



香港中文大學
The Chinese University of Hong Kong



香港中文大學醫學院
Faculty of Medicine
The Chinese University of Hong Kong



40th Anniversary
四十週年



Psychiatric complications of Long COVID:

Are we ready to receive the
challenges?

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Neuropsychiatric Problems

- Among general population during the COVID era
- Among Covid patients

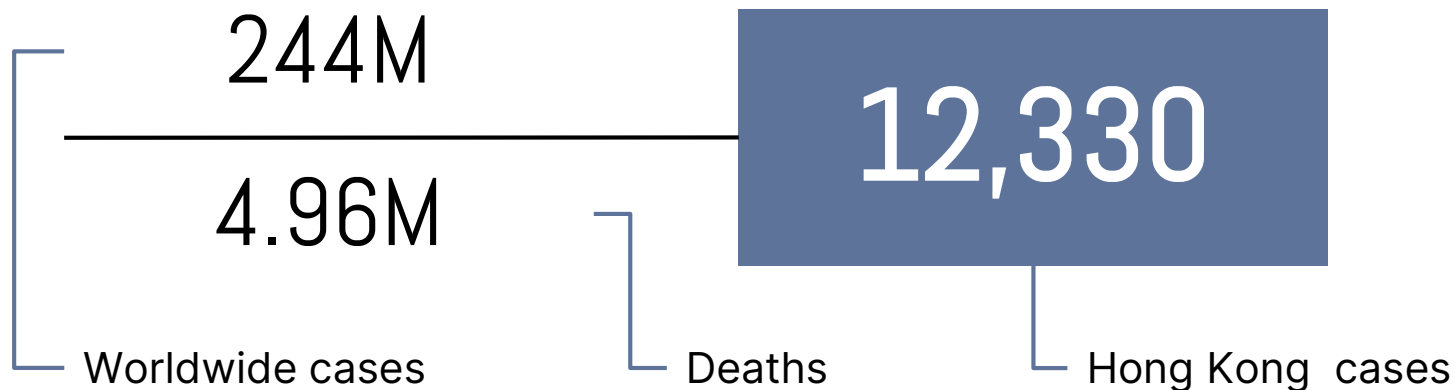
03

What can we do?

Challenges
Management

THE PANDEMIC

As of OCT 2021



COVID – Brief Overview

SARS-CoV-2 virus

Multisystem involvement

Mechanism of brain involvement

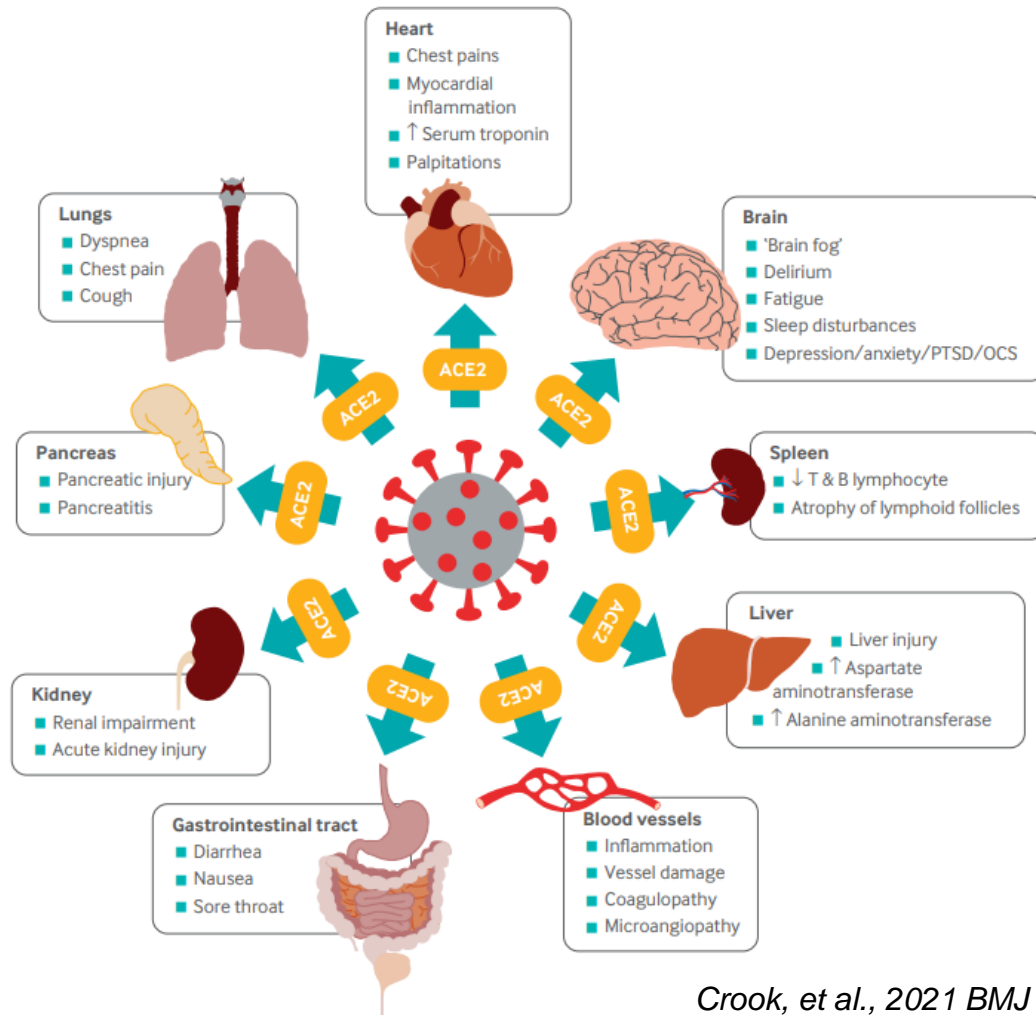
- Direct neurotrophism
- Immune activation
- Hypoxia, ischaemia etc

Psychosocial dimension

- Fear of infection
- Unprecedented social and activity restriction, quarantine
- Economic impact
- stigma

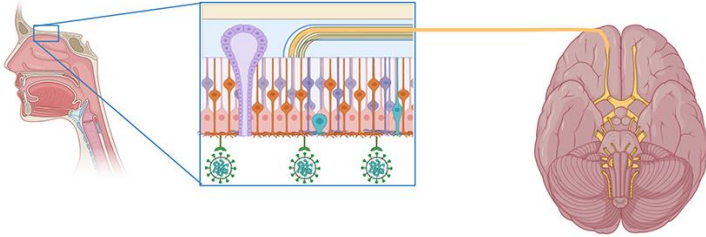
Multi-organ complications of covid-19 and long covid

- The SARS-CoV-2 virus gains entry into the cells of multiple organs via the ACE2 receptor
- The virus can cause a multitude of damage ultimately leading to numerous persistent symptoms



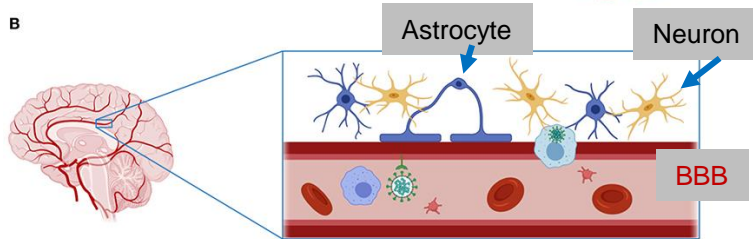
Possible Mechanisms of SARS-CoV-2 invasion to the central nervous system

A



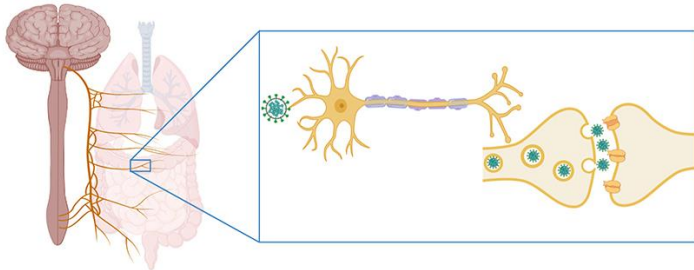
(A) SARS-CoV-2 can enter the CNS through the **olfactory bulb**. Olfactory epithelium is enriched with cells that express the receptor ACE2 and the protease cathepsin L.

B



(B) via the hematogenous route, attaching to the ACE2 receptor expressed in endothelial cells of the cerebral blood vessels, or inside an **immune cell**.

C



(C) Finally, SARS-CoV-2 can infect the nerve terminals of the vagus nerve located in the respiratory system and the **gastrointestinal tract**.

This figure was created with [BioRender](#).

COVID-19 and gut microbiota dysbiosis

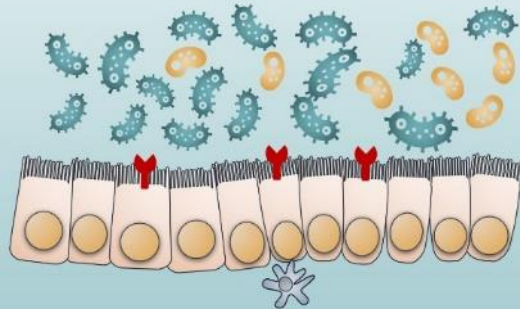
Health

Prevalent Commensals:

Eubacterium, *Faecalibacterium prausnitzii*,
Roseburia, *Lachnospiraceae* taxa



short-chain fatty acids (especially butyrate) producer
immunity maintenance
anti-inflammatory properties



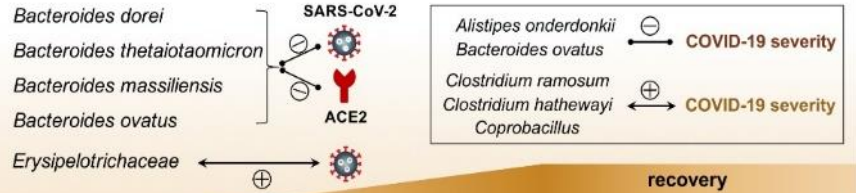
COVID-19

Commensal Symbionts ↓

Eubacterium ventriosum, *Faecalibacterium prausnitzii*, *Roseburia*, *Lachnospiraceae* taxa

