AETC AIDS Education & Training Center Program Southeast

Long COVID: The epidemic within a pandemic

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Disclosures

- I have no disclosures

Objectives

- Review the epidemiology of long COVID
- Review the pathogenesis of long COVID
- Discuss options for patients suffering from long COVID

What is long COVID

- CDC: Post-COVID conditions are a range of symptoms that can last weeks or months after being infected with the virus that causes COVID-19 or can appear weeks after infection.
- WHO: Post COVID-19 condition occurs in individuals with 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 alternate diagnosis

Early Descriptions of Long COVID

Persistent Symptoms in Patients After Acute COVID-19

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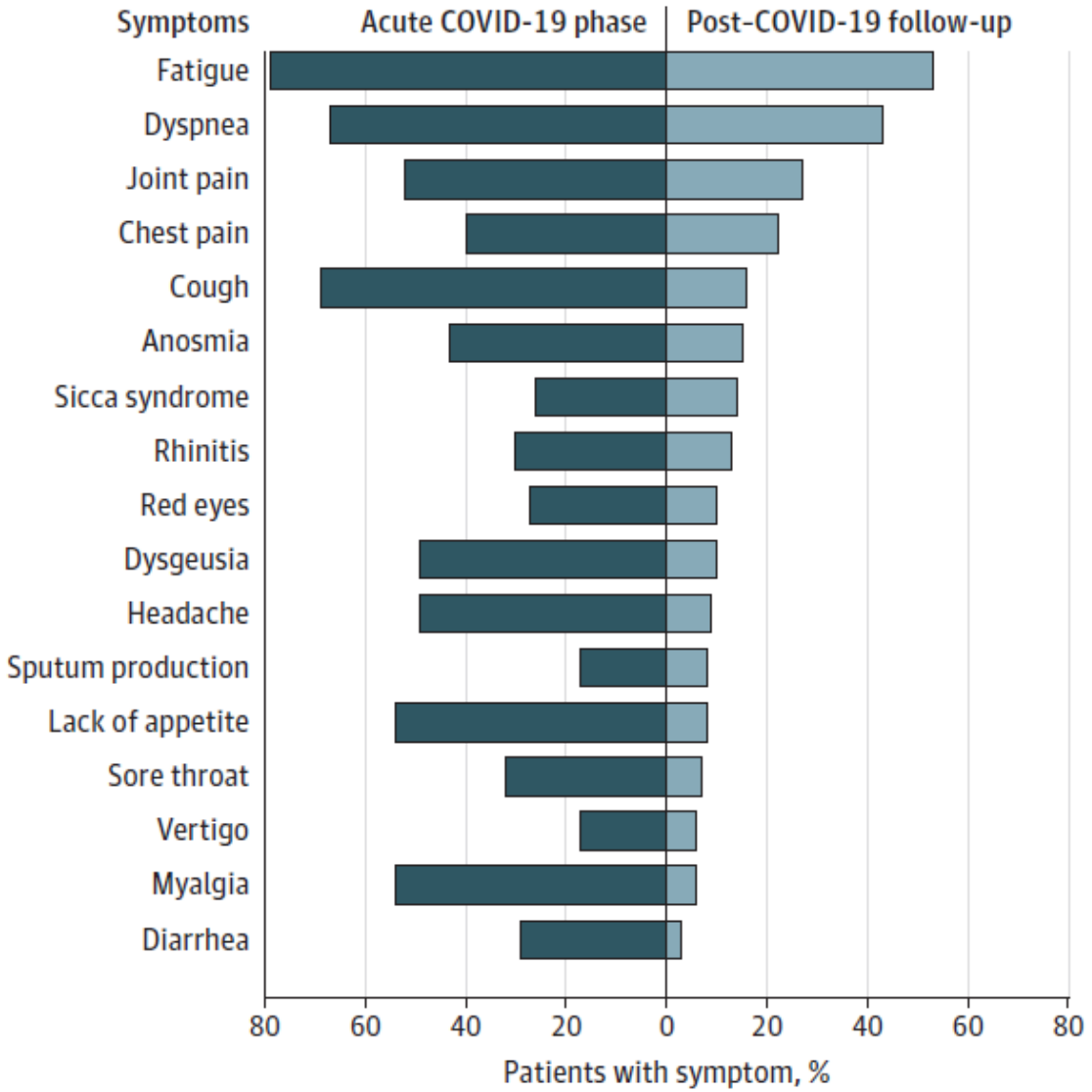
Figure. COVID-19–Related Symptoms



Persistent symptoms 3 months after a SARS-CoV-2 infection: the post-COVID-19 syndrome?

Yvonne M.J. Goërtz[1,2,3,9], Maarten Van Herck[1,2,3,4,9], Jeannet M. Delbressine[1], Anouk W. Vaes[1], Roy Meys[1,2,3], Felipe V.C. Machado[1,2,3], Sarah Houben-Wilke[1], Chris Burtin[4], Rein Posthuma[1,2,3], Frits M.E. Franssen[1,2,3], Nicole van Loon[1,5], Bita Hajian[1,2,3], Yvonne Spies[6], Herman Vijlbrief[6], Alex J. van 't Hul[7], Daisy J.A. Janssen[1,8] and Martijn A. Spruit[1,2,3,4]

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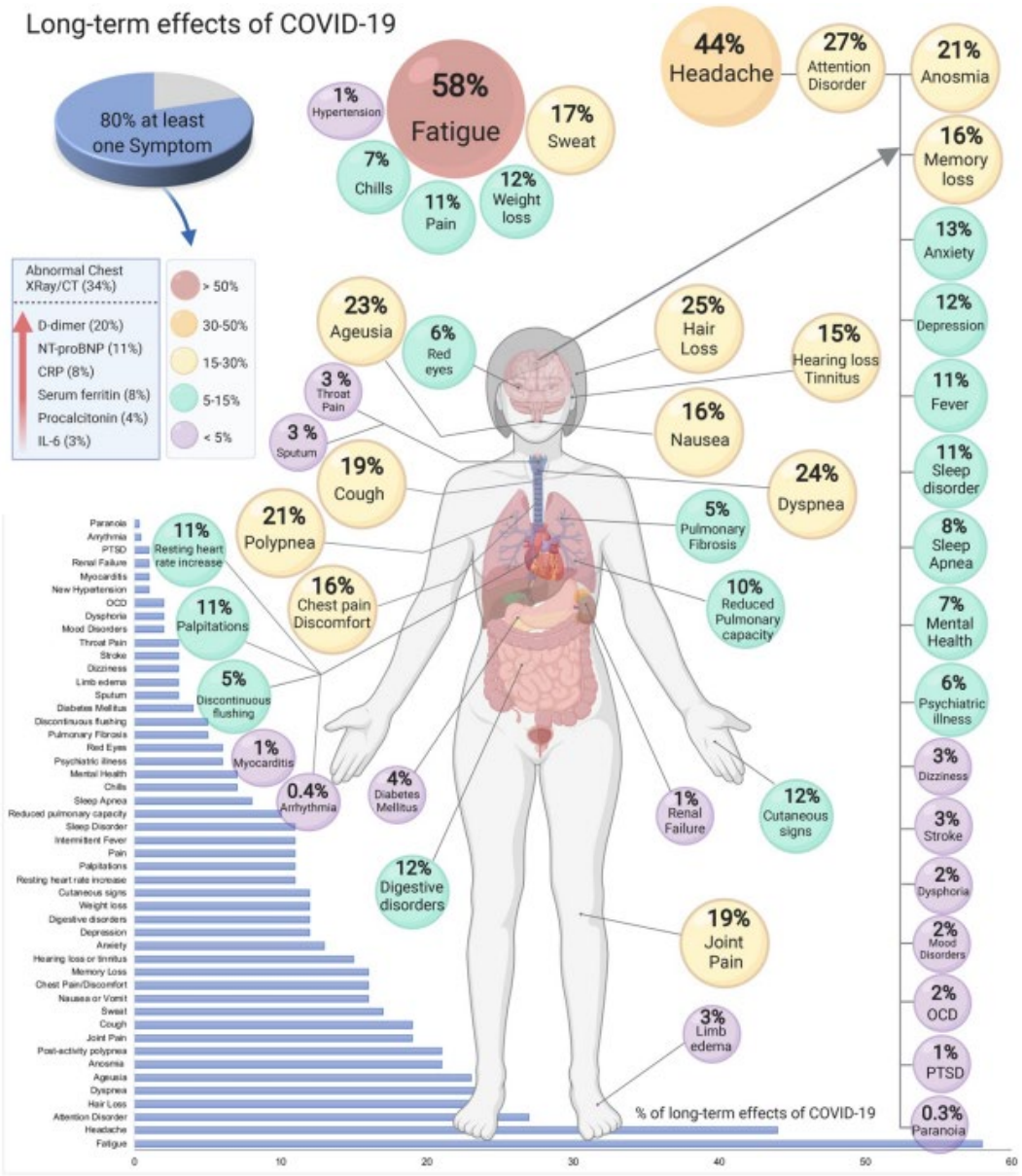
More than 50 Long-term effects of COVID-19:

