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Long COVID

IEQAS Conference 7th October 2021

Prof. Eoin Feeney

Consultant Physician in Infectious Diseases, SVUH

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The Atlantic

Jonno Rattman

HEALTH

UNLOCKING THE MYSTERIES OF LONG COVID

A growing number of clinicians are on an urgent quest to find treatments for a frighteningly pervasive problem. They've had surprising early success.

Coronavirus crisis

Long covid 'Swimming upstream on my own'

Marese McDonagh

Patient tells of 18-month wait to access a Covid clinic, says Mayo GP

Eight months after contracting Covid-19, Paula Gray still asks herself whether she really needs to do the most routine tasks because even taking a shower means "I'll pay for it later".

On Christmas Day after noticing that "the Cadbury's Roses and the turkey tasted the same", she tested positive and remembers thinking she'd have search for the appropriate specialty for their issue.

The long Covid clinic at St James's opened almost a year ago and caters only for Covid-19 patients who were treated at the hospital or hospital staff. They see 15 patients every Friday, including a "very small" cohort who got Covid-19 as far back as March 2020.

A spokesman for the UL Hospitals Group (covering Limerick, Clare and North Tipperary) said there was no designated long Covid clinics within its group. "Patients with suspected long Covid, however, may be, and are, referred to specialist clinics such as infectious diseases, respiratory, etc," he said.

A national approach to long Covid was being developed, with the HSE recruiting for the position of an implementation lead for a long Covid care model, the spokeswoman covering hospitals from Galway to Donegal said.

Kingston Mills, professor of experimental immunology at Trinity College, said the long Covid issue "will focus minds" when it comes to deciding whether to vaccinate under-12 year-olds. Given that British researchers had found 2-4 per cent of children developed it, he said: "We must stop that. We don't want children to be out of school for two months."

Claire Twomey (34), who contracted Covid-19 in March 2020, still suffers long Covid relapses. She eventually gave up her job in social care last January because she couldn't take the stress of being in and out. But as she can work from home she said she was luckier than many.

Paula Gray feels "80 per cent better" now. "But I do not know what the future is," she added.

■ Right, Paula Gray, from Co Sligo, has difficulty doing simple things like walking her dogs, Furball and Bella. Below left, Claire Twomey. MAIN PHOTOGRAPH: JAMES CONNOLLY

Long Covid has more than 200 symptoms, study finds

Calls for national screening programme as symptoms revealed range from brain fog to tinnitus

- Coronavirus - latest updates
- See all our coronavirus coverage

▲ A Covid-19 patient being treated in an ICU unit in India. People who have had the virus can later experience a variety of symptoms. Photograph: Xavier Galiana/AFP/Getty Images

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Overview

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- Long COVID definition
- Epidemiology
- Pathophysiology
- Treatments / interventions

- SVUH experience

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Definition of long COVID

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- No standardised definition: "long COVID", "long haulers", post-COVID syndrome, post-acute sequelae of COVID-19 (PASC)
- CDC guidelines
  - **Acute COVID-19 :** Up to 4 weeks post diagnosis
  - **Post-COVID conditions :** Symptoms that persist >4 weeks post diagnosis and are not explained by alternate diagnosis
- NICE guidelines on management of post-COVID:
  - **Acute COVID-19:** signs and symptoms up to 4 weeks
  - **Ongoing symptomatic COVID-19:** from 4 to 12 weeks
  - **Post-COVID-19 Syndrome:** more than 12 weeks, no other explanation

COVID-19 rapid guideline: managing the long-term effects of COVID-19.
Evaluating and caring for patients with Post-COVID Conditions : Interim Guidance https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-index.html

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Prevalence of long COVID

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Hospitalised patients

- Symptoms for up to 6 months in 15-76% of patients (~30%)
- Re-hospitalisation: up to 20%
- Follow-up post discharge: up to 80%

SARS and MERS

- 40% of SARS survivors had fatigue after 41.3 months
- 11-45% of SARS/MERS survivors abnormal lung function at 12 months
- 30% PTSD/depression at 6 months

Menges D et al. *PLoS One*. 2021
Lam MH et al. *Arch Intern Med*. 2009
Ahmed H et al. *J Rehabil Med* 2020

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Prevalence of long COVID

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- Very difficult to determine leading to broad estimates of prevalence
- Reported as 5-80% of individuals
- Often self-reported surveys
- Different definitions of what defines long COVID
- Lack of a control group

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Prevalence of long COVID

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Non-hospitalised patients

Table 2 | Long-term complications by age group in 247 home-isolated patients with COVID-19 at 6-month follow-up

Characteristic	All	0–15 years	16–30 years	31–45 years	46–60 years	Over 60 years
	% (*n*/*N*)	% (*n*)	% (*n*)	% (*n*)	% (*n*)	% (*n*)
	N = 247	*N* = 16	*N* = 61	*N* = 58	*N* = 67	*N* = 45
Age, median (IQR)	43 (27–55)	8 (6–12)	24(22–27)	37 (34–41)	53 (49–55)	67 (63–73)
Female gender	53% (131/247)	56% (9)	54% (33)	52% (30)	52% (35)	53% (24)
Status at 6 months						
Any symptoms	55% (136/247)	13% (2)*	52% (32)	59% (34)	61% (41)	60% (27)
Fever	2% (4/247)	0% (0)	0% (0)	5% (3)	1% (1)	0% (0)
Cough	6% (15/247)	0% (0)	0% (0)	9% (5)	4% (3)	16% (7)
Dyspnea	15% (38/247)	0% (0)	13% (8)	17% (10)	18% (12)	18% (8)
Palpitations	6% (15/247)	0% (0)	3% (2)	7% (4)	9% (6)	7% (3)
Stomach upset	6% (15/247)	6% (1)	5% (3)	7% (4)	6% (4)	7% (3)
Disturbed taste/smell	27% (67/247)	13% (2)	28% (17)	34% (20)	28% (19)	20% (9)
Fatigue	30% (69/231)	-[a]	21% (13)	31% (18)	33% (22)	36% (16)
Concentration problems	19% (44/231)	-[a]	13% (8)	19% (11)	21% (14)	24% (11)
Memory problems	18% (42/231)	-[a]	11% (7)	16% (9)	22% (15)	24% (11)
Sleep problems	5% (13/247)	0% (0)	5% (3)	7% (4)	4% (3)	7% (3)
Headache	11% (28/247)	0% (0)	11% (7)	14% (8)	9% (6)	16% (7)
Dizziness	10% (24/247)	0% (0)	7% (4)	10% (6)	10% (7)	16% (7)
Tingling in fingers	4% (9/247)	0% (0)	0% (0)	2% (1)	4% (3)	11% (5)