Opportunistic Pathogens ↑

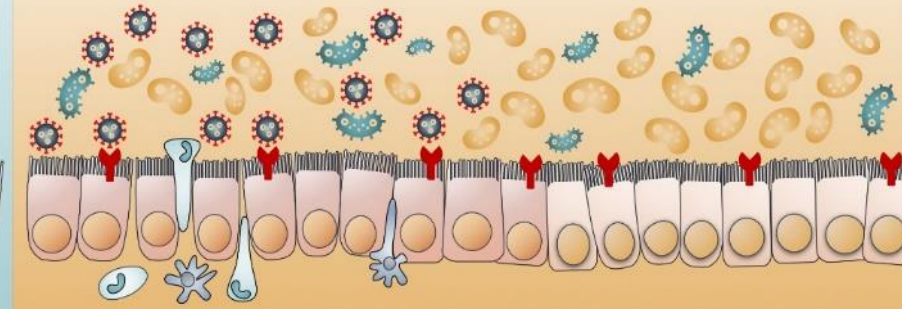
Clostridium hathewayi, *Actinomyces viscosus*, *Bacteroides nordii*



onset

prolonged alterations in the Gut Microbiome

recovery



Lower abundance of
Bifidobacterium pseudocatenulatum in
severe patients with
COVID 19 infection

Four *Bacteroides*
species inhibit the
SARS CoV2 viral load
and ACE2 receptor
expression



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Neuropsychiatric problems
among general public
during the COVID era

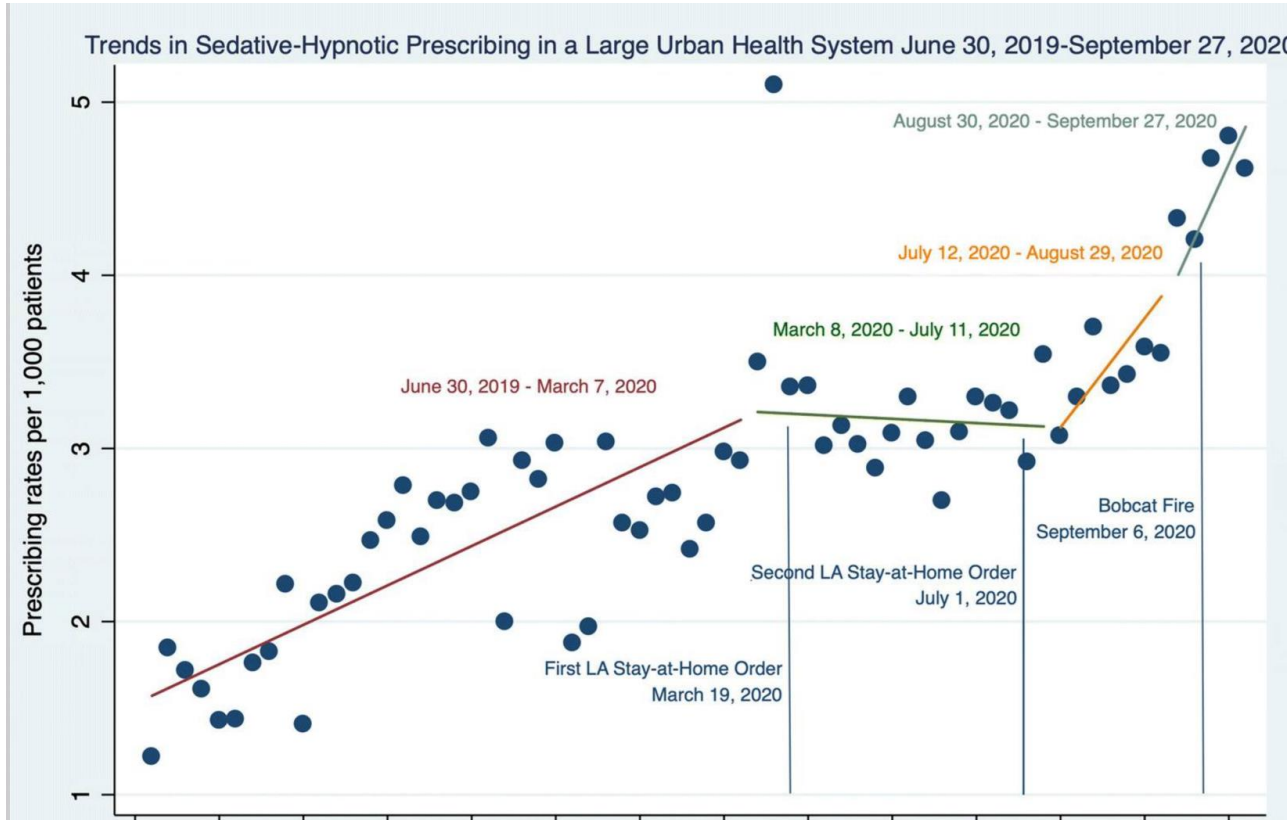
'Covid-somnia' / 'Corona-somnia'

Many studies and media reports reported increased risk of insomnia or non-specific sleep difficulties among general public during the COVID era.

For special groups like frontline HCWs during the early phase of pandemic, consistently reported insomnia prevalence up to 40-50%

Indirectly reflect by increase in sedative/anxiolytics demand from prescription database (Italy/US)

Sedative Hypnotic Prescribing Rate



ICOSS-International Covid Sleep Study

Aims:

How COVID-19 pandemic and infection has influenced on sleep, circadian rhythms, fatigue, daytime functioning and health in general adult populations.

Methods:

Online survey

N= ard 22 330 adults



Participating Countries/Regions



Findings



Insomnia & Mood Problems *Morin, et al., 2021 Sleep Medicine*

Clinical insomnia symptoms: **36.7%**
met criteria for a probable insomnia
disorder: **17.4%**
Probable Anxiety: **25.6%**
Probable Depression: **23.1%**

Greater risk of insomnia problems:

- Women,, COVID infection, Financial burden
- Confinement for 4-5 weeks
- Residents of Brazil, Canada, Norway, Poland, USA, and UK
- compared to residents from Asian countries



Evening-types show highest increase in mental health problems *Merikanto, et al., 2021, Sleep*

Evening-types:

- Poorer mental health, well-being, and quality of life
- Delayed sleep during working days
- Longer sleep duration

Sleep problems increased in all circadian types, but especially among **evening-types**, moderated by financial suffering and confinement

Findings



Social Jetlag and Insomnia

Brandão et al., 2021 Nature and Science of Sleep

Reduction in SJL: 46%

Increased in SJL: 20%

No Change: 34%

Changes of SJL (both reduced or increased):

- Later sleep timepoint
- More recurrent insomnia symptoms
- Reduced SJL → later bedtime



REM Sleep Behavior Disorder

Manuscript under review

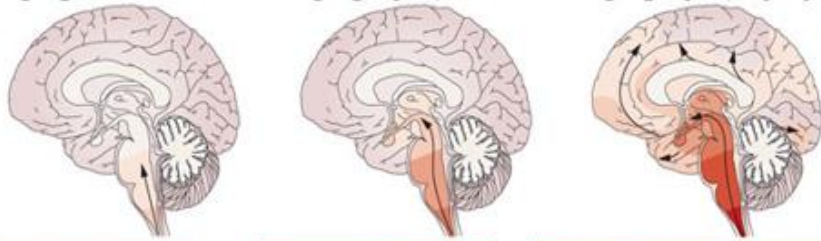
Possible RBD: 19.4%

Probable RBD: 3.1%

Greater risk of RBD:

- Male, younger age, COVID infection
- Smoking, alcohol, higher physical activity level
- Olfactory impairment
- Nightmare, OSA, Mood Problems

RBD and neurodegenerative disease



Stage 2---RBD

Stage 3-4---PD

Stage 5-6---Cognitive deficit

The risk for developing neurodegenerative diseases: 33.5% at five years follow-up, 82.4% at 10.5 years and 96.6% at 14 years.

Galbiati *et al.* 2019

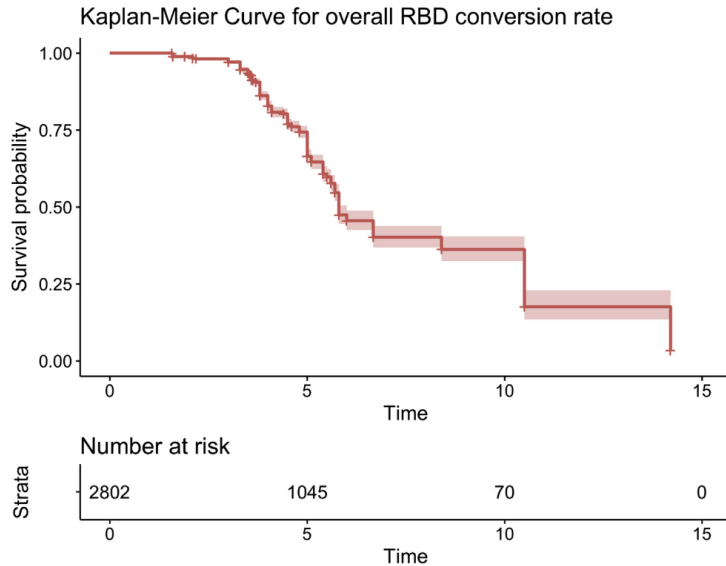


Fig. 4. Kaplan-Meier analysis plotting disease-free survival in RBD patients.

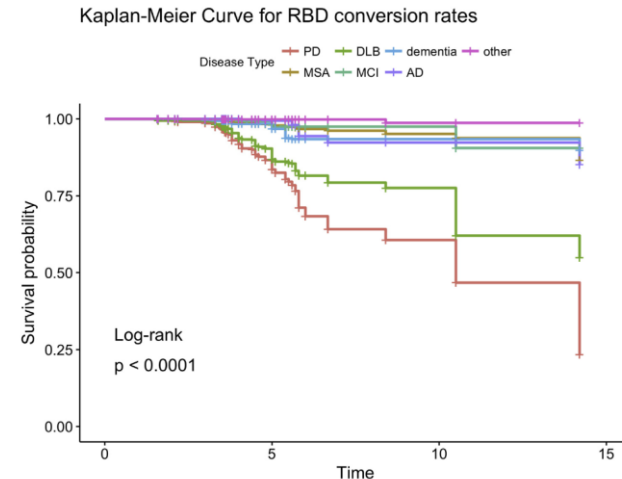


Fig. 5. Kaplan-Meier analysis plotting disease-free survival in RBD patients, stratified for neurodegenerative disease of conversion.



