

Episode 241 : Long COVID

Dear colleagues,

Again stimulated by some of you, I will dedicate this episode to some recent findings on underlying associations and mechanisms of long COVID or post-acute COVID syndrome (PACS). As you will see, this condition is quite common and debilitating.

Some lasting respiratory problems are expected and persistent anosmia/ageusia is well known as well, but as you will see, the syndrome is much broader and I will focus more on the neurological and cardiovascular symptoms here.

Recent papers also try to unravel the underlying mechanisms and understand the effect of vaccination. It will be an important task for our health system to address these issues, which were probably relatively neglected during the pandemic waves.

See: <https://www.icpcovid.com/en/news/18-february-episode-241-long-covid>

1) Neurological aspects

Ep 241-1: Meredith Wadman Science insider short summary of the next two papers

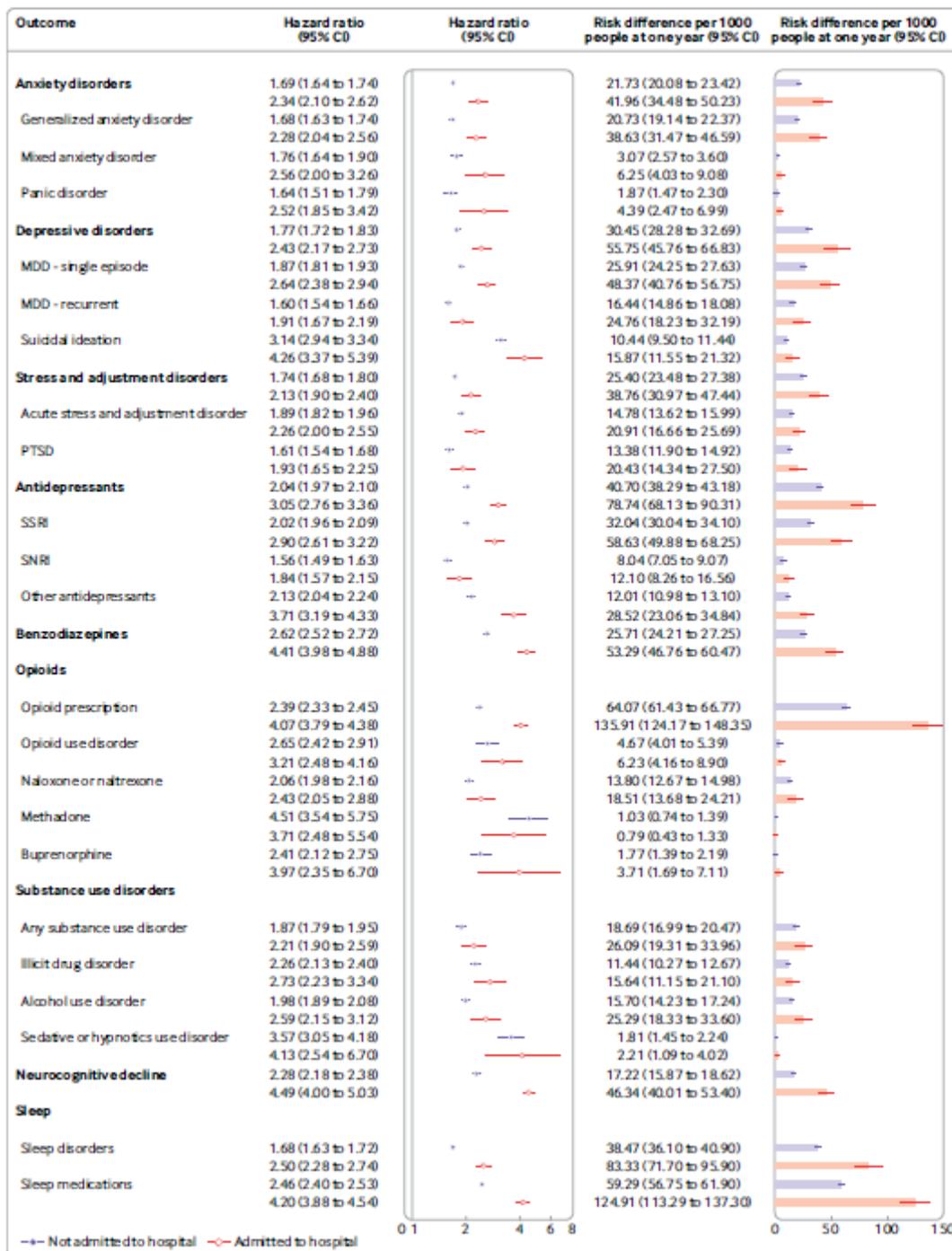
Ep 241-2: Yan Xie BMJ Jan 2022: a very large study on over 150,000 US adult subjects in the veterans administration VA (90 % male, 75 % white, mean age 63 yrs) surviving COVID without vaccination, compared with very large and similar VA control groups. They were followed up between 6-18 months

