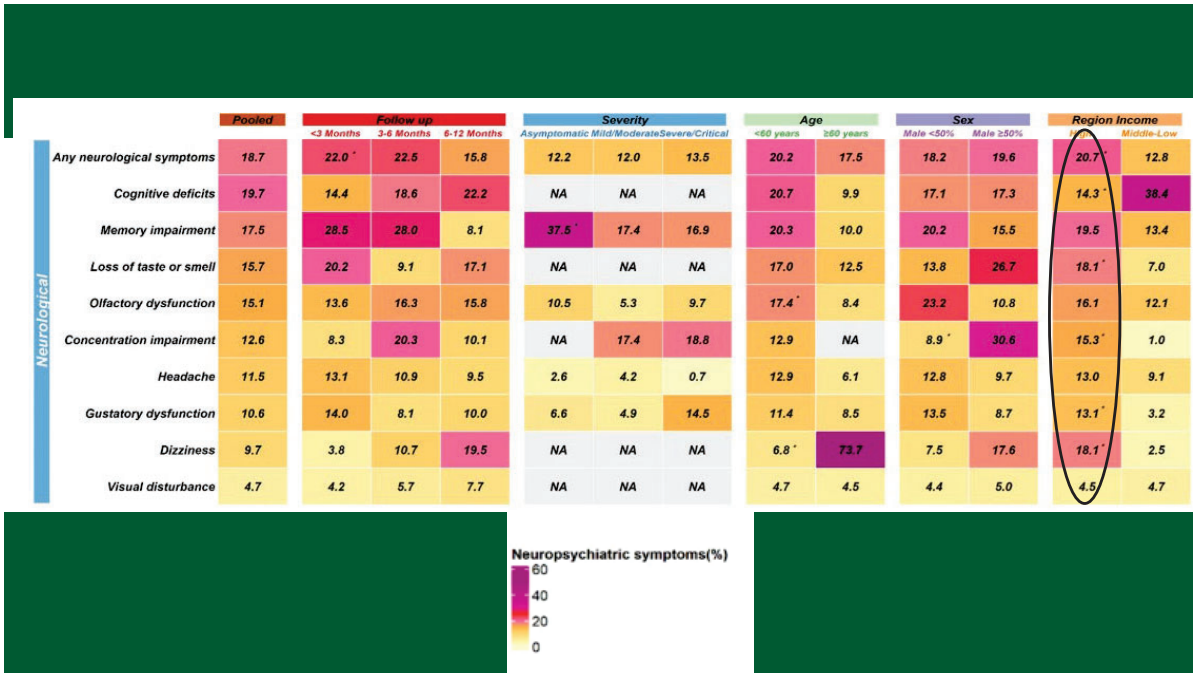
Neurological: Dizziness	9.7	3.8	10.7	19.5	NA	NA	NA	6.8 *	73.7	7.5	17.6	18.1 *	2.5
Neurological: Visual disturbance	4.7	4.2	5.7	7.7	NA	NA	NA	4.7	4.5	4.4	5.0	4.5	4.7

Neuropsychiatric symptoms(%)
60
40
20
0





Anxiety and Depression

Adults- Meta-analysis of 43 large studies prevalence of anxiety in the general population during the COVID-19 outbreak is 25% (95% CI 21%–29%).

Santabárbara J, et al Prog Neuropsychopharmacol Biol Psychiatry. 2021 Jul

Pediatrics - Pooled estimates obtained in the first year of the COVID-19 pandemic suggest that 1 in 4 youth globally are experiencing clinically elevated depression symptoms, while 1 in 5 youth are experiencing clinically elevated anxiety symptoms. These pooled estimates, which increased over time, are double of pre-pandemic estimates.

Racine N, et al JAMA Pediatr. 2021 Nov

Depression, anxiety, and post-traumatic stress disorder are the most often reported psychological problems in the literature (Yuan et al., 2021).

Some research found a rise in spousal violence and child abuse during the first weeks of lockdown (Fegert et al., 2020).