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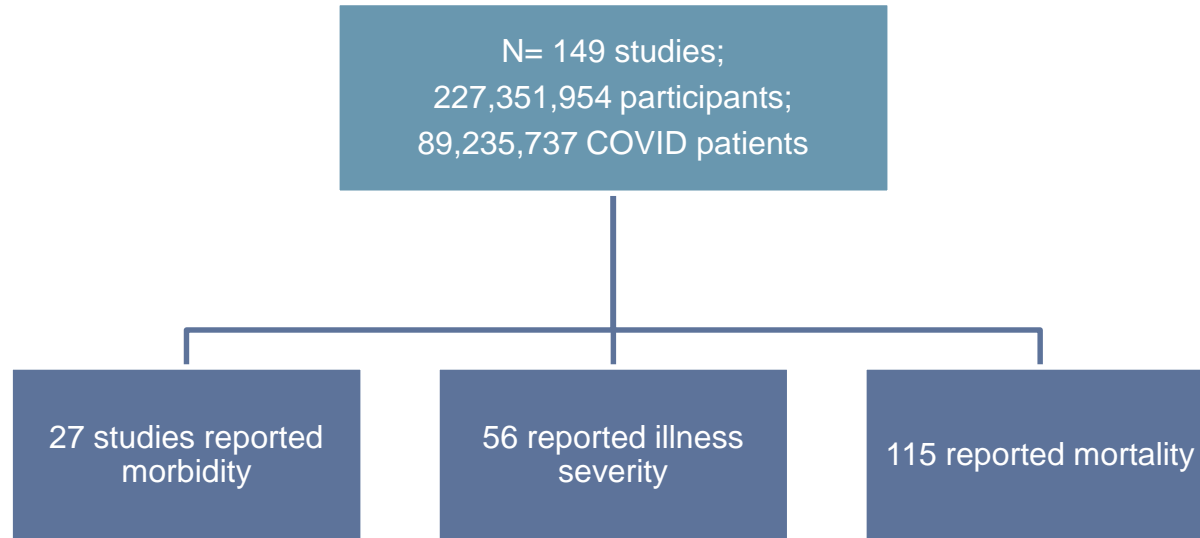
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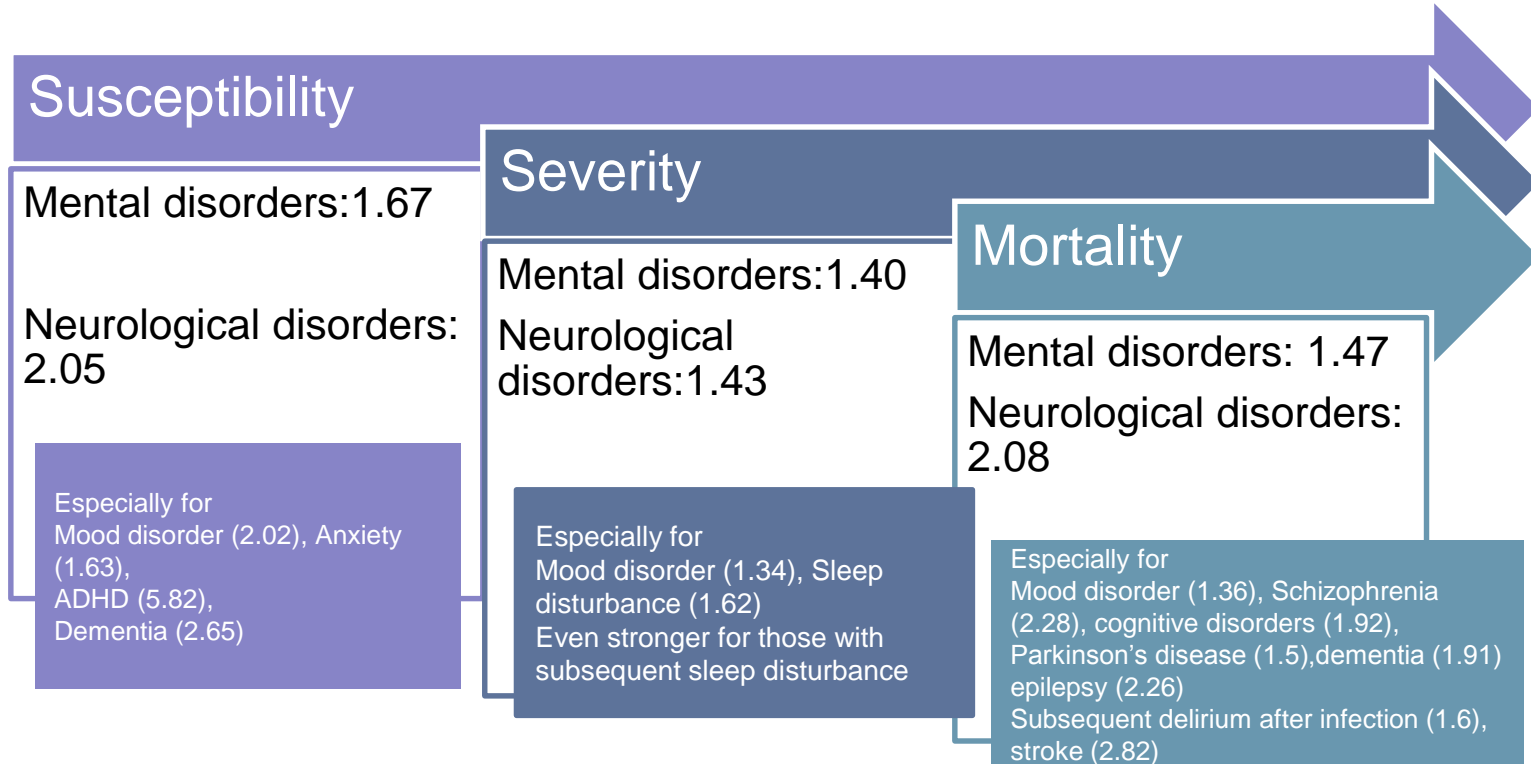
Neuropsychiatric problems and risk of COVID infection

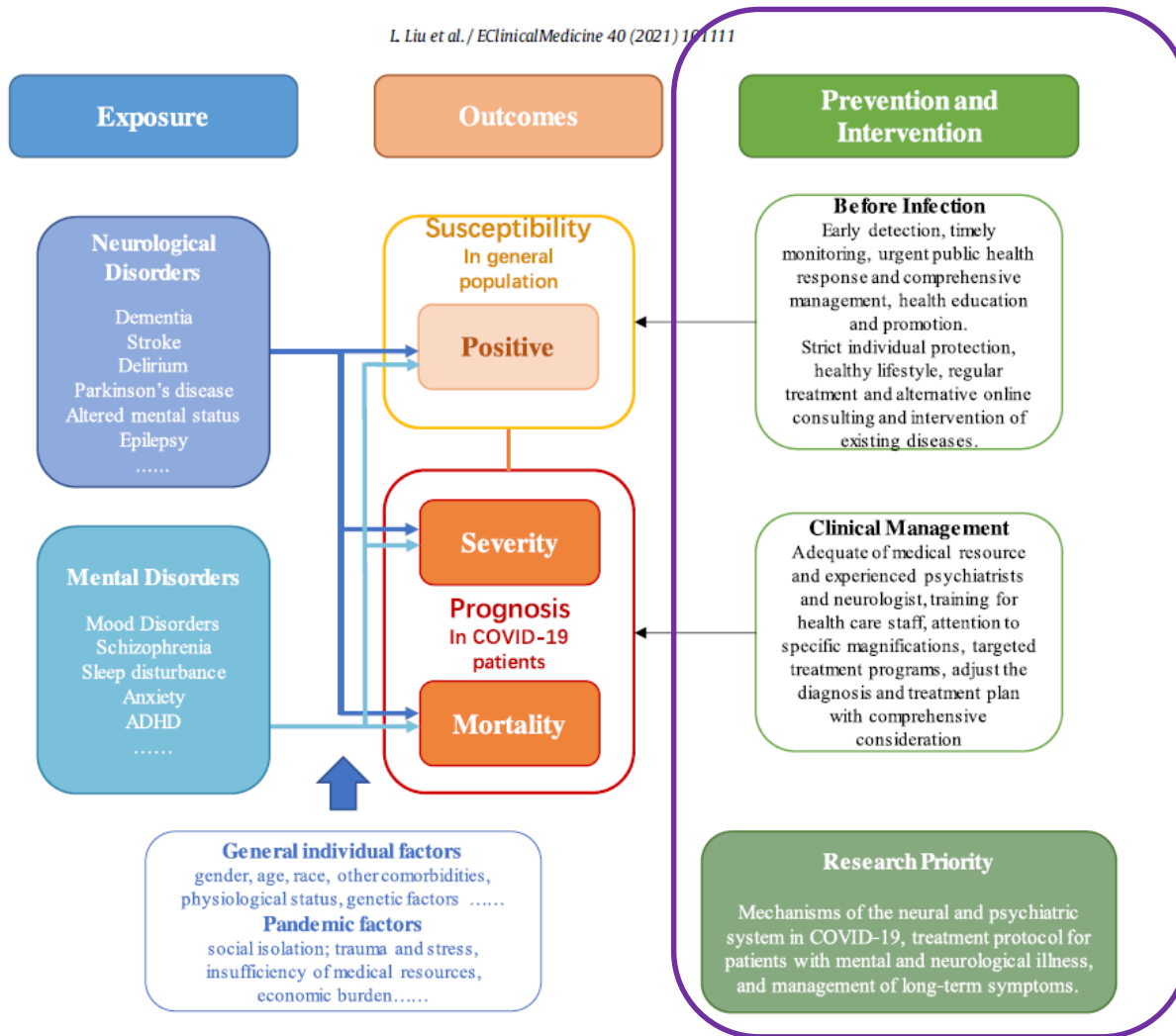
Mental and neurological disorders and risk of COVID-19 susceptibility, illness severity and mortality: A systematic review, meta-analysis and call for action