a systematic review and meta-analysis

Sandra Lopez-Leon MD, PhD[1,], Talia Wegman-Ostrosky MD, PhD[2], Carol Perelman, BSc[3], Rosalinda Sepulveda MD PhD [4], Paulina A Rebolledo, MD, MSc[5,6], Angelica Cuapio MD, Dr. Med[7], Sonia Villapol, PhD[8,9,*]*


Long-term effects of COVID-19
80% at least one Symptom
Abnormal Chest XRay/CT (34%)
D-dimer (20%)
NT-proBNP (11%)
CRP (8%)
Serum ferritin (8%)
Procalcitonin (4%)
IL-6 (3%)
> 50%
30-50%
15-30%
5-15%
< 5%
58% Fatigue
1% Hypertension
7% Chills
11% Pain
12% Weight loss
17% Sweat
44% Headache
27% Attention Disorder
21% Anosmia
16% Memory loss
13% Anxiety
12% Depression
11% Fever
11% Sleep disorder
8% Sleep Apnea
7% Mental Health
6% Psychiatric illness
3% Dizziness
3% Stroke
2% Dysphoria
2% Mood Disorders
2% OCD
1% PTSD
0.3% Paranoia
23% Ageusia
6% Red eyes
25% Hair Loss
15% Hearing loss Tinnitus
3 % Throat Pain
3 % Sputum
19% Cough
16% Nausea
24% Dyspnea
21% Polypnea
5% Pulmonary Fibrosis
16% Chest pain Discomfort
10% Reduced Pulmonary capacity
11% Resting heart rate increase
11% Palpitations
5% Discontinuous flushing
1% Myocarditis
0.4% Arrhythmia
4% Diabetes Mellitus
1% Renal Failure
12% Cutaneous signs
12% Digestive disorders
19% Joint Pain
3% Limb edema
Paranoia
Arrhythmia
PTSD
Renal Failure
Myocarditis
New Hypertension
OCD
Dysphoria
Mood Disorders
Throat Pain
Stroke
Dizziness
Limb edema
Sputum
Diabetes Mellitus
Discontinuous flushing
Pulmonary Fibrosis
Red Eyes
Psychiatric illness
Mental Health
Chills
Sleep Apnea
Reduced pulmonary capacity
Sleep Disorder
Intermittent Fever
Pain
Palpitations
Resting heart rate increase
Cutaneous signs
Weight loss
Digestive disorders
Depression
Anxiety
Hearing loss or tinnitus
Memory Loss
Chest Pain/Discomfort
Nausea or Vomit
Sweat
Cough
Joint Pain
Post-activity polypnea
Anosmia
Ageusia
Dyspnea
Hair Loss
Attention Disorder
Headache
Fatigue
0
10
20
30
40
50
60
% of long-term effects of COVID-19

Why should we care about Long-COVID?

Risk of persistent and new clinical sequelae among adults aged 65 years and older during the post-acute phase of SARS-CoV-2 infection: retrospective cohort study

Ken Cohen,[1] Sheng Ren,[1] Kevin Heath,[2] Micah C Dasmariñas,[1] Karol Giuseppe Jubilo,[1] Yinglong Guo,[1] Marc Lipsitch,[3] Sarah E Daugherty[1]

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http://dx.doi.org/10.1136/bmj-2021-068414

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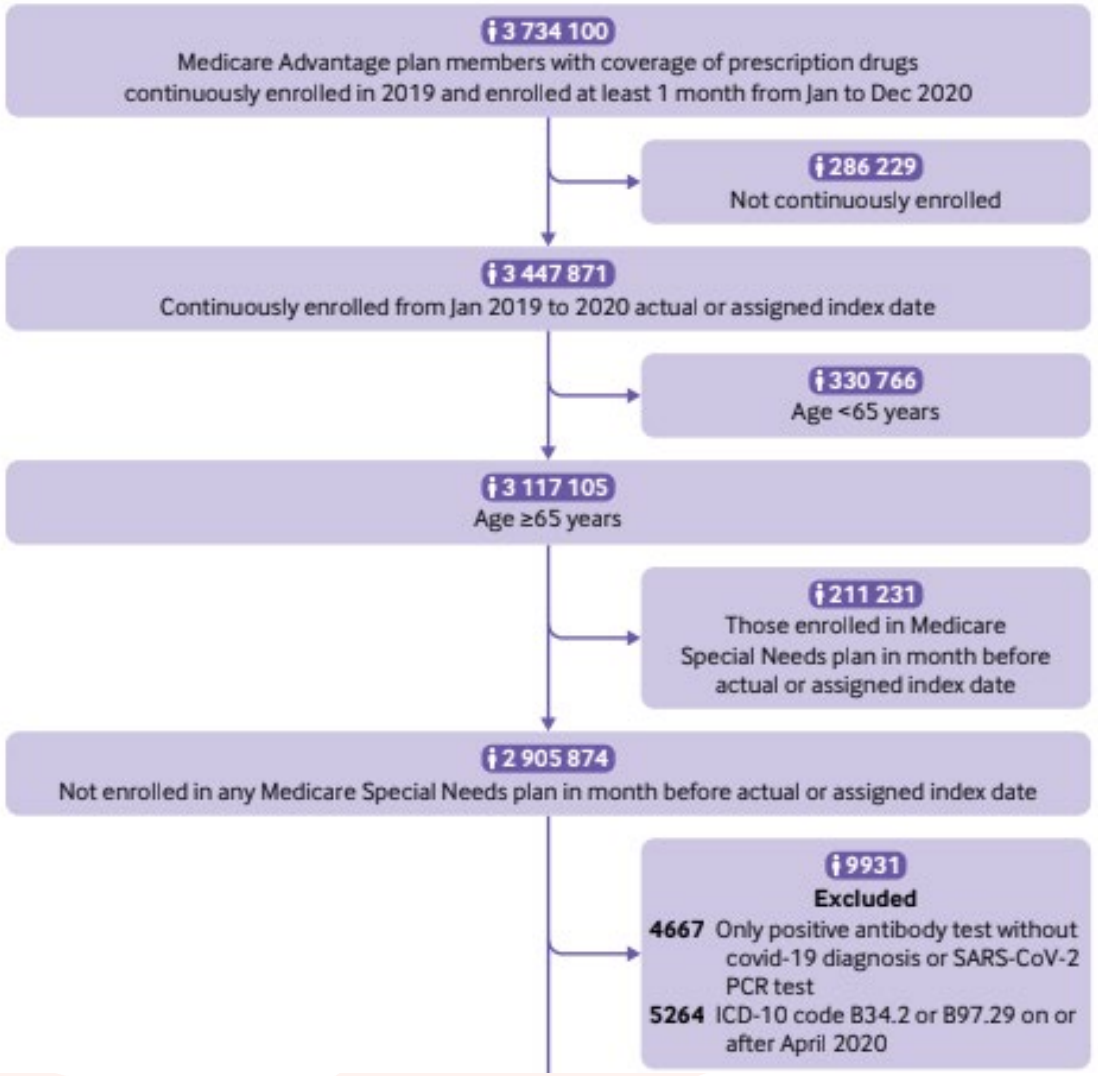
Methods

- Retrospective Cohort Study (UnitedHealth Group Clinical Research Database)
- Study Population: 65 y/o individuals enrolled in Medicare advantage plan from 2019 – date of diagnosis of SARS-CoV-2 infection (propensity matched to group that did not have covid)
- Outcomes
  - Presence of persistent and new sequelae at 21 days and 120 days (ICD 10 codes)