*Statistically significant difference at level $P < 0.05$ in univariable analysis using binomial logistic regression with age group 46–60 as reference group. *Children younger than 16 years were not assessed for these symptoms; therefore, $N = 231$ for these categories.

Conservative estimate: 10% of total COVID-19 cases will have symptoms for ≥6 months

Blomberg B et al. *Nat Med* 2021
Phillips S, Williams MA. *NEJM* 2021

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Post-COVID Symptoms

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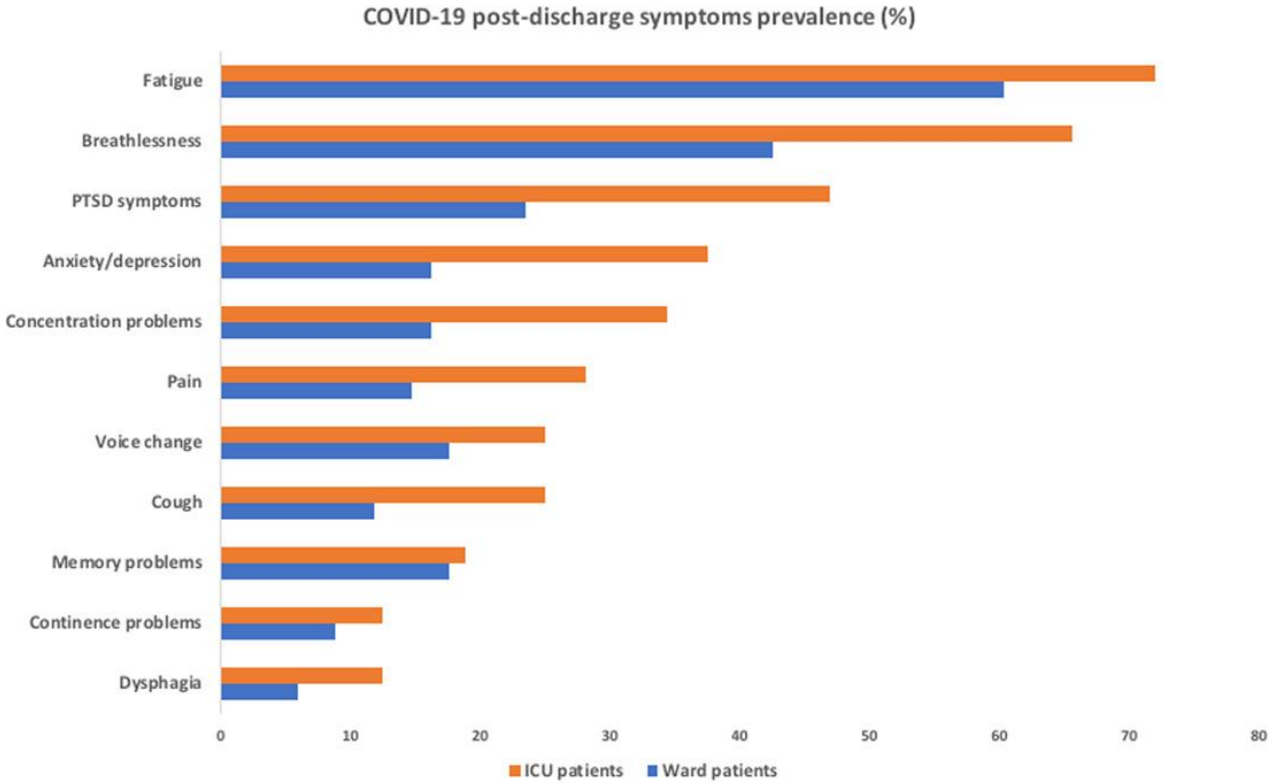

