

Long COVID immune correlates



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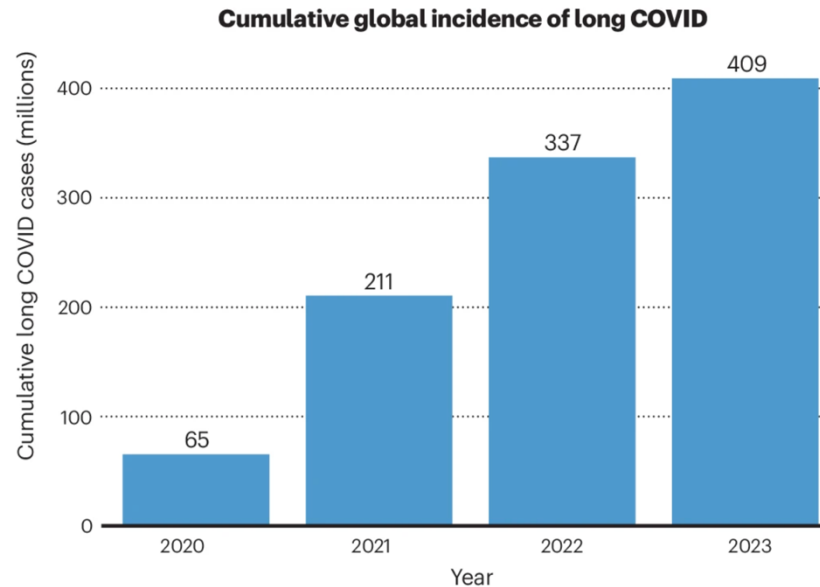
Long COVID – 6-years on and counting

- An enduring, persistent, disabling healthcare burden: some recover (perhaps 50%), some adapt and resume prior lifestyle, some do not recover or even worsen
- How to decode these pathophysiological pathways
- How to inform clinical trial strategies



The Long Covid global health challenge in context

From: [Long COVID science, research and policy](#)



Impact on global economies:

Lost GDP 0.5-2.3%

Lost workforce 3%

Annual economic impact \$1 trillion

From: Al-Aly, Z. et al, Nat Med., 2024

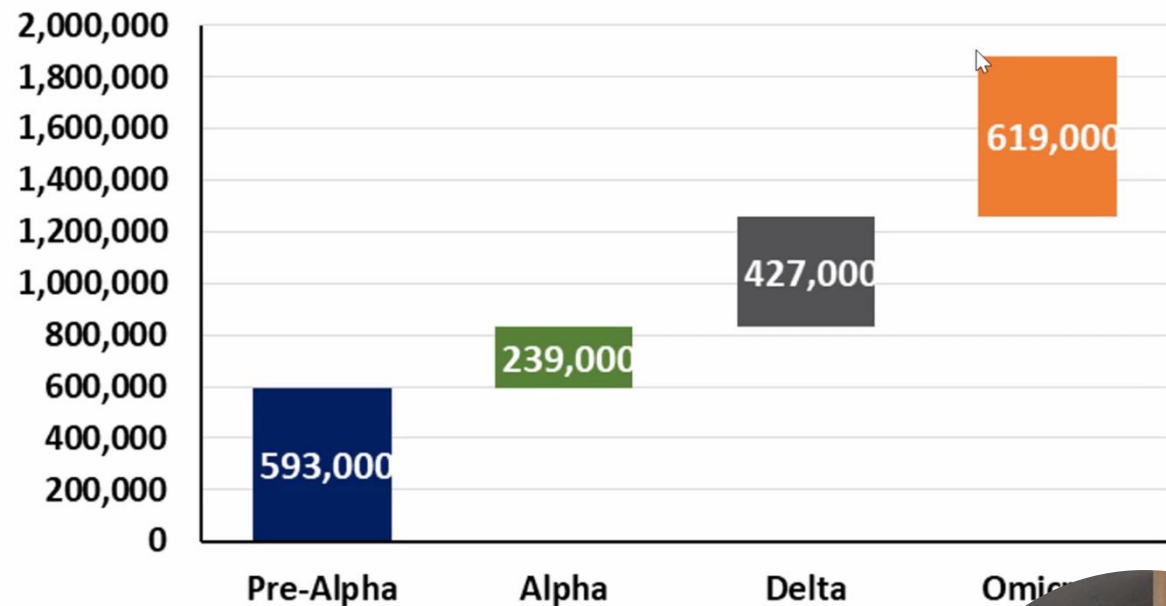


The challenge to our understanding of underlying mechanisms when the UK has added >600,000 to Long Covid caseload during breakthrough cases of a 'mild variant' in a predominantly triple-vaccinated population

indie_SAGE
The independent SAGE - Following the science

Number of People Living with Self-Reported Long Covid in the UK by Variant Type: Apr 4 - May 1, 2022

(Source: ONS Prevalence of ongoing symptoms following coronavirus (COVID-19) infection in the UK Reports)



All

Thanks to Bob Hawkins for the chart

<https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/datasets/alldatarelatingtoprevalenceofongoingsymptoms>



Virus reactivation in acute and long COVID-19

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 Check for updates

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Chronic viral infections are ubiquitous in humans, with individuals carrying multiple viruses that can reactivate during physiological stress, including severe illness¹. Notably, SARS-CoV-2 infection has been shown to reactivate chronic viruses such as Epstein–Barr virus and cytomegalovirus, yet the full extent, temporal dynamics and immunological impact of viral reactivation in COVID-19 remain incompletely understood^{2–7}. Here, leveraging multi-omic longitudinal data from 1,154 hospitalized patients with COVID-19 from the Immunophenotyping Assessment in a COVID-19 Cohort (IMPACC) study, we reveal significant reactivation of *Herpesviridae* and *Anelloviridae* during acute COVID-19, with distinct temporal dynamics for different viruses, and demonstrate that reactivation correlates with disease severity, host immune effects and clinical outcomes. Although our results do not establish causation between virus reactivation and clinical outcomes, we highlight the prevalence of chronic viral reactivation during acute COVID-19 and long COVID. Our findings challenge the prevailing view that chronic viral reactivation is primarily a consequence of immunosuppression, demonstrating that reactivations occur frequently in immunocompetent individuals during severe illness and in association with increased systemic inflammation. Additionally, we demonstrate persistence of viral reactivation in convalescence, and report an association of *Anelloviridae* with long COVID. This study provides immune, transcriptomic and metabolomic signatures of viral reactivation that could inform future strategies to prognosticate and treat acute COVID-19 and long COVID.

COVID can wake up a slew of dormant viruses inside you

Reactivation of typically harmless anelloviruses, in particular, seems to be linked with developing long COVID, study finds.

By [Max Kozlov](#)



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NEWS

HEALTH

COVID-19 can wake up dormant viruses in the body, large study confirms

Virus reactivations by SARS-CoV-2 could worsen initial symptoms and increase risk of Long Covid

5 AUGUST • 11:00 AM ET • BY CATHERINE DESJARDIS



Herpesvirus reactivation – supporting evidence

EBV parameter	Finding	Supportive of EBV involvement	Study cohort	Reference
Ab to: EA-D, VCA, EBNA-1	Ab signal for EBV reactivation strongly enhanced in LC group; EA-D Ab response correlated with symptom count	Strong	30xLC; 20xfully recovered	Gold et al., 2021
Ab to: EA-D, EBNA-1; plasma EBV viral load	Ab signal for EBV reactivation associated with LC fatigue and neurocognitive symptoms. No association with EBV viral load	Strong (with the caveat that this is early LC/post-acute infection)	Cohort: 249 post-acute COVID-19 at 4-months	Peluso et al., 2021
Ab to: EA-D, EBNA-1, CMV	EBV reactivation Ab signal associated with fatigue, OR 2.1	Strong (with the caveat that this is early LC/post-acute infection)	Cohort: 280 post-acute COVID-19	Peluso et al., 2022
REAP panel Ab profile against EBV gp23, gp42	Increased Ab reactivity to lytic/structural antigens, arguing for reactivation	Strong	Cohort: 273	Klein et al., 2023
T cell tetramer frequencies for EBV proteome epitopes	Significantly increased populations of EBV lytic antigen-specific CD69+CD137+ T cells, indicating recent activation	Strong	LC;56; Control: 20	Gao et al., 2020
Plasma EBV viral load	Potential prognostic marker of subsequent Long Covid	Of interest but with caveats: possible relevance to Long Covid predictive value of EBV viral load at acute infection	Acute, 1 st wave, severe COVID-19, 3-month follow-	



This protracted timecourse was predictable from prior experience with the very similar Long-SARS in 2003-2004. A 20-year perspective:

“None of our 50 patients got their old life back with time and treatment. Some were never able to return to work. Some had a trial of return to work and failed. Some had a trial of return to modified work, which then failed. Some had seniority to move to an easier position at work, which then failed. Some returned to being able to look after themselves completely, but could not return to work or sports”

John Patcai, Department of Medicine, University of Toronto

Oxford Open Immunology 2022; 3, Iqac0022



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The WILCO Study – 'Working out the Immunology of Long Covid'

Immunology Research
into COVID-19 and Long
Covid

Imperial College London IRAS ID:
295732



We're trying to understand why some people make a full recovery after COVID-19 while others go on to develop long-term symptoms. To do this, we are looking for volunteers to help us do research into the immune response following infection.