Lin L et al., 2021 EclinicalMedicine



Effect of Pre-existing mental and neurological on the risk of COVID





Important to understand the mechanisms of the neural and psychiatric systems in COVID-19



Adequate treatment approach for management of long-term symptoms



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Neuropsychiatric problems after COVID infection --Long COVID

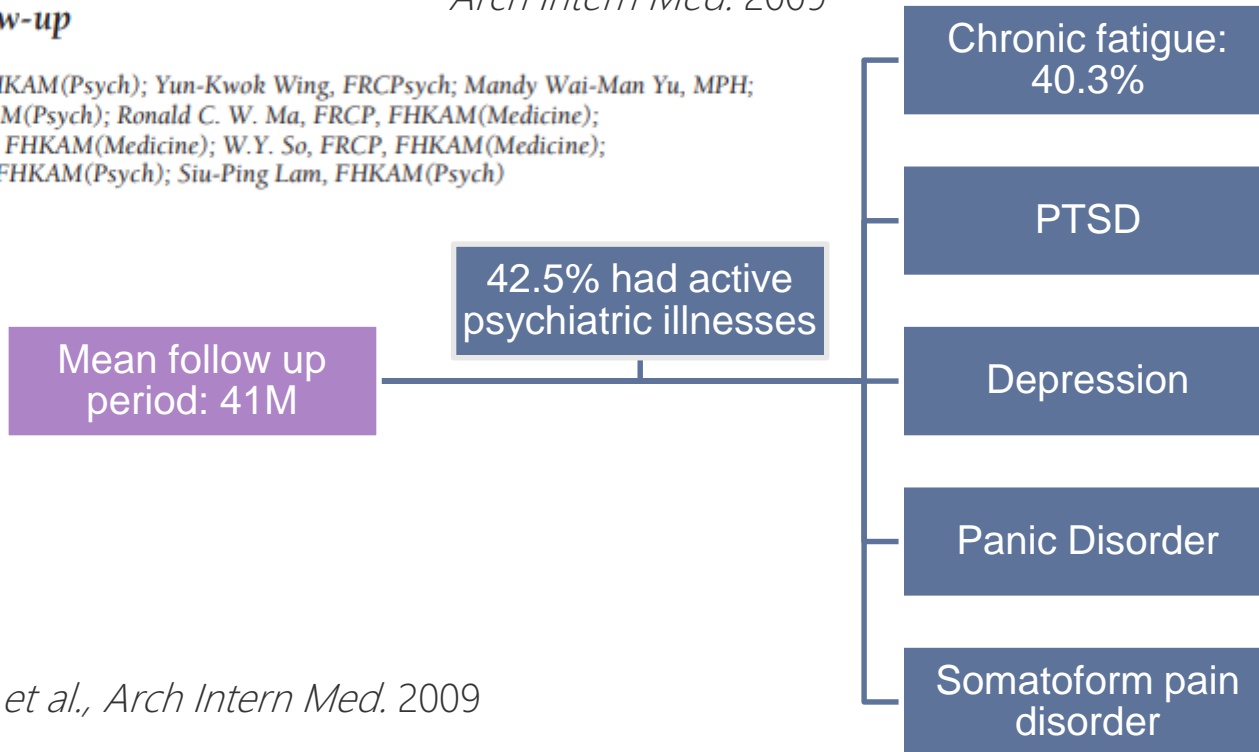
Experience learnt from SARS 2003

Mental Morbidities and Chronic Fatigue in Severe Acute Respiratory Syndrome Survivors

Long-term Follow-up

Arch Intern Med. 2009

Marco Ho-Bun Lam, FHKAM(Psych); Yun-Kwok Wing, FRCPsych; Mandy Wai-Man Yu, MPH;
Chi-Ming Leung, FHKAM(Psych); Ronald C. W. Ma, FRCP, FHKAM(Medicine);
Alice P. S. Kong, FRCP, FHKAM(Medicine); W.Y. So, FRCP, FHKAM(Medicine);
Samson Yat-Yuk Fong, FHKAM(Psych); Siu-Ping Lam, FHKAM(Psych)



Lam and Wing et al., Arch Intern Med. 2009



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How about in COVID recovery?

Definition of LONG COVID



A history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis

Long COVID
Long-haul COVID
Post COVID-19

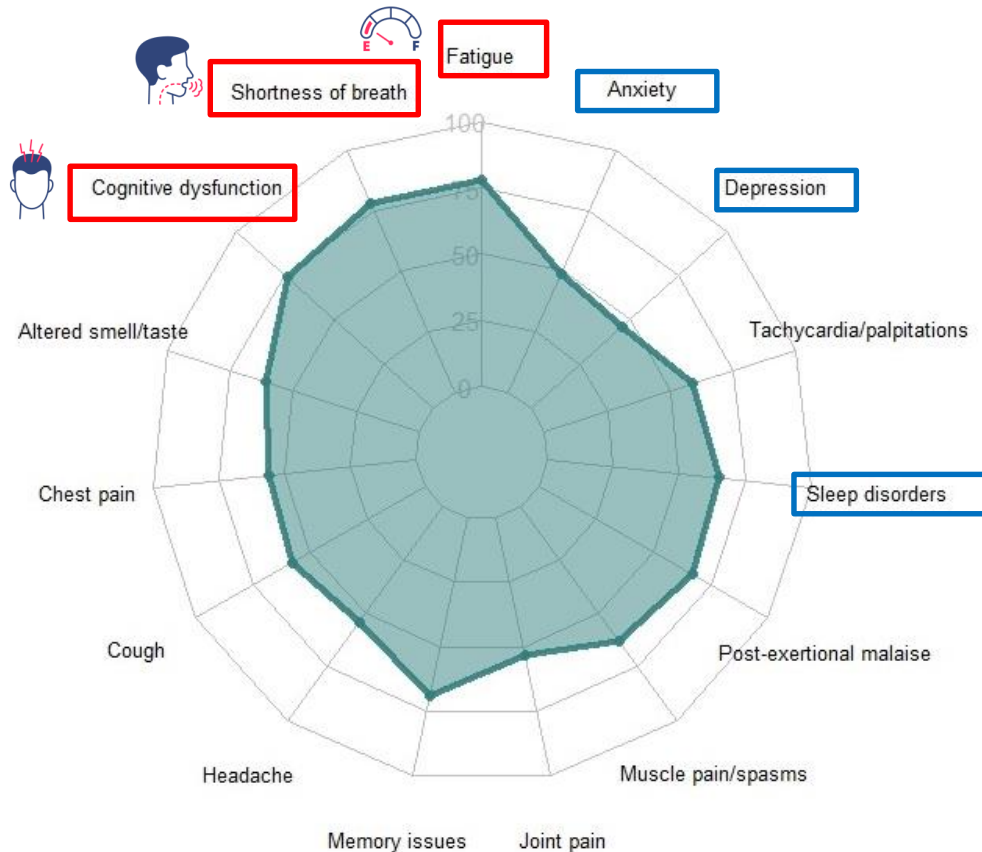


A clinical case definition of post COVID-19 condition by a Delphi consensus

6 October 2021



The MOST COMMON SYMPTOMS



Symptoms may be **new onset**, following initial recovery from an acute COVID-19 episode, or **persist** from the initial illness.

Symptoms may also **fluctuate or relapse** over time.

LONG COVID

- Could attribute to different underlying pathophysiologic processes
- Manifestation of the symptoms could be complicated by a number of factors (e.g., pre-existing condition, Sociodemographic factors)
- May share similarities with other post-viral conditions
- Frequency varies significantly in the literature due to the different definition used, sample heterogeneity , measurement methods.
- Could also affect children and adolescent but may need a separate definition for children.

6-month consequences of COVID-19 in patients discharged from hospital: a cohort study

Lancet 2021

Chaolin Huang, Lixue Huang*, Yeming Wang*, Xia Li*, Lili Ren*, Xiaoying Gu*, Liang Kang*, Li Guo*, Min Liu*, Xing Zhou, Jianfeng Luo, Zhenghui Huang, Shengjin Tu, Yue Zhao, Li Chen, Decui Xu, Yanping Li, Caihong Li, Lu Peng, Yong Li, Wuxiang Xie, Dan Cui, Lianhan Shang, Guohui Fan, Jiuyang Xu, Geng Wang, Ying Wang, Jingchuan Zhong, Chen Wang, Jianwei Wang†, Dingyu Zhang†, Bin Cao†*

1733 discharged covid patients; Mean age: 57.0; Median follow up: 186 days

Fatigue (63%)

Sleep difficulties
(26%)

Anxiety or
depression (23%)