Results

- 133,366 individuals identified who were infected with SARS-CoV-2 in 2020
- Propensity matched 132847 pairs for the primary group, 133266 matched pairs for the secondary, 113190 matched pairs for viral lower respiratory tract illness group


3 734 100
Medicare Advantage plan members with coverage of prescription drugs continuously enrolled in 2019 and enrolled at least 1 month from Jan to Dec 2020
286 229
Not continuously enrolled
3 447 871
Continuously enrolled from Jan 2019 to 2020 actual or assigned index date
330 766
Age <65 years
3 117 105
Age ≥65 years
211 231
Those enrolled in Medicare Special Needs plan in month before actual or assigned index date
2 905 874
Not enrolled in any Medicare Special Needs plan in month before actual or assigned index date
9931
Excluded
4667 Only positive antibody test without covid-19 diagnosis or SARS-CoV-2 PCR test
5264 ICD-10 code B34.2 or B97.29 on or after April 2020

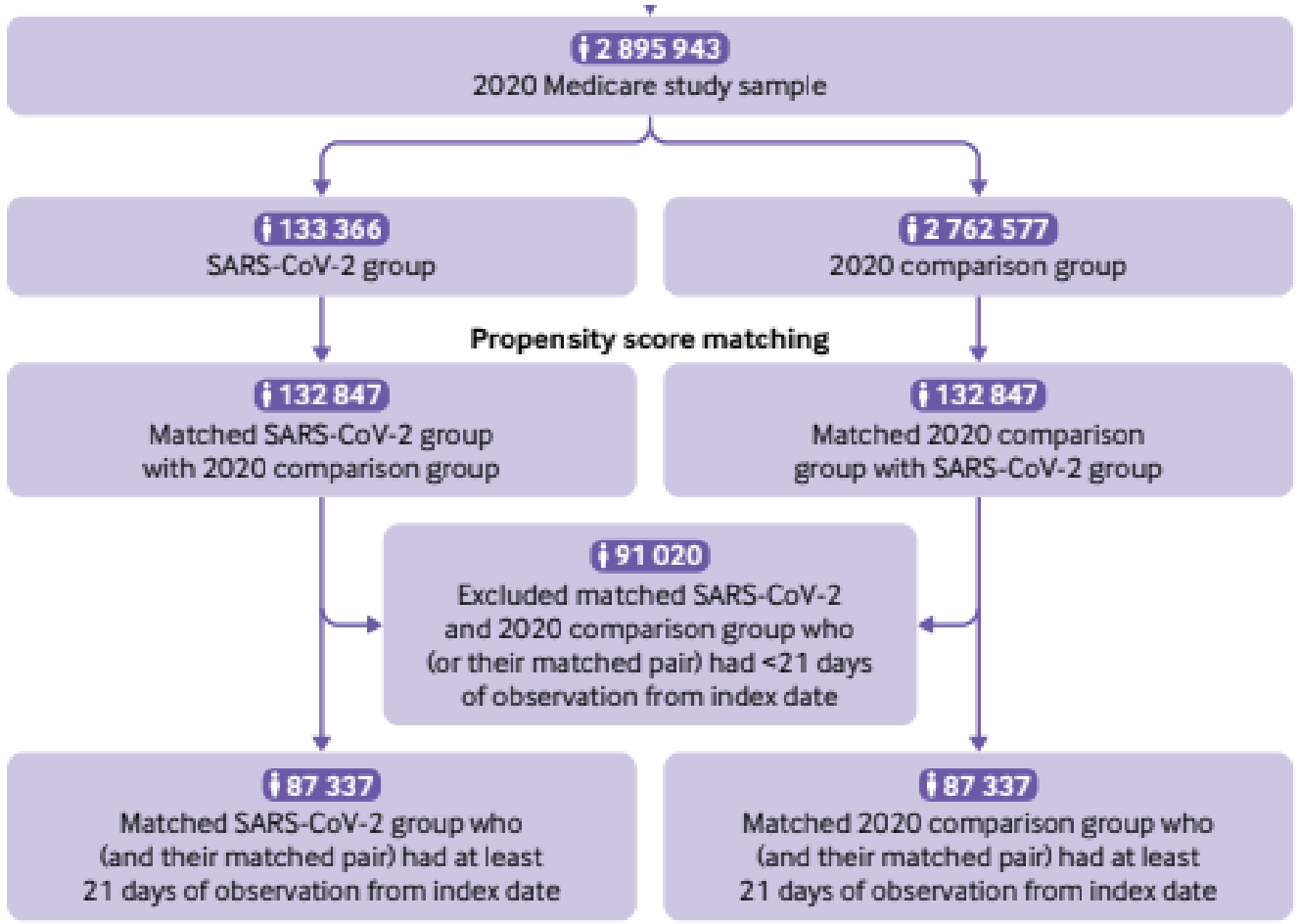


Fig 1 | Flowchart of 2020 cohort sample. PCR=polymerase chain reaction; ICD-10=international classification of diseases, 10th revision

Total No
Median (IQR) No of observation days
Mean (SD) age (years)
Median (IQR) age (years):
65-74
>74
Male sex
SES index:
Mean (SD)
Median (IQR)
Race:
White
Black
Asian
Hispanic
Other
Index month:
Before March
March
April
May
June
July
August
September
October
November
December

Previous comorbidity:
Any comorbidity†
1 comorbidity†
2 comorbiditiest
3 comorbiditiest
4 comorbiditiest
≥5 comorbiditiest
AIDS/HIV
Alcohol abuse
Anemia
Cerebrovascular disease
Chronic pulmonary disease
Coagulopathy
Congestive heart failure
Dementia
Depression
Drug abuse
Fluid and electrolyte disorders
Hypertension
Hypothyroidism
Liver disease
Lymphoma
Metastatic cancer
Moderate to severe liver disease
Myocardial infarction
Obesity
Other neurological disorders
Paralysis
Peptic ulcer disease
Peripheral vascular disease
Psychoses
Pulmonary circulation disorder
Renal failure

Previous conditions:
Alzheimer's dementia
Asthma
Cystic fibrosis
Immunodeficiency
Pulmonary fibrosis
Sickle cell disease
Smoking
Thalassemia
Type 1 diabetes
Type 2 diabetes
Mean (SD) previous inpatient length of stay (days)
Previous primary care physician visit (yes)
Mean (SD) No of previous primary care physician visit days
Previous cardiology visit (yes)
Mean (SD) No of previous cardiology visit days
Previous nephrology visit (yes)
Mean (SD) No of previous nephrology visit days
Region:
South
Midwest
Northeast
West
Unknown
Clinical characteristics‡:
Covid ICU visit (yes)
Covid hospital admission status (yes)
Diagnostic method§:
PCR test positive
Clinical diagnosis (not PCR test)

Results

- All individuals infected with SARS-CoV-2
  - 68% did not have new or persistent diagnoses in the post acute phase that required medical attention
  - 16% had one diagnosis that required medical attention
  - 16% had two or more in the post acute phase that required medical attention
- Among Hospitalized patients
  - 23.6% had at least 1 sequelae