COVID-19 lockout potentially influenced children and that family and community participation could prevent potential mental and physical health difficulties. These children's increased psychological symptoms may be due to a lack of assistance during such a stressful period. (Jiao et al., 2020)

Child telepsychiatry and psychotherapy advanced dramatically during this period, and the health-care system recognized and responded to these new types of care (Fegert et al., 2020).

It should be highlighted, however, that the effects of COVID-19 were not only psychological, but also social, economic, health, political, educational, labor and employment, ethnic-racial, freedom, and citizenship rights. These consequences are inextricably intertwined, resulting in socioeconomic disparities and injustices (Ferreira et al., 2020).

Regardless of their detrimental consequences on the person, anxiety, panic, and fear of infection have always been shown to encourage people to follow social distancing rules On the other side, persons experiencing similar psychological changes have seen a significant rise in the incidence of accidental accidents and suicides over time. (Holingue et al., 2020).

"The misinformation about the virus has spread more quickly than the sickness itself. Both healthcare providers and the public were subjected to contradictory claims about incubation periods, containment measures, and mitigation measures, such as hand washing, surface scrubbing, eye protection, social distancing, antigen and antibody testing, contact tracing, isolation periods, wearing masks, business closures, distance learning versus classroom teaching, the range of potential symptoms, the extent of asymptomatic spread, and the effectiveness of treatment."

Pandi-Perumal SR, et al, Alpha Psychiatry Jul 2022

C-MORE Study

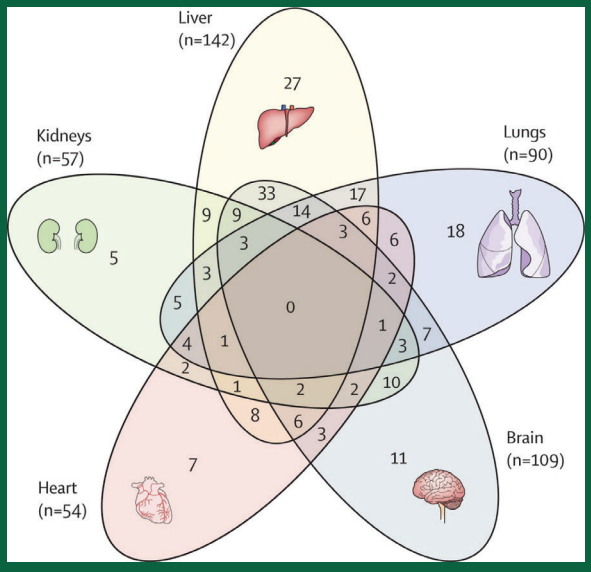
Multiorgan MRI findings after hospitalisation with COVID-19 in the UK a prospective, multicentre, observational cohort study Sep 22, 2023

259 COVID Patients, 59 Control

Multiorgan MRI (lungs, heart, brain, liver, and kidneys) with quantitative and qualitative assessment of images

Participants also underwent detailed recording of symptoms, and physiological and biochemical tests.

www.thelancet.com/respiratory Published online September 22, 2023 https://doi.org/10.1016/S2213-2600(23)00262-X



www.thelancet.com/respiratory Published online September 22, 2023 https://doi.org/10.1016/S2213-2600(23)00262-X

C-MORE Study

Sep 22, 2023

Our study demonstrates the substantial burden of multiorgan abnormalities in patients after hospitalisation for COVID-19, with nearly one in three patients having an excess burden of multiorgan injury.

Multiorgan MRI abnormalities were associated with severe and very severe persistent physical and mental health impairment after hospitalisation.

www.thelancet.com/respiratory Published online September 22, 2023 https://doi.org/10.1016/S2213-2600(23)00262-X

C-MORE Study Brain Results

White matter hyperintensities and small vessel disease were more common among (COVID) patients, who also had smaller grey matter volumes relative to controls in areas for:

Higher cognitive function, including memory and emotional processing and autonomic nervous function (hippocampus, amygdala, cerebellum, and thalamic nuclei),
Motor control (bilateral putamen),
Audiovisual processing (bilateral middle temporal gyrus),
Visual processing (bilateral cuneal and intracalcarine cortex)
Wakefulness or consciousness, and
Thermoregulation (thalamic nuclei).
Spatial memory formation (left posterior cingulate cortex),
Language processing and perception (supramarginal cortex),
Pain perception (insula).
Brain MRI abnormalities were more common among patients even after excluding patients who were critically ill with COVID-19.