Main outcome:

Significant increase in any type of mental disturbance examined investigated e.g. anxiety disorders, depressive disorders, stress and adjustment disorders, opioid use disorders, other (non-opioid) substance use disorders, neurocognitive decline, and sleep disorders with HR 1.2-1.94 (Fig 2 p. 7)

More in hospitalized than non-hospitalized, but the latter also increased (Fig 5 p. 9)

Higher risk than after seasonal influenza or other reasons for hospital admission.



Ep 241-3: Premraj J Neurol Sci Jan 2022: meta-analysis on 19 studies with over 11,000 patients > 3 months after acute COVID:

Main findings:

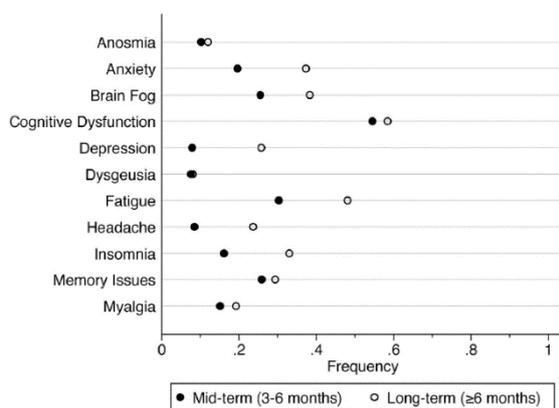
Key **neurological features** in post-COVID are fatigue, cognitive dysfunction (brain fog, memory issues, attention disorder) and sleep disturbances.

Psychiatric manifestations (sleep disturbances, anxiety, and depression) are common and increase significantly in prevalence over time.

Remarkably:

- Hospital admission: more memory disturbance, but reduced frequency of anosmia, anxiety, depression, dysgeusia, fatigue, headache, myalgia, and sleep disturbance as compared to non-hospitalized.
- ICU admission: fatigue, anxiety, depression, and sleep disturbances
- Neuropsychiatric symptoms appear to increase in prevalence over time, rather than resolve

Symptom	Cohort Size (N)	Frequency (95% CI)
Anosmia	3164	0.12 (0.07, 0.17)
Anxiety	3104	0.23 (0.13, 0.33)
Attention Disorder	1207	0.22 (0.10, 0.34)
Brain Fog	4329	0.32 (0.09, 0.55)
Depression	3104	0.14 (0.07, 0.21)
Dysgeusia	2703	0.11 (0.04, 0.17)
Fatigue	7173	0.37 (0.24, 0.50)
Headache	3675	0.10 (0.01, 0.21)
Memory Issues	5268	0.27 (0.18, 0.36)
Myalgia	7555	0.18 (0.04, 0.32)
Sleep Disturbances	8455	0.31 (0.18, 0.43)



2) Cardiovascular aspects

Remember: Ep 238-8: Yan Xie Nat Med Feb 2022 Increased cardiovascular risk post-COVID in veterans US

Individuals with COVID-19 are at increased risk of incident cardiovascular disease spanning several categories, including cerebrovascular disorders, dysrhythmias, ischemic and non-ischemic heart disease, pericarditis, myocarditis, heart failure and thromboembolic disease during 1 year post COVID

- Cardiovascular incidents increases depending on severity of acute phase
- Remarkably, CV incidents also present in those with less pre-existing cardiovascular risk factors (age, smoking, obesity etc)

= clear argument pro vaccination.