We are looking for people in any of these groups:

- Never had COVID-19 but have received COVID-19 vaccine doses
- Had COVID-19 and made a full recovery within 4-weeks (and may have since received vaccine doses)
- Had COVID-19 and have since suffered from the long-term symptoms described as Long Covid. These may include fatigue, 'brain-fog', exhaustion on walking, breathlessness, chest pain.

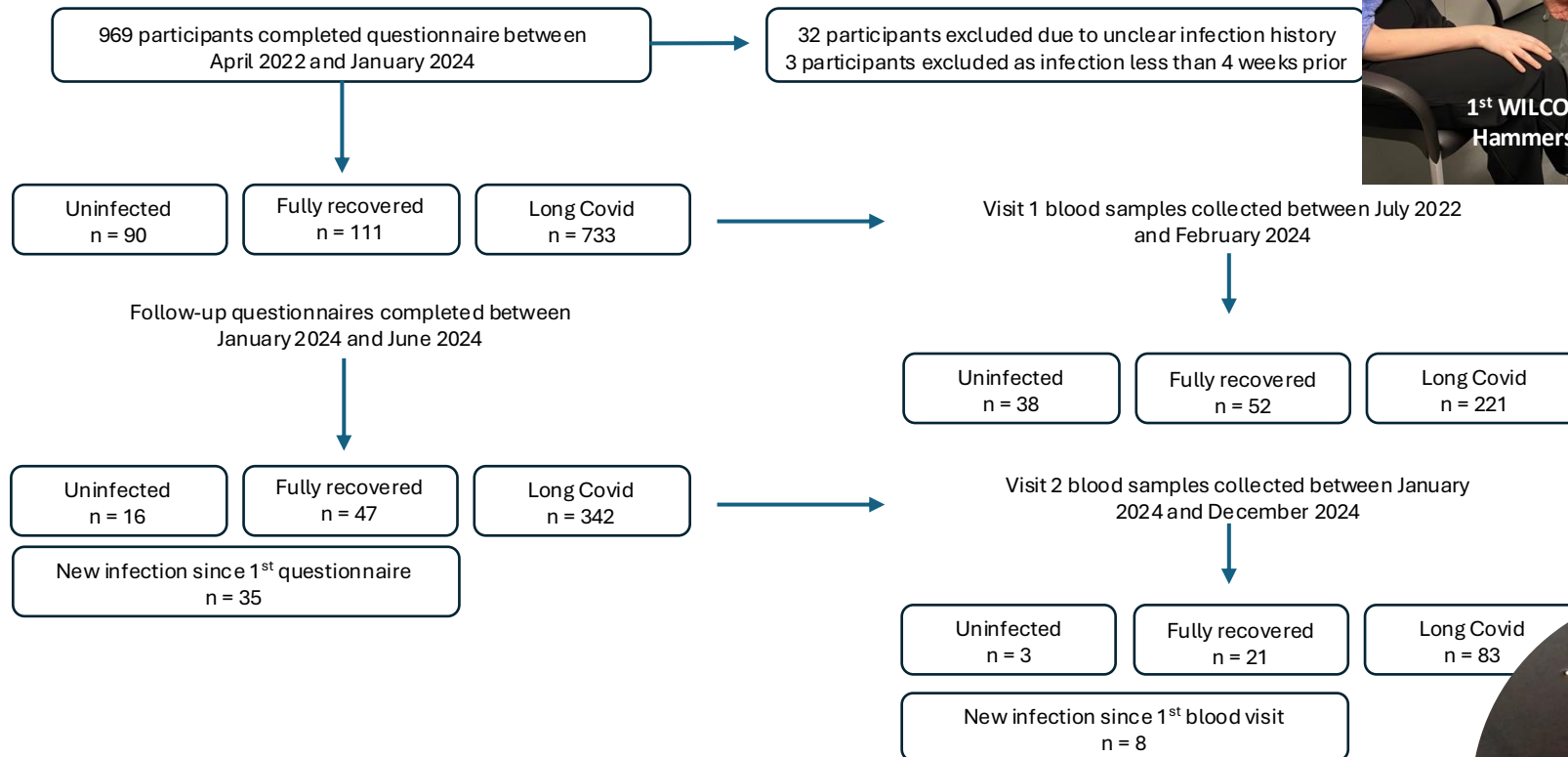
What the study involves - we would email you a short questionnaire and ask you to return it to us for analysis. We will then invite people showing specific sets of symptoms to pay a visit to the hospital where we will take a small blood test, about the size of an egg-cup of blood. This will be taken to our lab for analysis of immunity to the virus and other features of immune function. We may invite you for a repeat test around 4-months later. We may also ask you to do a '6-minute walk test' and donate a stool sample.

If you might be interested in taking part please contact the investigator,
Prof Danny Altmann: altmannlongcovidstudy@imperial.ac.uk



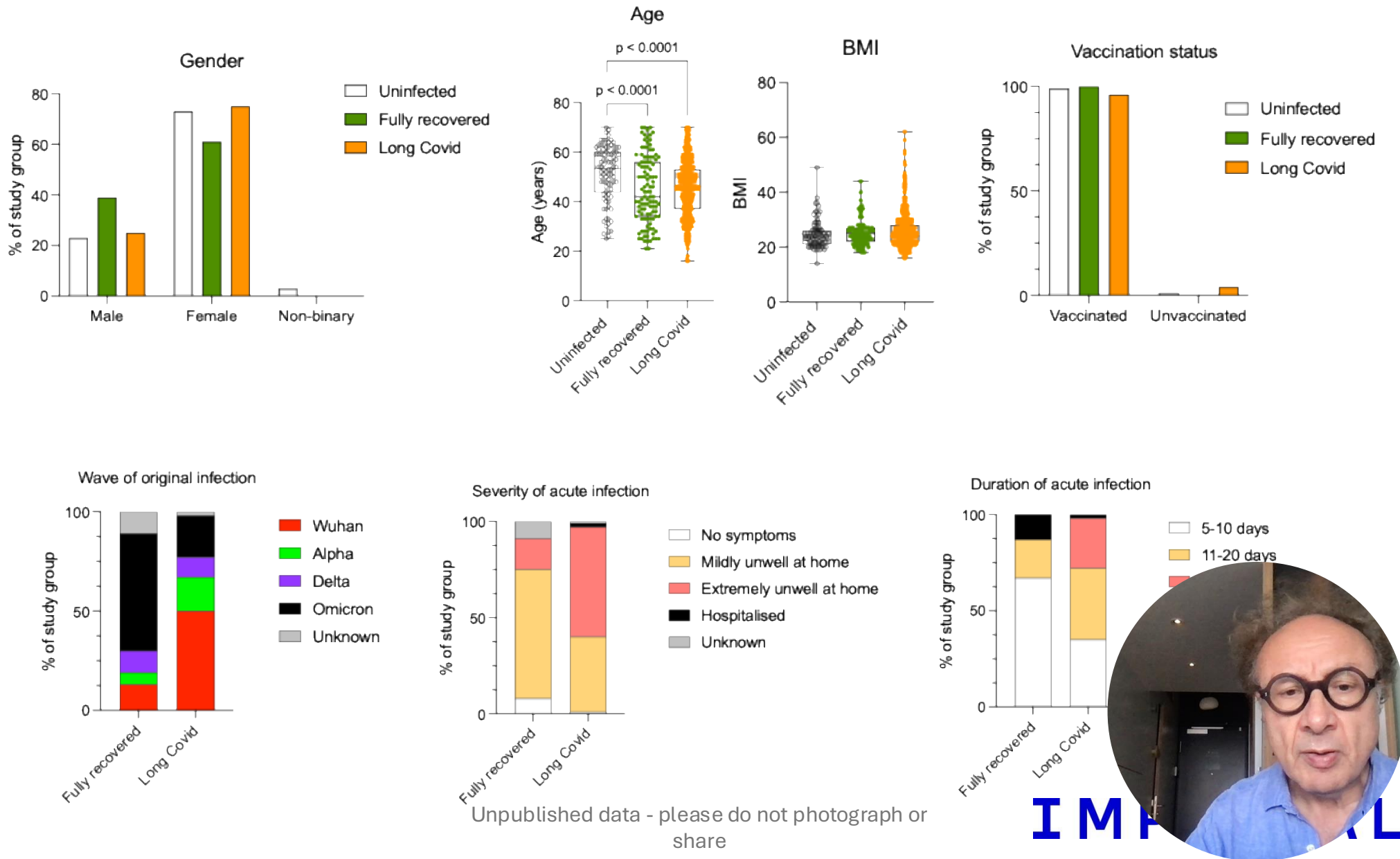
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Adult WILCO consort diagram

