



## Long Covid : updates

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Defining  
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# Outline

- How long is Long Covid?
- Covid vs flu
  - 2023 rematch
  - 2024 rematch
  - Long Covid vs Long flu
- Mechanisms
- Reflections on challenges and opportunities

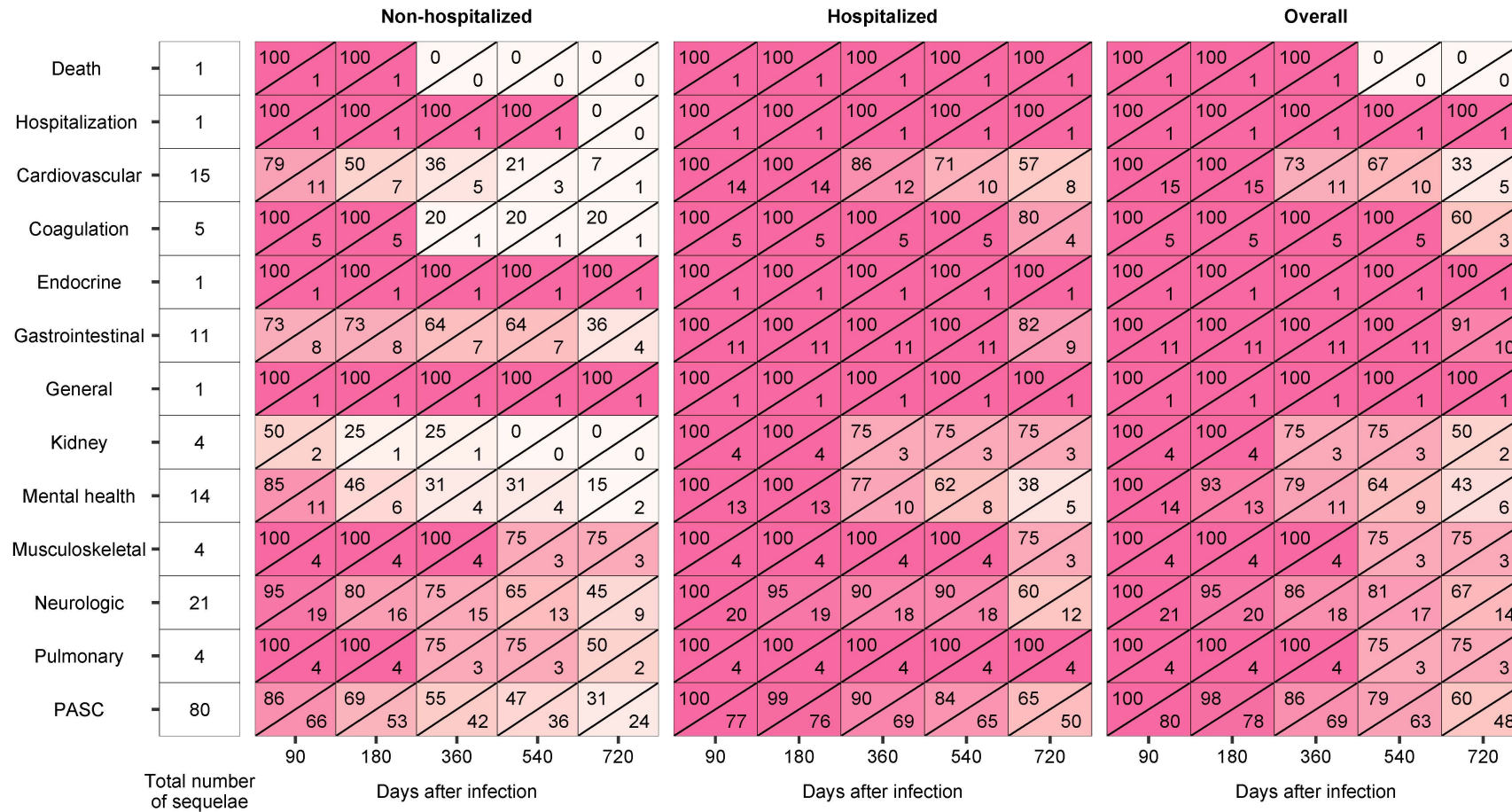




# How long is long Covid?

# How long is Long Covid?

Bowe et al.  