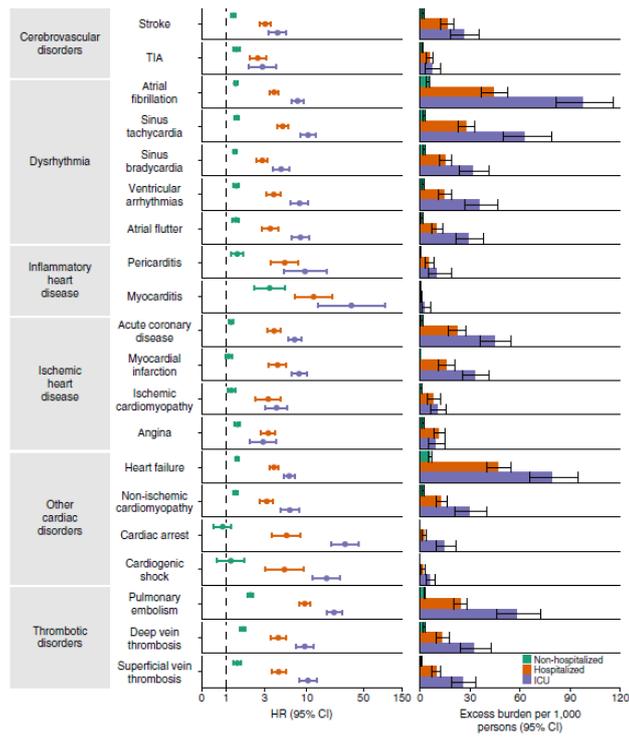


Fig. 5 | Risks and 12-month burdens of incident post-acute COVID-19 cardiovascular outcomes compared with the contemporary control cohort by care setting of the acute infection. Risks and burdens were assessed at 12 months in mutually exclusive groups comprising non-hospitalized individuals with COVID-19 (green), individuals hospitalized for COVID-19 (orange) and individuals admitted to intensive care for COVID-19 during the acute phase