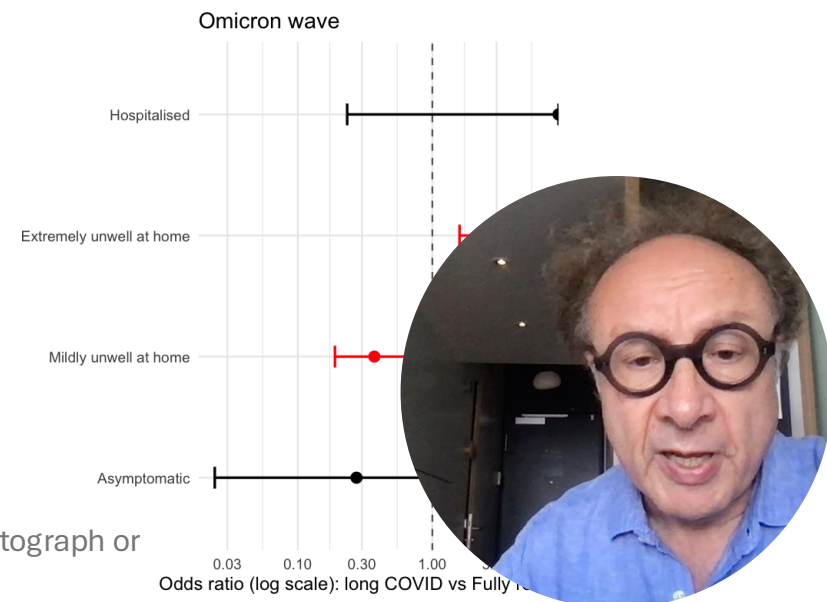
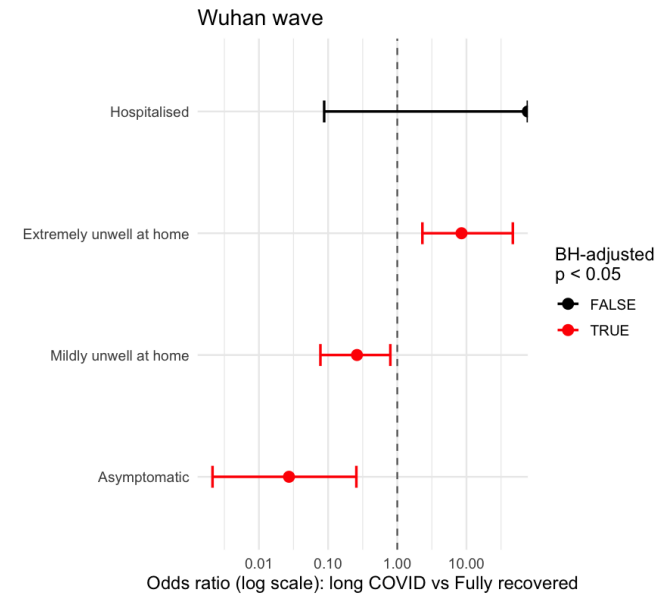
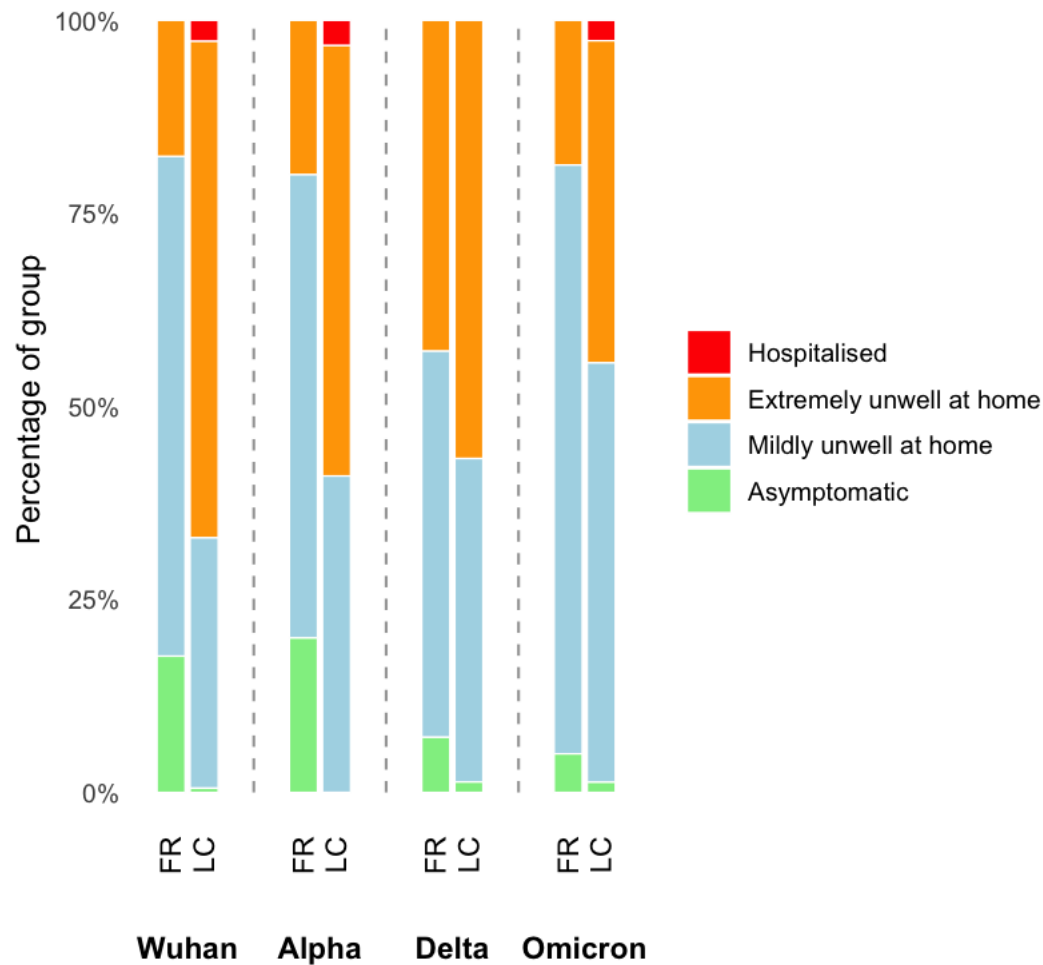


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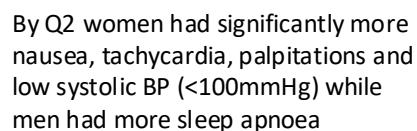
Adult WILCO participant characteristics at Q1



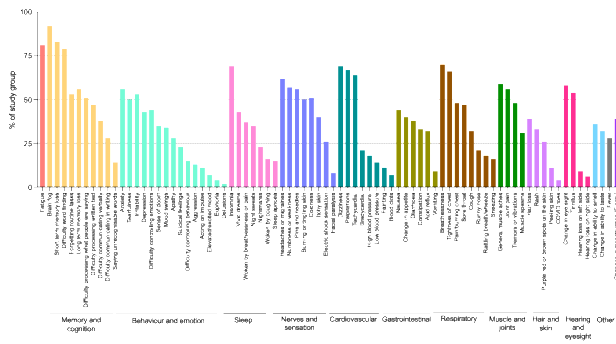
Severity of acute SARS-CoV-2 infection linked to LC irrespective of infecting VOC



