

Long COVID-19

Treatable Traits Masterclass

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“Long COVID does not exist, it is a made-up illness”

“SARS-CoV-2 is just like any other virus”

“Long COVID is the same as Chronic Fatigue”

Long COVID can be managed like any other chronic illness”

What causes Long COVID ?



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In moderate or severe acute COVID-19

1. Lung alveolar injury and DAD

SARS-CoV-2 destroys type 2 pneumocytes via ACE-2 receptor binding
Viral replication, cytokines, cell death, apoptosis, exudates etc

2. Thrombosis of alveolar microcirculation

Coagulopathy and epithelial dysfunction impairs gas exchange

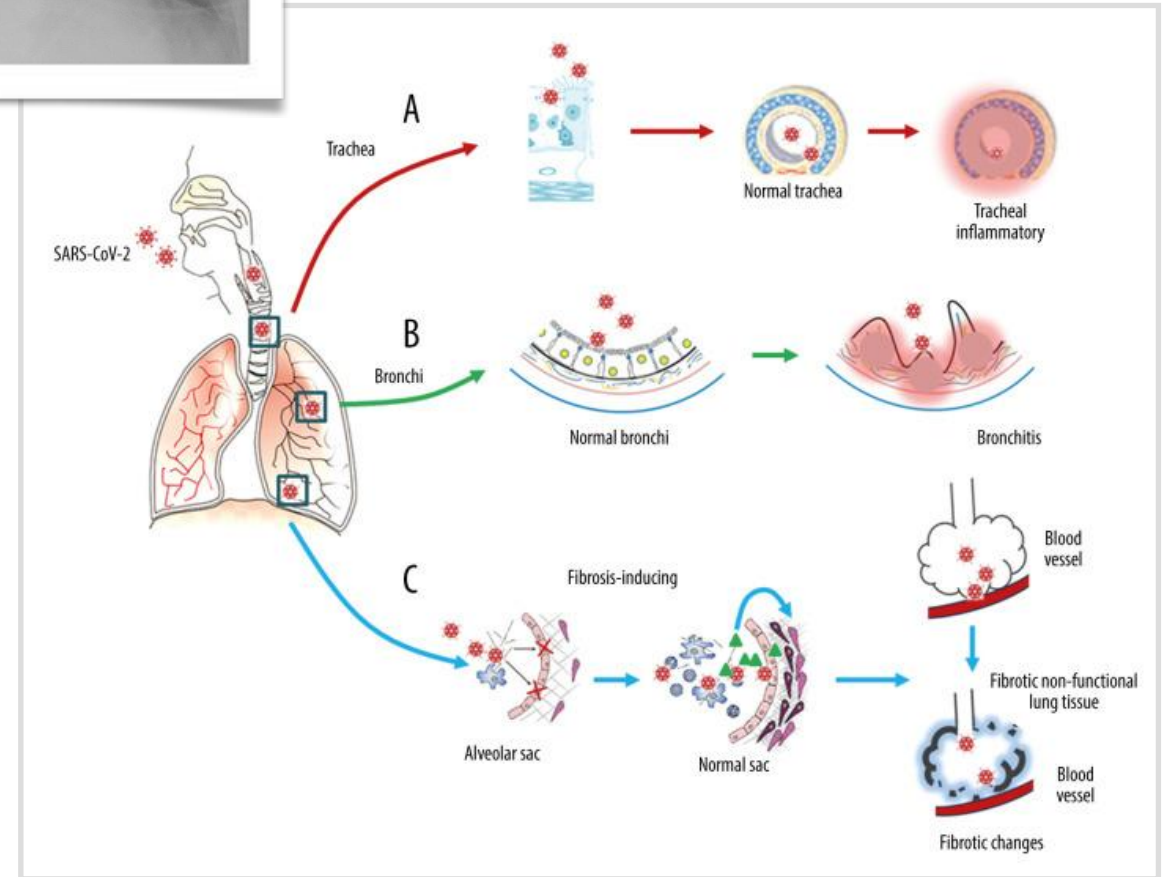
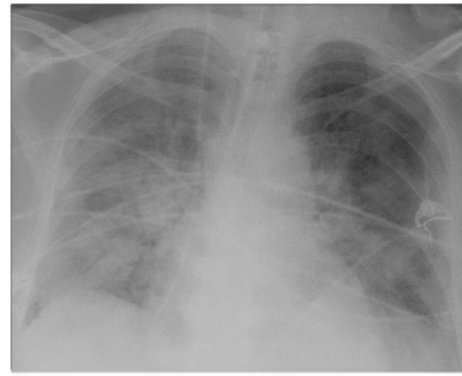
3. Airway injury from pro-inflammatory cytokines

Inflammation of trachea, bronchi, bronchioles

4. Nerve injury

In mild or minimally symptomatic acute COVID-19

1. All of above (with the exception of #1 "DAD")
2. Immune dysregulation
3. Disruption to Kyneuranine and other pathways of BBB
4. Dysbiosis of the lung and gut microbiome