COVID Long Hauler

~~COVID Long Hauler~~

Long COVID

~~COVID Long Hauler~~

~~Long COVID~~

Post-acute sequelae of SARS-CoV-2 infection (PASC)

Post-acute sequelae of SARS-CoV-2 infection (PASC)

Defined as ongoing, relapsing, or new symptoms or conditions present 30 or more days after infection

Short- and long-term effects of PASC have substantial impacts on health-related quality of life, earnings, and health care costs

Defining PASC precisely is difficult because it is heterogeneous, composed of conditions with variable and potentially overlapping etiologies (eg, organ injury, viral persistence, immune dysregulation, autoimmunity, and gut dysbiosis)

Thaweethai et al. Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection. *JAMA.* 2023;329(22):1934–1946.

What percentage of adults ever had Long COVID or currently have Long COVID, and did it differ by sex?

- In 2022, 6.9% of adults ever had Long COVID and 3.4% of adults currently had Long COVID (Figure 1).

Figure 1. Percentage of adults who ever had Long COVID or currently have Long COVID, by sex: United States, 2022

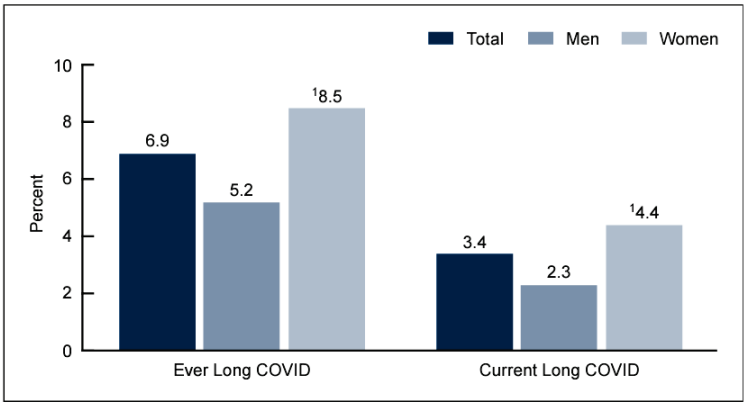


Figure 2. Percentage of adults who ever had Long COVID or currently have Long COVID, by age group: United States, 2022

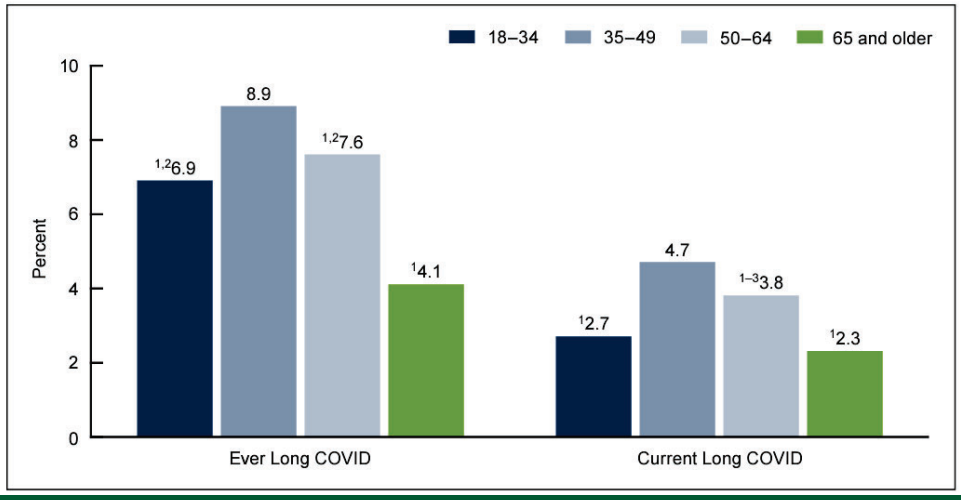


Figure 3. Percentage of adults who ever had Long COVID or currently have Long COVID, by race and Hispanic origin: United States, 2022