Nature Medicine  
2023

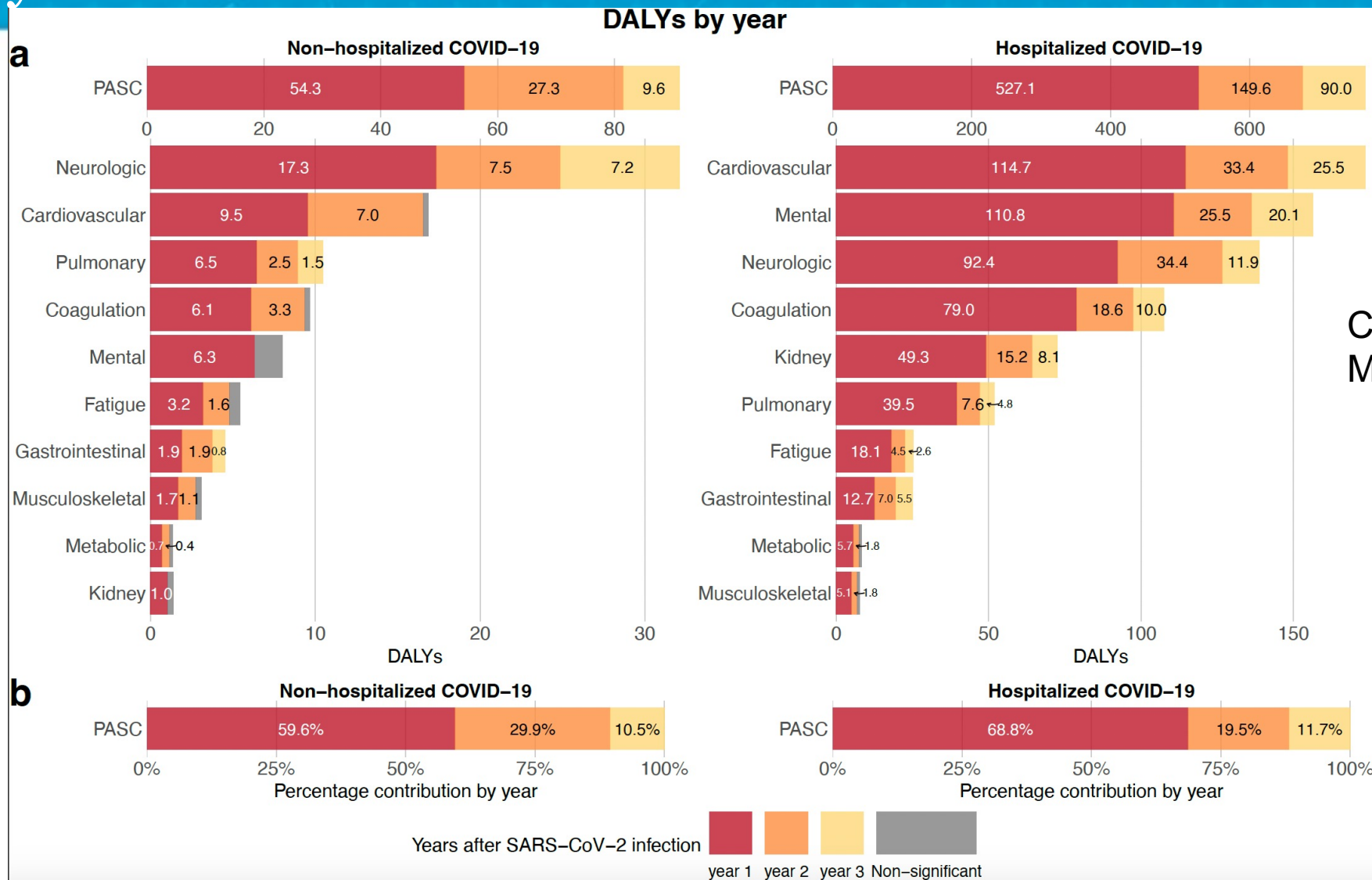


X / Y  
X = Percentage of sequelae at increased risk  
Y = Number of sequelae at increased risk

Percent of sequelae at increased risk  
0 25 50 75 100



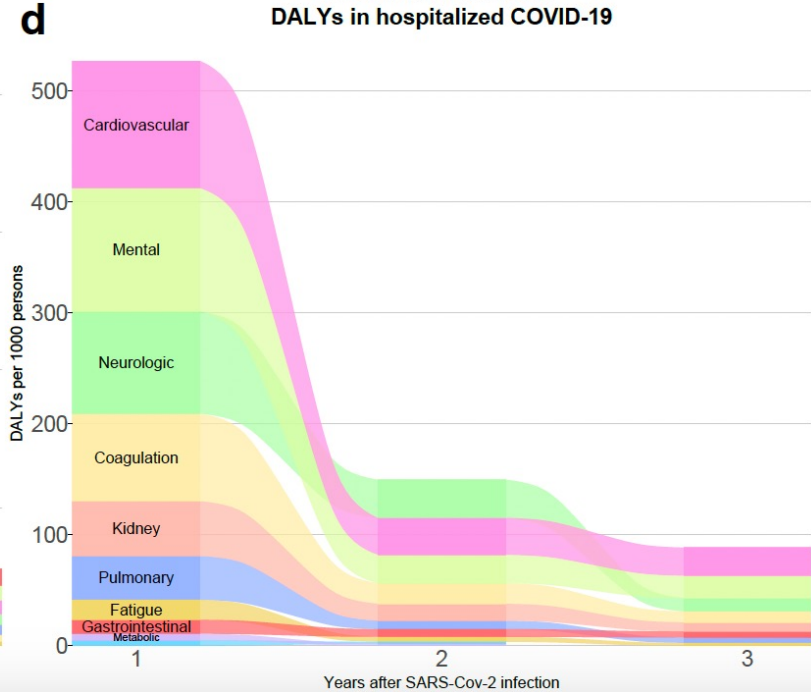
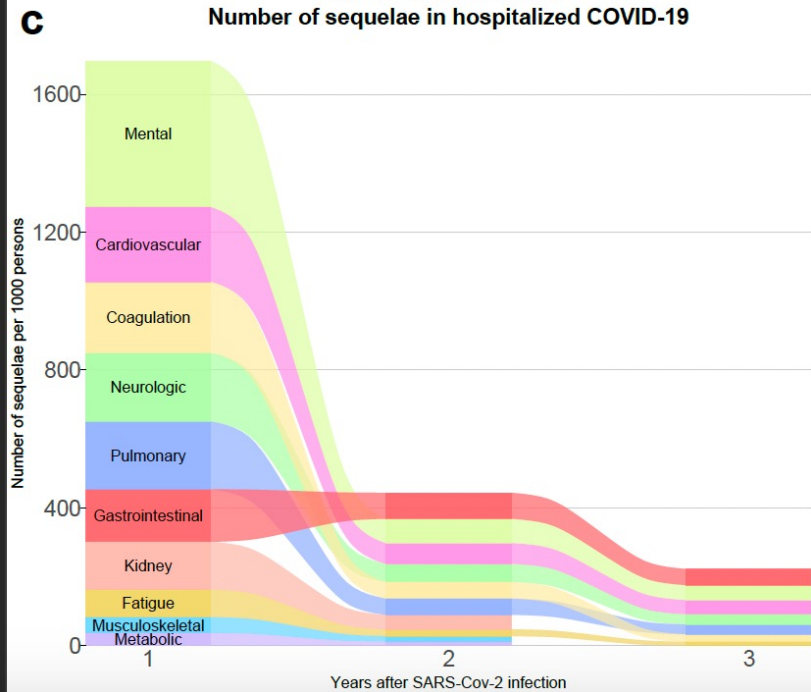
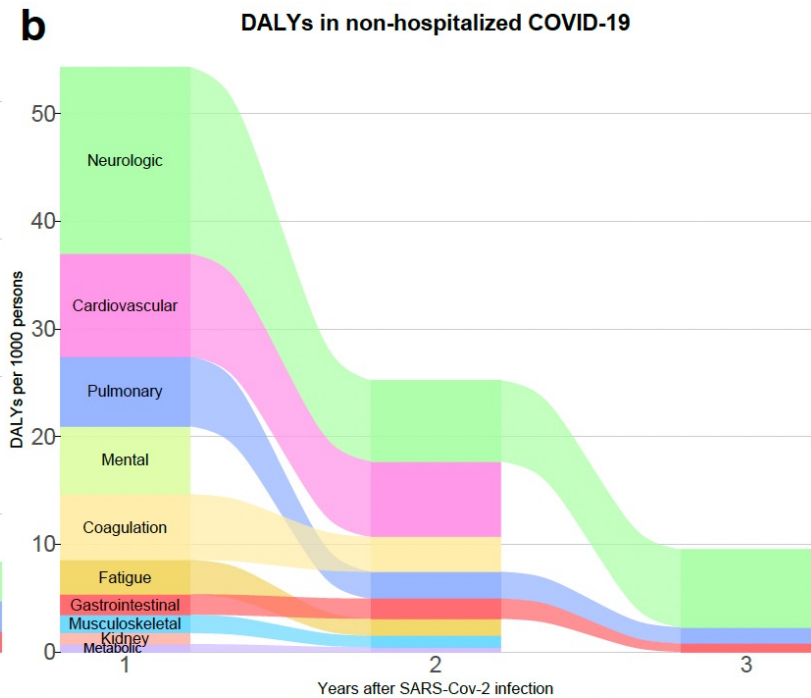
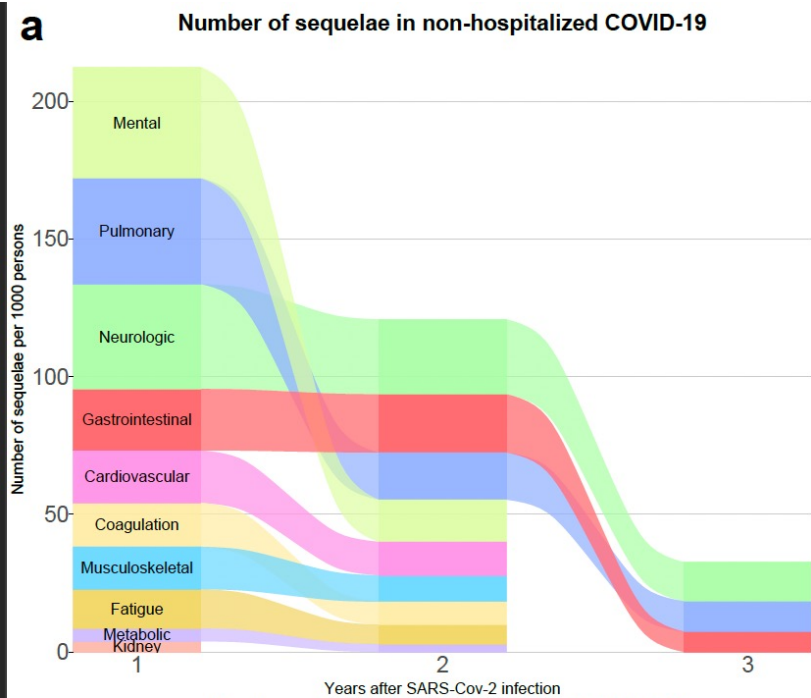
# 3-year outcomes of PASC