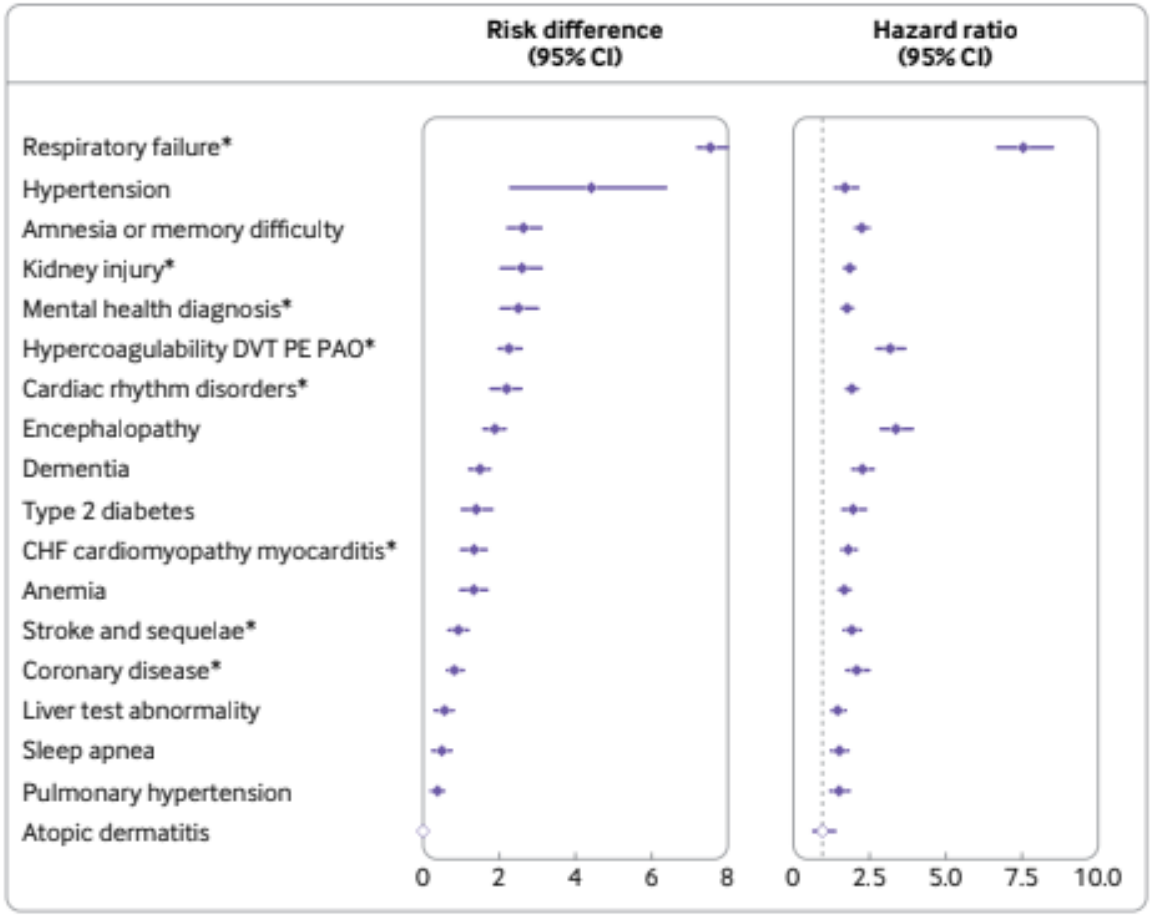


Fig 2 | SARS-CoV-2 group versus 2020 comparison group for risk difference per 100 individuals (left) and hazard ratio (right) for clinical sequelae in post-acute phase. Clinical sequelae are diagnoses with incidence ≥ 1 per 100 in the SARS-CoV-2 group at 120 days after the start of the post-acute phase (index date +21 days) and highest in hierarchy if an aggregate or group diagnosis is noted. This rule was adopted to avoid confidence intervals that were too wide to display. Symptoms are not displayed. eTables 4a-b list all associations for each of the 53 outcomes. Symbols indicate significant risk difference or hazard ratio (Bonferroni corrected P value ≤0.05); atopic dermatitis=negative control. *Aggregate diagnosis includes all subdiagnoses (eTable 1). DVT=deep vein thrombosis; PE=pulmonary embolism; PAO=peripheral arterial occlusion; CHF=congestive heart failure

Key Discussion Points

- Some of the most common sequelae that required medical attention included:
  - Chronic respiratory failure
  - Cardiac rhythm disorders
  - Acute coronary syndromes
  - Hypercoagulability
  - Neurological disorders
- In a population of adults aged ≥65 years after acute infection with the SARS-CoV-2 virus, we found that 32% of individuals were diagnosed as having one or more persistent or new clinical sequelae that required medical attention during the post-acute phase of the illness, 11 percentage points higher than a comparator cohort.

Who gets long COVID?

Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19

Maxime Taquet[1,2]*, **Quentin Dercon**[1], **Sierra Luciano**[3], **John R. Geddes**[1,2], **Masud Husain**[4,5], **Paul J. Harrison**[1,2]

Citation: Taquet M, Dercon Q, Luciano S, Geddes JR, Husain M, Harrison PJ (2021) Incidence, co-occurrence, and evolution of long-COVID features: A 6-month retrospective cohort study of 273,618 survivors of COVID-19. PLoS Med 18(9): e1003773. https://doi.org/10.1371/journal.pmed.1003773

Methods

- Retrospective Cohort Study from EHR (TriNetX Analytics)
- 81 million patients, including 273,618 COVID-19 Survivors
- Looked at incidence at 3 and 6 months after diagnosis
- 9 core features of long-COVID

Breathing difficulty
Fatigue/malaise
Chest/throat pain
Headache
Anxiety/Depression
Abdominal symptoms
Myalgia
Pain
Cognitive Symptoms

Methods

- Matched cohort study
  - Primary Cohort was all patients with a confirmed diagnosis of COVID-19
  - Compared to a matched cohort of influenza patients (negative COVID-19)
- Study Population
  - All patients over 10 who were alive at the end of follow up.
  - January 2020 – December 2020

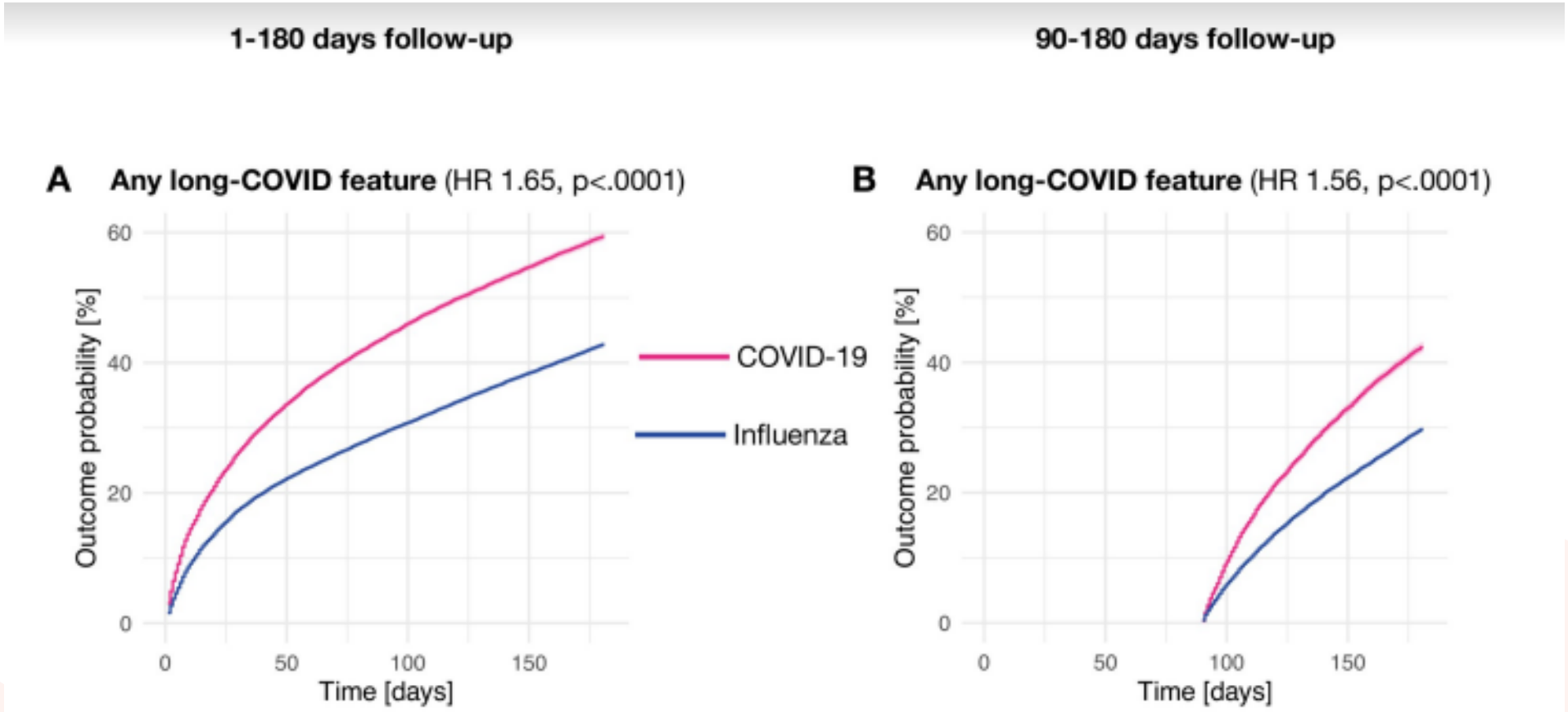
Results

- 273,618 patients with COVID were identified
- 114,449 patients with influenza were available for matching

Table 1. COVID-19 cohort, and for COVID-19 and influenza cohorts after propensity score matching. Only characteristics with a prevalence higher than 5% in the unmatched COVID-19 cohort are presented here; for additional baseline characteristics and outcomes, see Tables A and B in S1 Tables.