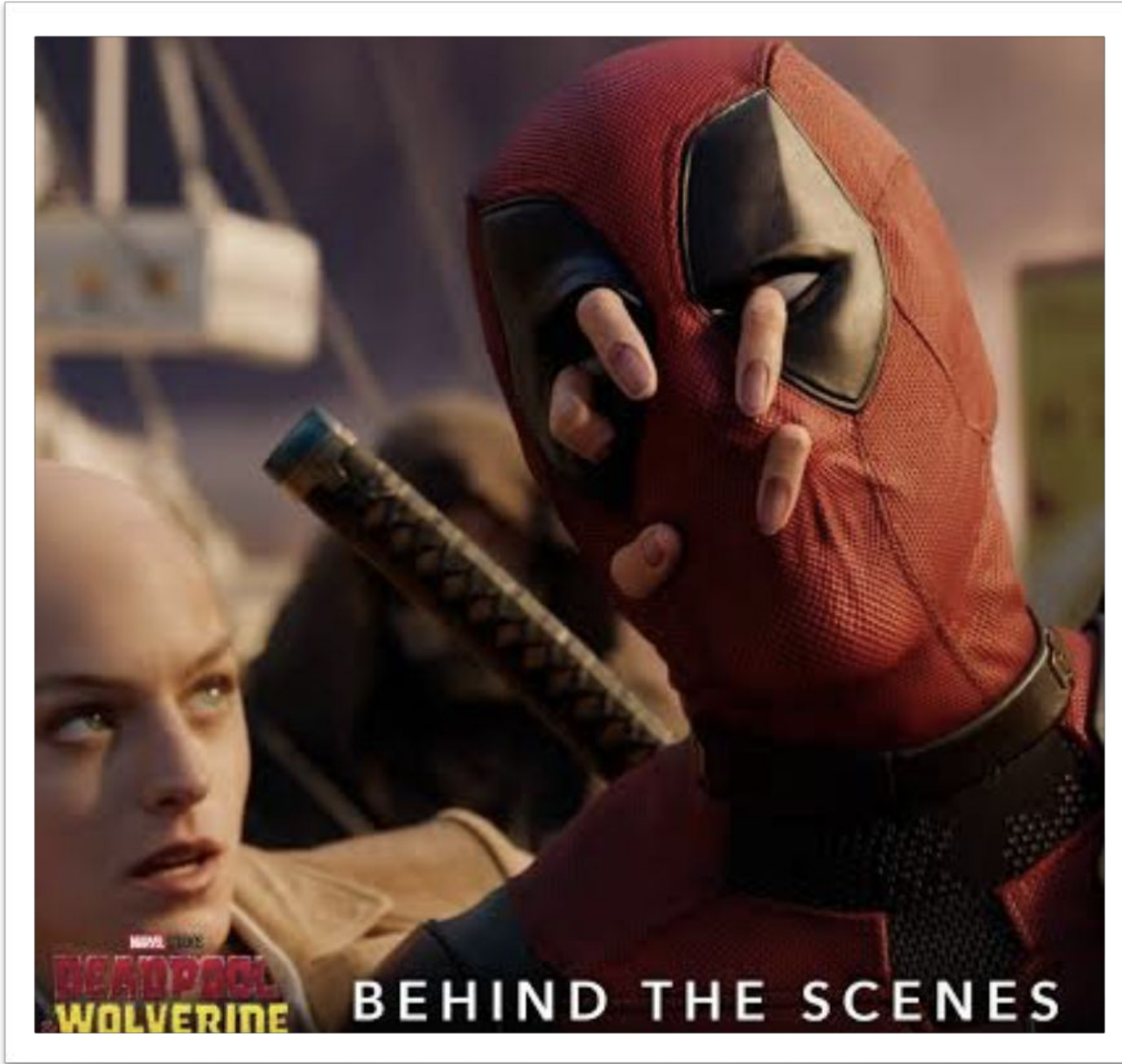
* Wang, F., Kream, R.M. and Stefano, G.B., 2020. Long-term respiratory & neurological sequelae of COVID-19. Medical science monitor. 26

** Phetsouphanh, Chansavath, et al. "Improvement of immune dysregulation in individuals with long COVID at 24-months following SARS-CoV-2 infection." Nature Communications 15.1 (2024): 3315.

SARS-CoV-2 Nucleocapsid protein = Cassandra Nova (?)



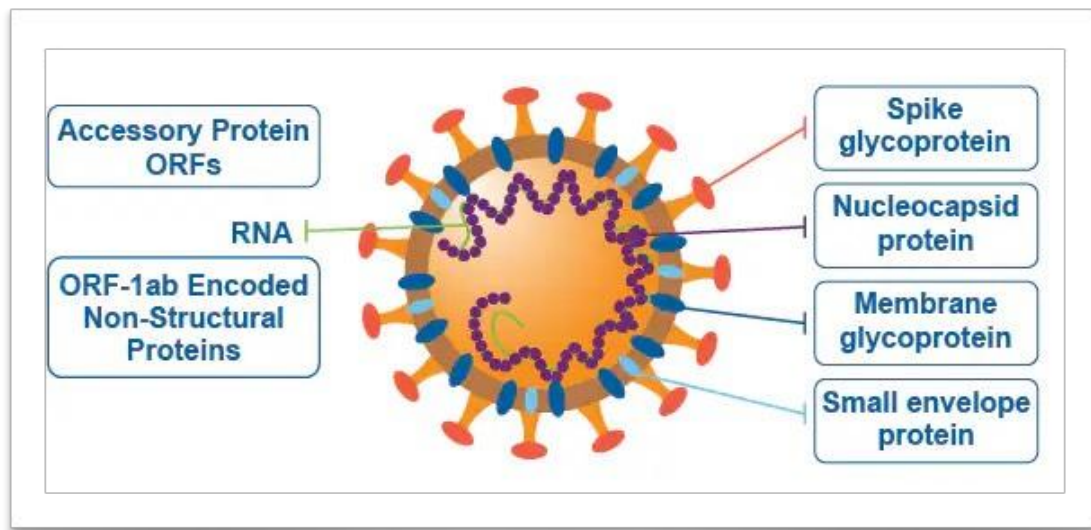
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Viral entry into host

**Subsequent persistent change in
host inflammatory response**

The cause of Long COVID = Immune dysregulation



- Measurable Humoral & Cellular Immune dysfunction
- IgG NC (SARS-CoV-2) of @ 1-3 weeks
 - **87.5% @3m, 38.6% @6m, 26.6% @12m***
- + associated with persistent symptoms & pneumonia*
- **Increased PDL-1 & TIM-3** expression on CD4 + & CD8+ cells to **eight months but not at 24 months****

PDL-1 important role in resolving inflammatory responses

TIM-3 associated with autoimmune disease and cancer

- Increased IF-gamma IF-B **with re-infection**

* Chansaenroj J, Yorsaeng R et al. Long-term specific IgG response to SARS-CoV-2 nucleocapsid protein in recovered COVID-19 patients. *Scientific reports*. 2021 Dec 1;11(1):23216.

** Phetsouphanh C, Jacka B et al. Improvement of immune dysregulation in individuals with long COVID at 24-months following SARS-CoV-2 infection. *Nature Communications*. 2024 Apr 17;15(1):3315.

LONG-COVID-19



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What?