Halpin SJ et al. *J Med Virol* 2020

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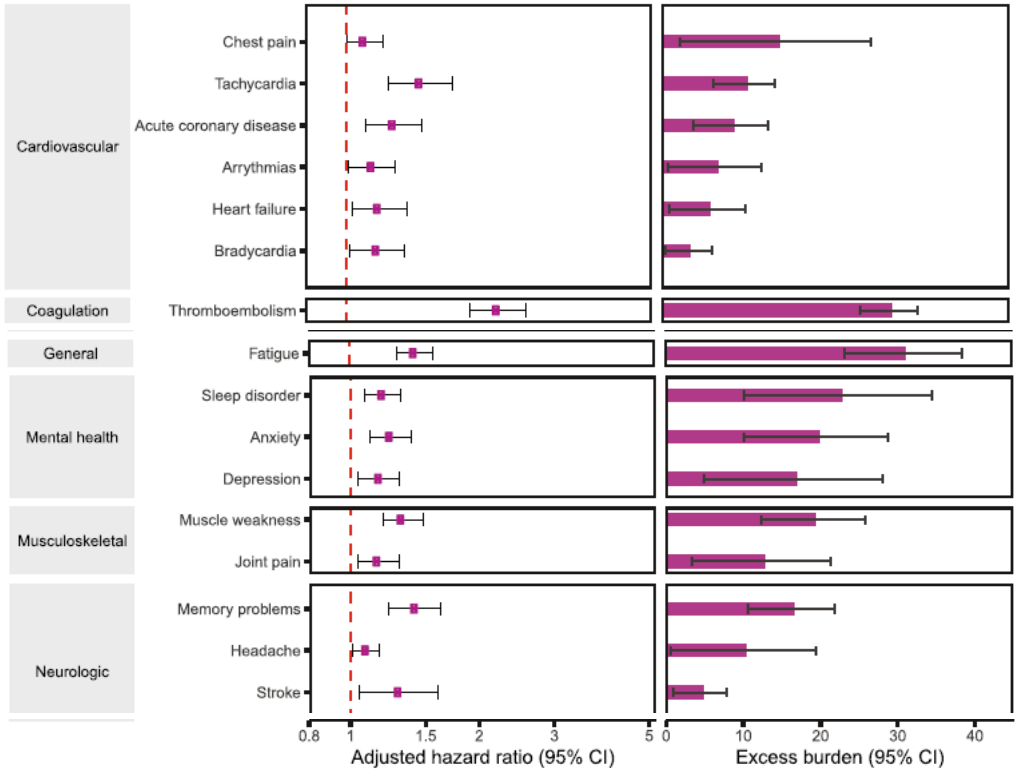
COVID vs Influenza



Higher risk of developing new medical conditions in COVID-19 compared to without COVID-19 (+4.95%) and those with viral lower respiratory tract infection (+1.65%).

Daugherty SE et al. *BMJ*. 2021

Adapted from Al-Aly Z et al. *Nature* 2021

Post-COVID Symptoms

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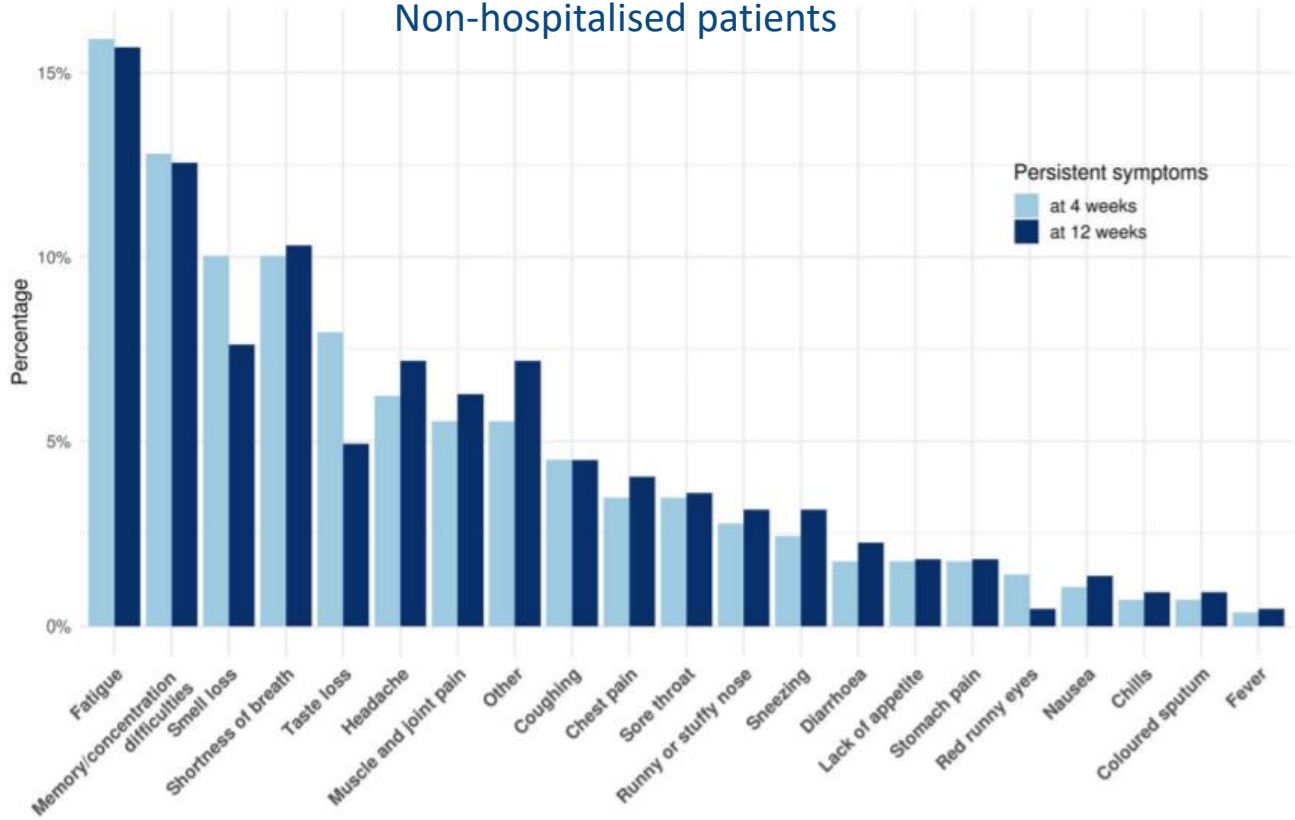
Non-hospitalised patients