Cai et al. Nature Medicine 2024

# 3-year outcomes of PASC

Cai et al. Nature Medicine 2024







# Even a remote mild SARS-CoV-2 infection can have health effects 3 years later

Cai, Xie, Al-Aly, Nature Medicine 2024

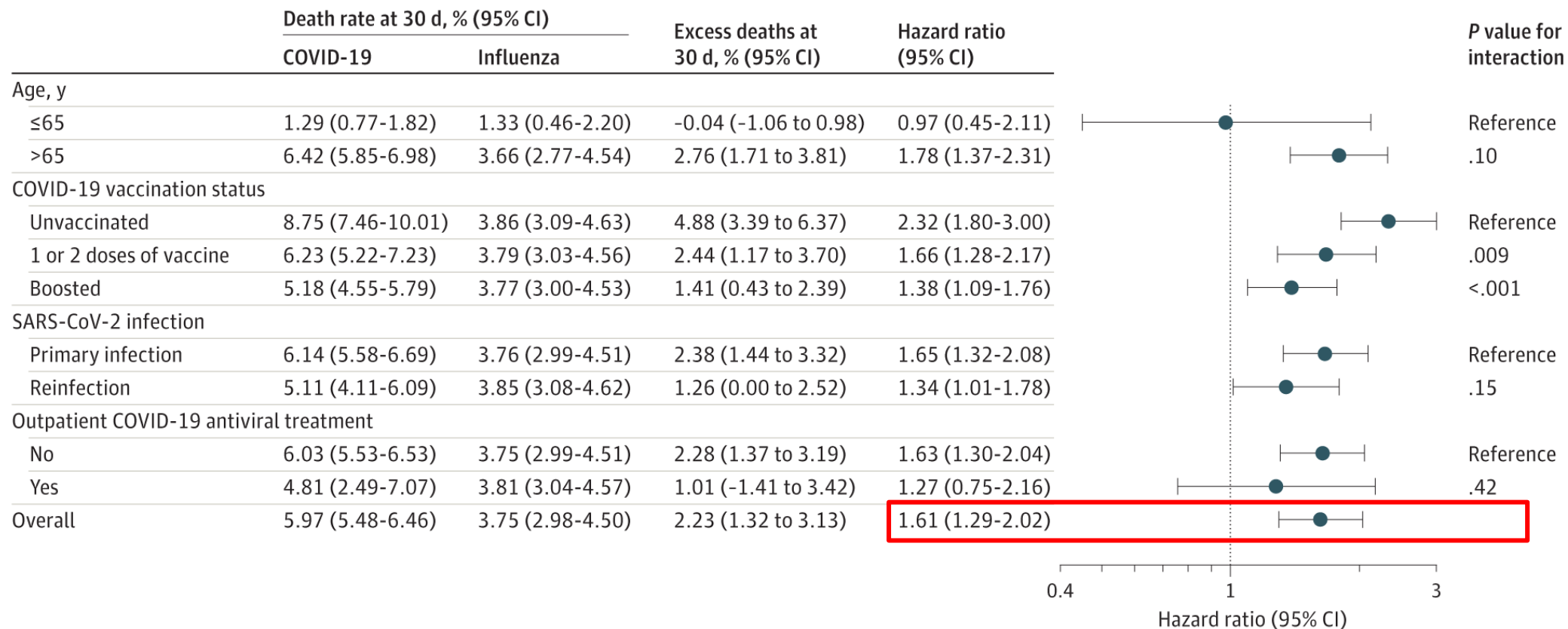




## Covid vs flu



# Covid vs flu: 2023 rematch





Then we almost drank the Kool-Aid



# Covid vs flu: 2024 rematch

**Table 2. Risk of Death in People Hospitalized for COVID-19 Compared With Seasonal Influenza and in Those Hospitalized for COVID-19 Before vs During the JN.1-Predominant Era**