The persistence of symptoms beyond 3 months *

Why is it important?

- Reduced QoL
- Social impact and stigma
- Economic & Professional impairment

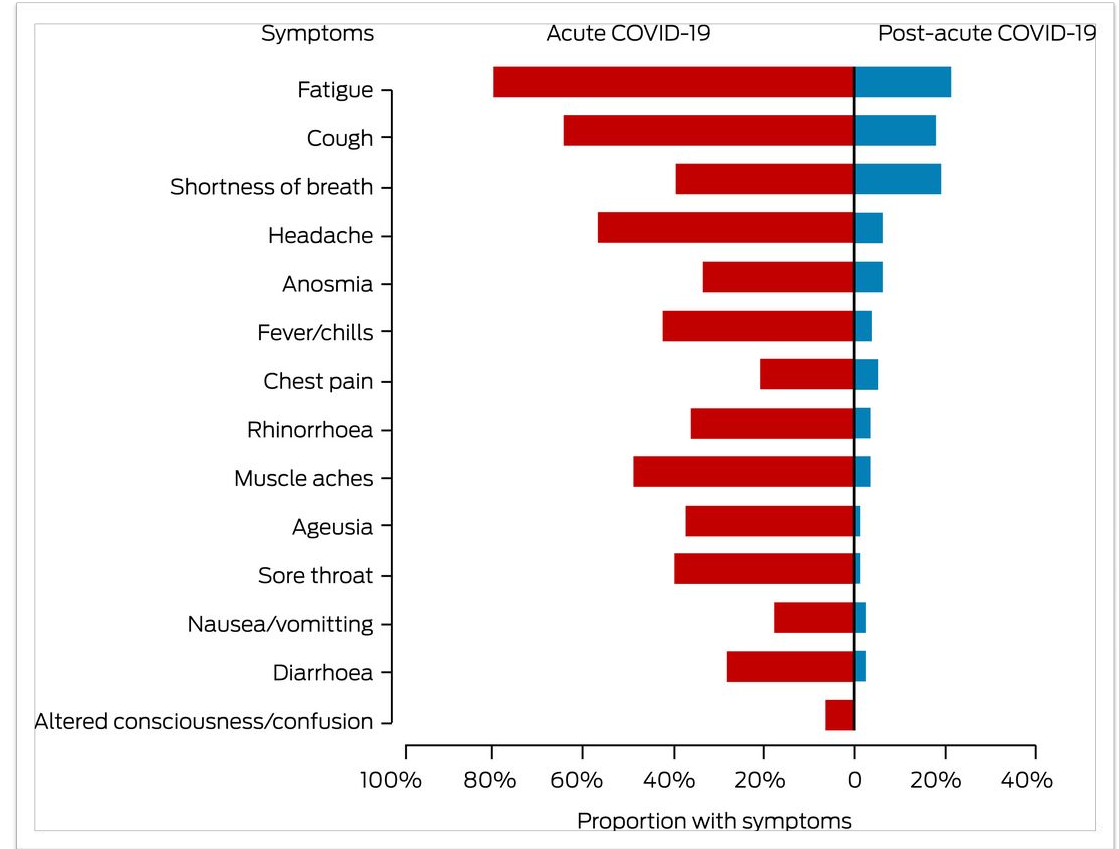


Figure: Darley et al MJA 2021

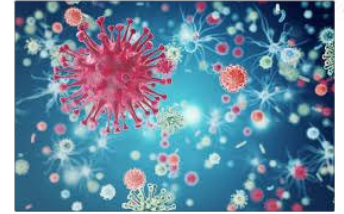
* World Health Organization. A clinical case definition of post COVID-19 condition by a Delphi consensus, 6 October 2021.

Most common Long COVID symptoms

1. Fatigue
2. "Brain fog"
3. SOB + / - cough
4. Pain including chest pain
5. Mental health + / - sleep disturbance



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Natarajan, Arun, et al. "A systematic review and meta-analysis of long COVID symptoms." *Systematic reviews* 12.1 (2023): 88.

Lewthwaite, Hayley, et al. "Treatable traits for long COVID." *Respirology* 28.11 (2023): 1005-1022

Who gets Long COVID ?

Anyone !

Severity of acute COVID-19 was NOT a predictor of mild cognitive impairment post COVID *

Risk Factors

- **Un-vaccinated (or under-vaccinated)**
- Severity of acute COVID infection (hospital, symptoms)
- Female gender
- Co-morbidities (HT, DM, Auto-immune, Immunosuppressed)
- Stress at time of acute COVID #
- Low self-esteem

* Cysique LA, Jakabek D, Bracken SG, Allen-Davidian Y, Heng B, Chow S, Dehghani M, Staats Pires A, Darley DR, Byrne A, Phetsouphanh C. The kynurenine pathway relates to post-acute COVID-19 objective cognitive impairment and PASC. *Annals of Clinical and Translational Neurology*. 2023 Aug;10(8):1338-52.

** Romero-Rodríguez, Esperanza, et al. "Hospital admission and vaccination as predictive factors of long COVID-19 symptoms." *Frontiers in Medicine* 9 (2022): 1016013.

Slurink, Isabel et al. "Who develops long COVID? Longitudinal pre-pandemic predictors of long COVID and symptom clusters in a representative Dutch population." *Int J.ID*.144 (2024): 107048.

Challenges with the diagnosis of Long COVID



There are so many !!