	COVID-19 (unmatched)	COVID-19 (matched)	Influenza (matched)
COHORT SIZE	273,618	106,578	106,578
DEMOGRAPHICS			
Age; mean (SD); y	46.3 (19.8)	39.4 (18.4)	38.3 (19.7)
Sex; n (%) female	152,157 (55.6)	62,293 (58.4)	61,419 (57.6)
Race; n (%)			
White	159,028 (58.1)	70,243 (65.9)	70,128 (65.8)
Black or African American	50,329 (18.4)	19,349 (18.2)	18,583 (17.4)
Unknown	54,131 (19.8)	12,565 (11.8)	13,693 (12.8)
Ethnicity; n (%)			
Hispanic or Latino	43,254 (15.8)	9,014 (8.5)	8,944 (8.4)
Not Hispanic of Latino	151,246 (55.3)	72,644 (68.2)	72,075 (67.6)
Unknown	79,118 (28.9)	24,920 (23.4)	25,559 (24.0)
COMORBIDITIES; n (%)			
Overweight and obesity	50,209 (18.4)	19,080 (17.9)	18,182 (17.1)
Hypertensive disease	83,970 (30.7)	28,188 (26.4)	26,189 (24.6)
Type 2 diabetes mellitus	43,127 (15.8)	12,087 (11.3)	11,254 (10.6)
Asthma	29,556 (10.8)	17,097 (16.0)	16,418 (15.4)
Nicotine dependence	20,091 (7.3)	12,602 (11.8)	12,111 (11.4)
Substance misuse	29,240 (10.7)	16,187 (15.2)	15,446 (14.5)
Mood disorders	42,041 (15.4)	19,933 (18.7)	18,916 (17.7)
Anxiety disorders	52,299 (19.1)	25,731 (24.1)	24,302 (22.8)
Ischemic heart diseases	24,980 (9.1)	7,990 (7.5)	7,350 (6.9)
Other forms of heart disease	49,825 (18.2)	16,688 (15.7)	15,654 (14.7)
CKD	18,455 (6.7)	5,310 (5.0)	5,029 (4.7)
Neoplasms (any)	52,535 (19.2)	20,945 (19.7)	19,474 (18.3)

	COVID-19 (unmatched)	COVID-19 (matched)	Influenza (matched)
OUTCOMES, % from 1 day to 6 months post-diagnosis (95% CI)			
Anxiety/Depression	22.82 (22.48–23.14)	26.69 (26.14–27.24)	19.79 (19.47–20.11)
Chest/Throat pain	12.60 (12.34–12.86)	12.80 (12.36–13.22)	7.17 (6.97–7.38)
Abnormal breathing	18.71 (18.41–19.02)	18.43 (17.96–18.90)	9.72 (9.48–9.95)
Myalgia	3.24 (3.09–3.38)	3.67 (3.42–3.91)	2.23 (2.12–2.35)
Fatigue	12.82 (12.56–13.09)	12.59 (12.16–13.03)	6.81 (6.60–7.00)
Headache	8.67 (8.44–8.90)	10.53 (10.14–10.90)	7.98 (7.75–8.19)
Abdominal symptoms	15.58 (15.26–15.87)	17.34 (16.84–17.83)	11.42 (11.16–11.66)
Cognitive symptoms	7.88 (7.69–8.08)	5.56 (5.28–5.85)	3.16 (3.02–3.30)
Pain	11.60 (11.33–11.87)	12.09 (11.67–12.54)	8.34 (8.13–8.56)
Any	57.00 (56.59–57.43)	59.37 (58.72–60.00)	42.77 (42.38–43.16)
OUTCOMES, % from 3 months to 6 months post-diagnosis (95% CI)			
Anxiety/Depression	15.49 (15.21–15.77)	19.24 (18.59–19.90)	14.27 (13.97–14.57)
Chest/Throat pain	5.71 (5.53–5.90)	6.48 (6.08–6.91)	3.79 (3.63–3.96)
Abnormal breathing	7.94 (7.72–8.16)	9.08 (8.62–9.54)	4.69 (4.51–4.87)
Myalgia	1.54 (1.44–1.64)	2.05 (1.82–2.28)	1.27 (1.17–1.36)
Fatigue	5.87 (5.68–6.06)	6.38 (5.99–6.79)	3.73 (3.58–3.89)
Headache	4.63 (4.47–4.80)	6.66 (6.25–7.07)	5.08 (4.89–5.27)
Abdominal symptoms	8.29 (8.06–8.51)	10.69 (10.16–11.22)	6.84 (6.64–7.06)
Cognitive symptoms	3.95 (3.80–4.10)	3.01 (2.74–3.29)	1.83 (1.71–1.94)
Pain	7.19 (6.98–7.39)	8.53 (8.06–9.00)	5.53 (5.33–5.72)


1-180 days follow-up
90-180 days follow-up
A
Any long-COVID feature (HR 1.65, p<.0001)
B
Any long-COVID feature (HR 1.56, p<.0001)
Outcome probability [%]
Time [days]
COVID-19
Influenza
0
20
40
60
0
50
100
150