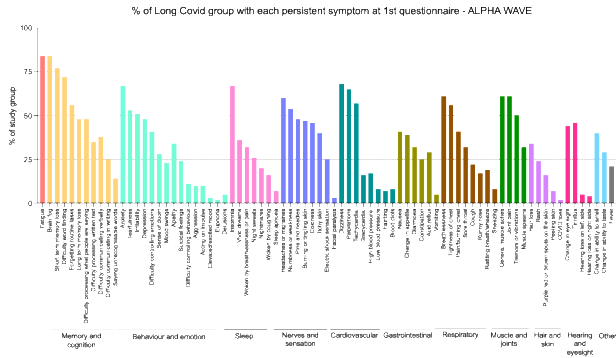
Female



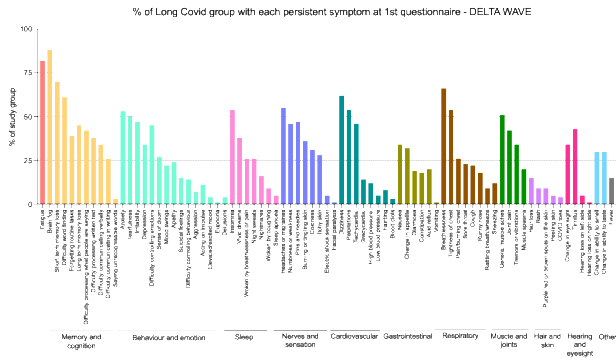
Wuhan wave



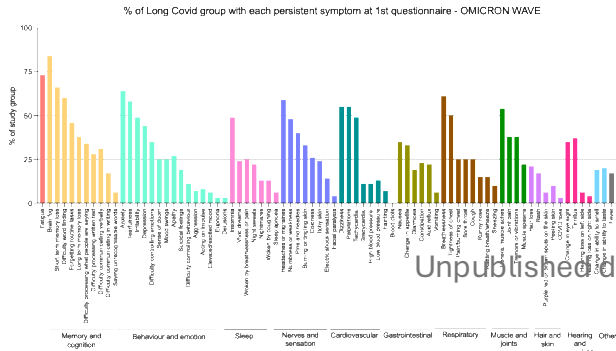
Alpha wave



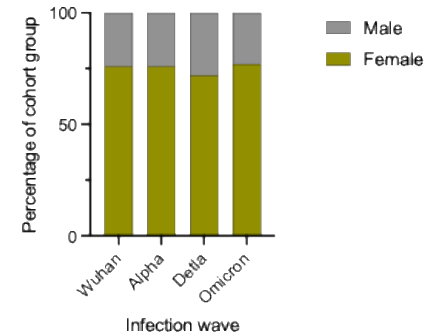
Delta wave



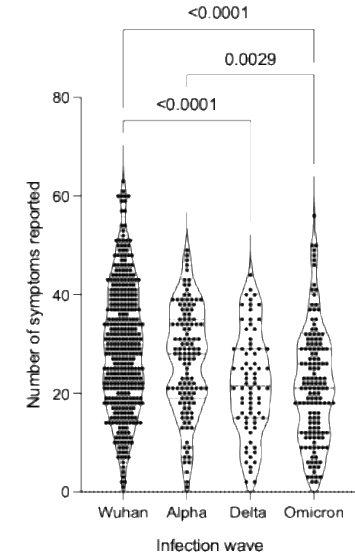
Omicron wave



Sex split across the different waves



Number of symptoms reported by infection wave

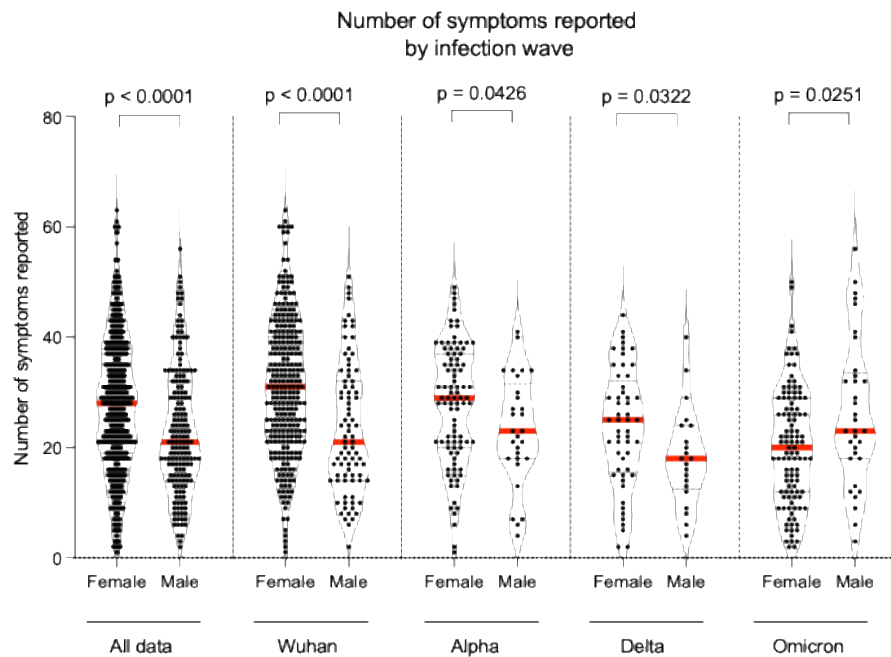


More persistent symptoms following SARS-CoV-2 infection during the Wuhan wave compared to Delta and Omicron waves.

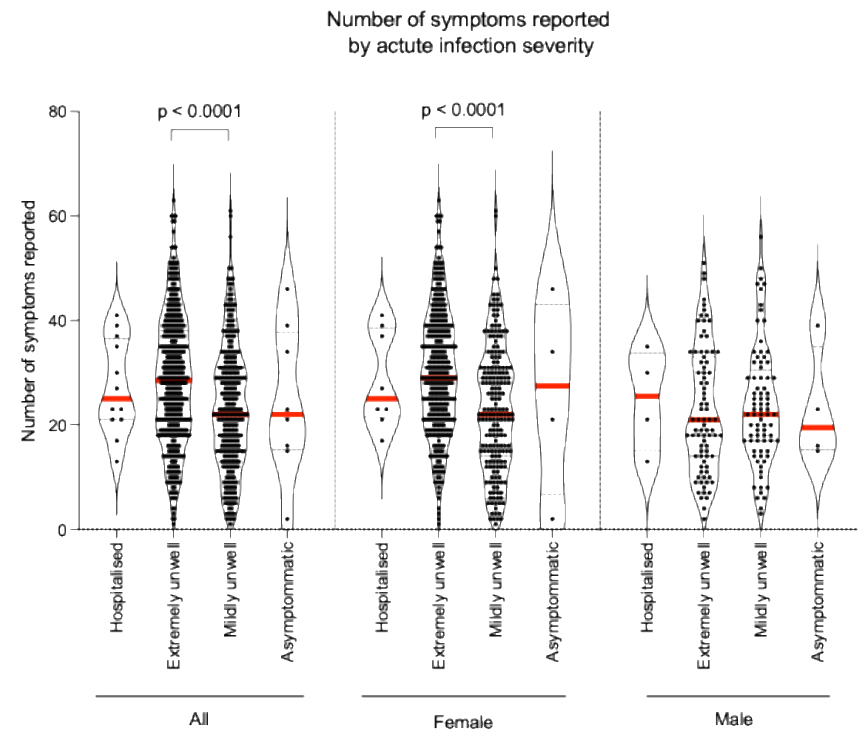


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Persistent symptoms more common in women than men irrespective of SARS-CoV-2 VOC in pre-Omicron infection waves