3 Key Challenges



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1. The diagnosis is not considered
2. There is no single diagnostic test
3. Long COVID in co-morbid patients



Prevention of Long COVID

DIAGNOSIS

PCR testing if RAT negative

MITIGATION

Anti-virals reduce severe disease

Reduce Long COVID by 26% compared to no treatment*

PREVENTION and MANAGEMENT of Acute-COVID

- *Metformin* at the time of diagnosis reduced Long COVID
- 14 days; 500mg, 500mg BD, 500mg/1000mg
- >6.3% at day 300 versus 10.4% (p=0.012)**
- *Tocilizumab, Baricitinib, Dexamethasone* for hospitalised Acute COVID-19

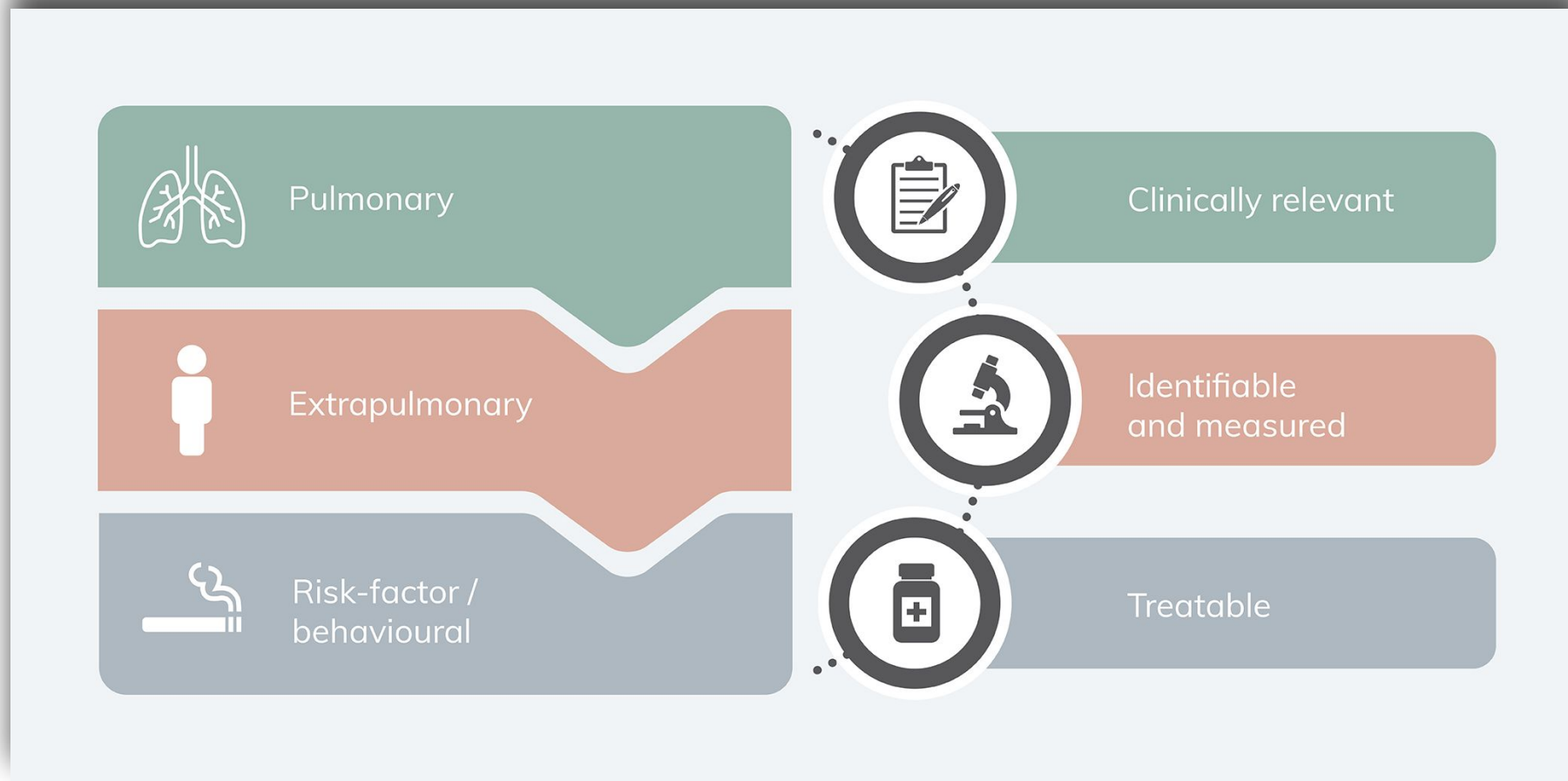
* Xie et al. Nirmatrelvir and the Risk of Post-Acute Sequelae of COVID-19, MedRx, 2022

** Bramante, C.T. et al. 2022. Randomized trial of metformin, ivermectin & fluvoxamine for Covid-19. NEJM.



Treatable Traits for Long COVID

Personalised medicine focusing on measurable abnormalities with an existing evidence base for treatment



Treatable Traits in long COVID



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1. Respiratory

Asthma & COPD
Infectious/Inflamm bronchitis &
Pneumonia
PE and microvascular clotting

2. Cardiac

Myocarditis/Pericarditis
Ischaemia & Cardiac failure
Arrhythmia & POTS

3. Sleep

Insomnia & Hyper-somulence
OSA
PLMS

4. Mood Disorder

Anxiety/Depression
Panic disorder/PTSD

5. Autoimmune

Polyarthrits and myalgia
Inflammatory pain syndrome
SLE like disorder

6. Neuropathic

Painful neuropathy
Radiculopathy
PLMS

7. Immunodeficiency

Recurrent infections
Reactivation of chronic viruses

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INVITED REVIEW SERIES: TREATABLE
TRAITS—PERSONALIZED MEDICINE
FOR LIFE IN AIRWAY DISEASE

Respirology WILEY

Treatable traits for long COVID

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Abstract

Long COVID, or post-acute COVID-19 sequelae, is experienced by an estimated one in eight adults following acute COVID-19. Long COVID is a new and complex chronic health condition that typically includes multiple symptoms that cross organ systems and fluctuate over time: a one-size-fits-all approach is, therefore, not likely to be appropriate

Lewthwaite, Hayley, et al. "Treatable traits for long COVID." *Respirology* 28.11 (2023): 1005-1022.