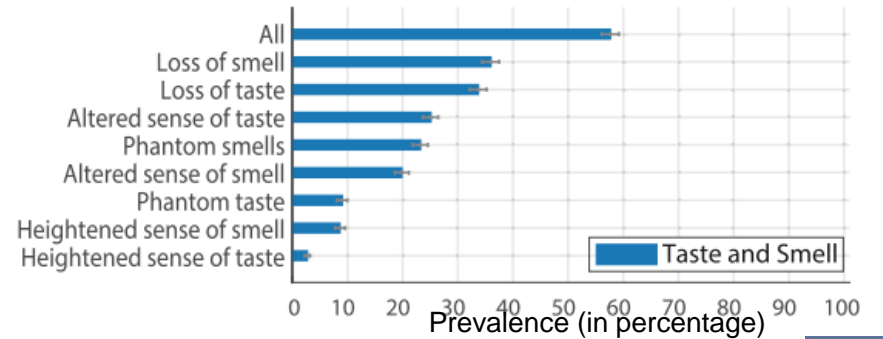
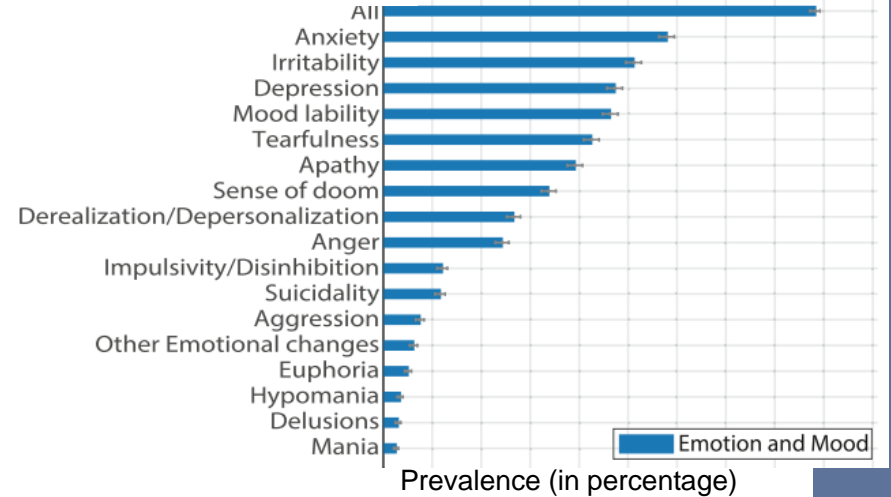
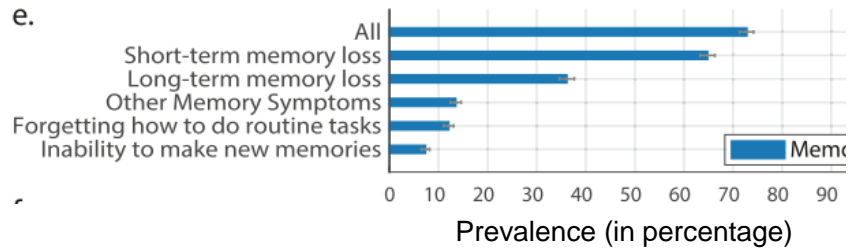
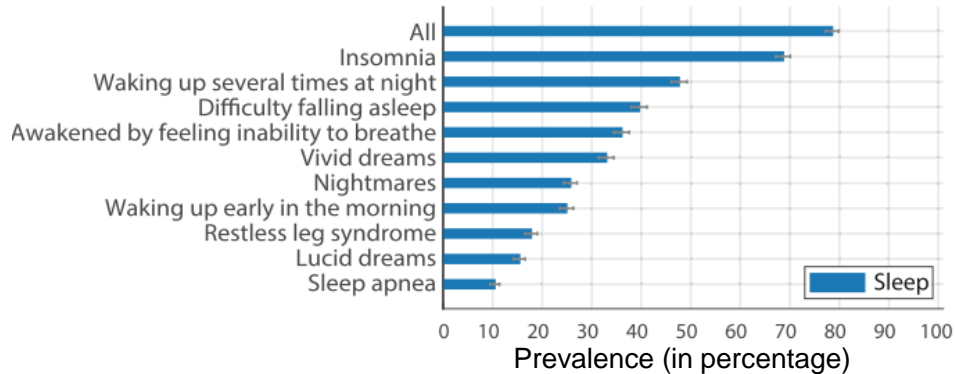
Diffusion impairment
(22% - 56%
depending on
severity)

Characterizing long COVID in an international cohort: 7 months of symptoms and their impact

Davis et al., *EClinicalMedicine*, 2021

Hannah E. Davis^{a,1}, Gina S. Assaf^{a,1}, Lisa McCorkell^{a,1}, Hannah Wei^{a,1}, Ryan J. Low^{a,b,1}, Yochai Re'em^{a,c,1}, Signe Redfield^a, Jared P. Austin^{a,d}, Athena Akrami^{a,b,1,*}

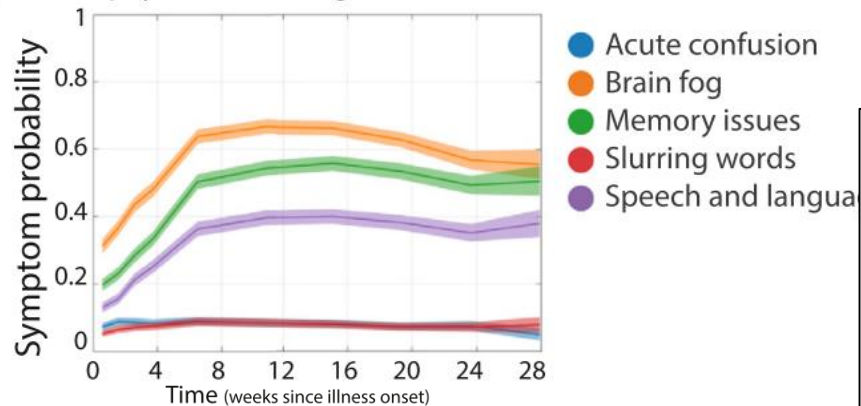
Symptoms experienced at any point



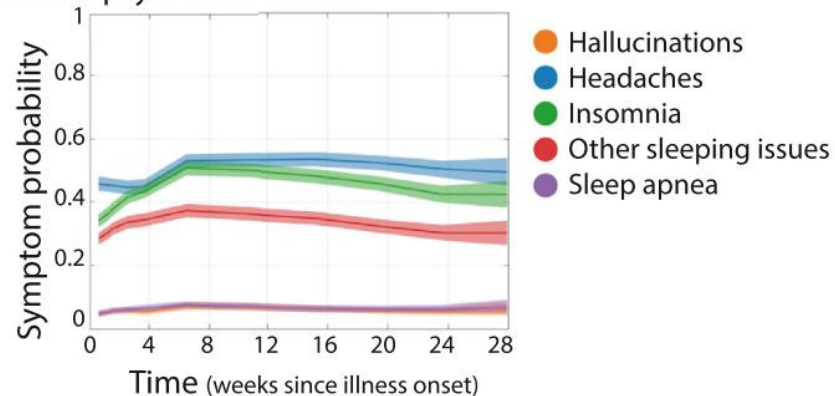
Symptoms over time

Davis et al., *EClinicalMedicine*, 2021

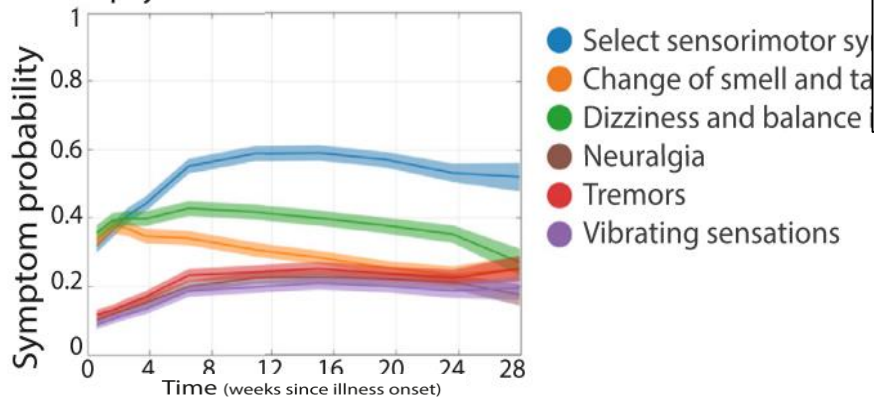
j. Neuropsychiatric - cognitive



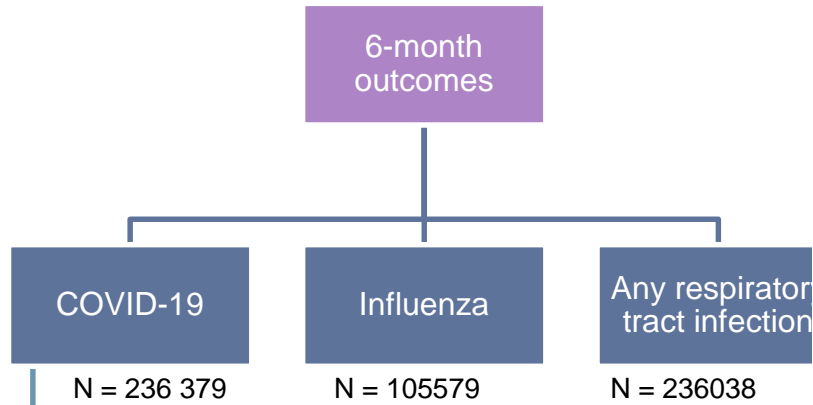
l. Neuropsychiatric - other



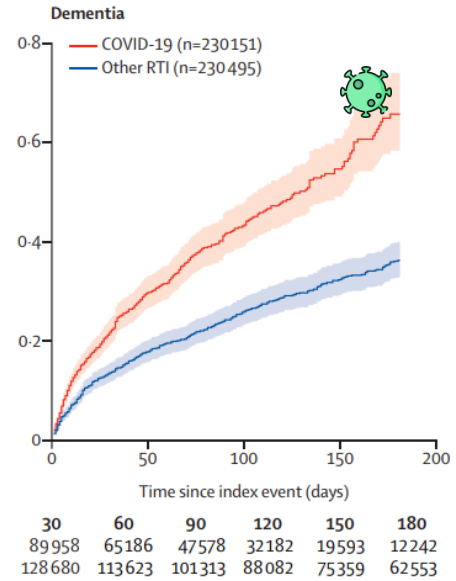
k. Neuropsychiatric - sensorimotor



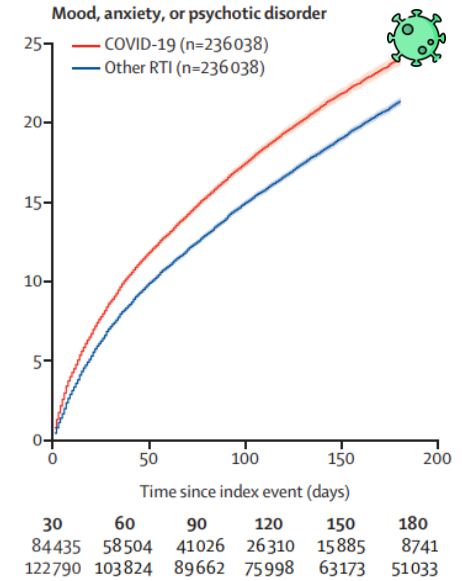
6-Month Neurological and Psychiatric outcomes associated with different severity



Neurological and psychiatric outcomes
 Whole sample: 34%
 Hospitalized: 39%;
 Intensive Therapy Unit: 46%
 Encephalopathy: 62%