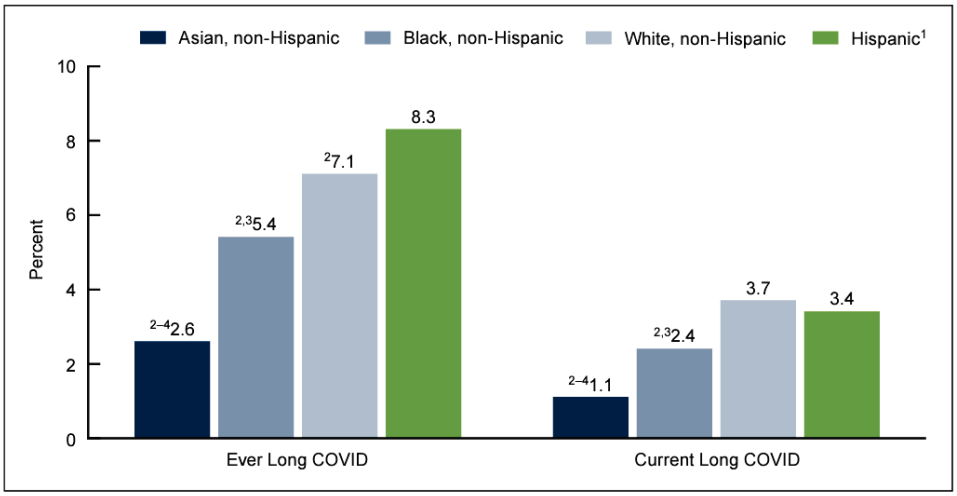


Figure 4. Percentage of adults who ever had Long COVID or currently have Long COVID, by family income as a percentage of the federal poverty level: United States, 2022