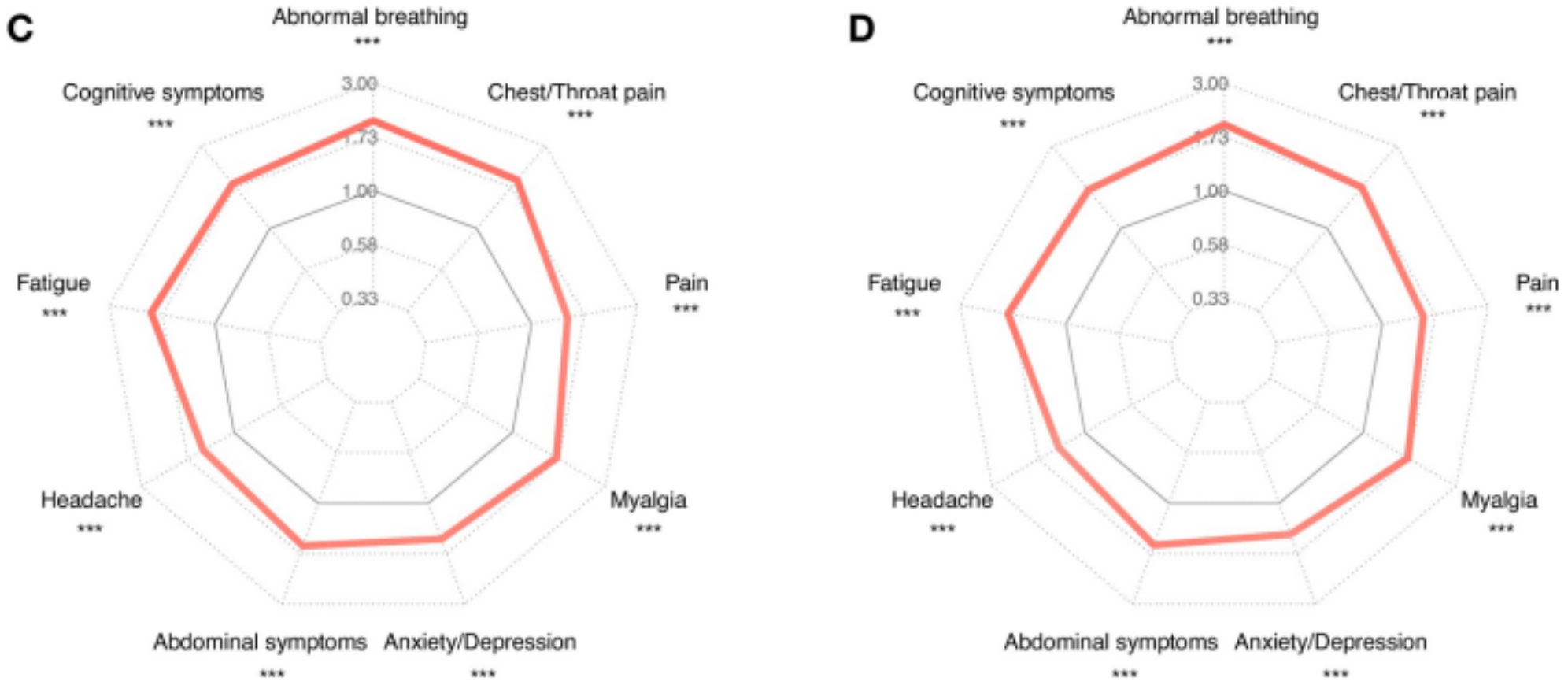
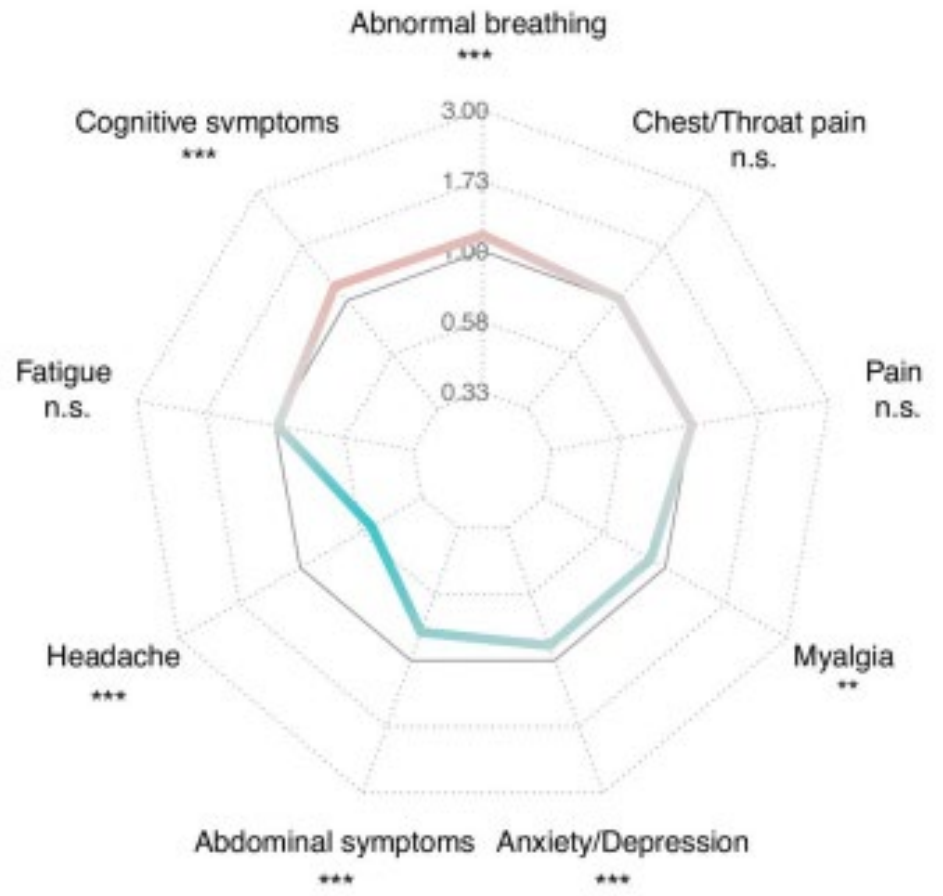
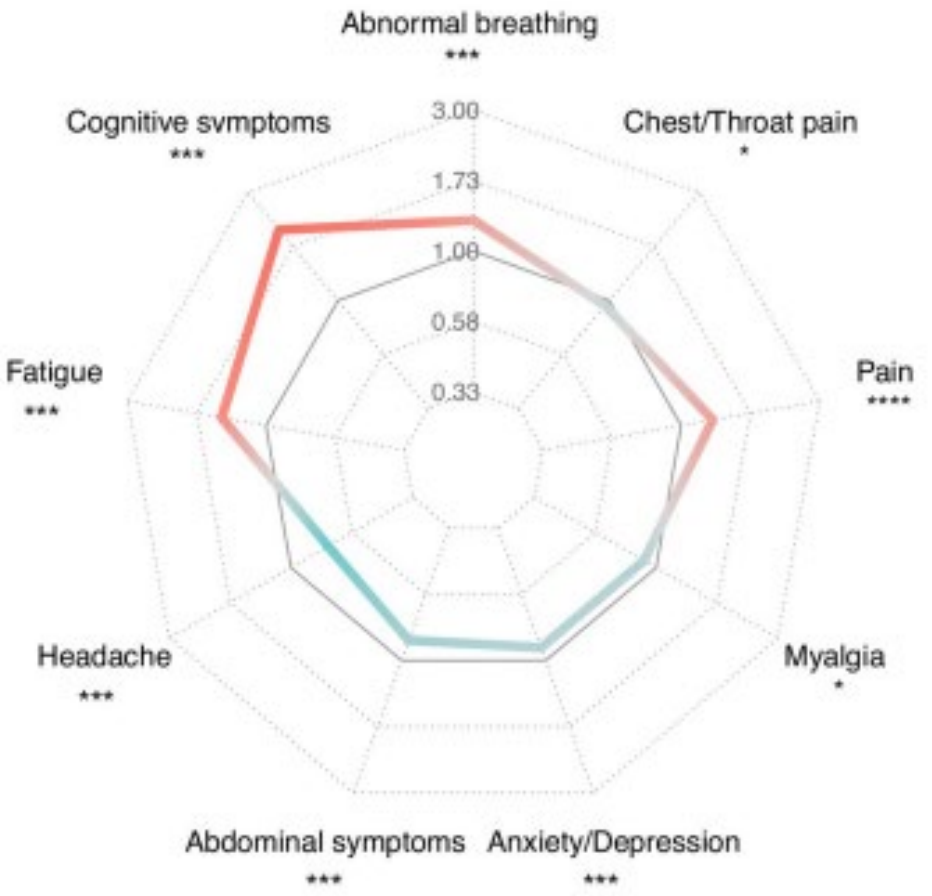


Fig 2. (A, B) Kaplan–Meier curves showing the emergence of long-COVID features over 6 months (A) and specifically over the "long" phase from 3 to 6 months (B) in the cohorts of patients diagnosed with COVID-19 and the matched cohort of patients diagnosed with influenza. (C, D) HRs of individual long-COVID features comparing the cohort of patients with COVID-19 to the matched cohort of patients with influenza. $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. All long-COVID features are more common after COVID-19 than after influenza. For Kaplan–Meier curves of individual long-COVID features, see Fig A in S1 Fig. COVID-19, Coronavirus Disease 2019; HR, hazard ratio.