HR = 1.88 – 1.95



HR = 1.40 -1.85

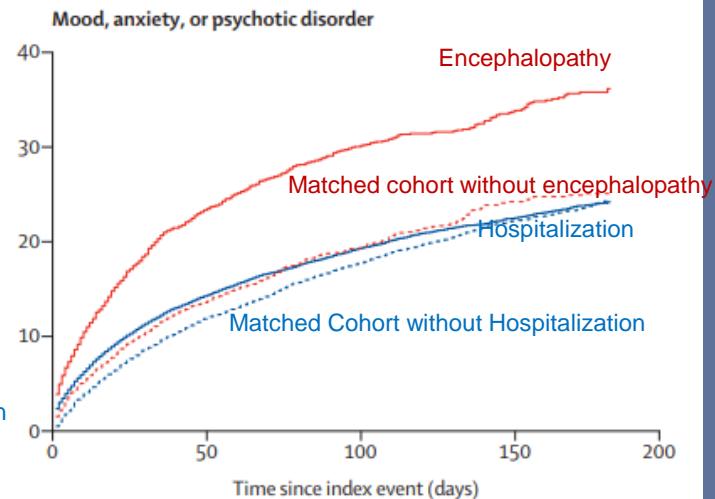
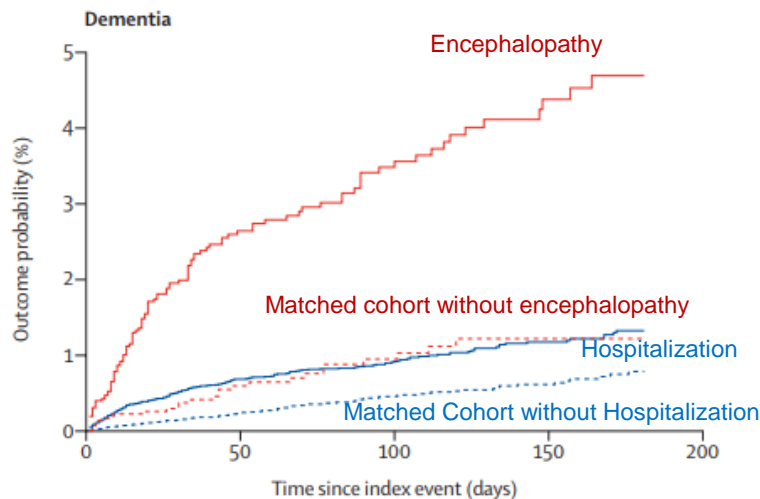
Patients without hospitalization after COVID-19 compared with those after influenza or other RTIs

	COVID-19 vs influenza in patients without hospitalisation (N=96 803)*		COVID-19 vs other RTI in patients without hospitalisation (N=183 731)*	
	HR (95% CI)	p value	HR (95% CI)	p value
Dementia	1.88 (1.27–2.77)	0.0008	1.95 (1.55–2.45)	<0.0001
Mood, anxiety, or psychotic disorder (any)	1.49 (1.45–1.54)	<0.0001	1.18 (1.15–1.21)	<0.0001
Mood, anxiety, or psychotic disorder (first)	1.85 (1.72–1.99)	<0.0001	1.40 (1.32–1.48)	<0.0001
Mood disorder (any)	1.49 (1.43–1.55)	<0.0001	1.22 (1.19–1.26)	<0.0001
Mood disorder (first)	1.78 (1.61–1.96)	<0.0001	1.37 (1.27–1.47)	<0.0001
Anxiety disorder (any)	1.48 (1.43–1.54)	<0.0001	1.16 (1.13–1.19)	<0.0001
Anxiety disorder (first)	1.80 (1.67–1.94)	<0.0001	1.37 (1.30–1.45)	<0.0001
Psychotic disorder (any)	1.93 (1.63–2.28)	<0.0001	1.44 (1.27–1.62)	<0.0001
Psychotic disorder (first)	2.27 (1.56–3.30)	<0.0001	1.49 (1.15–1.93)	0.0016
Substance use disorder (any)	1.26 (1.19–1.33)	<0.0001	1.11 (1.07–1.17)	<0.0001
Substance use disorder (first)	1.21 (1.05–1.38)	0.0054	0.89 (0.81–0.97)	0.013
Insomnia (any)	1.52 (1.42–1.63)	<0.0001	1.18 (1.12–1.24)	<0.0001
Insomnia (first)	2.06 (1.82–2.33)	<0.0001	1.51 (1.38–1.66)	<0.0001
Any outcome	1.47 (1.44–1.51)	<0.0001	1.16 (1.14–1.17)	<0.0001
Any first outcome	1.83 (1.71–1.96)	<0.0001	1.28 (1.23–1.33)	<0.0001

Details on cohort characteristics are presented in the appendix (pp 37–40). HR=hazard ratio. RTI=respiratory tract infection. *Matched cohorts.

Table 4: HRs for the major outcomes in patients without hospitalisation after COVID-19 compared with those after influenza or other RTIs

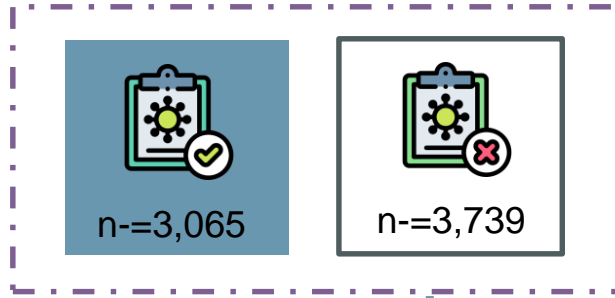
Higher risk in the group who had encephalopathy than for the matched cohort who did not



	Total	30	60	90	120	150	180
Encephalopathy	4704	2627	1929	1425	1036	717	583
Matched cohort without encephalopathy	5094	2562	2010	1419	986	986	986
Hospitalisation	42434	19428	13970	10567	7611	5427	3616
Matched cohort without hospitalisation	42877	18719	13904	10329	7017	5174	2697

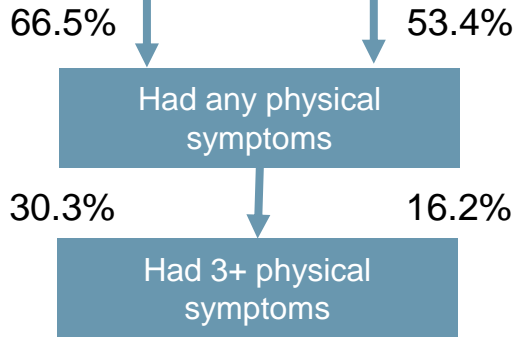
	Total	30	60	90	120	150	180
Encephalopathy	6221	2640	1734	1217	888	575	351
Matched cohort without encephalopathy	6221	2729	1910	1417	955	633	437
Hospitalisation	45167	18072	12352	8933	6068	3976	2501
Matched cohort without hospitalisation	45167	18092	12874	9170	5925	3653	2001

How about in Children and Adolescents ?



No difference in the distribution of **mental health and fatigue** scores

After 3 months

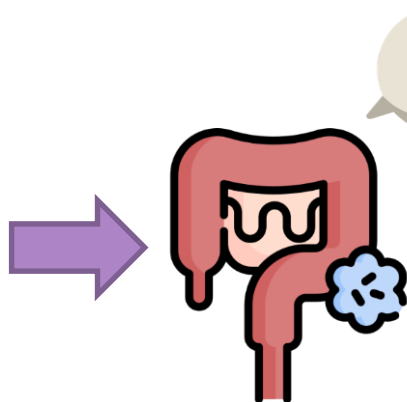
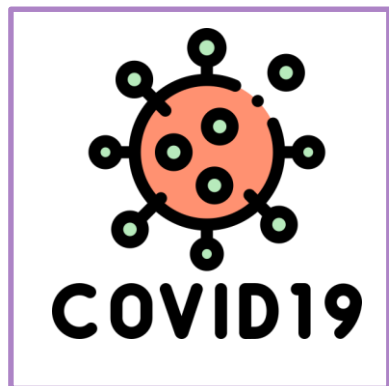


“Post-COVID is different in children and adolescents to adults and one should not extrapolate from the adult literature to decide policy and services for children and adolescents.”

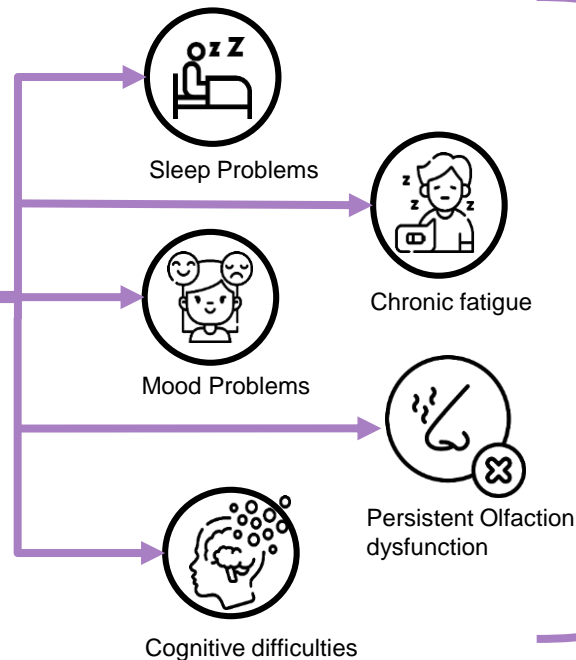
Hong Kong Data – Ongoing project

Long COVID - **neuropsychiatric** sequelae associated with altered **gut microbiota**?

Study design: Prospective longitudinal follow up of COVID-19 survivors and the general population age-sex matched non-COVID controls.