	Death rate at 30 d, % (95% CI)		Adjusted hazard ratio (95% CI) <sup>a</sup>
	Unadjusted	Adjusted <sup>a</sup>	
<b>Hospitalized for COVID-19 compared with hospitalized for seasonal influenza</b>			
COVID-19	5.70 (5.20-6.19)	5.70 (5.20-6.19)	1.35 (1.10-1.66)
Seasonal influenza	3.04 (2.40-3.79)	4.24 (3.47-5.01)	
<b>Hospitalized for COVID-19 before compared with during JN.1-predominant era<sup>b</sup></b>			
Before JN.1-predominant era	5.77 (5.05-6.48)	5.46 (4.76-6.16)	1.07 (0.89-1.28)
During JN.1-predominant era	5.64 (4.95-6.33)	5.82 (5.12-6.51)	

<sup>a</sup> Model adjusting through inverse probability weights where the overall COVID-19 group is the target population. Variables adjusted for included age, self-reported race, sex, Area Deprivation Index, smoking, use of long-term care, BMI, eGFR, systolic and diastolic blood pressure, COVID-19 vaccination status, influenza vaccination status, cancer, cardiovascular disease, chronic lung disease, coronary artery disease, dementia, diabetes, hyperlipidemia, HIV, immune dysfunction, liver diseases, peripheral artery diseases, number of outpatient visits and hospital admissions, number of blood panel tests,

number of medications received, number of Medicare outpatient visits and hospital admissions within 1 year before beginning of follow-up, hospital bed capacity, and hospital bed occupancy at the participants' health care facility within the week of the admission. The calendar date of the admission was additionally adjusted for in COVID-19 vs seasonal influenza.

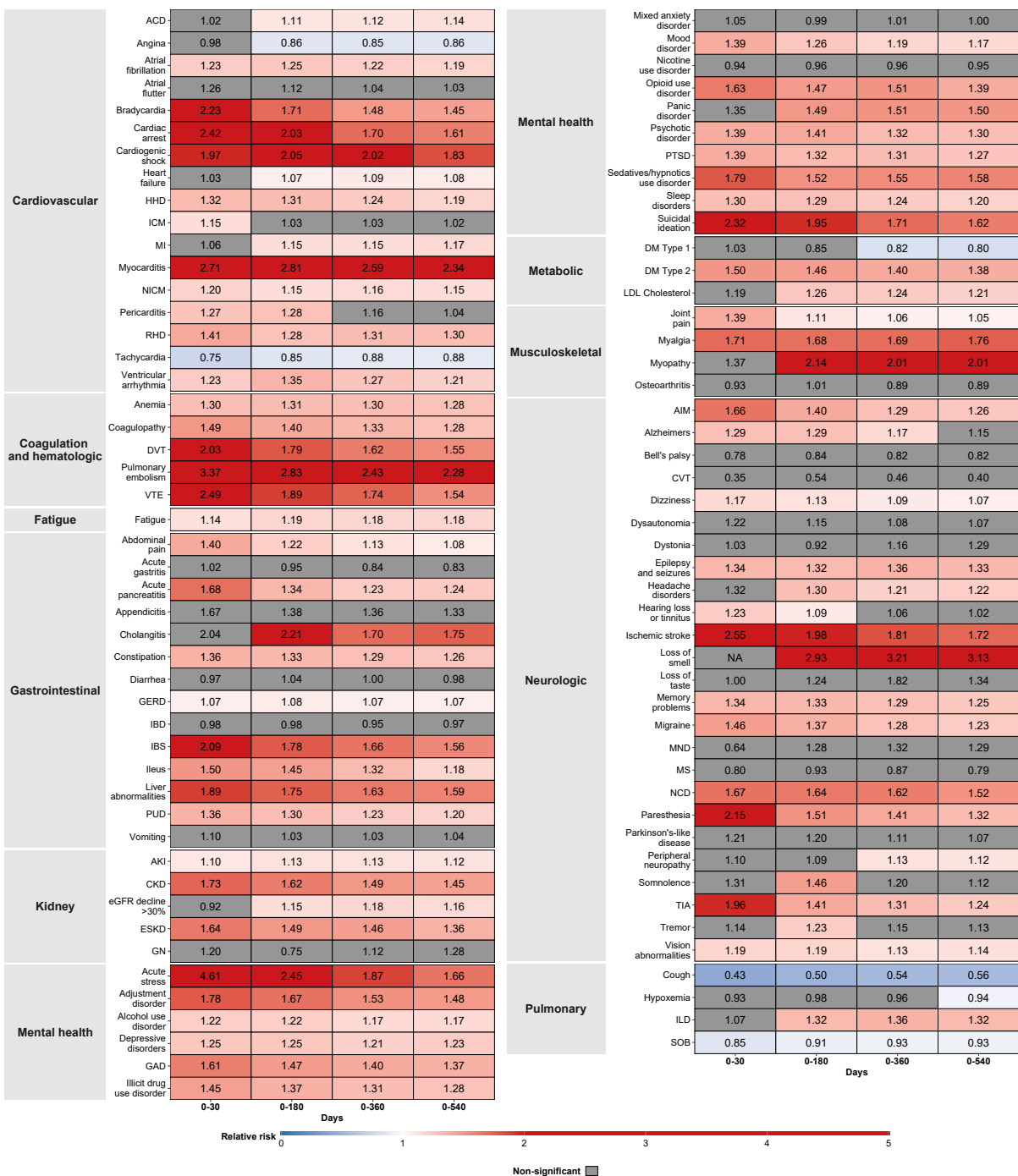
<sup>b</sup> JN.1-predominant era defined as beginning on December 24, 2023.