Bliddal S et al. *Sci Rep* 2021

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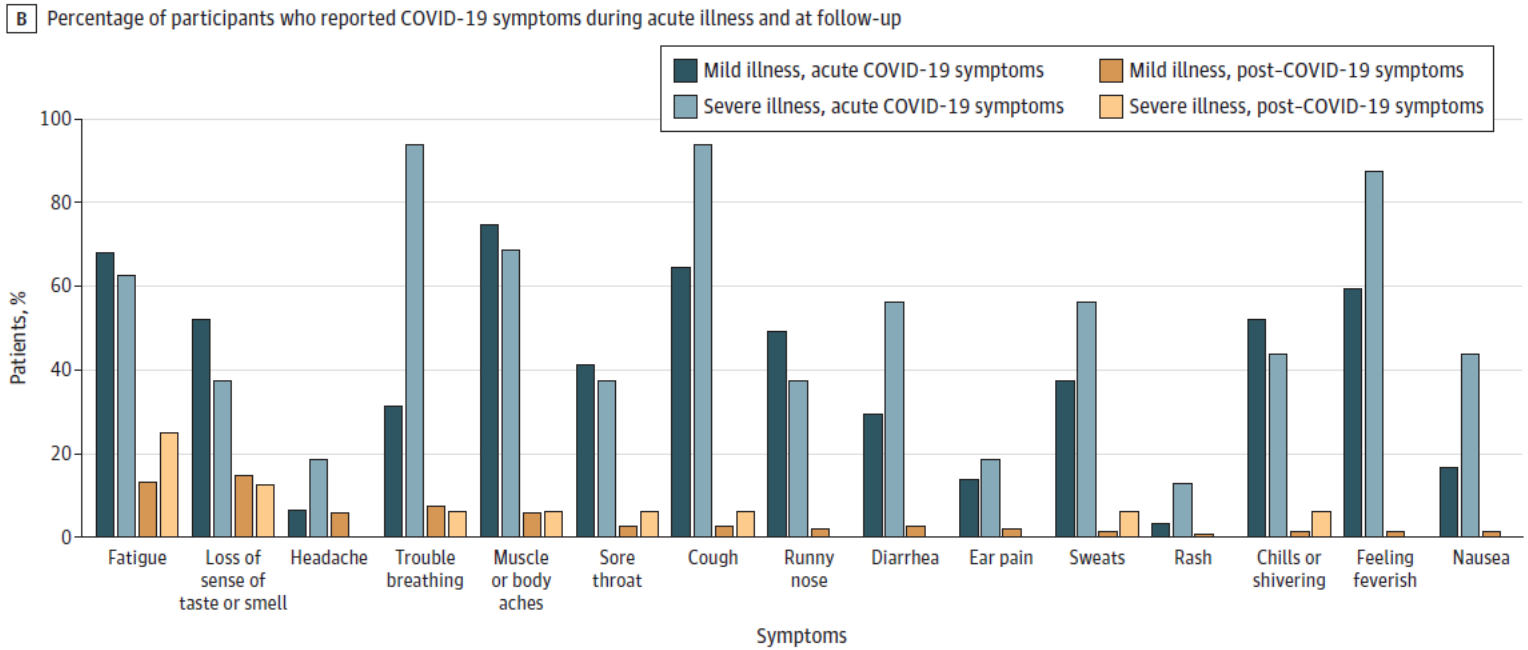
Post-COVID Symptoms



Logue JK et al. *JAMA Netw Open*. 2021

6- month neurological and psychiatric outcomes in 236379 survivors of COVID-19: a retrospective cohort study using electronic health records

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236,379 participants

6 months post COVID

ICU, Hospitalised and non-hospitalised patients

- Incidence of a neurological or psychiatric diagnosis in the following 6 months was 33·62%
- Incidences greater in patients who had required hospitalisation, markedly so in those requiring ICU
- Incidence and relative risk of neurological and psychiatric diagnoses were also increased even in patients with COVID-19 who did not require hospitalisation.
- Anxiety, Mood, Substance use and Insomnia
- Psychiatric sequelae are widespread and persist up to, and probably beyond, 6 months.

Taquet, Geddes, Husain, Luciano & Harrison, 2021 (Lancet Psychiatry)

Psychologic effects

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- Meta-analysis
- 215 studies
- Predominantly in hospitalised patients and during the acute illness

Table 2 Overall meta-analytical estimates of point prevalence of neurological or neuropsychiatric symptoms

Symptom/syndrome	Studies	n	Point prevalence (%)	95% CI	I^2
Headache	84	64 613	20.7	16.1 to 26.1	99.0%
Myalgia	76	66 268	25.1	19.8 to 31.3	99.1%
Fatigue	67	21 101	37.8	31.6 to 44.4	98.7%
Anosmia	63	15 975	43.1	35.2 to 51.3	98.8%
Dysgeusia	52	13 686	37.2	29.8 to 45.3	98.6%
Dizziness/vertigo	26	47 619	6.4	4.0 to 10.0	97.1%
Altered mental status	19	49 326	8.2	4.4 to 14.8	99.0%
Anosmia at follow-up	11	3182	11.8	5.5 to 23.5	98.5%
Depression	10	43 128	23.0	11.8 to 40.2	99.3%
Anxiety	9	42 566	15.9	5.6 to 37.7	99.5%
Sleep disorder	8	42 221	23.5	12.0 to 40.9	98.9%
Ischaemic stroke	8	5258	1.9	1.3 to 2.8	61.7%
Other CVD	6	43 701	1.6	0.3 to 7.9	98.7%
Dysgeusia at follow-up	6	2065	11.7	5.1 to 25.0	96.7%
Seizure	5	41 929	0.06	0.06 to 0.07	0.0%
Haemorrhagic stroke	5	3074	0.4	0.3 to 0.7	0.0%
Visual defect	5	678	3.0	1.9 to 4.5	0.0%
Hearing impairment	4	557	2.0	1.1 to 3.5	0.0%
Tinnitus	4	455	3.5	1.7 to 7.4	51.8%
Weakness	3	221	40.0	27.9 to 53.5	45.4%

CVD, cardiovascular disease.