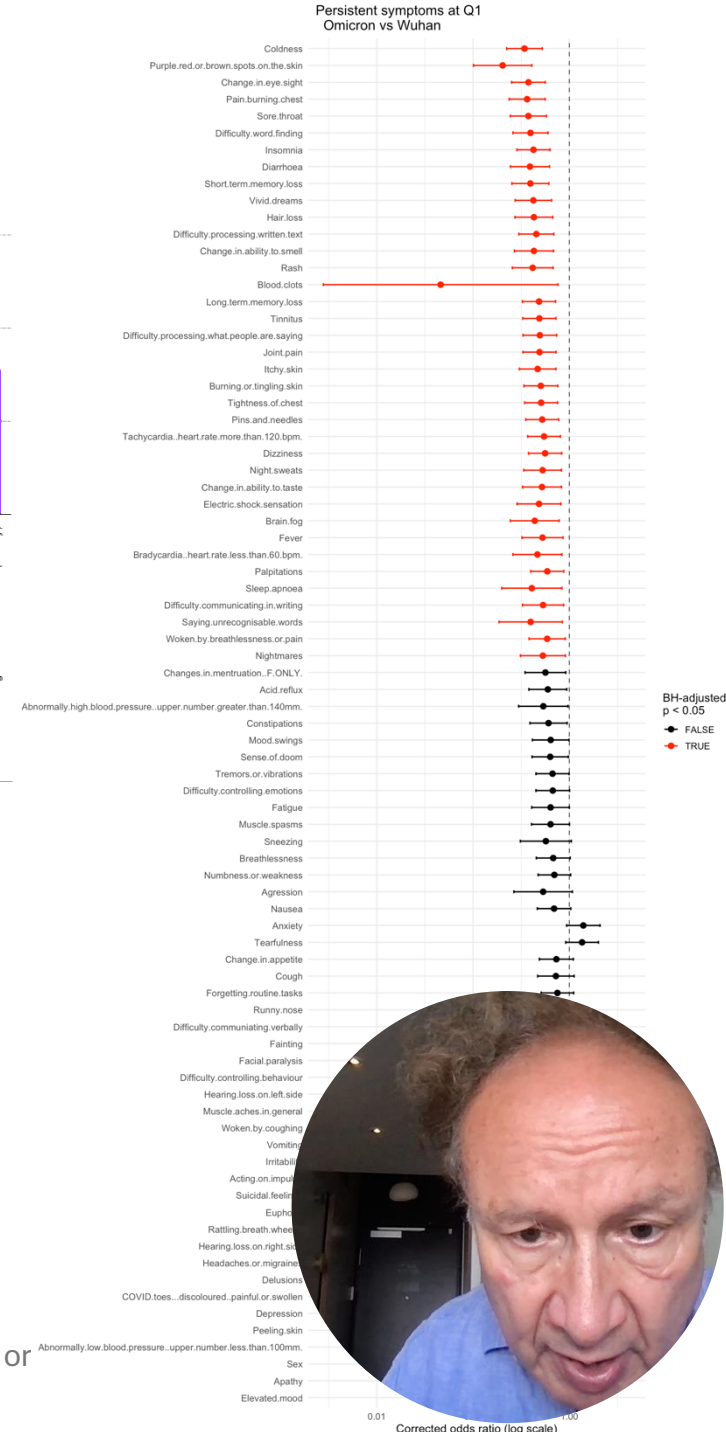
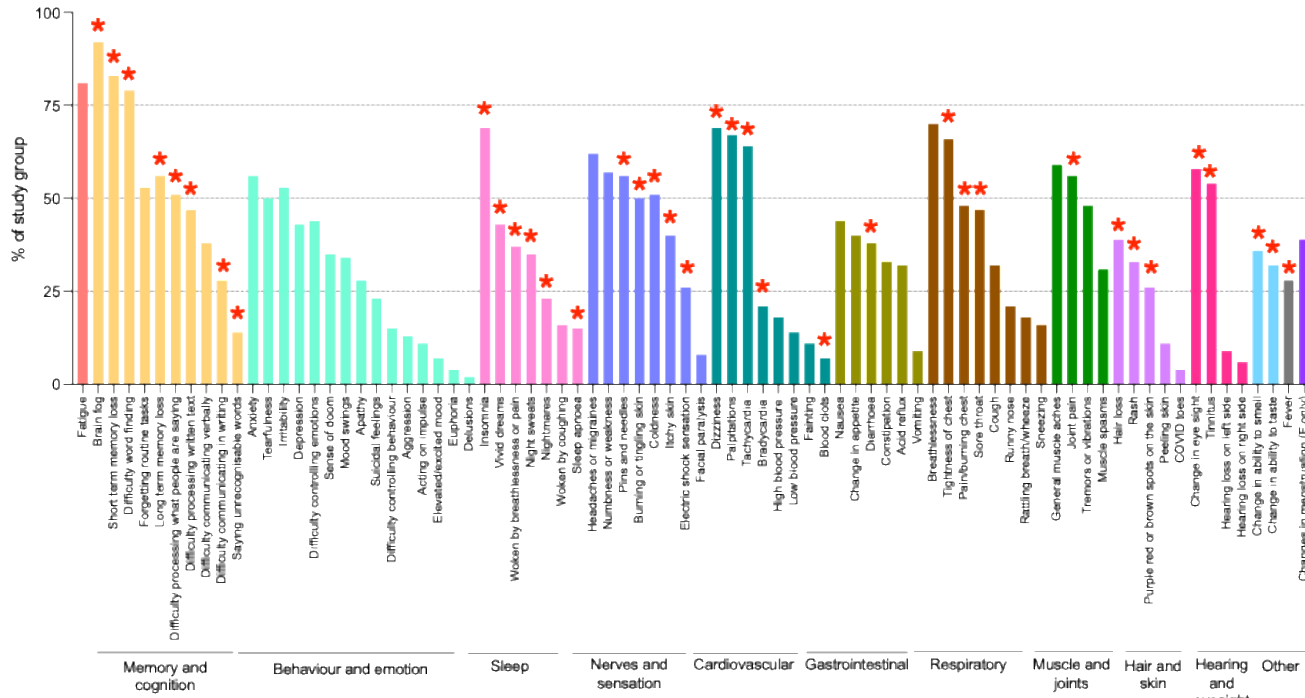
Persistent symptoms more common in women following severe acute SARS-CoV-2 infection

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% of Long Covid group with each persistent symptom at 1st questionnaire - WUHAN WAVE

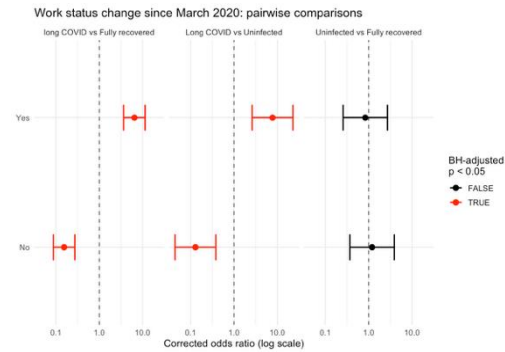
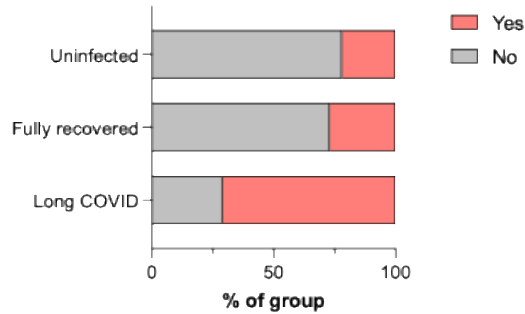


Some persistent symptoms more common following a SARS-CoV-2 infection during the Wuhan wave compared to the Omicron wave.

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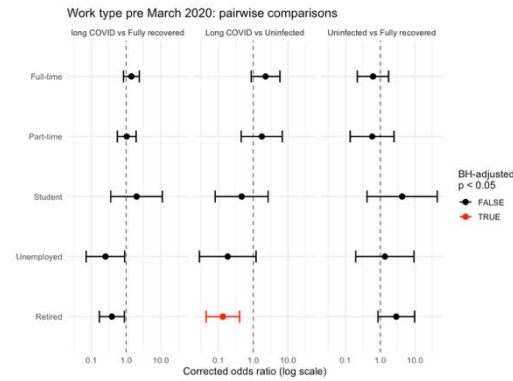
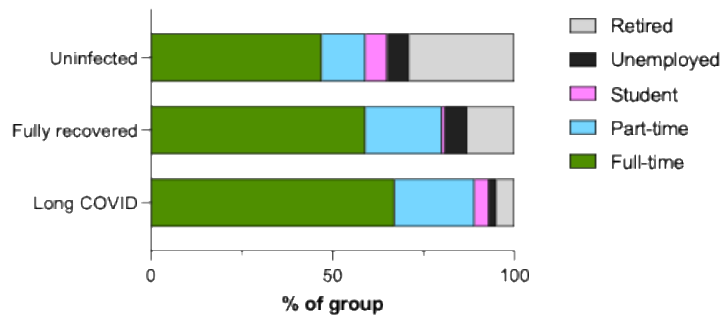
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Change of employment status since March 2020



