Key Scientific Publications

May-June 2023

Connections between ME/CFS and Long COVID

frontiers | Frontiers in Medicine

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ME/CFS and Long COVID share similar symptoms and biological abnormalities: road map to the literature

Anthony L. Komaroff[1]* and W. Ian Lipkin[2]

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Considerable similarities in symptoms, few differences

Symptom	ME/CFS	Long COVID	Symptom	ME/CFS	Long COVID
Fatigue	✓	✓	Poor appetite	✓	✓
Post-exertional malaise	✓	✓	Orthostatic intolerance	✓	✓
Headaches	✓	✓	Palpitations	✓	✓
Sleep disorder	✓	✓	Breathlessness	✓	✓
Impaired reasoning	✓	✓	Nausea and diarrhea	✓	✓
Impaired memory	✓	✓	Chills	✓	✓
Impaired attention	✓	✓	Cough	✓	✓
Secondary depression	✓	✓	Decreased smell and taste		✓
Secondary anxiety	✓	✓	Rash and hair loss		✓
Reduced activity	✓	✓	Painful lymph nodes	✓	
Myalgia/arthralgia	✓	✓	Chemical sensitivities	✓	
Muscle weakness	✓	✓	Tinnitus	✓	
Hot and cold spells	✓	✓			

First publication from the RECOVER study: Confirming what we already know

JAMA | Original Investigation

Development of a Definition of Postacute Sequelae of SARS-CoV-2 Infection

Tanayott Thaweethai, PhD; Sarah E. Jolley, MD, MS; Elizabeth W. Karlson, MD, MS; Emily B. Levitan, ScD; Bruce Levy, MD; Grace A. McComsey, MD; Lisa McCorkell, MPP; Girish N. Nadkarni, MD, MPH; Sairam Parthasarathy, MD; Upinder Singh, MD; Tiffany A. Walker, MD; Caitlin A. Selvaggi, MS; Daniel J. Shinnick, MS; Carolin C. M. Schulte, PhD; Rachel Atchley-Challenner, PhD; RECOVER Consortium Authors; Leora I. Horwitz, MD; Andrea S. Foulkes, ScD; for the RECOVER Consortium

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Defining PASC

- This study involved nearly 10,000 adults from the RECOVER adult cohort

- Examined 37 symptoms experienced by patients across multiple body areas and organs

- Developed a scoring system to help find out which adults may have Long COVID, comparing people who were COVID-infected with people who were COVID-uninfected

- The 12 symptoms that best differentiated people who were COVID-infected from those who were COVID-uninfected were included in the score

- Each symptom was assigned a different number of points

- People who had 12 or more points were considered likely to have Long COVID

- Symptoms included: post exertional malaise, fatigue, brain fog, dizziness, gastrointestinal symptoms, heart palpitations, issues with sexual desire or capacity, change in smell or taste, thirst, chronic cough, chest pain, and abnormal movements.

Table 2. Model-Selected Symptoms That Define PASC and Their Corresponding Scores[a]

Symptom	Log odds ratio	Score
Smell/taste	0.776	8
Postexertional malaise	0.674	7
Chronic cough	0.438	4
Brain fog[b]	0.325	3
Thirst	0.255	3
Palpitations	0.238	2
Chest pain[b]	0.233	2
Fatigue[b]	0.148	1
Sexual desire or capacity	0.126	1
Dizzines	0.121	1
Gastrointestinal	0.085	1
Abnormal movements	0.072	1
Hair loss	0.049	0