## Long term health effects of Covid Flu



Figure 2

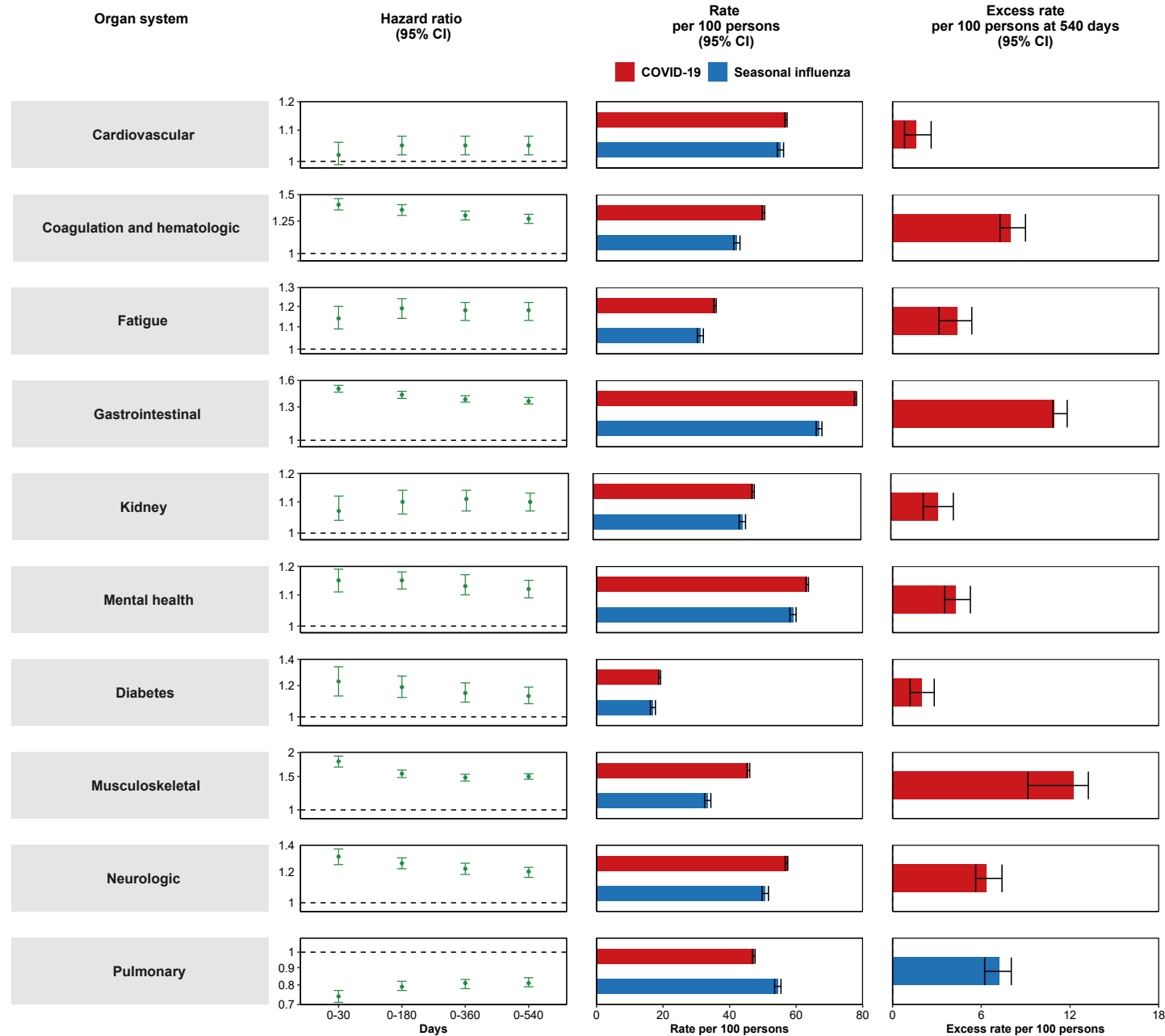


# Risks of 94 health outcomes

Risk is higher in COVID for 64 of 94 health outcomes

Xie et al. Lancet Infectious Diseases

Figure 3  
A



# Excess burden in COVID-19 vs flu

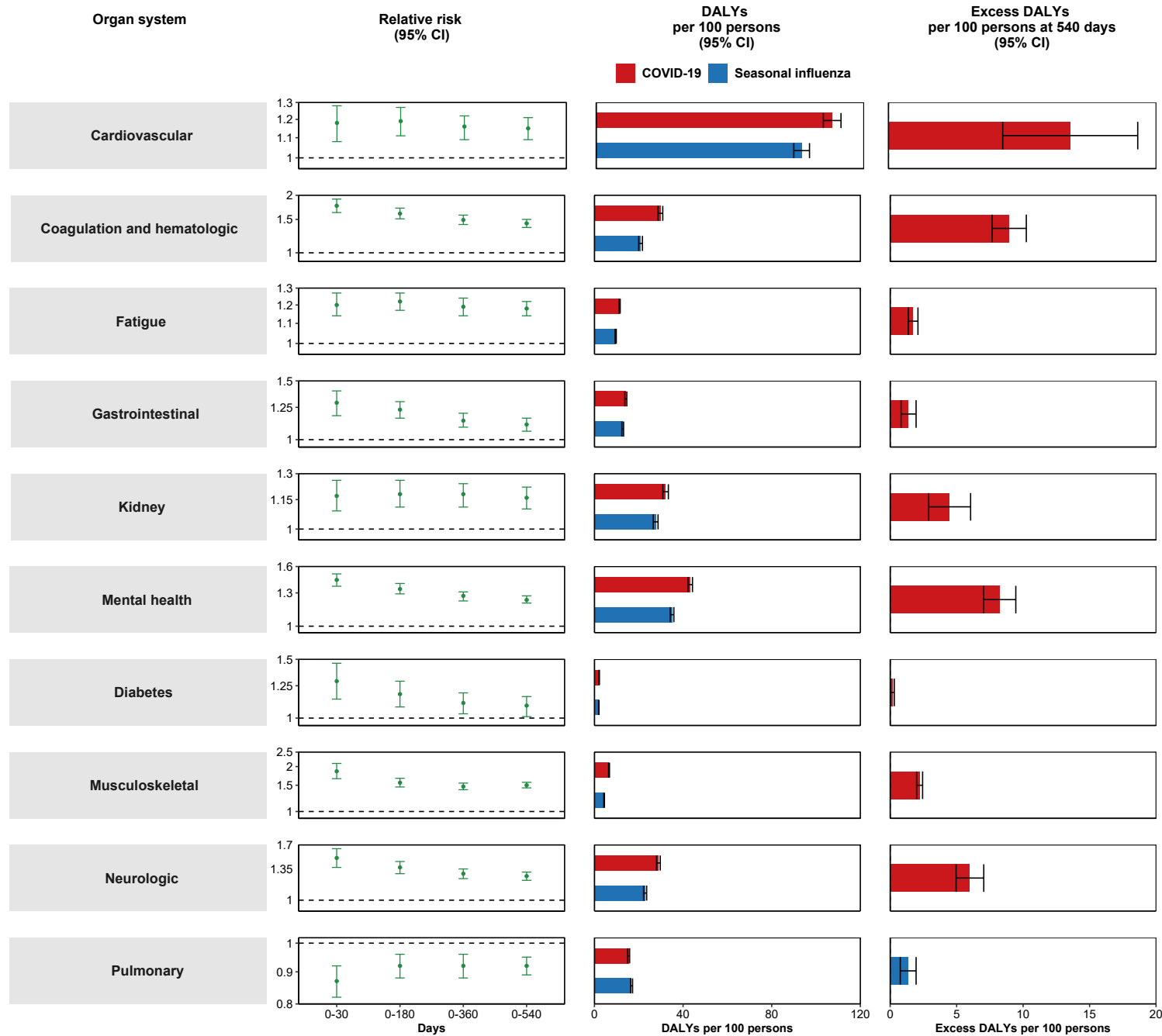
Xie et al. Lancet Infectious Diseases



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Figure 3  
B

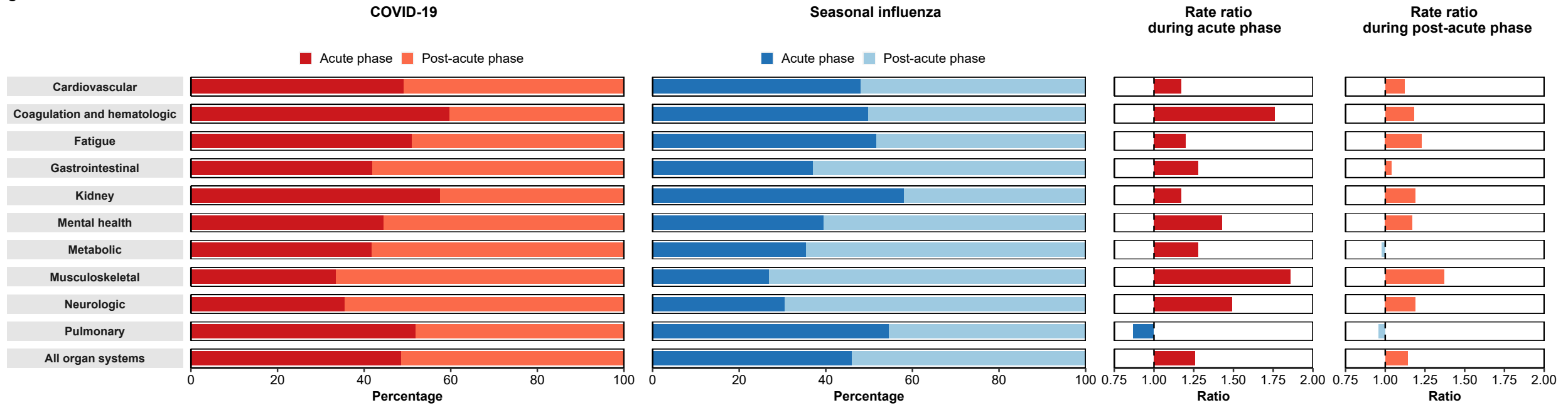