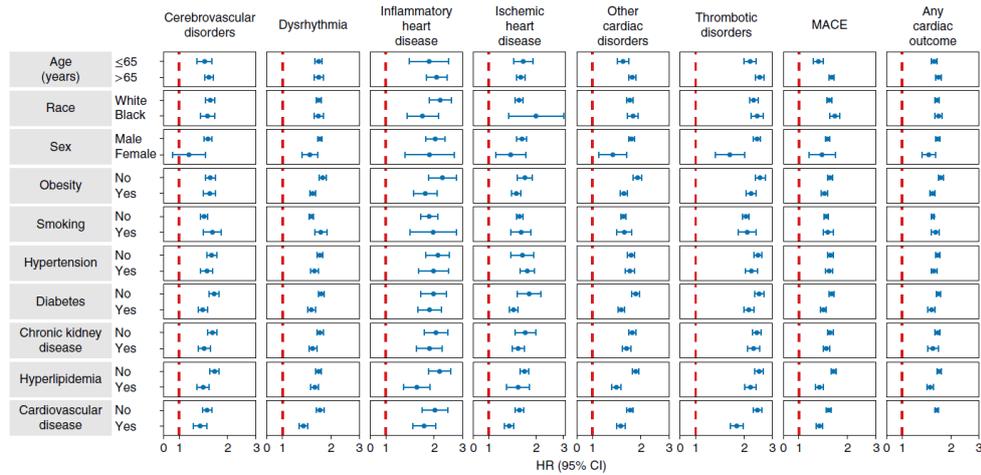


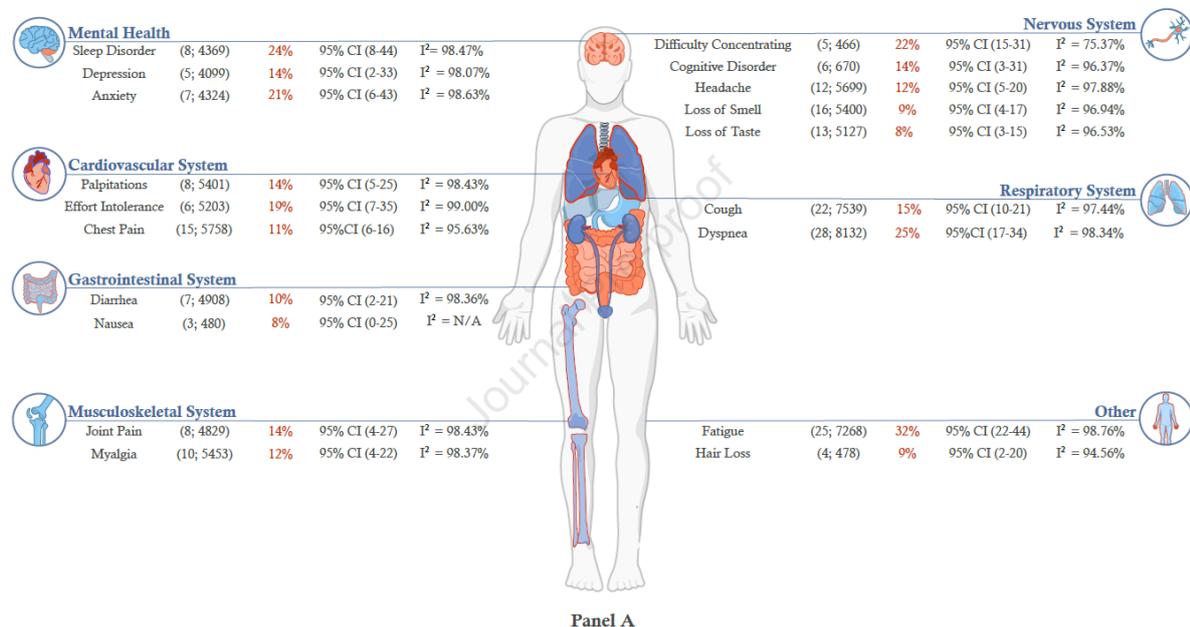
Fig. 4 | Subgroup analyses of the risks of incident post-acute COVID-19 composite cardiovascular outcomes compared with the contemporary

3) **Meta-analysis**

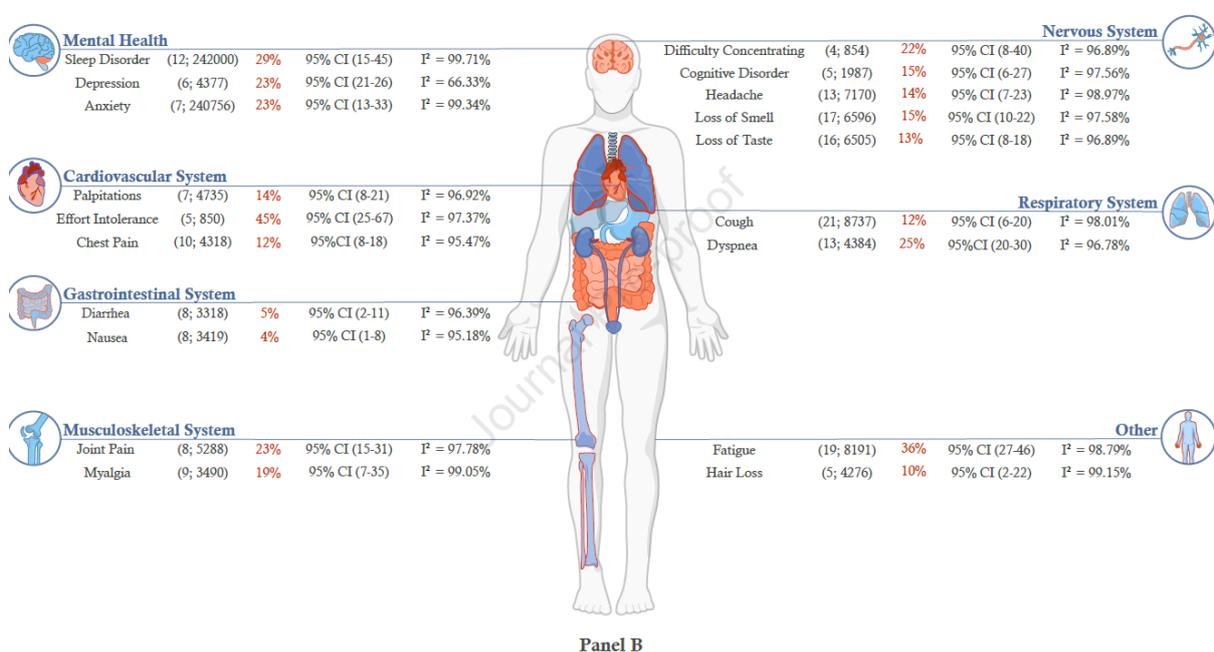
Ep 241-4: Alkodaymi Clin Micro Infect Feb 2022: Meta-analysis on 63 studies and over 250,000 COVID patients.