Neurology and Neuropsychiatry of COVID-19: a systematic review and meta-analysis of the early literature reveals frequent CNS manifestations and key emerging narratives (Rogers et al., 2021)

SVUH Psychology Service Referrals

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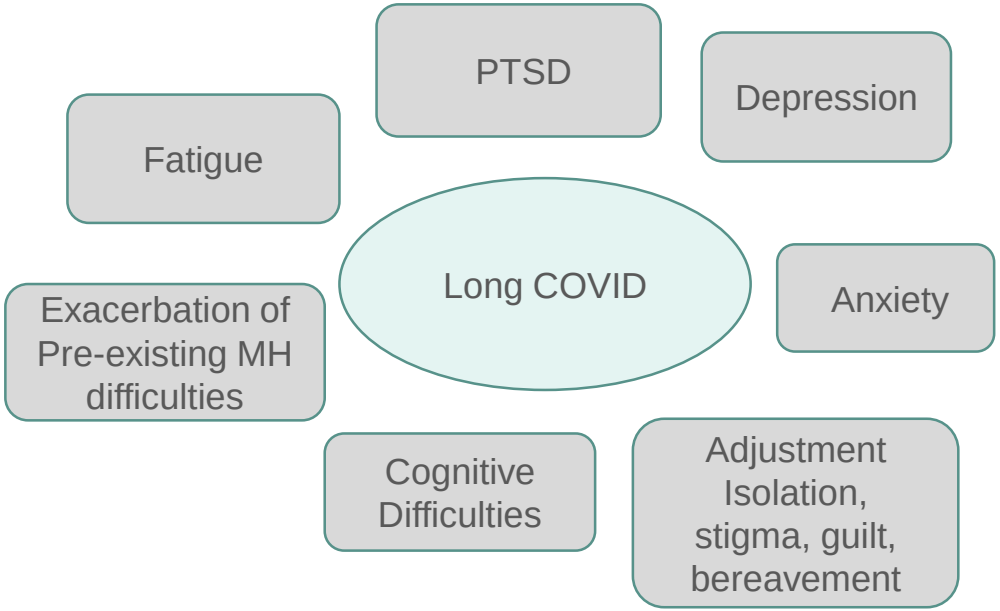
- 120 referrals (November 2020-August 2021)
- 75% Female
- Age 42.7 years (Range 18 – 73)
- 94 have had input to date – 26 on waiting list



AIID Cohort - Ireland

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- Patients from the All Ireland Infectious Diseases cohort study with symptoms >4 weeks post acute symptom onset
- PCR confirmed COVID-19
- 233 patients –SVUH, MMUH and Beaumont (89% of patients from SVUH)

Demographics

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Age (years) (median, IQR)	43 (36-54)
Gender: Female (n (%))	173 (74%)
Hospitalised (n (%))	75 (32%)
Time from symptom onset, weeks (Median, IQR)	18 (10-29)
Initial COVID-19 illness disease severity (n (%))	
Mild	180 (77.3%)
Moderate	24 (10.3%)
Severe	11 (4.7%)
Critical	12 (5.2%)
BMI kg/m^2 (Median, IQR)	27.41 (23.75 - 32.28)
HCW (n (%))	155 (66%)
Doctor	13 (8%)
Nurse	90 (58%)
Healthcare assistant	16 (10%)
Other	36 (23%)

Data from Dr.Grace Kenny

AIID Cohort symptoms

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Symptom %	Symptom %
Fatigue 81.9%	Confusion 2.2%
Dyspnea 69%	Joint pain 22.8%
Chest pain 41%	Myalgia 15.5%
Palpitations 33.6%	Abdominal pain 4.7%
Cough 15.9%	Nausea 5.6%
Poor concentration 33.2%	Diarrhoea 2.6%
Headache 20.7%	Sore throat 5.6%
Dizziness 12.1%	Rash 4.7%
Anosmia 11.6%	Fever 4%

Data from Dr.Grace Kenny

MCA - Symptom clusters

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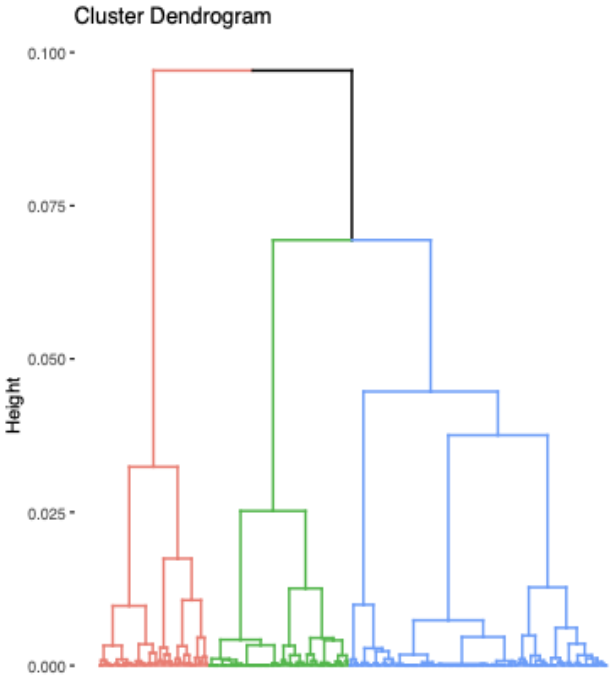
- Cluster one – fewer symptoms, fatigue predominant
  - 2.23 symptoms
- Cluster two – shortness of breath, palpitations, chest pain
  - 4.52 symptoms
- Cluster three – joint pain, myalgia, headache
  - 6.08 symptoms