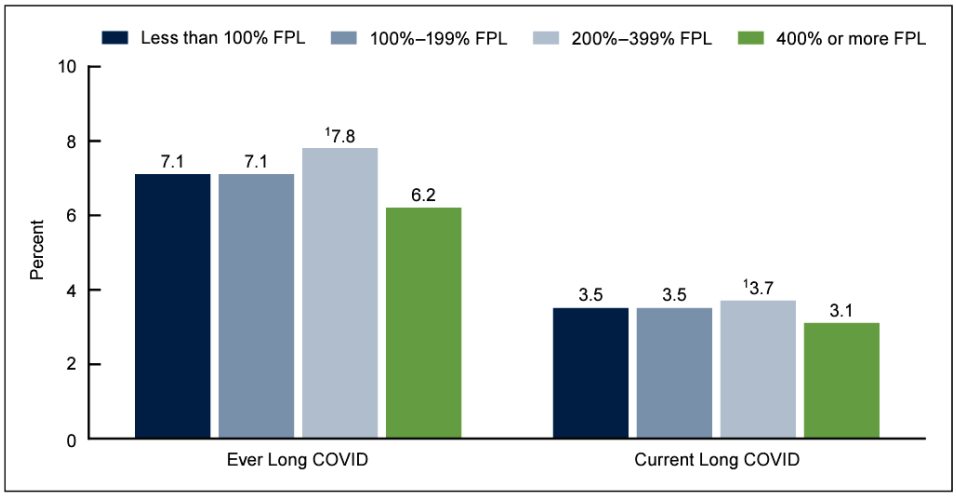
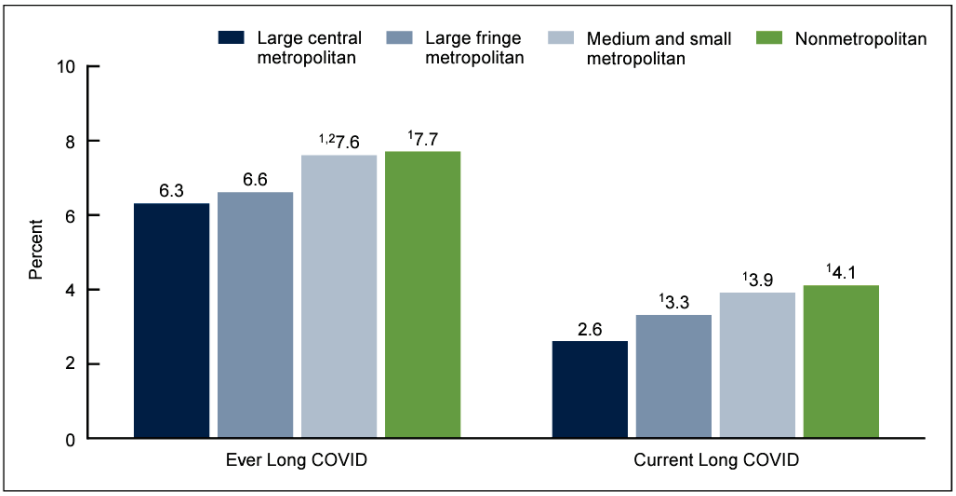
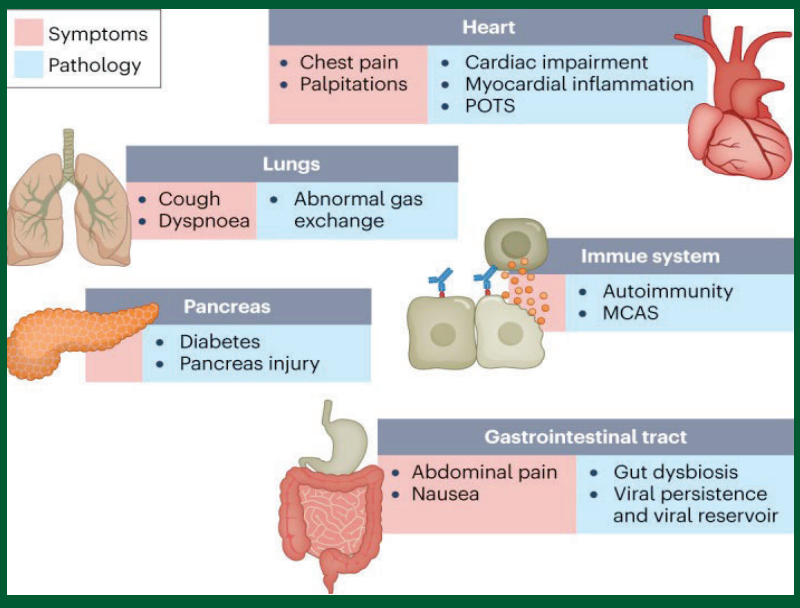
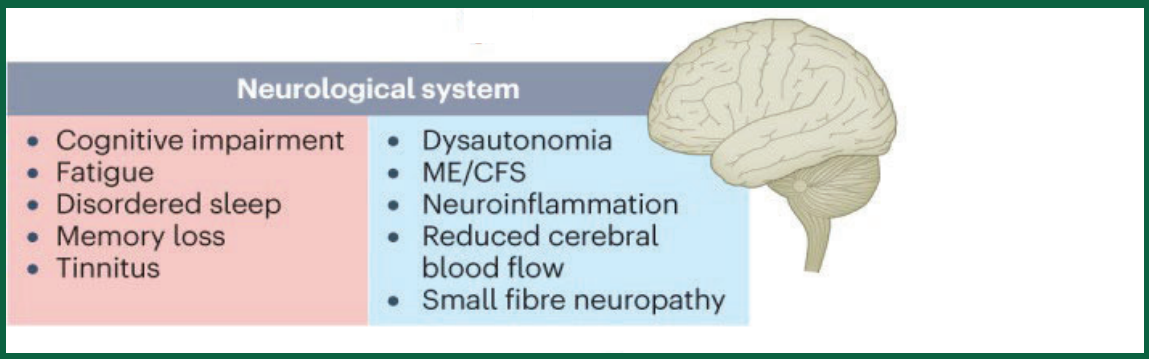