Overview of symptoms:

Estimated prevalence 3-6 months after acute COVID



Estimated prevalence 6-9 months after acute COVID



Determining factors: male gender, diabetes and severity of acute phase

Limitations:

- Not always a suitable control group
- Lack of standardized methodology, symptom terminology, use of “umbrella terms”...

- Severity of COVID illness not always clear

Hypothetical mechanisms:

- 1) COVID-19 patients with chronic symptoms may harbor the virus in several potential tissue reservoirs across the body, which may not be identified by nasopharyngeal swabs
With delayed viral clearance due to immune exhaustion resulting in chronic inflammation and impaired tissue
- 2) Sequelae of COVID-19 organ involvement during acute infection,
- 3) Auto-immunity: cross reactivity of SARS-CoV-2-specific antibodies with host proteins
- 4) Mitochondrial dysfunction and impaired immunometabolism,
- 5) Alterations in microbiome leading to long-term health consequences of COVID-19 (88–91).

4) **PACS in people with HIV**

Ep 241-5: Peluso medRxiv 14 Feb 22 in a small study comparing HIV + and HIV- subjects

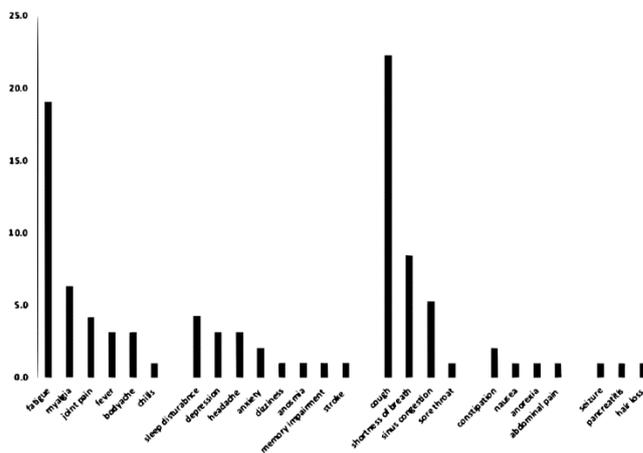
- HIV(+) status was strongly associated with PASC (odds ratio 4.01, p=0.008).
- Proportion of PD-1+ (= “exhausted”) CD4+ T cells and levels of certain inflammatory markers (IL-6, TNF-alpha, and IP-10) were associated with persistent symptoms.

Ep 241-6: Pujari Inf Infl Dis May 2021: **PACS among people living with HIV in western India**

Long COVID amongst 94 subjects was defined as at least one symptom after 30 days of illness onset.

43 % of HIV (+) subjects, with moderate-severe illness as the only significant risk factor. In 10 % it persisted for 100 days.