Dysbiosis
associated with
coronavirus



Captured
by **Digital
Mental
Health
Platform**

**Hidden
under-
detected**

Supported by

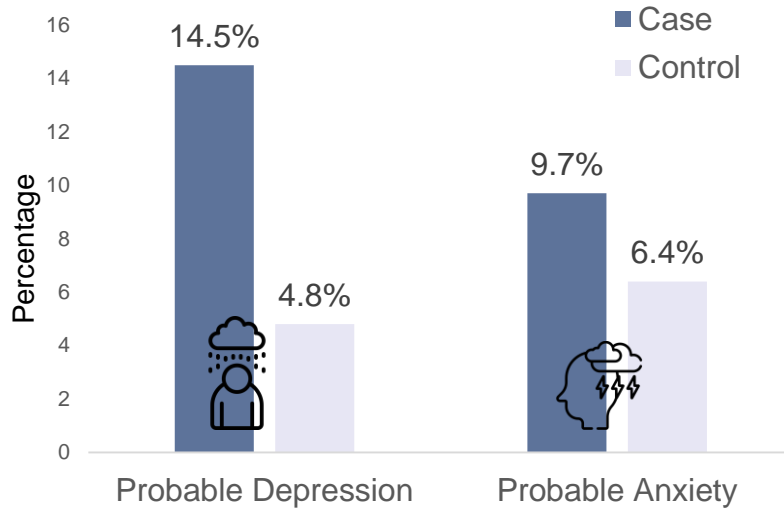


Research Fund Secretariat
Food and Health Bureau
The Government of the Hong Kong Special Administrative Region

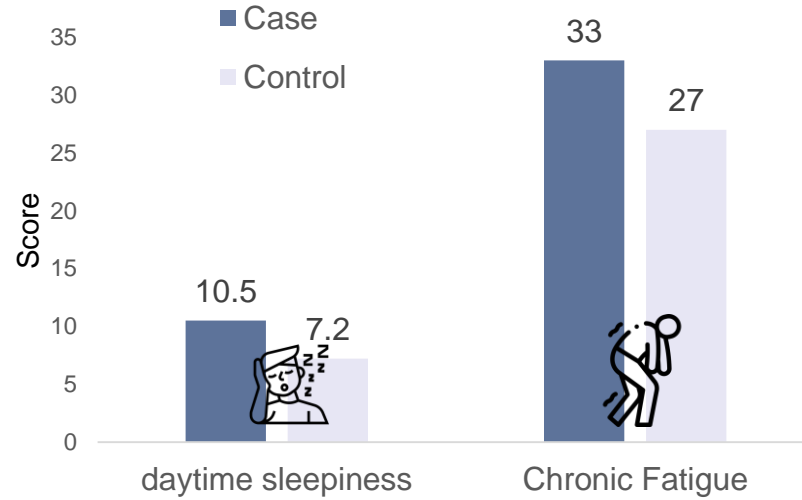
Preliminary data

N = 62 (31 cases + 31 controls); mean age: 54yrs

The prevalence of mental health problems



Fatigue and Daytime Sleepiness Score





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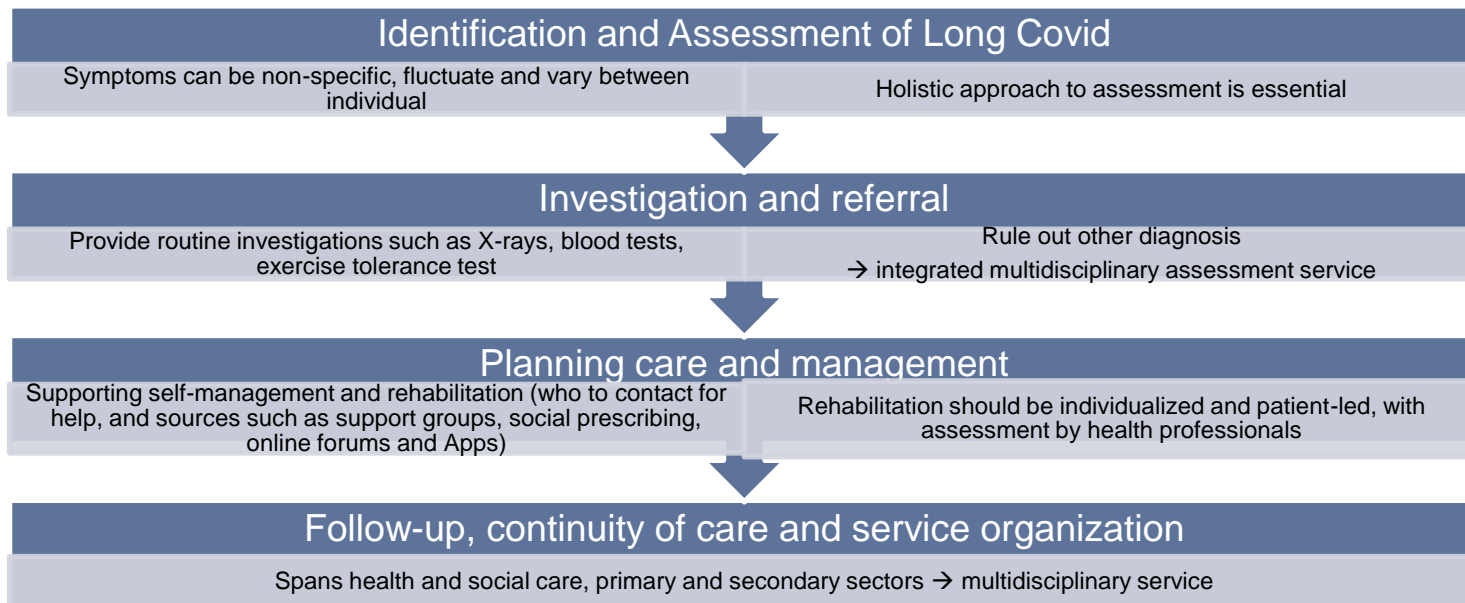
Assessment and Treatment for LONG COVID

Are we ready to receive the challenges?

Joint guideline on the management of long COVID

NICE, SIGN and the Royal College of General Practitioners have published a joint guideline on identifying and managing the long-term effects of COVID-19 ('long COVID') in adults, young people and children.

- A holistic approach to assessment is essential
- There is no unique approach to evaluating possible long COVID.



Assessment of LONG COVID

- No laboratory test can distinguish long covid from other etiologies
- Basic panel of lab tests might be considered between 4-12weeks
- Additional testing after 12 weeks if symptoms persisted

Basic diagnostic tests to consider ≥4 weeks after SARS-CoV-2 infection (or sooner if clinically indicated)	
<u>Category</u>	<u>Laboratory tests</u>
Blood count, electrolytes, and renal function	Complete blood count with possible iron studies to follow, basic metabolic panel, urinalysis
Liver function	Liver function tests or complete metabolic panel
Inflammatory markers	C-reactive protein, erythrocyte sedimentation rate, ferritin
Thyroid function	TSH and free T4
Vitamin deficiencies	Vitamin D, vitamin B12
Specialized diagnostic tests* to consider ≥12 weeks after SARS-CoV-2 infection (or sooner if clinically indicated)	
<u>Category</u>	<u>Laboratory tests</u>
Rheumatological conditions	Antinuclear antibody, rheumatoid factor, anti-cyclic citrullinated peptide, anti-cardiolipin, and creatine phosphokinase
Coagulation disorders	D-dimer, fibrinogen
Myocardial injury	Troponin
Differentiate symptoms of cardiac versus pulmonary origin	B-type natriuretic peptide
* The specialized diagnostic tests should be ordered in the context of suggestive findings on history and physical examination	

Source: Centers for Disease Control and Prevention Center for Preparedness and Response

Assessment of LONG COVID

Symptom checklist and assessment tools to monitor the LONG COVID condition

Self-reported
questionnaires

Cognitive
Assessment

Exercise Tolerance
test

Blood pressure and
heart rate

Specific imaging tests for evaluation of Long covid? Brain MRI with brain fog?
More evidence is needed

*Source: Centers for Disease Control and
Prevention Center for Preparedness and
Response*

Management of LONG COVID

The guidelines for treating and managing long covid is evolving.

Summary of NICE, SIGN, and RCGP rapid guideline for managing the long-term effects of covid-19



Self-management and supported self-management

Self-monitoring;

Provide adequate information and advices for self-management

Investigation and referral

Comprehensive examinations



Support for older people and children

Consider **additional support and referral** for specialist advice, especially for children and older people