Figure 5. Percentage of adults who ever had Long COVID or currently have Long COVID, by urbanization level: United States, 2022







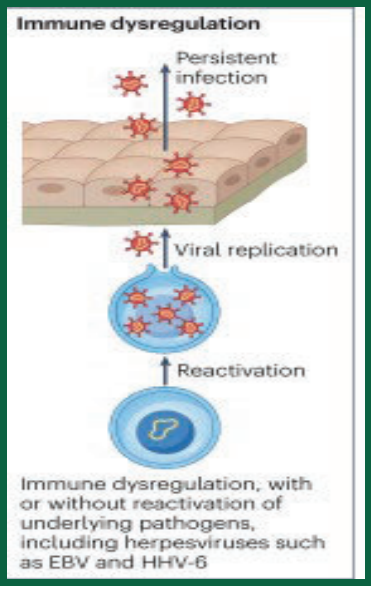
In a meta-analysis, fatigue was found in 32% and cognitive impairment was found in 22% of patients with COVID-19 at 12 weeks after infection [1].

Cognitive impairments in long COVID are debilitating, at the same magnitude as intoxication at the UK drink driving limit or 10 years of cognitive ageing [2]

1 Ceban, et al Brain Behav Immun. 2022 Mar;101:93-135

2 Holdsworth, et al PLoS One. 2022 Jun 10;17(6)

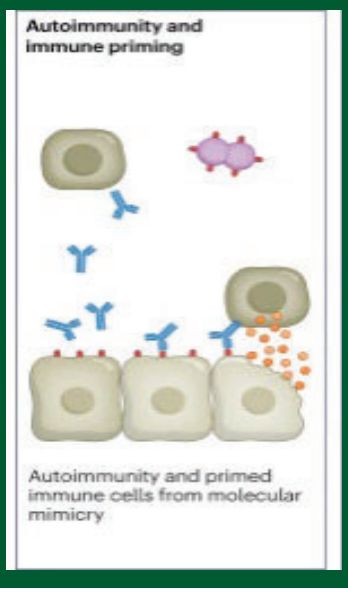
Theories on Pathophysiology of Long COVID



Theories on Pathophysiology of Long COVID

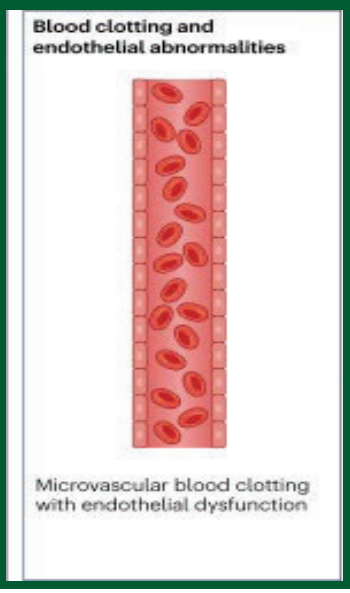
Impacts of SARS-CoV-2 on the microbiota and virome (including SARS-CoV-2 persistence)

Theories on Pathophysiology of Long COVID



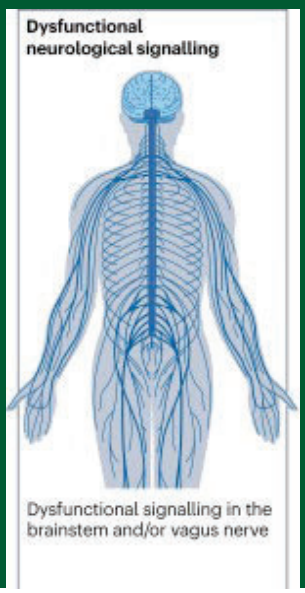
Autoimmunity and primed immune cells from molecular mimicry