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Symptom Clusters

- Cohort 1 is more characteristic of Sars-CoV-2 specifically (loss of smell and taste)
- Cohorts 3 and 4 are similar to ME/CFS
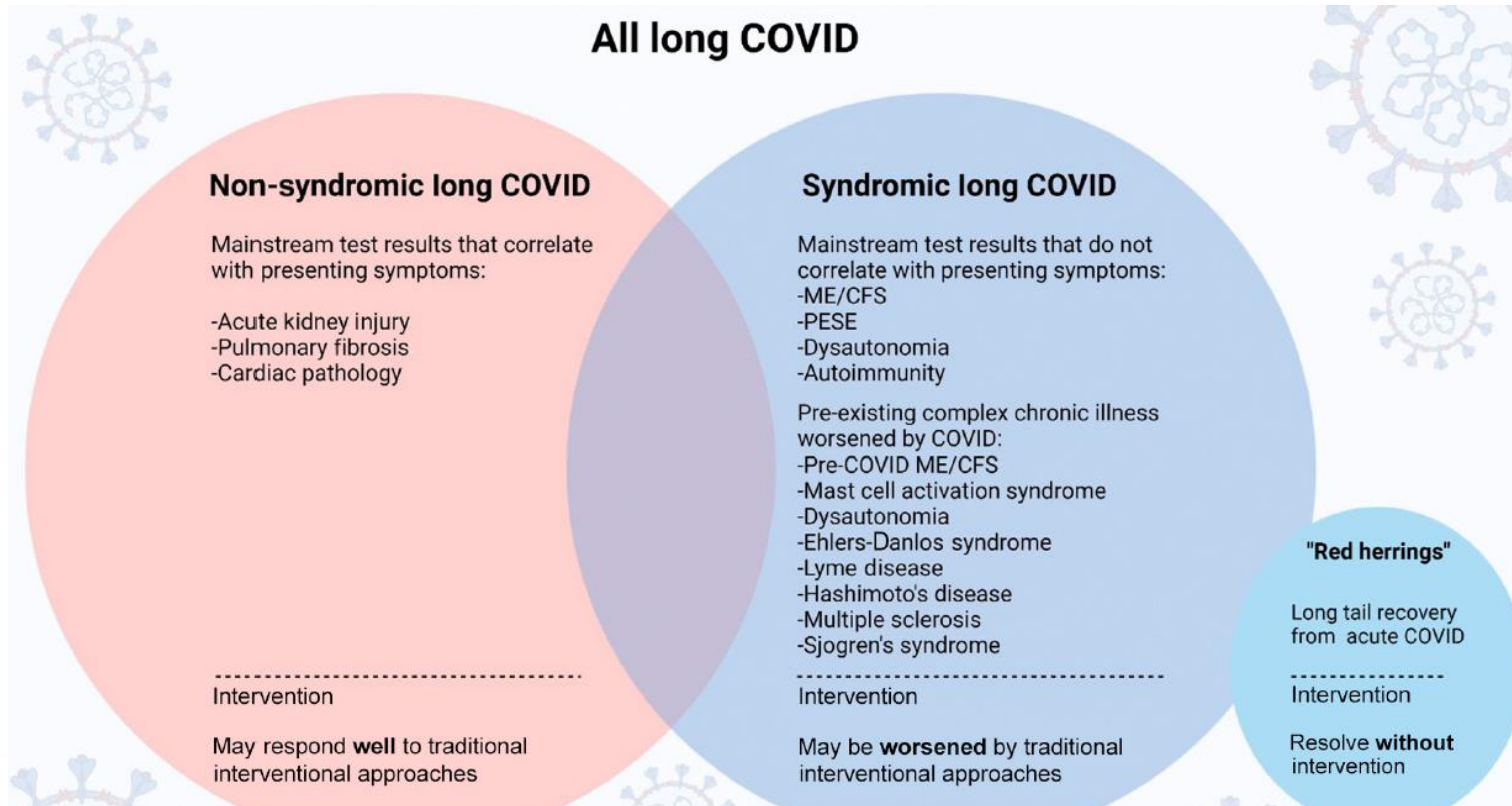- Cohort 2 has more pronounced dysautonomia