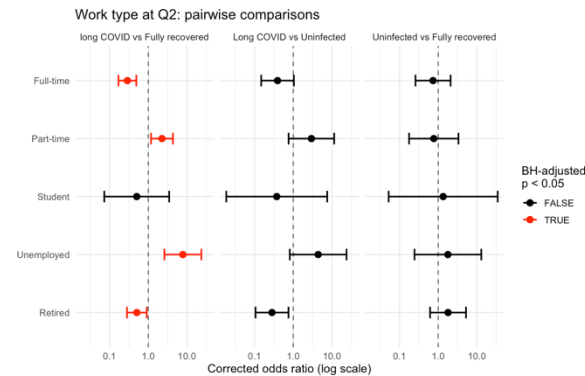
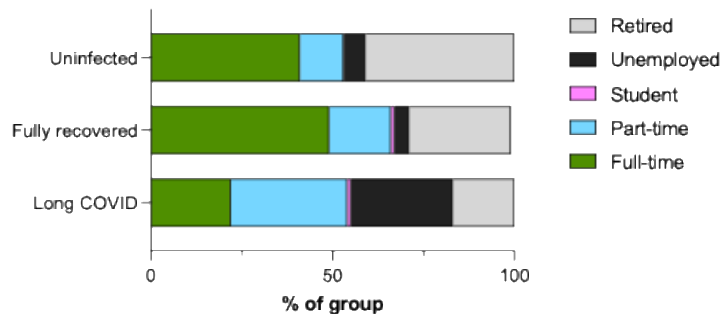
Change in employment status of people with LC comparing pre- and post-pandemic

Employment status pre-March 2020



No difference in employment status pre-pandemic

Employment status at Q2



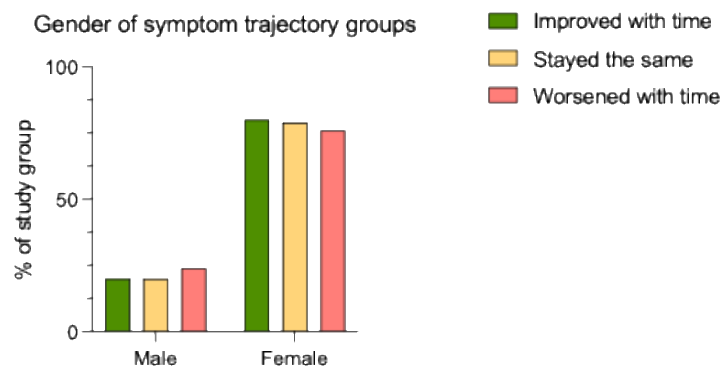
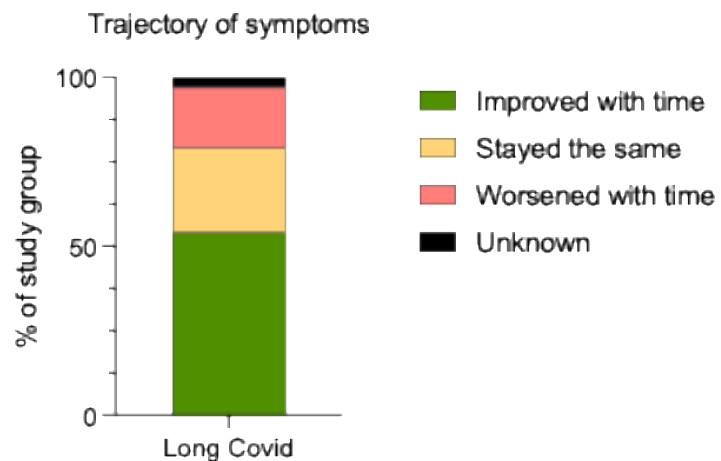
People with LC more likely to be unemployed working at Q2 than had full-time work within infected

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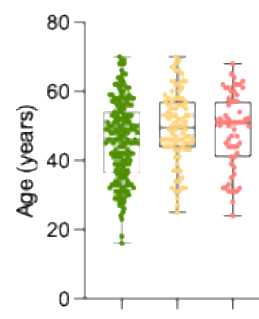
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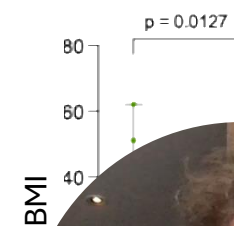
Adult WILCO Q2 cohort longitudinal symptom trajectory



Age of symptom trajectory groups



BMI of symptom trajectory groups



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These trajectories – improved versus ‘deep LC’ are not obviously distinguished by:

- Gender
- Ethnicity
- Age
- BMI
- Infecting VoC
- ‘proxies for persistent virus reservoir’ – S, N Ab or T cells, IFI27 transcription



Experimental design for longitudinal RNAseq analysis of an age/sex matched WILCO sub-study cohort

SARS-CoV-2 infection



FR - Fully recovered within 4/52 after acute SARS-CoV-2 infection



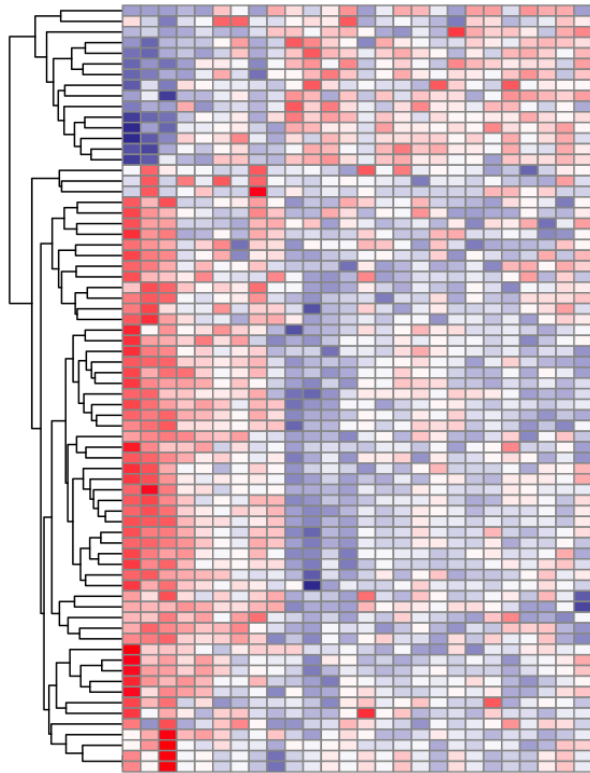
LC Improved - Long COVID – (persistent symptoms lasting >3/12 after acute SARS-CoV-2 infection) with symptoms having improved after 18/12 additional f/u



Deep LC - Long COVID (persistent symptoms lasting >3/12 after acute SARS-CoV-2 infection) with symptoms having got worse after 18/12 additional f/u



RNAseq analysis of the three well characterized groups (FR, LC Improved & Deep LC) longitudinally across two time points.



72 differentially expressed genes
between three groups at V1



FR - Fully recovered within 4/52 after
acute SARS-CoV-2 infection;



LC Improved - Long COVID – (persistent
symptoms lasting >3/12 after acute
SARS-CoV-2 infection) with symptoms
having improved after 18/12 additional
f/u