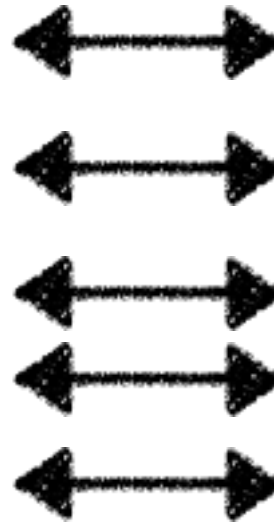
FATIGUE



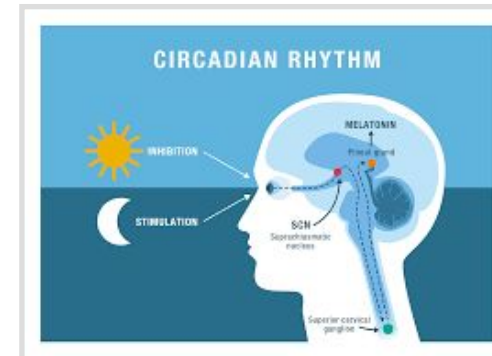
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COALITION



1. Assess sleep hygiene, quantity & quality
2. Alcohol intake
3. Mood disorders common
4. Consider untreated OSA, PLMS
5. Chronic pain
6. GIT dysfunction
7. Post exertional malaise



1. Sleep diary, fluid restriction, melatonin
2. Brief intervention
3. “This way up”, pharmacotherapy
4. CPAP, MAS, positional tx, Iron replacement
5. Analgesia, Naltrexone, SSRI
6. Dietary change, pre/pro-biotics
7. **Pacing, prescribed exercise intensity**



Dyspnoea



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COALITION

Life threatening

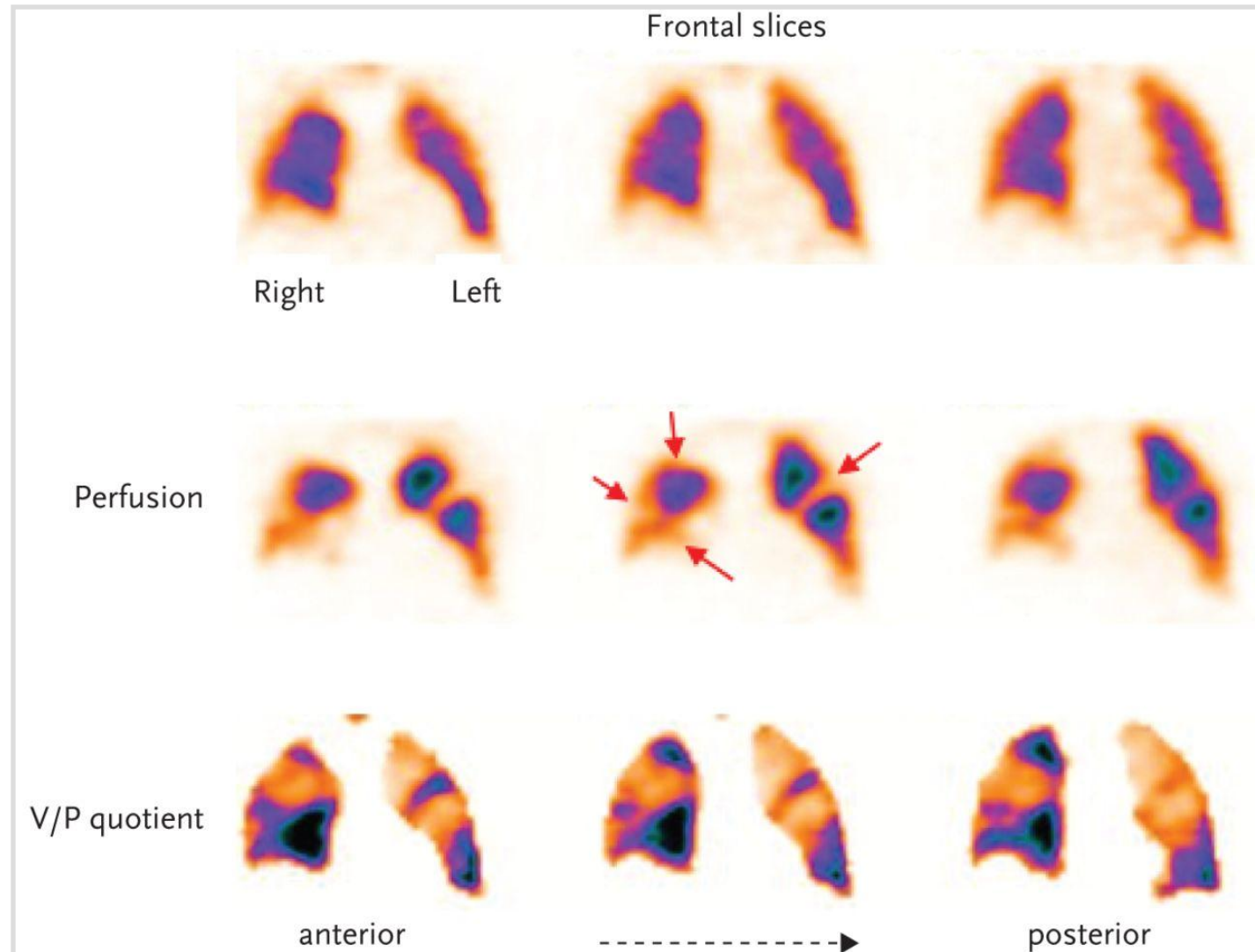
- PE
- Pneumonia/COP
- Arrhythmia
- Myocardial ischaemia/infarct

Important

- Asthma
- Pleural effusion
- Cardiac failure

Annoying & Disabling

- Chronic hyper-ventilation
- Anxiety/Panic disorder
- Dysfunctional breathing



Cough



IMMUNISATION
COALITION

Life threatening

Pneumonia

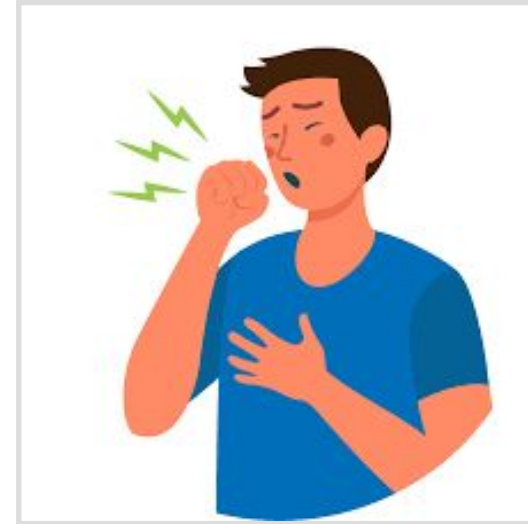
- COPD/Asthma (severe)
- Lung cancer

Important

- Infectious bronchitis
- COPD/Asthma (mild-mod)