Theories on Pathophysiology of Long COVID



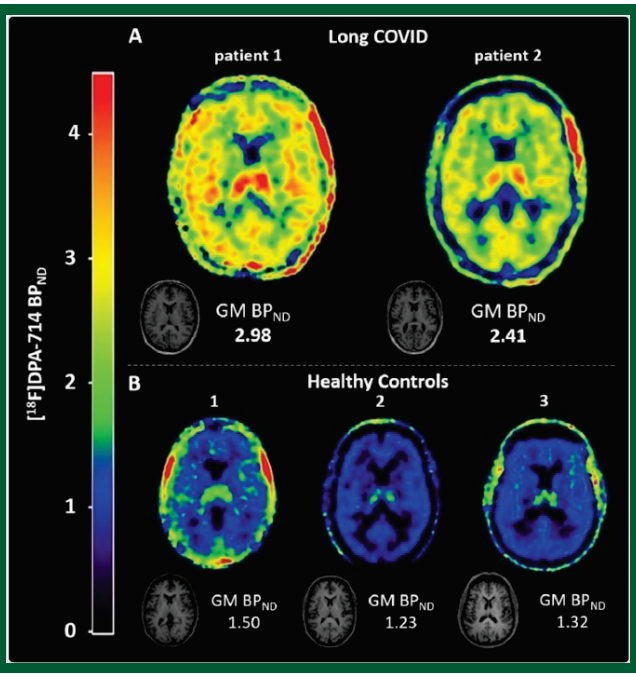
Microvascular blood clotting with endothelial dysfunction

Theories on Pathophysiology of Long COVID



Long COVID is associated with extensive in-vivo neuroinflammation on [18F]DPA-714 PET

(MS related isotope)



Visser, et al medRxiv 2022

Hamster models exhibited an ongoing inflammatory state involving T cell and myeloid activation, production of pro-inflammatory cytokines, and an interferon response that was correlated with anxiety and depression-like behaviours in the hamsters, with similar transcriptional signatures found in the tissue of humans who had recovered from COVID-19

Frere et al, Sci Transl Med. 2022 Sep

Long COVID Working Case Definition – NIH

More than 200 symptoms are associated with long COVID.

"Long COVID is not just one syndrome; it's a syndrome of syndromes"

- Post-exertional malaise
- Fatigue
- Brain fog
- Dizziness
- Gastrointestinal symptoms
- Palpitations
- Changes in sexual desire or capacity
- Loss of or change in smell or taste
- Thirst
- Chronic cough
- Chest pain
- Abnormal movements

Thaweethai et al. Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection. *JAMA.* 2023;329(22):1934–1946.

Long COVID Working Case Definition - NIH

Four Clusters
Cluster 1 loss of or change in smell or taste
Cluster 2 by post-exertional malaise and fatigue
Cluster 3 by brain fog, post-exertional malaise, and fatigue
Cluster 4 by fatigue, post-exertional malaise, dizziness, brain fog, gastrointestinal symptoms, and palpitations

Long COVID more common and more severe manifestations in people infected **before** Omicron.

NIH RECOVER Initiative

RECOVER-NEURO - web-based training program called BrainHQ and transcranial direct current stimulation

RECOVER-VITAL - SARS-CoV-2 persistence; up to 25 days nirmatrelvir/ritonavir (Paxlovid)

RECOVER-SLEEP - melatonin and sleep coaching

RECOVER-AUTONOMIC - postural orthostatic tachycardia syndrome (POTS)

Summary

COVID-19 Pandemic has had widespread pathophysiologic effects across the world, with multi-organ involvement

Neurologic after-effects appear to be long-lasting and variable

Psychologic pathology has both physiologic and emotional basis from the trauma of the lockdowns and response

I want to be more like Sir William Osler or at least have that mustache

Questions?