# Excess DALYs in COVID-19 vs flu

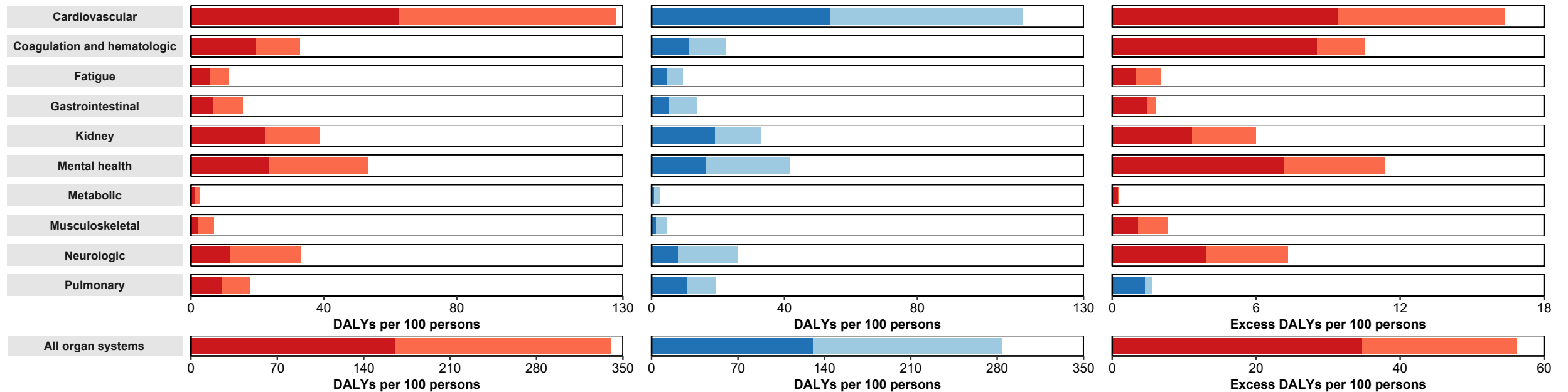
Xie et al. Lancet Infectious Diseases



Figure 5  
C



D





# SARS-CoV-2 remains a more serious threat to human health than flu

- More Covid cases than flu
- Covid is year-round – flu is seasonal
- Covid leads to more hospitalization than flu
- Covid leads to more death than flu
- Both Covid-19 and flu have long tails –
  - Long Covid is worse than Long Flu



Has the risk of PASC changed over the course of the pandemic?