Data from Dr.Grace Kenny

Symptom clusters

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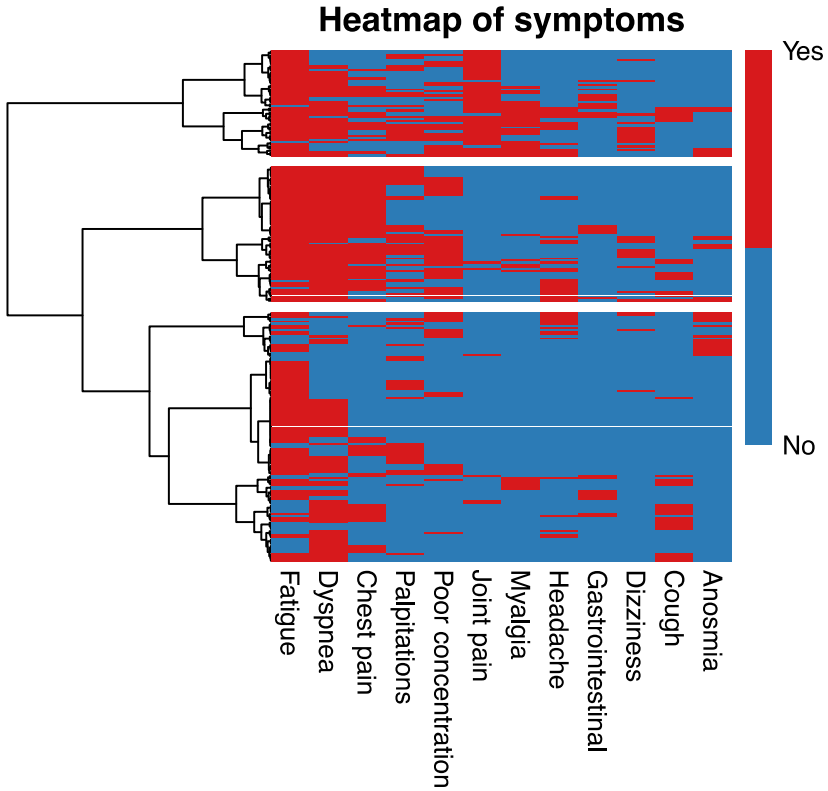

Data from Dr.Grace Kenny

Symptom clusters

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	Cluster 1 n = 108	Cluster 2 n = 87	Cluster 3 n = 37	P value
Age (median, IQR)	44 (32,55)	42 (35, 52)	47 (40,55)	0.48
Female (n (%))	70 (64.8%)	70 (80.4%)	32 (86.5%)	**<0.01**
BMI (median (IQR))	26.5 (23.5, 30.2)	27.7 (23.6, 33.1)	29.5 (25.1, 33.7)	0.09
Mild disease (%)	75 (69%)	76 (87%)	29 (78%)	0.07
Outpatient management (%)	67 (62%)	65 (74.7%)	26 (70.3%)	0.16
TFSO weeks (median, IQR)	15.5 (9-27.2)	19.9 (13-27.8)	22.7 (10-37.9)	**0.01**
Healthcare worker (%)	60 (55%)	63 (72%)	31 (83.8%)	**<0.01**
Time off work (median, IQR weeks)	6 (2-12)	12 (6-24)	10 (7.5-24)	**<0.01**
MRC score (median, IQR)	1 (1-2)	3 (2-3)	2 (2-3)	**<0.01**
ED attendance (n of patients attending (%))	28 (26%)	43 (49%)	15 (45%)	**<0.01**

Data from Dr.Grace Kenny

Symptom clusters

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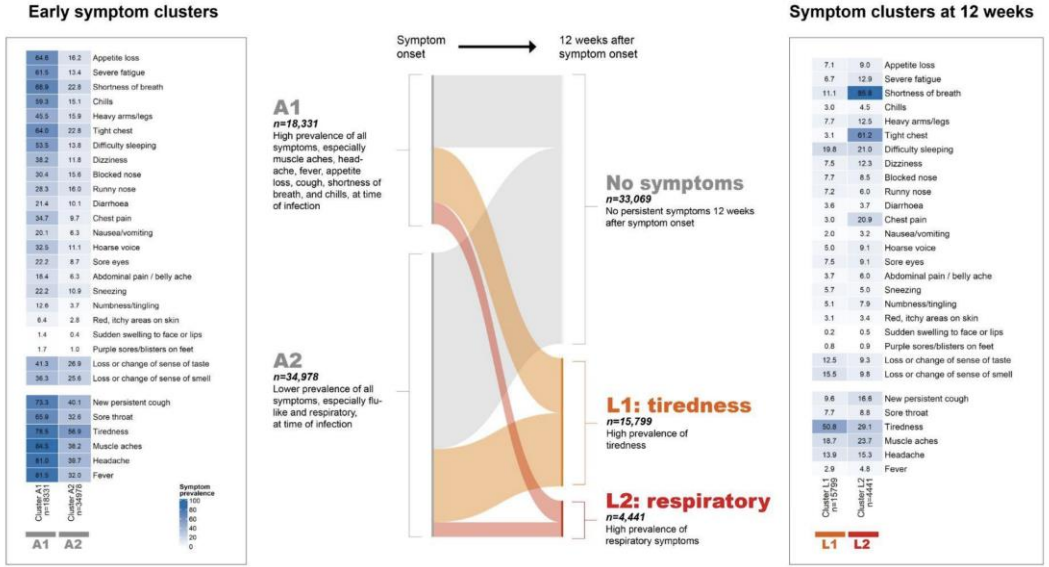
Figure 3 Results of clustering on symptom profile at time of symptom onset and then reclustering at 12 weeks, using CLARA (partitioning around medoids) algorithm. Central Sankey plot shows transitions between early and 12-week clusters. Two stable clusters of symptomatic infections were identified at t0: cluster A1 was characterised primarily by higher prevalence of flu-like symptoms (muscle aches, headache, fever, appetite loss, chills) and respiratory symptoms (shortness of breath, tight chest, new persistent cough). Two stable clusters were identified at 12 weeks. Cluster L1 ("tiredness cluster") had high prevalence of tiredness. Cluster L2 ("respiratory cluster") was a smaller subset of 4,441 participants who had high prevalence of shortness of breath and tight chest as well as chest pain.