Symptoms



4) **Underlying mechanisms of PACS**

Ep 241-7: Vijayakumar Immunity March 2022 on immune profiling of broncho-alveolar lavage in people with ongoing respiratory symptoms 3-6 months after acute COVID

- 1) **Abnormal BAL** (but not plasma) **proteome**: most upregulated compared to controls:

Elevated Albumin, Lactic Dehydrogenase (LDH), Thyroxine-binding globulin (SERPINA7), dipeptidyl peptidase 4 (DPP4), plasma serine protease inhibitor (SERPINA5), kallikrein-related peptidase-6 (KLK6), lymphatic vessel endothelial hyaluronic acid receptor 1 (LYVE1), amphiregulin (AREG), factor 3 (F3), Fms-related tyrosine kinase 3 ligand (FLT3LG), glutaminyl-peptide cyclotransferase (QPCT), metallo proteinase-3 (MMP3), and Proto-oncogene tyrosine-protein kinase Src (SRC)

Interpretation: evidence of apoptosis, epithelial damage and repair.

- 2) Elevated levels of **tissue-resident CD8 T cells**, higher **B cell numbers** and **differentiating monocytes**, all linked to impaired lung function and persistent abnormalities on CT scan.

Most aberrant values returned to normal at 1 year after acute COVID

→ these abnormalities are markers, consequence of lung damage but not predisposing factors

Ep 241-8: Yapeng Su Cell Jan 2022 on predictors of post-acute COVID syndrome (PACS) or long COVID.

Four different PACS syndromes are distinguished: respiratory viral (42%), neurological (25%), anosmia/dysgeusia (18%), and gastrointestinal (GI; 9%).

Previously already associations suggested between PACS and

- Acute disease severity
- Unresolved SARS-CoV-2 viral fragments
- Auto-antibodies

A very complex analysis of proteomics, SARS-CoV-2 viremia, activation of EBV, CMV, T cell subsets and clinical factors. Just some highlights

- 1) Clinical predictors:
 - Type 2 diabetes associates with fatigue, respiratory symptoms (cough as PACS)
 - Coronary heart disease and cough at enrolment with anosmia/dysgeusia
 - Female sex associates with neurological symptoms and dyspnea
 -
- 2) Low cortisol was associated with respiratory symptoms
- 3) Virology:
 - Nasal swab SARS-CoV-2 viral load predictive for anosmia/dysgeusia
 - Viremia of both SARS-CoV-2 and EBV predictive for memory issues
 - EBV viremia also associated with fatigue and sputum production
- 4) Antibodies to SARS-CoV-2 and to auto-antigens (type 1 IFN and nuclear antigens) were inversely correlated with each other.
 - Neurological PASC associated with higher anti-SARS-CoV-2 Nucleoprotein Ab
 - GI PASC and sputum production rather associated with auto-antibodies
 - IFN- α 2 auto-Abs uniquely associated with respiratory viral PASC
- 5) SARS-COV-2 specific T cells
 - For patients reporting GI PASC, SARS-CoV-2 specific T cells exhibited undifferentiated phenotypes during acute disease and elevated cytotoxic characteristics at time of PACS
 - By contrast, in patients with respiratory viral symptoms, SARS-CoV-2 specific T cells followed the opposite trend
- 6) Bystander activation of CMV specific T cells associates with GI PACS

Detectability of most PASC factors at COVID-19 diagnosis emphasizes the importance of early disease measurements for understanding emergent chronic conditions and suggests treatment strategies.

5) **The effectiveness of vaccination against long COVID**

Ep 241-9 : UK Health Security Agency review

- 1) Effectiveness of vaccination BEFORE infection: 6 out of 8 studies indicate that fully vaccinated subjects are half as likely to develop long COVID than unvaccinated.
- 2) Effect of vaccination in long COVID cases is less clear: in 3 out of 4 studies more subjects reported improvement, but worsening was also reported.

Limitations:

- Heterogeneity in long COVID definition
- Only observational studies.

CONCLUDING REMARKS

Long-COVID/PACS is a very heterogeneous syndrome, which needs to be better defined and studied. It is evident that predisposing factor, such as age and co-morbidities are important, but apparently previously healthy young people are also suffering from this condition. .

It will be important to unravel the mechanisms, which could include persistence of virus, long-lasting inflammation, auto-immunity, metabolic disturbances, tissue damage....

Vaccination has a role to play in prevention and maybe also as part of a therapeutic approach. In any case, a multidisciplinary therapy, involving physicians, physiotherapists and psychologists will be needed to address these various aspects in an integrated way.

Best wishes,

Guido