Annoying & Disabling

- GORD
- Post-infectious cough/ cough hyper-sensitivity
- Post-nasal drip



Easy
Fast
Accurate
Reliable
Versatile
Hygienic
Portable
Affordable



Chest Pain



IMMUNISATION
COALITION

Life threatening

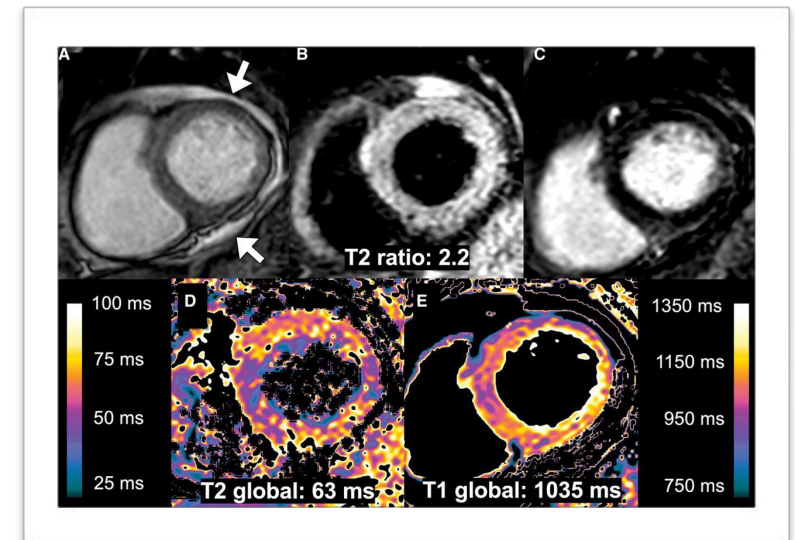
- PE
- Myocardial ischaemia/infarct
- Pneumonia

Important

- Myocarditis/Pericarditis
- Pleuritis
- Rib fracture/muscle tear

Annoying & Disabling

- Neuropathic
- Costochondritis
- Anxiety/Panic disorder

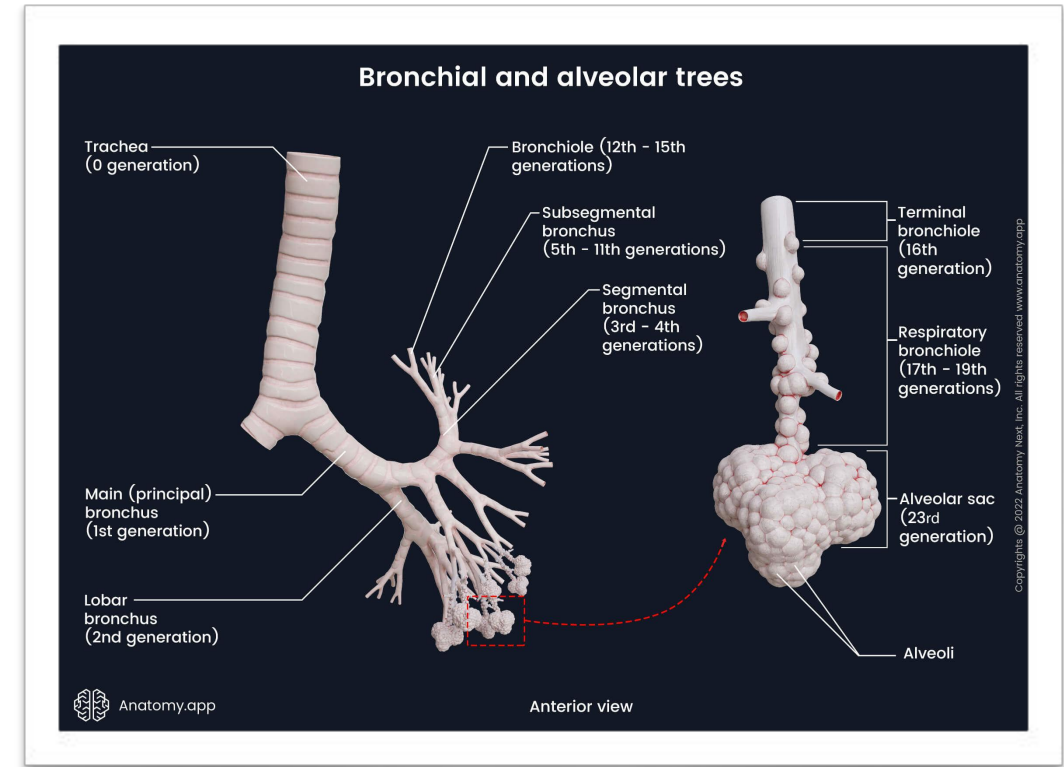


* Oaklander AL. et al. Neurology Neuroimmunology & Neuroinflammation, 2022



Small Airway Dysfunction (SAD)

- Bronchioles of the distal airways narrowed, inflamed, remodelled, mucous secretion
- Associated SOB, cough, wheeze, chest pain and tightness
- Characteristic of asthma, COPD but also post infective conditions
- Airflow obstruction, gas trapping and hyper-inflation
- Lung function testing and (CT, VQ imaging)