Male vs Female



Age 45+ vs Age 10–44



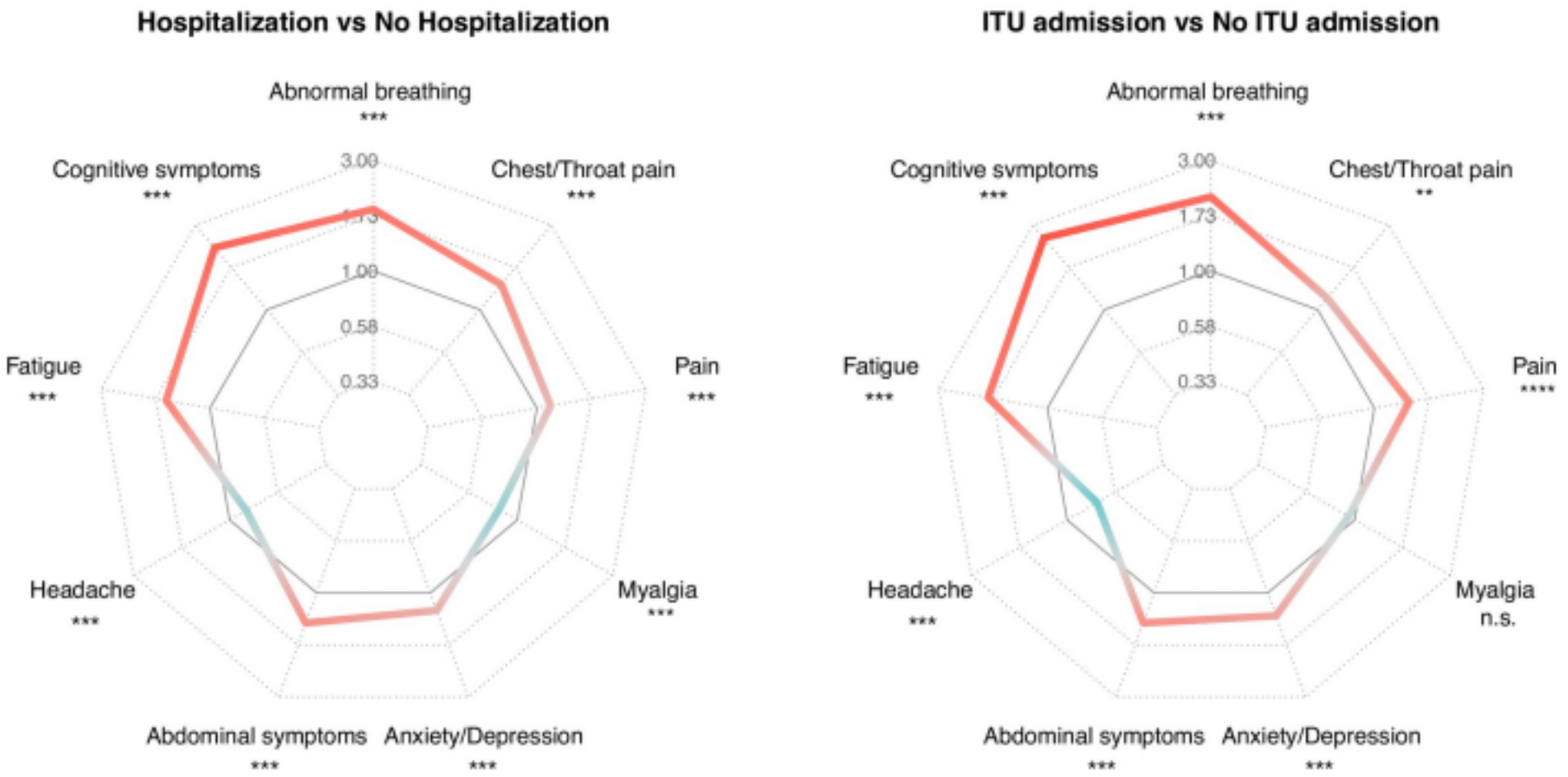


Fig 5. Spider plots summarizing the HRs for each long-COVID feature in subgroups based upon sex, age, and severity of COVID-19 as proxied by requiring hospitalization or ITU admission. HRs are shown comparing the first named group with the second named group. HRs greater than 1 are in red; HRs less than 1 in blue. Significance indicated by asterisks, $^{*}p < 0.05$, $^{**}p < 0.01$, $^{***}p < 0.001$. Each comparison is based on propensity score–matched cohorts; for baseline characteristics, see Tables M-T in S1 Tables). For spider plots of all subgroup analyses, see Fig AE in S1 Fig. COVID-19, Coronavirus Disease 2019; HR, hazard ratio; ITU, intensive treatment unit.

Table V – Comparison in the 6-month incidence of any pain, between patients with COVID-19 and a matched cohort of patients with influenza. Any pain in this analysis refers to the composite endpoint of chest/throat pain, headache, myalgia, other pain (as defined in Supplementary Methods 4) or abdominal and pelvic pain (a subcategory of the abdominal symptoms also defined in Supplementary Methods 4).

Patients with COVID-19	Matched patients with influenza	Comparison	
6-month incidence, % (95% CI)	6-month incidence, % (95% CI)	HR (95% CI)	p-value
34.15 (33.64-34.65)	23.98 (23.67-24.29)	1.53 (1.49-1.56)	< 0.0001

Long covid—mechanisms, risk factors, and management

Harry Crook,[1] Sanara Raza,[1] Joseph Nowell,[1] Megan Young,[1] Paul Edison[1,2]

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http://dx.doi.org/10.1136/bmj.n1648

Table 1 | Summary of studies that have explored the persisting symptoms post-covid-19 infection, or during long covid

Study reference	Number of subjects in study	Hospitalized / non-hospitalized	Study design	Time to assessment (average)	Symptoms (% of patients)	
Carfi A, et al, 2020[15]	143	Hospitalized	Case series	60.3 days after onset	Fatigue (53.1%); dyspnea (43.4%);	joint pain (27.3%); chest pain (21.7%)
Mandal S, et al, 2020[16]	384	Hospitalized	Cross sectional (analytic)	54 days post-hospital discharge	Fatigue (46.6%); cough (28.6%);	breathlessness (56.25%); poor sleep quality (57%)
Halpin SJ, et al, 2020[17]	100	Hospitalized (32 ICU treated, 68 ward treated)	Cross sectional (analytic)	48 days after onset	Fatigue (64%); breathlessness (48%);	neuropsychological (30%); speech and swallow (8%)
Dennis A, et al, 2020[13]	201	Hospitalized: n=37; non-hospitalized: n=164	Cross sectional (analytic)	140 days after onset	Fatigue (98%); muscle ache (87.6%); shortness of breath (87.1%); headache (82.6%); joint pain (78.1%);	fever (75.1%); chest pain (73.6%); sore throat (71.1%); diarrhea (59.2%)
Tenforde MW, et al, 2020[18]	274	Non-hospitalized	Cross sectional (survey)	14-21 days after onset	Fatigue (38%); cough (46%); headache (18%); body ache (20%); loss of taste (28%); loss of smell (27%); diarrhea (14%);	congestion (32%); dyspnea (31%); nausea (13%); sore throat (18%); chest pain (20%); abdominal pain (18%); confusion (20%)
Goertz YMJ, et al, 2020[19]	2113	Hospitalized: n=112; non-hospitalized: n=2001	Cross sectional (survey)	79 days after onset	Fatigue (87%);dyspnea (71%);	chest tightness (44%);cough (29%)
Townsend L, et al, 2020[20]	128	Hospitalized: n=71; non-hospitalized: n=57	Cross sectional (analytic)	72 days after initial symptoms	Fatigue (52.3%)	
Boscolo-Rizzo P, et al, 2020[21]	187	Non-hospitalized	Cross sectional (survey)	28 days after onset	Loss of taste or smell (10.6%)	
Paderno A, et al, 2020[22]	151	Non-hospitalized	Cohort study	30 days after onset	Olfactory dysfunction (17%);	gustatory dysfunction (11%)
Puntmann VO, et al, 2020[23]	100	Hospitalized: n=33; non-hospitalized: n=67	Cohort study	71 days after onset	Cardiac involvement (78%); troponin levels (71%); ongoing myocardial	inflammation (60%); shortness of breath (36%)

What about Long-COVID and Vaccination?