Pathogenesis of long COVID

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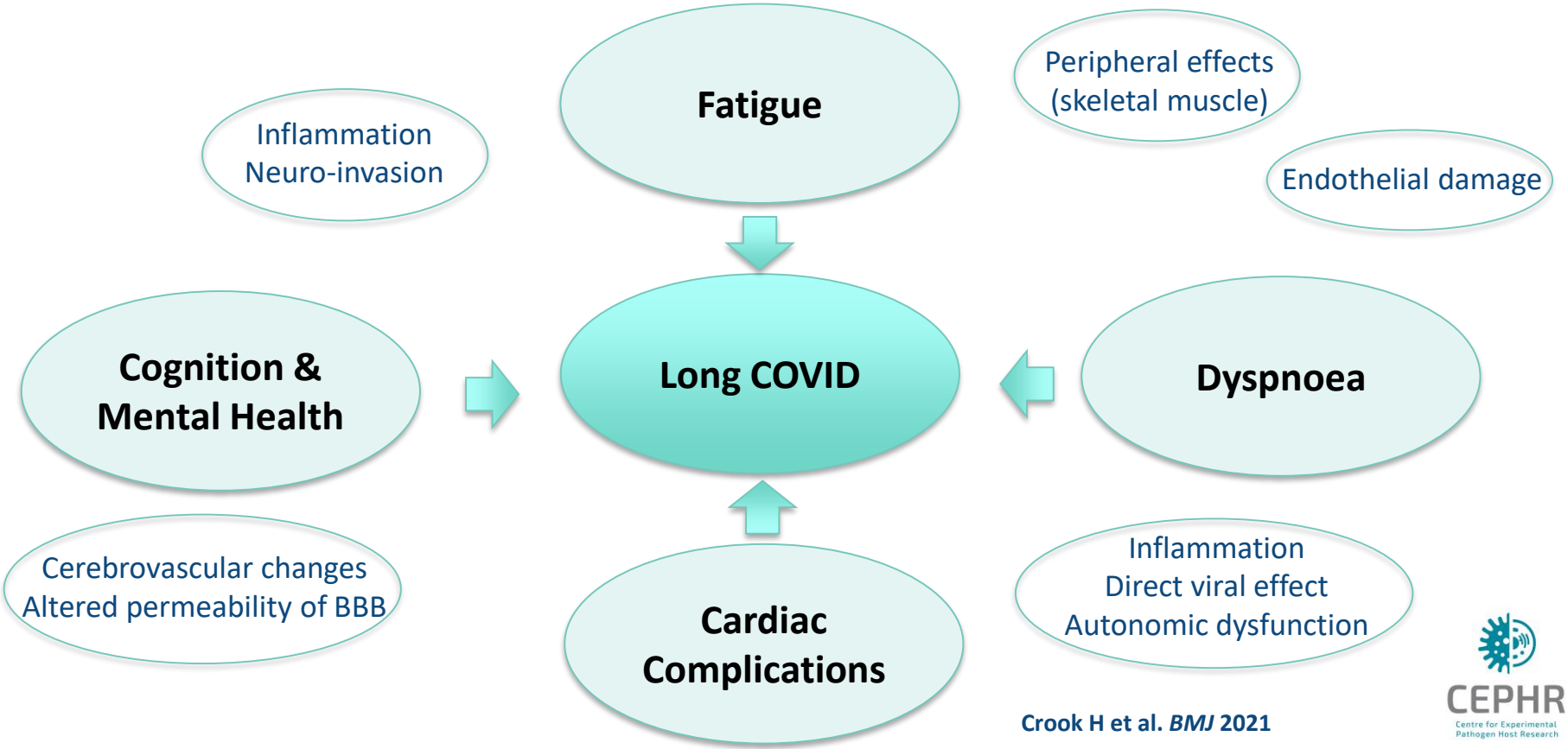

Crook H et al. *BMJ* 2021

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Proposed pathogenesis

- Fatigue
  - Muscular weakness
  - Neural cell invasion by SARS-CoV2
  - Increased blood brain barrier permeability
- Dyspnoea
  - Subtle differences in pulmonary gas exchange
  - Muscular weakness / fatiguability of respiratory muscle
  - Cardiac abnormalities
- Palpitations / chest pain
  - Autonomic dysfunction
  - Myocarditis/ Reduced cardiac relaxation

Crook H et al. *BMJ* 2021
Aiyegbusi et al. Journal Royal Society of Medicine 2021

Assessment of Long COVID patient

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- 15% of post COVID patients are readmitted within 2 months of discharge
- 30% within 6 months
  - More likely if older, underlying lung conditions

- Need to carefully look for alternative cause for patient's symptoms

- Antibody tests often performed to diagnose COVID-19 if no PCR performed
  - 10% of patients with proven COVID-19 will have negative antibody test

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Assessment of Long COVID patient

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Table 2. System-based conditions reported following SARS-CoV2 infection

Body System	Conditions (subject to change and not mutually exclusive)
Cardiovascular	Myocarditis, heart failure, pericarditis, orthostatic intolerance (e.g., postural orthostatic tachycardia syndrome (POTS))
Pulmonary	Interstitial lung disease, reactive airway disease
Renal	Chronic kidney disease
Dermatologic	Alopecia
Rheumatologic	Reactive arthritis, fibromyalgia, connective tissue disease
Endocrine	Diabetes mellitus, hypothyroidism
Neurologic	Transient ischemic attack/stroke, olfactory and gustatory dysfunction, sleep dysregulation, altered cognition, memory impairment, headache, weakness, and neuropathy
Psychiatric	Depression, anxiety, and post-traumatic stress disorder (PTSD), psychosis
Hematologic	Pulmonary embolism, arterial thrombosis, venous thromboembolism, or other hypercoagulability
Urologic	Incontinence, sexual dysfunction
Other	Weight loss, dysautonomia, vitamin D deficiency, allergies and mast cell activation syndrome, reactivation of other viruses, pain syndromes, and progression of comorbid conditions

As more is learned about the natural history of SARS-CoV-2 infection, this list of symptoms and conditions will likely change over time.