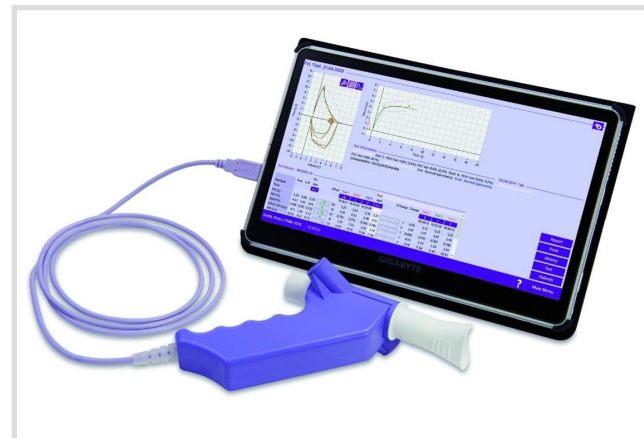
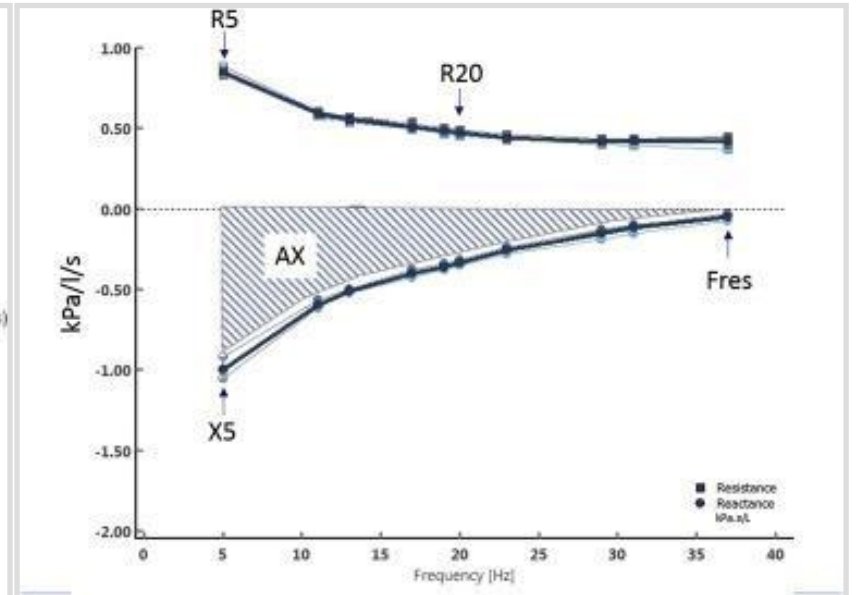
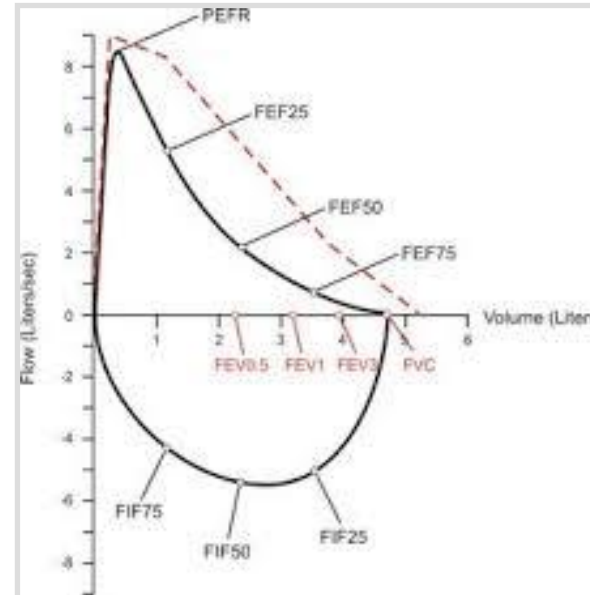


SAD



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- Spirometry and Oscillometry
- Reduced FEF 25-75, FEV1
- Increased Resistance (R5, R5-19)
- Reduced Reactance (X5)



SAD

- n=163 Symptomatic Long COVID
- NO prior asthma !
- Oscillometry detected SAD
- Older, higher BMI, HT
- More symptomatic

76% !!

Byrne, A., Lees, N., Asgary, E., & Stumbles, E. (2023).

Prevalence of abnormal oscillometry among ambulatory

Long COVID patients. ERJ 62 (suppl 67)

Table 1: Differences between patients with and without small airway disease (SAD) at the first visit

Variable	SAD present (n=123)	SAD absent (n=40)	P-value
Demographic Data			
• Age (mean ± SD)	52.93 ± 14.88	42.18 ± 15.56	<0.001
• Sex (Female, %)	76 (61.8%)	20 (50%)	0.188
• BMI (mean ± SD)	29.07 ± 6.5	24.44 ± 3.98	<0.001
Comorbid Conditions (%)			
• Hypertension	40 (32.5%)	4 (10%)	0.005
• DM	18 (14.6%)	2 (5%)	0.107
• Depression	21 (17.1%)	11 (27.5%)	0.149
• Anxiety	23 (18.7%)	10 (25%)	0.389
• GORD	13 (10.6%)	4 (10%)	0.919
• Obesity	27 (22%)	3 (7.5%)	0.040
• IHD	13 (10.6%)	0 (0%)	0.032
• Sleep apnoea	22 (17.9%)	3 (7.5%)	0.113
• Dyslipidaemia	11 (8.9%)	1 (2.5%)	0.175
• Smoking	7 (5.7%)	0 (0%)	0.123
Time between first infection and first visit (median (IQR))	305 (184, 474)	334.5 (225.5, 498.75)	0.784
HOPE survey (median (IQR))			
• Pre-COVID symptoms score	11 (5, 22.25)	8 (3, 15.75)	0.014
• Symptoms score	42.5 (24.75, 55.25)	36 (27, 53.5)	0.096
• Pre-COVID functional score	0.5 (0, 4)	0 (0, 2)	0.333
• Functional score	16.5 (4, 23)	18 (8, 25)	0.355
• Pre-COVID overall score	8 (5, 9)	8 (7, 9)	0.411
• Overall score	4 (3, 6.25)	4 (2, 5.75)	0.138



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SAD improves over time

- Followed over 18 months
- Oscillometry not spirometry detects change
- With SAD improved with time
- No SAD did not change
- Those treated with ICS/LABA improved

Byrne, A., Lees, N., Asgary, E., & Stumbles, E. (2023).

Prevalence of abnormal oscillometry among ambulatory

Long COVID patients. ERJ 62 (suppl 67)

Treatable Traits in Long COVID: Inhaled corticosteroids for small airway dysfunction among symptomatic Long COVID patients without known Asthma.