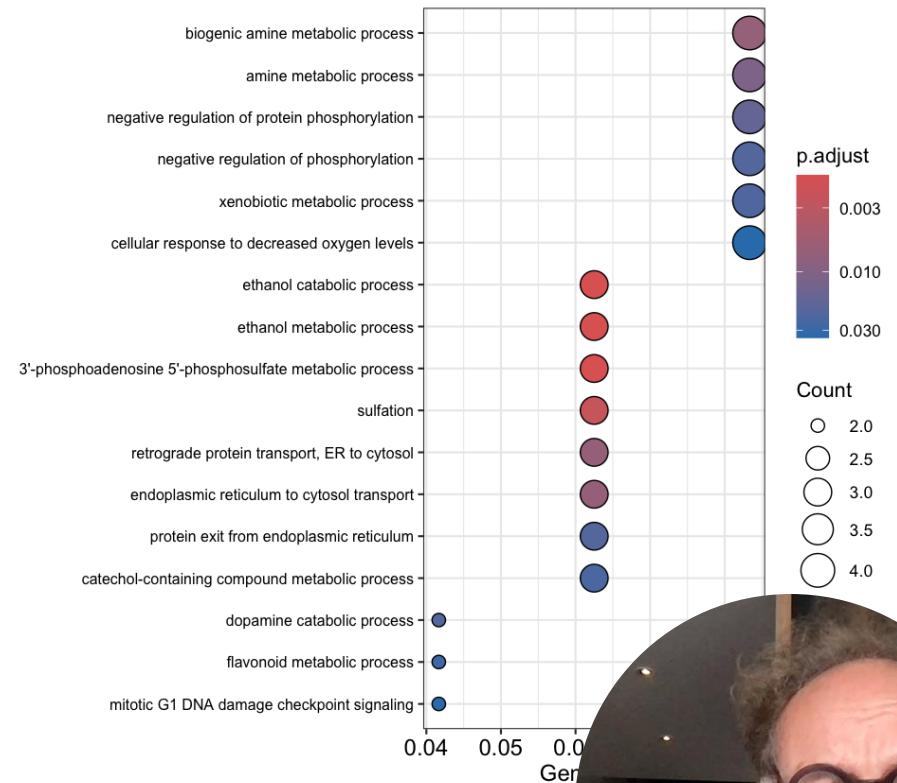
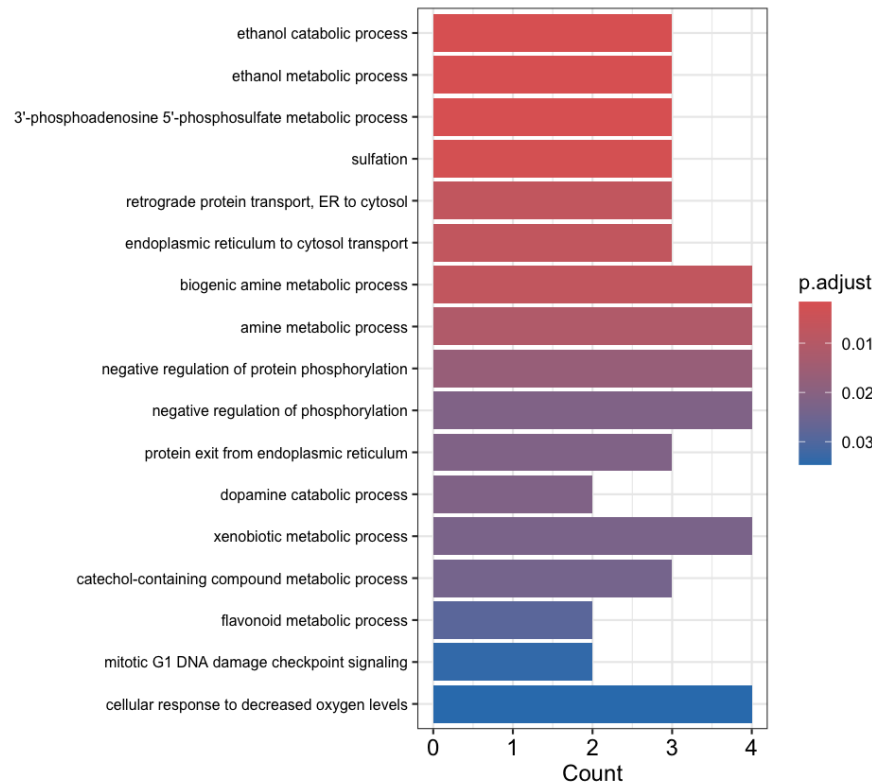
Deep LC - Long COVID (persistent
symptoms lasting >3/12 after
SARS-CoV-2 infection) with
having got worse after 18/12
f/u

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58 of sig. genes pull apart FR and Deep - LC GO term enrichment

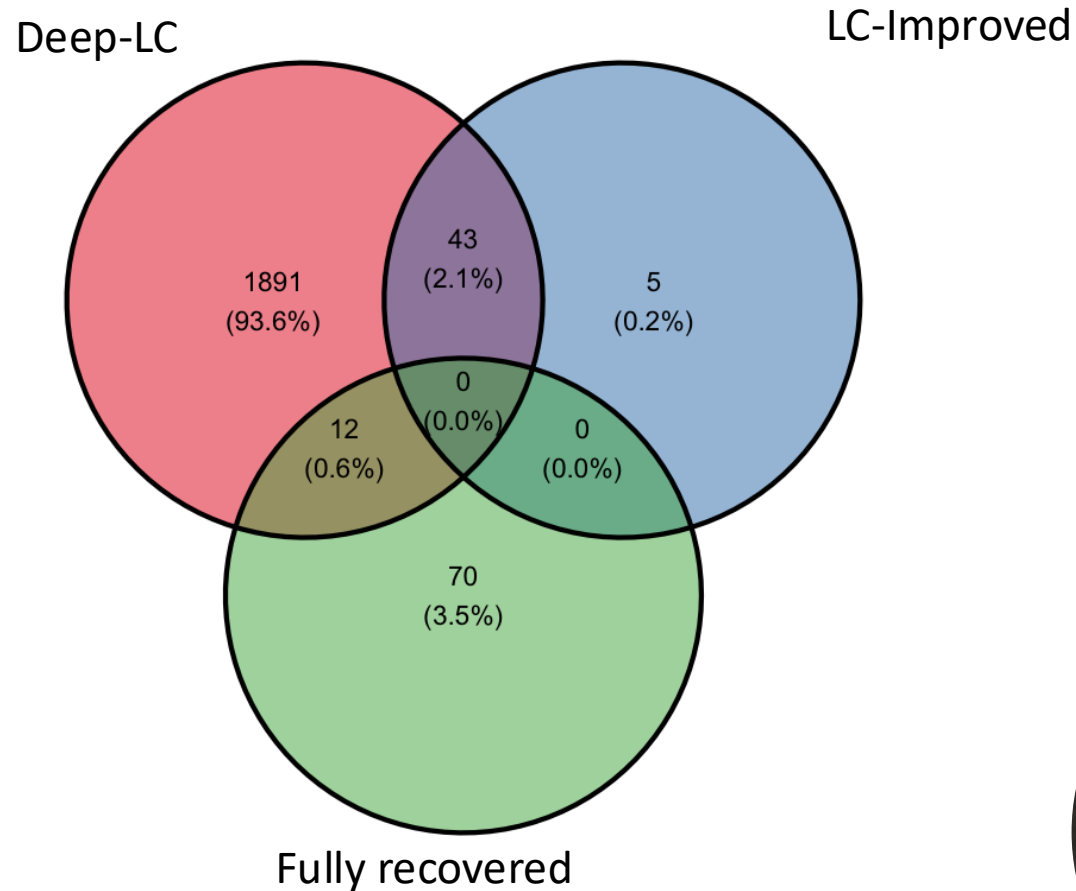


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Paired analysis comparing timepoint V1 and V2 for the three clinical trajectory groups – what changed?