B Symptom frequencies by PASC status

	1 (n=477)	2 (n=405)	3 (n=587)	4 (n=562)
Fatigue[a]	66	84	94	94
Fever, sweats, or chills	27	26	28	56
Postexertional malaise[a]	55	99	99	94
Swelling of legs	22	23	18	40
Chest pain[a]	13	26	14	50
Palpitations[a]	38	59	44	86
Hair loss[a]	29	31	21	59
Skin color changes	10	17	16	38
Skin pain	5	6	8	18
Skin rash	12	16	17	32
Hearing	40	38	40	62
Vision	19	20	25	51
Abdominal pain	7	11	12	36
Dry mouth	29	42	26	55
Gastrointestinal[a]	42	60	45	88
Teeth	18	21	17	43
Thirst[a]	30	48	20	62
Back pain	26	31	32	58
Foot pain	15	19	15	36
Joint pain	32	33	36	64
Muscle pain	27	33	34	60
Weakness	24	33	41	67
Abnormal movements[a]	5	10	8	33
Brain fog[a]	38	0	100	94
Dizziness[a]	31	56	62	94
Headache	23	26	37	64
Smell or taste[a]	100	3	6	53
Tremor	14	14	15	34
Anxiety	18	17	30	40
Depression	17	17	32	44
Sexual desire or capacity[a]	29	33	35	66
Sleep disturbance	18	22	32	49
Chronic cough[a]	33	43	16	43
Shortness of breath	22	30	31	58
Sleep apnea	30	36	32	44
Throat pain	5	5	7	24
Bladder	20	25	23	49

Cluster

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Feature Review

Long COVID: pathophysiological factors and abnormalities of coagulation

Simone Turner,[1] M. Asad Khan,[2] David Putrino,[3] Ashley Woodcock,[4,5] Douglas B. Kell [iD],[1,6,7,8,*] and Etheresia Pretorius [iD] [1,6,9,*]

EBV Rearing its Ugly Head

Non-SARS-CoV-2 viral agents		
Reactivation of latent herpesviruses	*Positive studies:* (354–359) *Negative studies:* (360)	*Positive studies:* in acute COVID-19, reactivation EBV is frequent (361) (or only modest) (362, 363), as is reactivation of HHV-6, HHV-7 and CMV (361, 363, 364). *Positive studies in Long COVID:* (7, 365, 366)

Systematic review with meta-analysis of active herpesvirus infections in patients with COVID-19: Old players on the new field

Ana Banko [1,*], Danijela Miljanovic [1], Andja Cirkovic [2]

[1] Institute of Microbiology and Immunology, Faculty of Medicine, University of Belgrade, Belgrade, Serbia
[2] Institute for Medical Statistics and Informatics, Faculty of Medicine, University of Belgrade, Belgrade, Serbia

There was a 6 times higher chance for active EBV infection in patients with severe COVID-19 than in non-COVID-19 controls

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Chronic viral coinfections differentially affect the likelihood of developing long COVID

[1]Division of HIV, Infectious Diseases, and Global Medicine, [2]Division of Experimental Medicine, and [3]Department of Epidemiology and Biostatistics, UCSF, San Francisco, California, USA. [4]Monogram Biosciences Inc., South San Francisco, California, USA. [5]School of Pharmacy, [6]Department of Neurology, and [7]Division of Cardiology, UCSF, San Francisco, California, USA.

- 280 adults with prior SARS-CoV-2 infection assessed for the presence and types of LC symptoms and prior medical history (including COVID-19 history and HIV status) and performed serological (blood) testing for EBV and CMV using a commercial laboratory.

- LC symptoms, such as fatigue and neurocognitive dysfunction, at a median of 4 months following initial diagnosis, were independently associated with serological evidence suggesting recent EBV reactivation (early antigen–diffuse IgG positivity) or high nuclear antigen (EBNA) IgG levels but not with ongoing EBV viremia.

- Serological evidence suggesting recent EBV reactivation (early antigen–diffuse IgG positivity) was most strongly associated with fatigue (OR = 2.12).

- LC symptoms were also observed in people with no EBV reactivation

- Underlying HIV infection was also independently associated with neurocognitive LC (OR = 2.5).

- Interestingly, participants who had serologic evidence of prior CMV infection were less likely to develop neurocognitive LC (OR = 0.52).