Table 2: Longitudinal data for visits 1, 2, 3, and 4 in non-asthmatic patients with and without SAD

Parameter	SAD				P-value	No SAD				P-value
	Visit 1	Visit 2	Visit 3	Visit 4		Visit 1	Visit 2	Visit 3	Visit 4	
FOT parameters (median (IQR))										
R5 (cmh2a/L/s)	3.6 (3.03, 4.77)	3.56 (2.89, 4.75)	3.38 (2.89, 4.49)	3.26 (2.78, 3.85)	0.001	2.55 (2.21, 2.96)	2.53 (2.19, 3.04)	2.54 (2.16, 3.01)	2.99 (2.66, 3.16)	0.494
R19 (cmh2a/L/s)	2.79 (2.34, 3.56)	2.77 (2.37, 3.6)	2.76 (2.1, 3.52)	2.89 (1.98, 3.06)	0.017	2.45 (2.08, 2.84)	2.4 (2.11, 2.82)	2.3 (2.19, 2.54)	2.64 (2.56, 3.05)	0.552
R5-19 (cmh2a/L/s)	0.73 (0.5, 1.26)	0.74 (0.37, 1.35)	0.6 (0.48, 1.26)	0.64 (0.34, 0.88)	0.422	0.12 (0, 0.32)	0.15 (-0.05, 0.34)	0.21 (-0.03, 0.57)	0.15 (-0.13, 0.53)	0.682
AX (cmh2a/L)	9.2 (6.39, 16.16)	8.8 (5.18, 17.31)	9.56 (5.25, 15.21)	7.12 (4.86, 10.44)	0.053	2.85 (2.33, 3.42)	3.09 (1.97, 4.6)	2.6 (2.05, 3.85)	3.51 (2.51, 5)	0.494
X5 (cmh2a/L/s)	-1.56 (-2.19, -1.22)	-1.51 (-2.34, -1.08)	-1.55 (-1.9, -1.05)	-1.18 (-1.6, -1.05)	0.120	-0.87 (-1, -0.75)	-0.91 (-1.07, -0.7)	-0.85 (-1.04, -0.72)	-1 (-1.2, -0.94)	0.552
FRES	19.19 (15.74, 23.11)	18.51 (15.52, 22.29)	19.07 (15.72, 22.4)	17.25 (14.24, 18.79)	0.721	11.49 (10.48, 12.53)	11.72 (9.97, 14.99)	11.21 (10.16, 12.53)	12.4 (10.16, 15.77)	0.272
Spirometry data (mean ± SD)										
FVC (L)	3.58 ± 0.99	3.63 ± 1.19	3.78 ± 1.11	3.54 ± 1.04	0.274	3.88 ± 1.05	3.83 ± 1.27	3.58 ± 0.95	3.51 ± 0.94	0.406
FEV1 (L)	2.83 ± 0.85	2.85 ± 1	2.95 ± 0.97	2.71 ± 0.96	0.662	3.17 ± 0.85	3.12 ± 0.91	3.03 ± 0.84	2.7 ± 0.73	0.277
FEV1/FVC (%)	0.8 ± 0.15	0.78 ± 0.11	0.77 ± 0.11	0.75 ± 0.13	0.645	0.86 ± 0.37	0.92 ± 0.56	0.78 ± 0.1	0.77 ± 0.02	0.621
FEF 25-75 (L/s)	2.78 ± 1.17	2.85 ± 1.26	2.83 ± 1.14	2.48 ± 1.16	0.831	3.05 ± 1.11	2.85 ± 1	2.78 ± 1.19	2.31 ± 0.72	0.556



IMMUNISATION
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Case study

48 year old

Female schoolteacher

Acute SARS-CoV-2, Jan 2022 + on PCR

3 prior vaccinations

GP referral 4 months post acute

Acute symptoms

- Rhinorrhea, loss smell/taste, sore throat, myalgia, cough, SOB, chest pain, lethargy
- ED presentation with chest pain but not hypoxic and no admission

Post-Acute

- Chest pain despite naproxen 500mg BD
- Slow resolution of taste/smell

Long COVID

- Fatigue, lethargy, “brain fog”
- Sleeps 7pm til 7am, pain/anxiety, delayed sleep phase
- Unable to work full time (2 days/week only)
- STOP BANG 4/8 and ESS 15/24



Case Study

48 year old

Female schoolteacher

Acute SARS-CoV-2, Jan 2022 +

Initial Investigations

- Nasoendoscopy showed candidiasis and mild turbinate hypertrophy
- Bloods, PFT, CT chest, Sleep study

Initial Management

- Amphotericin 10mg lozenge
 - 10mg amitryptilline nocte
 - Follow-up 2 months later
 - Came with niece (recalled little of 1st consult)
-
- Mild improvement in mood, pain sleep onset, variably compliant (50% time)
 - DSS no OSA (2/hr), no PLMS, 360min sleep, 83% sleep efficiency
 - Still very tired and sleepy with ESS 15/24

Case Study

48 year old

Female schoolteacher

Acute SARS-CoV-2, Jan 2022 +

Management

- Has increased amitriptyline to 20mg note
- Still struggling with sleepiness
- Armodafonil 150mg at 8am (private script)
- Psychologist/Physio/Rehab physician referrals at Long COVID clinic
- ESS reduced to 7 from 15/24 when on armodafonil
- Pain improved, still memory impairment and migraines
- Neurologist review

18 months Post infection

- Migraines improved with “ajovy”
- Sleep better, still impaired memory
- Cholesterol elevated 6.5 , commenced atorvastatin 40mg

Case Study

48 year old

Female schoolteacher

Acute SARS-CoV-2, Jan 2022 +

24 months post infection

- Overall much better
- Not back to baseline
- Atorvastatin seemed to help a little initially
- Amitryptiline changed to duloxetine but flare in pain
- Armodafonil 150mg 8am on school days
- Transient flare in symptoms after booster COVID vaccine
- Working 4 of 5 days per week

Research



IMMUNISATION
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- Lewthwaite, H., Byrne A., Brew, B. and Gibson, P.G., 2023. Treatable traits for long COVID. *Respirology*, 28(11), pp.1005-1022.
- Cysique LA, Jakabek D, Bracken SG, Byrne A, Phetsouphanh C. et al. The kynurenine pathway relates to post-acute COVID-19 objective cognitive impairment and PASC. *Annals of Clinical and Translational Neurology*. 2023 Aug;10(8):1338-52.
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