Cutoff $p < 0.05$

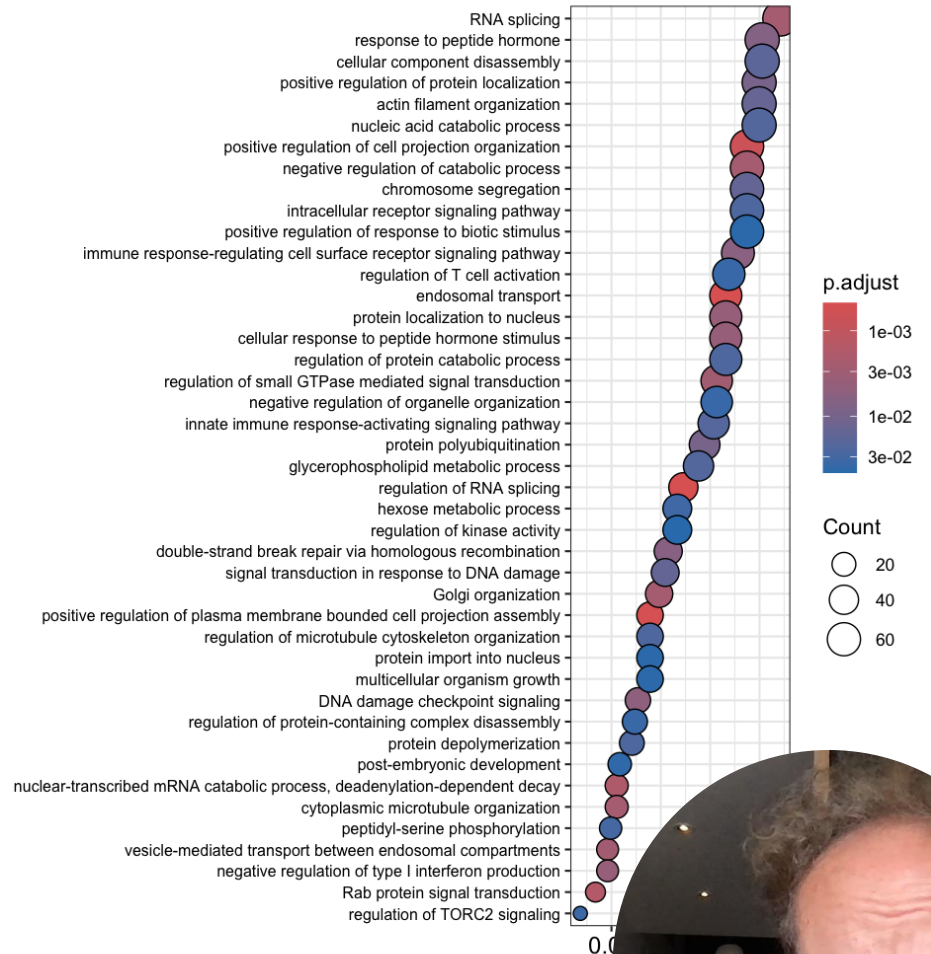
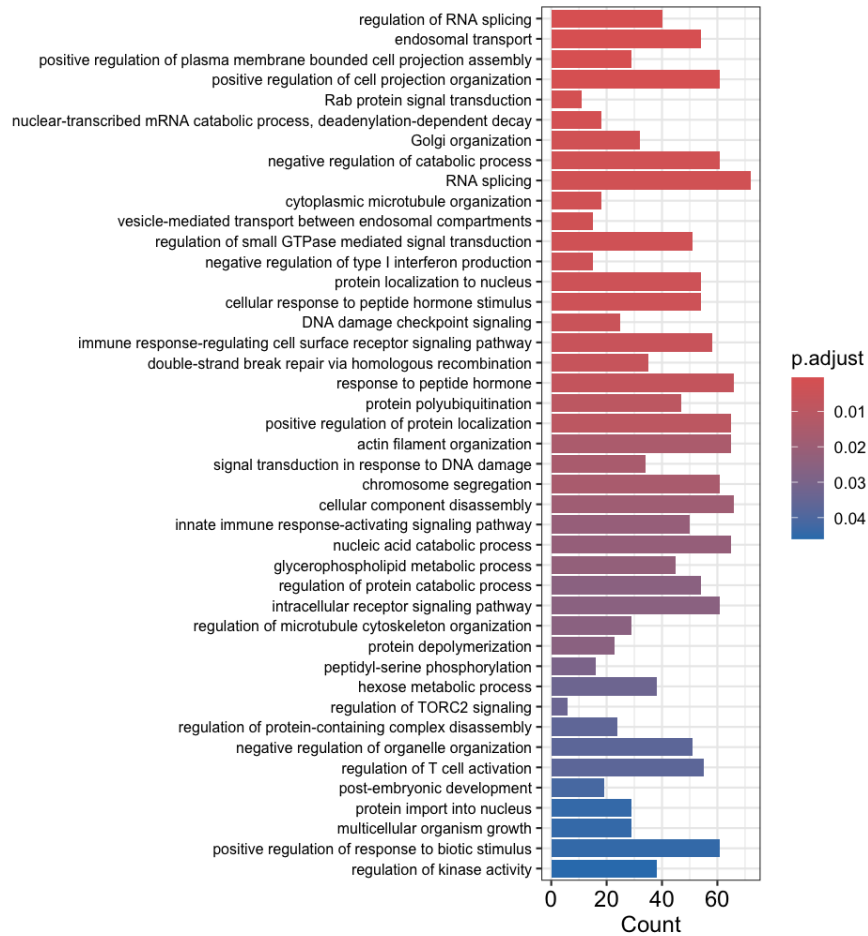
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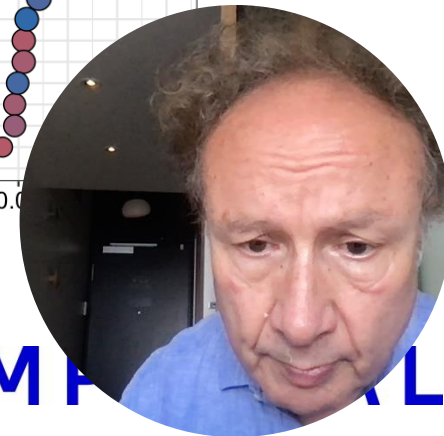
For 1,946 genes that change between V1 and V2 in the Deep-LC group

Statistically sig. GO terms (simplified) = 43



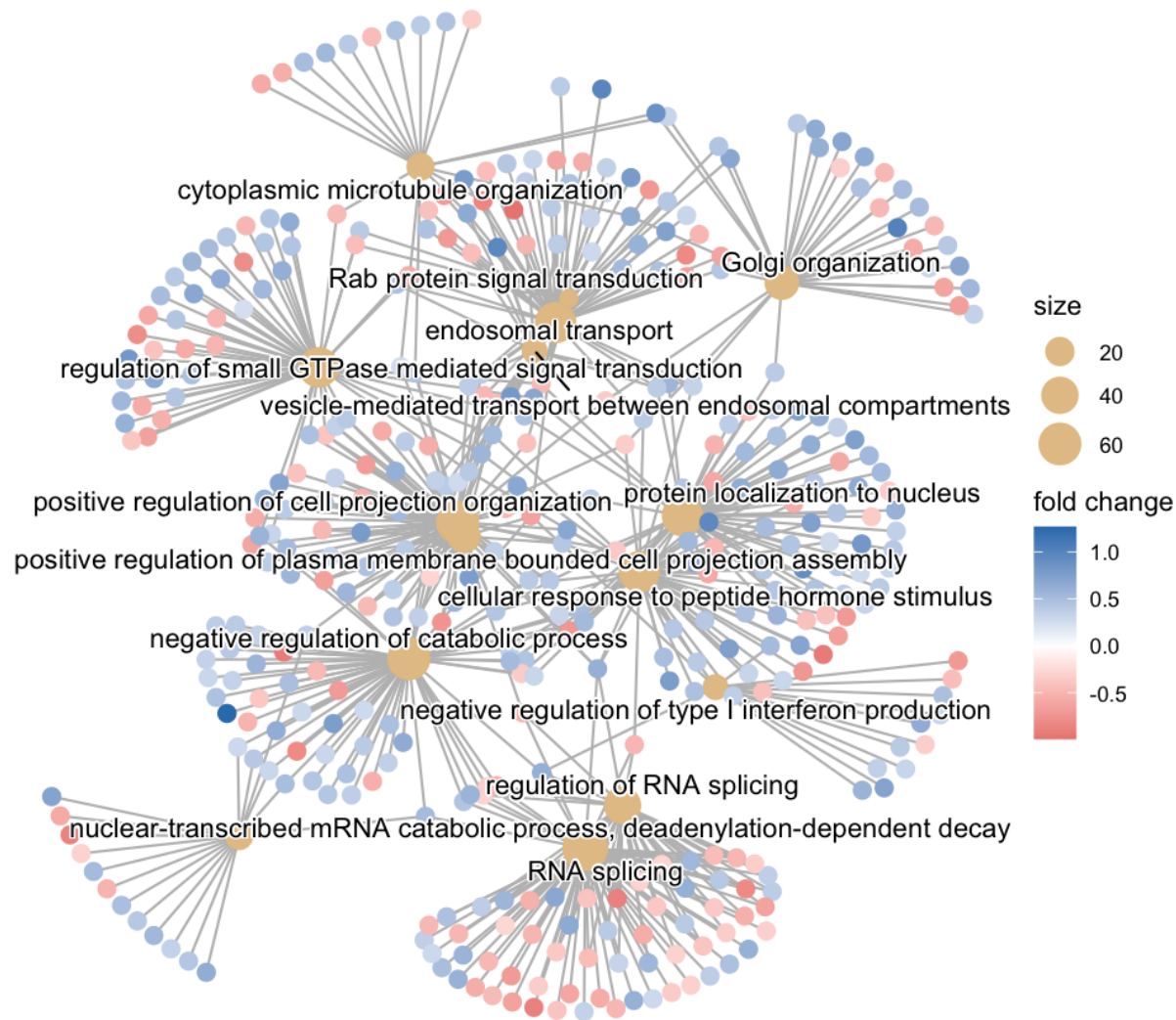
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Top 15 GO terms as a CNETplot

for 1,946 genes that change between V1 and V2 in the Deep-LC group



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Differential transcripts in LC implicate targets – druggable targets - associated with:

- energy expenditure and metabolic rate
- chronic pain and anxiety
- neurotransmitter metabolism
- CNS injury and regeneration



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WILCO (Working out the Immunology of Long COVID) Project

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