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- Anti-SARS-CoV-2 antibodies were analyzed in plasma and saliva from non-vaccinated ME/CFS (n=95) and healthy donors (n=110)
- Reactivation of human herpesviruses 1-6 (HSV1, HSV2, VZV, EBV, CMV, HHV6), and human endogenous retrovirus K (HERV-K) was detected by anti-viral antibody fingerprints in saliva

- At 3-6 months after mild/asymptomatic SARS-CoV-2 infection, virus specific antibodies in saliva were substantially induced signifying a strong reactivation of latent viruses (EBV, HHV6 and HERV-K) in both cohorts.
- In patients with ME/CFS, antibody responses were significantly stronger, in particular EBV-encoded nuclear antigen-1 (EBNA1) IgG were elevated in patients with ME/CFS, but not in HDs
- EBV-VCA IgG was also elevated at baseline prior to SARS-infection in patients compared to HDs

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*CORRESPONDENCE
Eirini Apostolou
Eirini.Apostolou@liu.se
Anders Rosén
Anders.Rosen@liu.se

Saliva antibody-fingerprint of reactivated latent viruses after mild/asymptomatic COVID-19 is unique in patients with myalgic-encephalomyelitis/chronic fatigue syndrome

Eirini Apostolou[1]*, Muhammad Rizwan[1], Petros Moustardas[1], Per Sjögren[2,3], Bo Christer Bertilson[2,3], Björn Bragée[2,3], Olli Polo[3] and Anders Rosén[1]*

[1]Division of Cell Biology, Department of Biomedical and Clinical Sciences, Linköping University, Linköping, Sweden, [2]Division of Family Medicine and Primary Care, Department of Neurobiology, Care Sciences and Society, Karolinska Institute, Stockholm, Sweden, [3]ME-center, Bragée Clinics, Stockholm, Sweden

- Evidence of altered and chronically aroused anti-viral profile against latent viruses in ME/CFS
- SARS-CoV-2 infection even in its mild/asymptomatic form is a potent trigger for reactivation of latent herpesviruses (EBV, HHV6) and endogenous retroviruses (HERV-K)
- Detected by antibody fingerprints locally in the oral mucosa (saliva samples)
- This has not been shown before because the antibody elevation is not detected systemically in the circulation/plasma

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Outpatient treatment of COVID-19 and incidence of post-COVID-19 condition over 10 months (COVID-OUT): a multicentre, randomised, quadruple-blind, parallel-group, phase 3 trial

Carolyn T Bramante, John B Buse, David M Liebovitz, Jacinda M Nicklas, Michael A Puskarich, Ken Cohen, Hrishikesh K Belani, Blake J Anderson, Jared D Huling, Christopher J Tignanelli, Jennifer L Thompson, Matthew Pullen, Esteban Lemus Wirtz, Lianne K Siegel, Jennifer L Proper, David J Odde, Nichole R Klatt, Nancy E Sherwood, Sarah M Lindberg, Amy B Karger, Kenneth B Beckman, Spencer M Erickson, Sarah L Fenno, Katrina M Hartman, Michael R Rose, Tanvi Mehta, Barkha Patel, Gwendolyn Griffiths, Neeta S Bhat, Thomas A Murray*, David R Boulware*

- The goal of the trial was to see whether taking metformin, fluvoxamine, or ivermectin during the acute phase could reduce the risk of severe outcomes and/or later developing long Covid.
- All three medications have been used for many years to treat other unrelated conditions. Metformin is a medication that's been commonly used to treat diabetes.
- To be enrolled into the trial, all participants had to be experiencing Covid-19 symptoms for fewer than seven days and had had a clearly positive SARS-CoV-2 test within the three days prior.
- Participants were overweight, the median body mass index (BMI) ended up being 29·8 kg/m2.
- Those taking metformin when sick with Covid-19 were 41% less likely to have eventually developed long Covid than those taking only a placebo (6·3% compared to 10.4% of those who had received placebo only)
- The difference was even greater (63% lower) among those who had started taking metformin within three days of first experiencing Covid-19 symptoms
- Metformin likely worked through suppressing the acute infection / inflammation
- The study definition of Post-Covid is very different from post-Covid ME

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