July 17, 5:00 pm ET

Twitter/X @zalaly



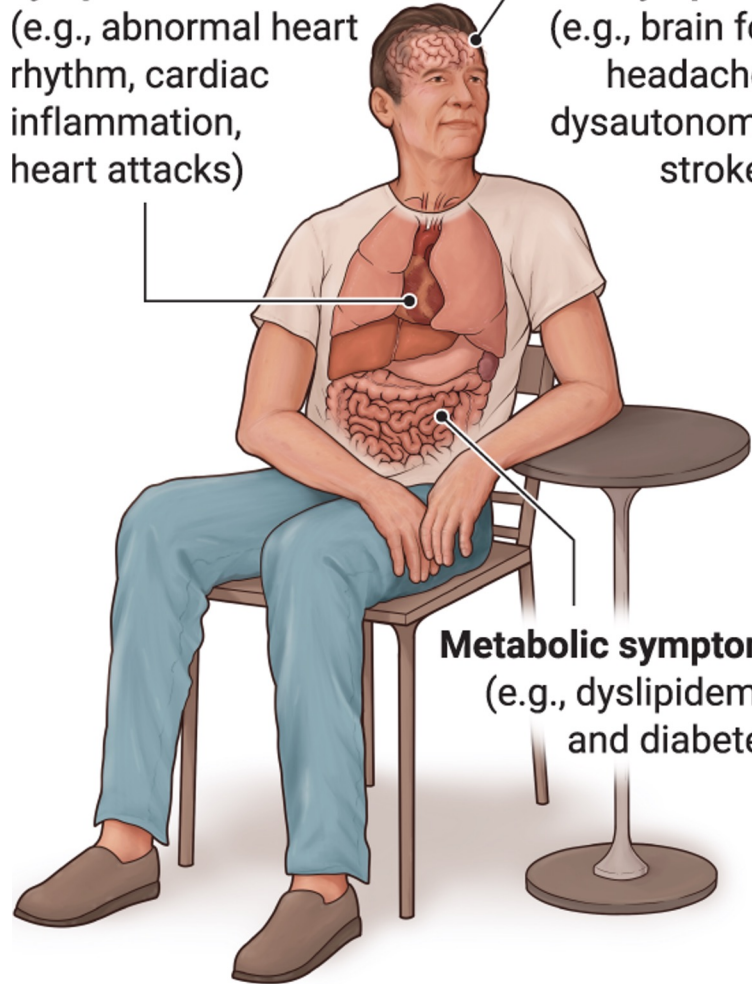
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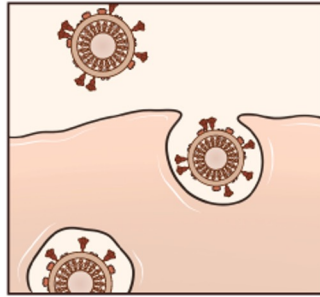
# Mechanisms of Long Covid

**Cardiovascular symptoms**  
(e.g., abnormal heart rhythm, cardiac inflammation, heart attacks)

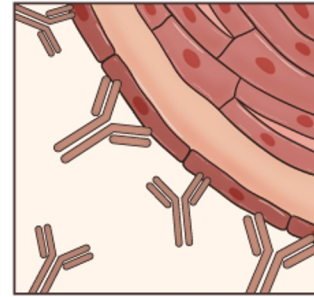
**Neurologic symptoms**  
(e.g., brain fog, headaches, dysautonomia, strokes)



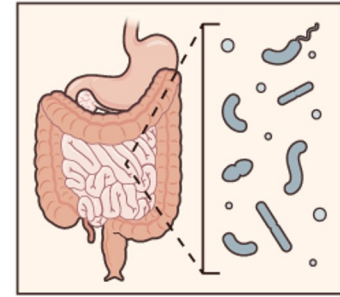
**Metabolic symptoms**  
(e.g., dyslipidemia and diabetes)



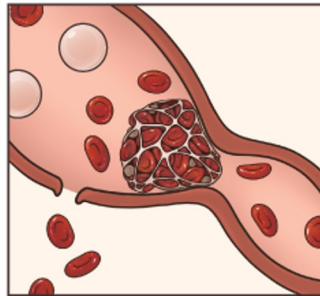
**Viral persistence**  
may cause inflammation and reactivate dormant viruses.



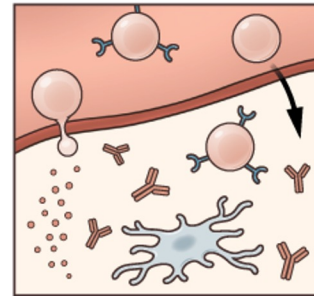
**Immune dysregulation**  
may increase immune reactivity.



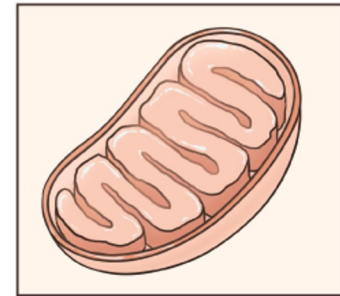
**Microbiome dysbiosis**  
may impair gut-brain signaling and metabolic regulation.