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Assessment of Long COVID patient

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- Full history and physical examination
- Vital signs; BP, HR, orthostatic measurements, SpO2
- 6 minute walk test
- FBC, U&E, LFTs, CRP, ferritin, TFTs
- CXR
- ECG

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Focused assessment

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- Cardiac symptoms
  - Holter, echocardiogram, stress test, cardiac CT, cardiac MRI
- Respiratory symptoms
  - Pulmonary function tests, CT chest
- Neurologic symptoms
  - MOCA, CT brain, MRI brain
- Pain symptoms
  - Autoantibodies / rheumatologic conditions, muscle enzymes
- Psychologic symptoms
  - Depression screening (Hospital Anxiety and Depression Scale)

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Management of Long COVID

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- Most patients can be managed in primary care
- Reassurance and support important for all patients
- Self management tools / online tools can be helpful
  - Rehabilitation / exercise programs
  - Breathing programs
- Encourage the setting of realistic goals
- Provide advice, support for support groups
- Provide support for employers / families

https://www.nice.org.uk/guidance/ng188/

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Specialised clinics

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- Structured around physician / medical team
- Physiotherapy
- Psychology
- Occupational therapy
- Rehabilitation medicine
- Clear referral pathways to appropriate specialities
  - Respiratory
  - Cardiology
  - Psychiatry
  - Neurology

https://www.nice.org.uk/guidance/ng188/

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Fatigue

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TABLE 1 PASC fatigue assessment recommendations

#	Statement
1	Patients should be assessed for fatigue patterns throughout their normal day to guide activity recommendations.
1a	Patients should be assessed for their responses to initiating and escalating activity on their fatigue.
1b	Patients should be evaluated for changes in daily functioning and activity levels.
1c	Patients' physical functioning and endurance should be assessed to inform activity and therapy recommendations. (Examples of tests that can be chosen based on an individual's activity tolerance: 30 s sit to stand[55]; 2-min step (seated or standing)[56]; 6 min walk test[57]; 10 m walk test[58]).
2	Clinicians should assess for changes in activities of daily living, independent activities of daily living, school, work, and avocational (ie, hobbies)
3	A full patient history with review of preexisting conditions should be conducted
4	Patients should be evaluated for conditions that may exacerbate fatigue symptoms and warrant further testing and potential subspecialty referral (see Table 2). Particular areas include: • Sleep • Mood, including anxiety, depression and PTSD. Note: Patients often report dissatisfaction with their care because of their persistent symptoms being attributed to psychological factors. It is important to note that mood disorders may be secondary to persistent medical issues or one of many factors leading to fatigue. • Cardiopulmonary • Autoimmune • Endocrine
5	A medication review should be conducted to investigate medications that may be contributing to fatigue. Of note, antihistamine, anticholinergic, and antidepressant/anxiolytic medications can contribute to fatigue in patients with PASC.
6	The following basic lab workup should be considered in new patients or those without lab workup in the 3 months before visit including complete blood count with differential, chemistries including renal and hepatic function tests, thyroid stimulating hormone, c-reactive protein or erythrocyte sedimentation rate, and creatinine kinase. Other laboratory tests may be considered based on the results of these tests or if there is specific concern for comorbid conditions as outlined in Table 2.

Abbreviations: PASC, postacute sequelae of SARS-CoV-2 infection; PTSD, posttraumatic stress disorder.

PM&R 2021;13:1027-43

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Fatigue

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TABLE 4 PASC fatigue treatment recommendations

#	Statement
1	Begin an individualized and structured, titrated return to activity program.
2	Discuss energy conservation strategies.
3	Encourage a healthy dietary pattern and hydration.
4	Treat, in collaboration with appropriate specialists, underlying medical conditions, such as pain, insomnia/sleep disorders (including poor sleep hygiene), and mood issues that may be contributing to fatigue.

Abbreviation: PASC, postacute sequelae of SARS-CoV-2 infection.

PM&R 2021;13:1027-43

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Long COVID Rehab Programme

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- Physiotherapy led with MDT education sessions
  - Clinical Specialist PT Rebecca Sweeney and Senior PT Eimear Dolan
  - OT, MSW, Psychology, SLT,PT, Nutrition and Dietetics

- 6 week self management programme
  - 2 x combined aerobic / strength training sessions p/w
  - Virtual via Web Ex Platform

- Referral via ID team at Long COVID clinic
  - Referral form with clearance to exercise
  - Individualised 1:1 assessments
  - Exercise prescription +/- IMT

Physiotherapy Results

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	Average Pre	Average Post	Average Change
Sub. max METs	5.7	7.9	+2.3
Est. max METs	6.9	9.0	+2.1
30 sec STS	11.8	12.9	+1.1
PHQ	8.2	6.9	-1.3
GAD 7	5.5	5.0	-0.5
SGRQ	52.2	38.9	-13.2
Working Status - Full time - Reduced capacity - Not working	 - 33% - 11% - 56%	 - 56% - 22% - 22%	 - + 23% - + 11% - - 34%

Summary

ST. VINCENT'S UNIVERSITY HOSPITAL
Elm Park

- Symptoms which persist after COVID-19 are common
- Various symptoms have been described, which may cluster into particular groups
- Many patients miss work / attend the ED
- There are significant psychological effects on individuals
- No unifying pathophysiology has been determined
- Symptom management, MDT input and rehabilitation form the basis of treatment

CEPHR
Centre for Experimental Pathogen Host Research

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