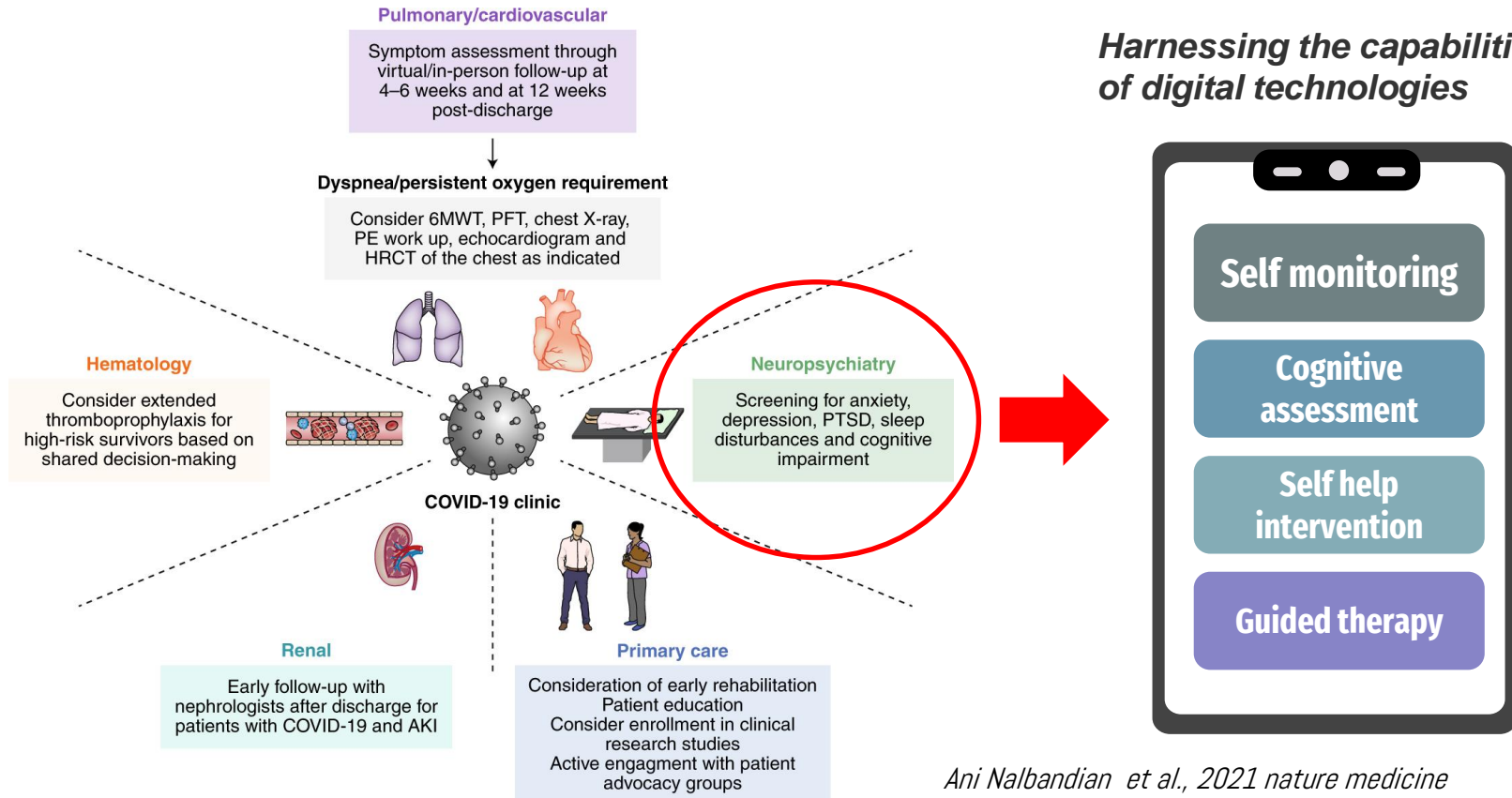
Multidisciplinary rehabilitation

Assess **physical, psychological and psychiatric** aspects of rehabilitation

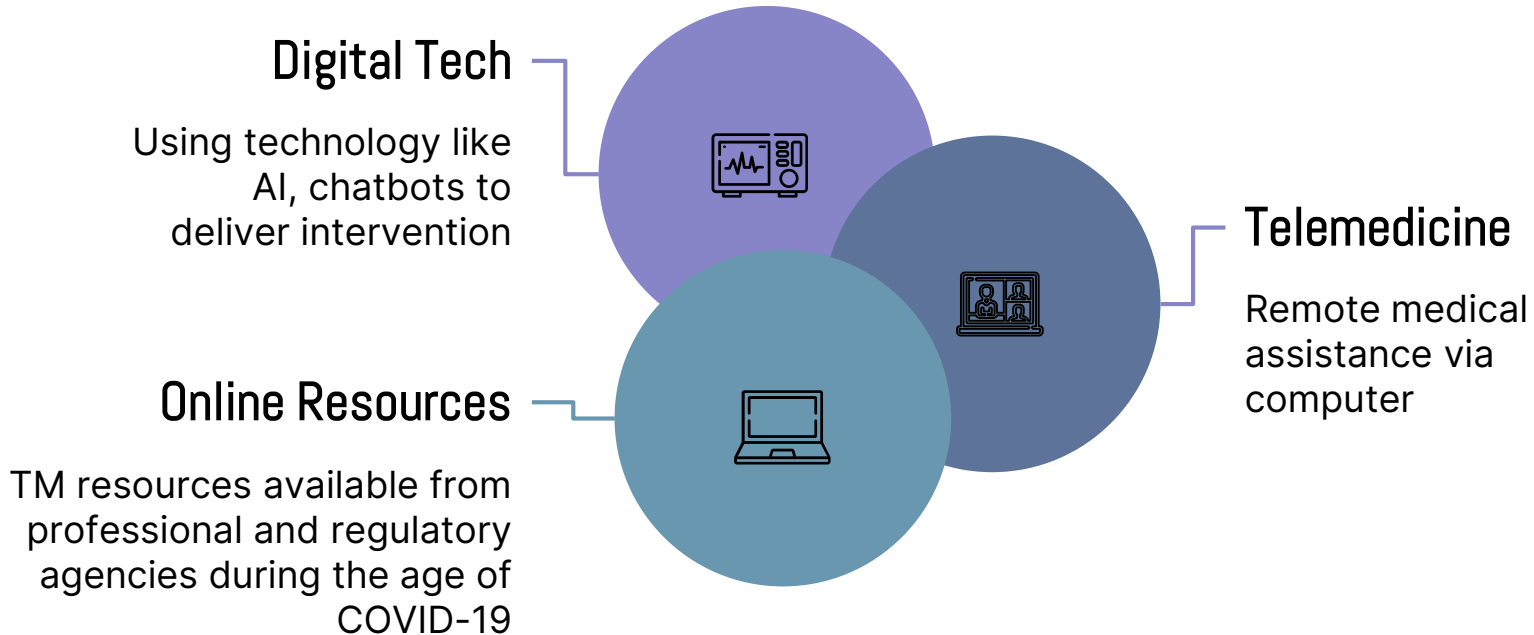
Work with person to develop personalized rehabilitation and manage plan - Encourage people to monitor progress

Management **of fatigue should be a key component**, followed by cognitive impairment

Multi-disciplinary management



Telemedicine can help

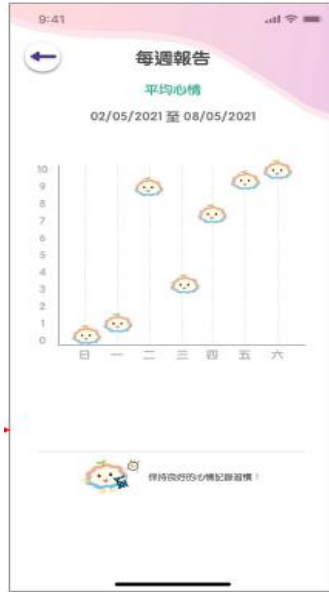


Digital Mental Health Platform – Assessment

Mood and Sleep record



Self-assessment



1. **Dynamic assessment** of the **multiple facets** of mental health and cognitive status over a time period
2. Allow timely and ambulatory measurement



Digital Mental Health Platform – Intervention



9:41

Cancel

抑鬱症是甚麼?

抑鬱症是一種常見情緒障礙，會對患者的情緒、思維以及日常行為，例如睡眠、飲食、工作學習等產生負面影響。長時間的情緒低落以及對一向喜歡做的事情失去興趣是抑鬱症的兩個主要表現。

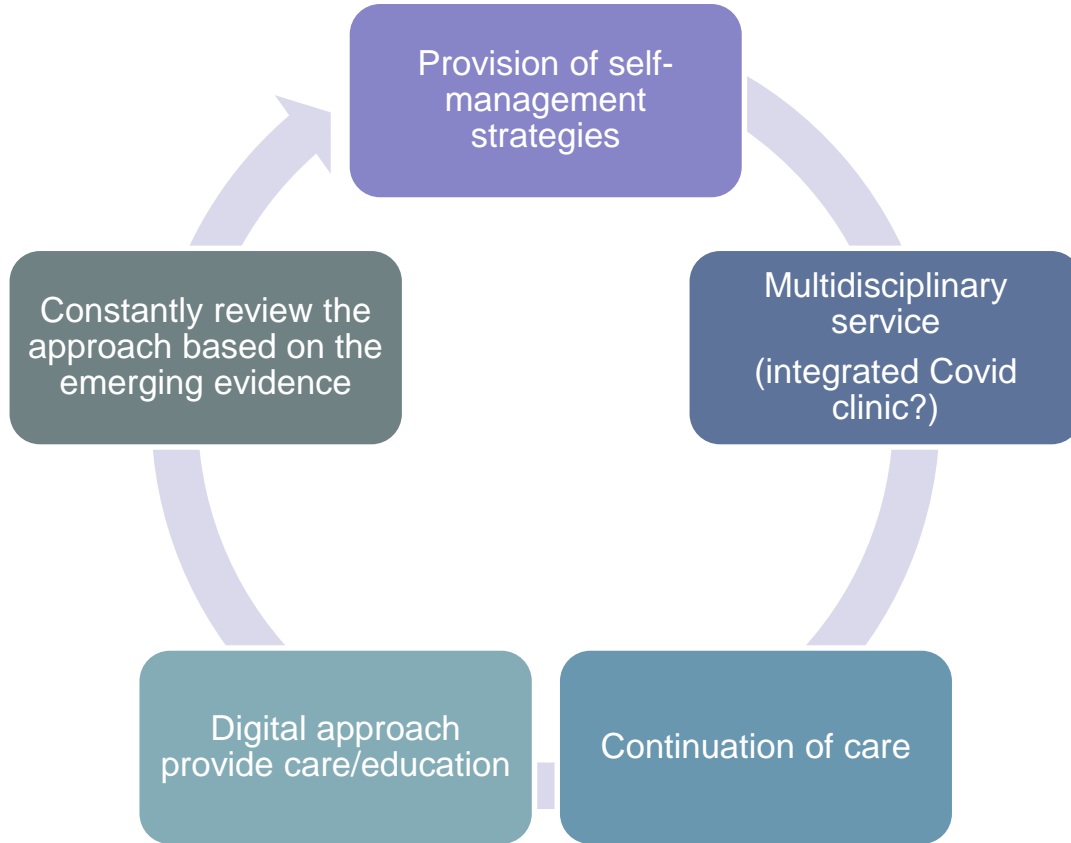
常見的症狀:

- 長時間地感到情緒低落或者沮喪憂傷
- 對於你平時喜歡的事情喪失興趣或者在做這些事情的過程中體會不到愉快感
- 食欲改變 (明顯減退或者增加) ，或者儘管你沒有刻意改變飲食習慣，仍出現體重減輕或者增加的情況
- 入睡困難，早醒，或者嗜睡
- 經常覺得疲倦，缺乏精力
- 經常感覺煩躁，難以靜坐或坐立不安，或者語速或動作明顯減慢 (這些情況必須嚴重到已經被他人察覺)
- 缺乏自信，對前途悲觀，或者經常對做過的事情感到後悔，經常自責

Transdiagnostic approach:

- Targeting Sleep, Depression and Anxiety
- Treatment components and sequence will be formulated based on participants' profile
- Self-pace, fully-automated approach

Implication to policy



Summary

- The pandemic has impacted every aspect of life, resulting in increased sleep and mental problems in the general population.
- Long COVID is very common in COVID survivors regardless of the severity of the acute infection
- Fatigue, brain fog and shortness of breath are the common long-lasting symptoms.
- Management of Long COVID is still evolving, a multidisciplinary management is necessary.
- Digital approach is a potential and cost-effective way to monitor and manage long covid



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40th Anniversary
四十週年



Thank You!