**Endothelial inflammation**  
may activate coagulation cascades and elicit microthrombosis.



**Neuronal inflammation**  
may result from activated microglia and immune cells.

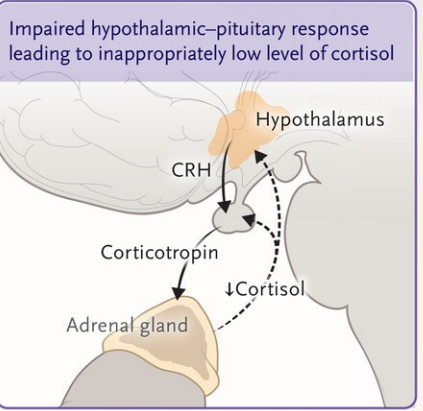
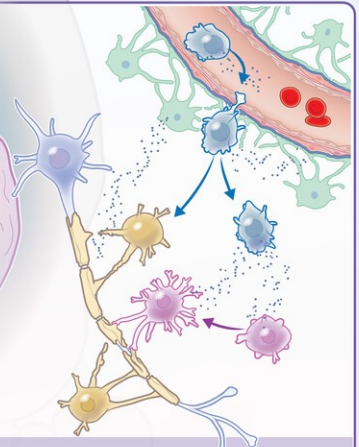
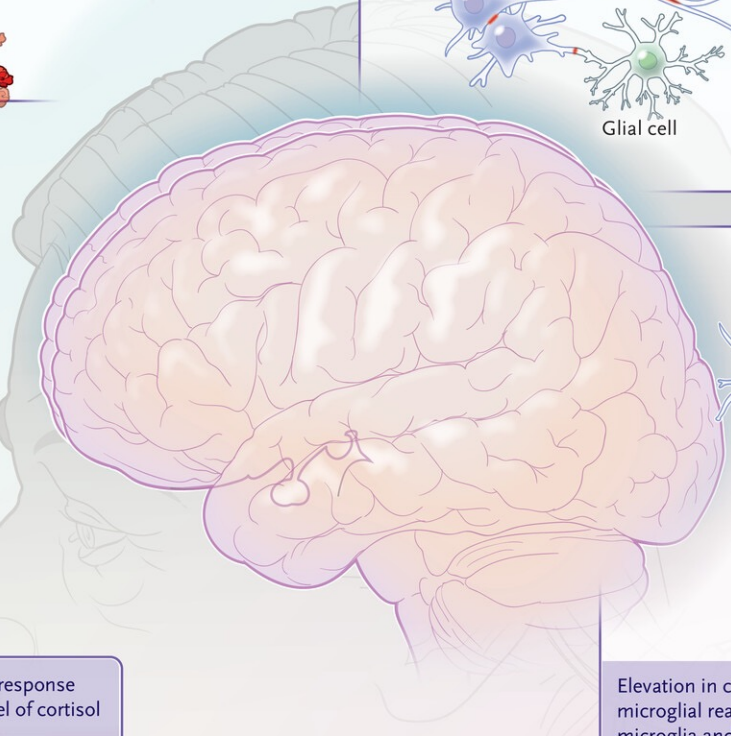
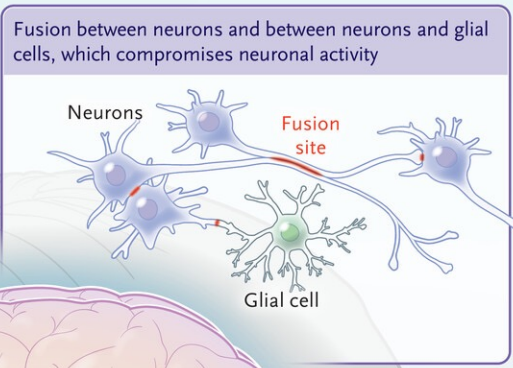
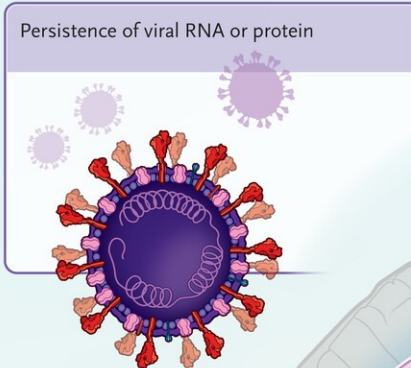


**Mitochondrial dysfunction**  
may impair metabolism and lead to fatigue and metabolic symptoms.

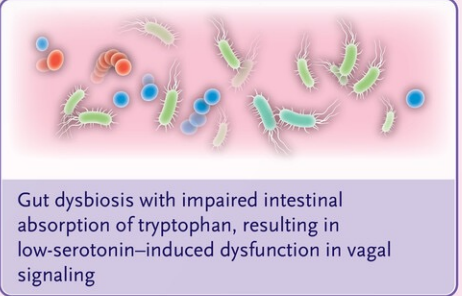
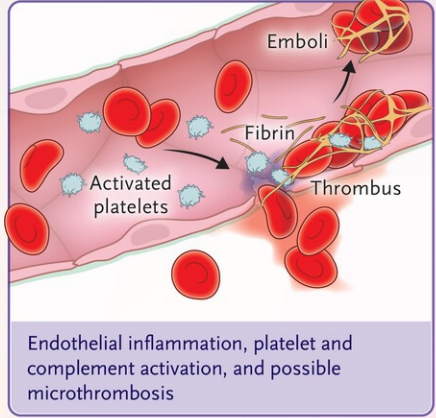


# Putative Mechanisms of Neurologic Involvement in Long Covid

Al-Aly and Rosen, NEJM 2024



Elevation in cytokine levels and increased microglial reactivity; activation of hippocampal microglia and reduced neurogenesis; persistent loss of oligodendrocytes and myelinated axons



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# The long shadow of Covid

- The toll of hospitalization and death from acute covid is the tip of the iceberg
- Long Covid
  - Disease and disability
  - Life expectancy
  - Impact on health systems
  - Development and educational attainment
  - Economic implications
  - Impact on SDG
  - Social implications



# Reflections on challenges and opportunities

- Challenges:
  - Care of people with Long Covid remains suboptimal
  - Prevention strategies are underutilized
  - No treatment
  - No consensus on terms, definitions and clinical endpoints (outcomes)
  - No systems to measure the burden of infection-associated chronic illness
  - Long term risks of infections (5, 10, 15 years) unknown
  - Politicization of public health (misinformation, disinformation, anti vaccine and anti science)



# Reflections on challenges and opportunities

- Opportunities:
  - Patients as partners
  - Scope and scale of the pandemic – an historical opportunity
    - Long Covid and other infection-associated chronic illnesses
  - Prevention (ventilation and air filtration, vaccines, antivirals)
  - Treatment
  - Data systems and expertise
    - Surveillance and epidemiology of post-acute illness
    - Real-time real-world evidence generation
  - Preparedness and resilience for the next pandemic

# Summary

- A SARS-CoV-2 infection can lead to sequelae 3 years after infection
- SARS-CoV-2 is more serious threat to health than flu
  - Covid leads to more hospitalization than flu
  - Covid leads to more death than flu
- Both Covid-19 and flu have long tails – Long Covid is worse than Long Flu



Thank you

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