Long Covid after Breakthrough COVID-19: the post-acute sequelae of breakthrough COVID-19

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Methods

- Primary Question: Do people with breakthrough infection experience post-acute sequelae?
- Veterans Health Administration Electronic Medical Record Utilized
- Cohort Construction
  - Breakthrough COVID19
  - COVID19 infection, no prior vaccination
  - Hospitalized with COVID
  - Hospitalized with influenza
  - No history of COVID Test or Flu

Methods

- Looked at a panel of Symptoms
- Time points:
  - 30 days (Acute Phase)
  - 6 months
- Based vaccinated status on CDC guidance (14 days after last shot)

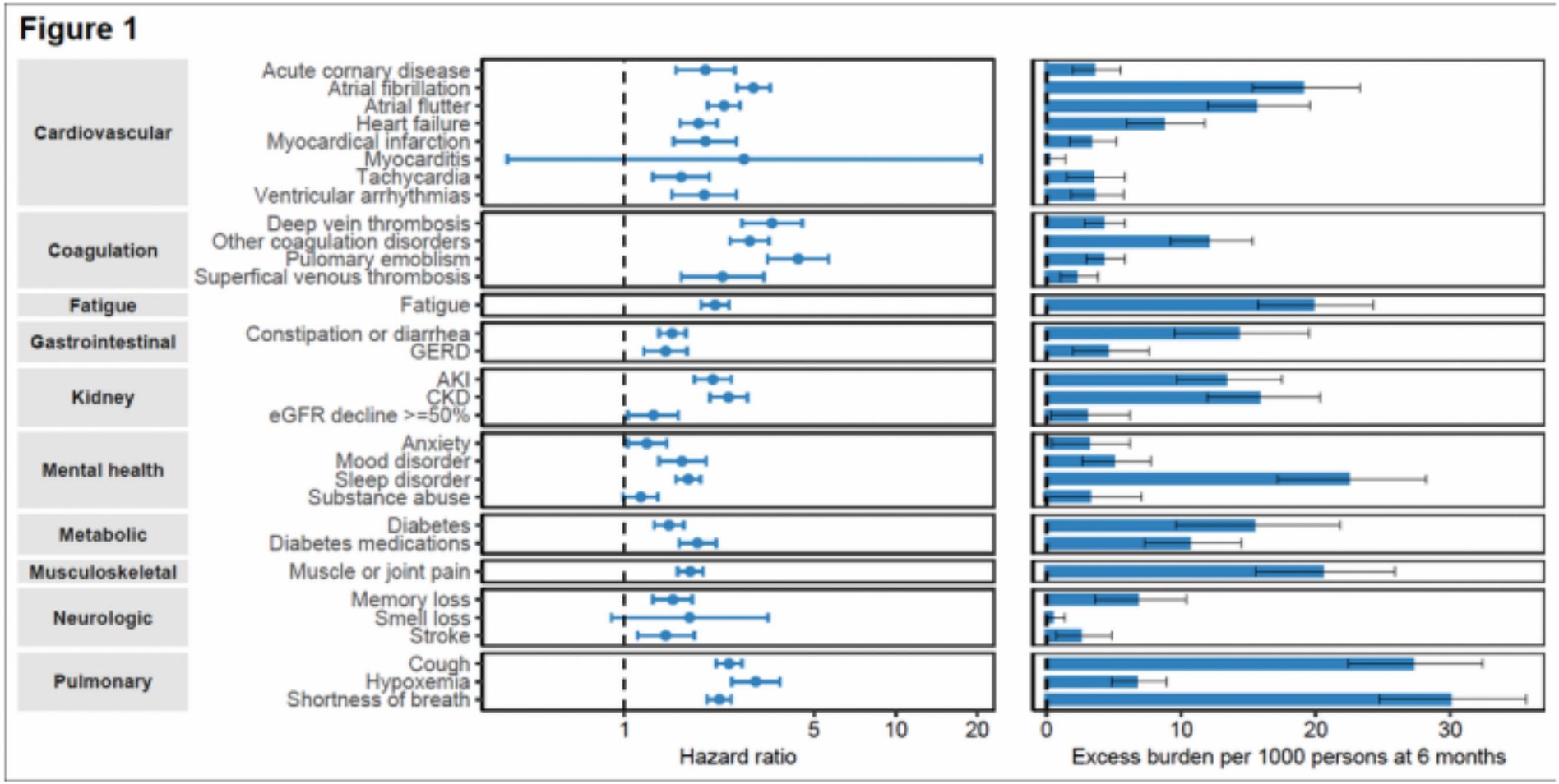


Figure 1

Risk and 6-month excess burden of post-acute sequelae in people with breakthrough COVID-19 compared to the control group. Incident outcomes were assessed from 30 days after the positive COVID-19 test to end of follow-up. All results are in comparison to the control group that consisted of those with no record of a positive COVID-19 test. Adjusted hazard ratios (dots) and 95% confidence intervals (error bars) are presented, as are estimated excess burden (bars) and 95% confidence intervals (error bars). Burdens are presented per 1000 persons at 6 months of follow-up. AKI, acute kidney injury; CKD, chronic kidney disease; GERD, gastroesophageal reflux disease.

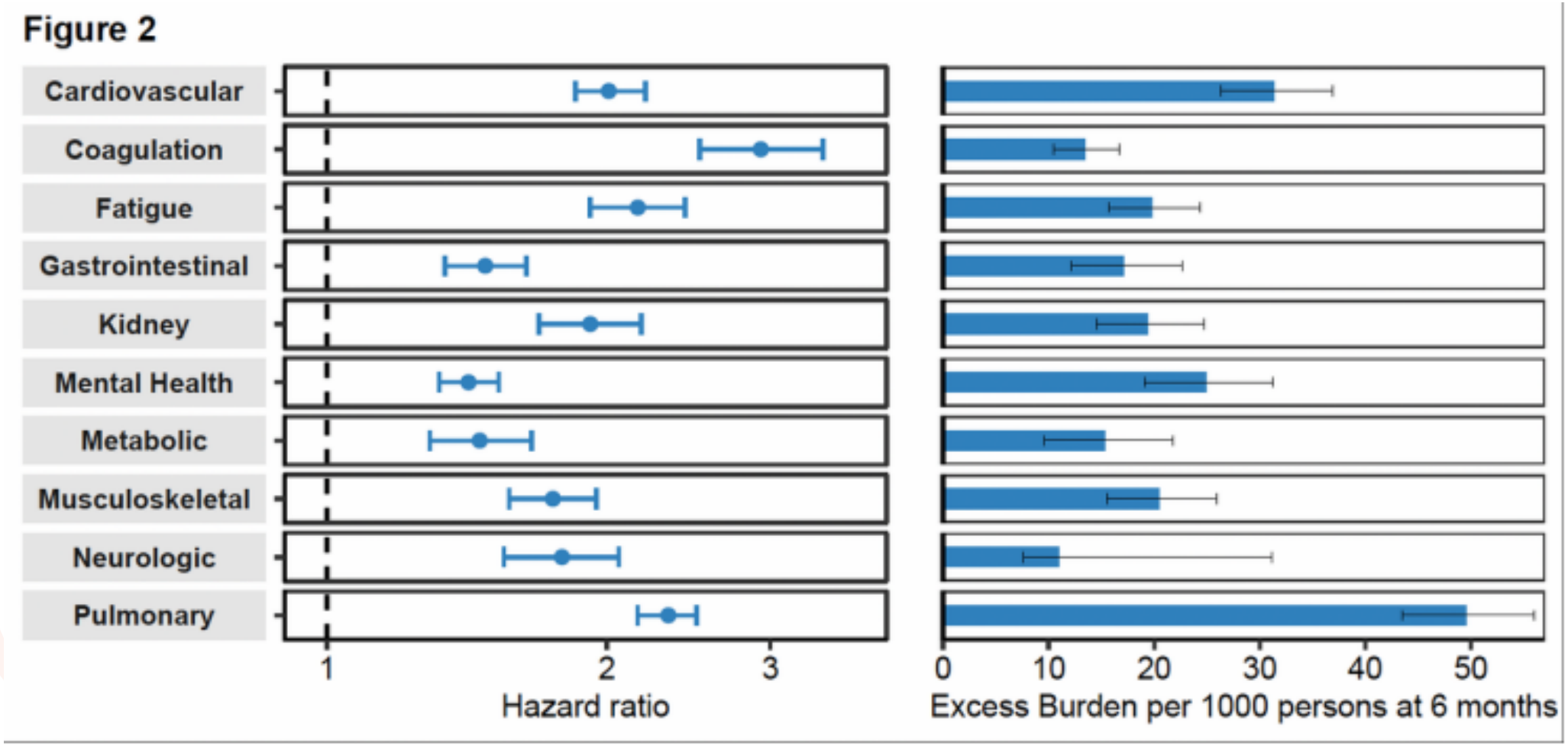


Figure 2

Risk and 6-month excess burden of post-acute sequelae by organ system in people with breakthrough COVID-19 compared to the control group. Incident outcomes were assessed from 30 days after the positive COVID-19 test to end of follow-up. All results are in comparison to the control group that consisted of those with no record of a positive COVID-19 test. Adjusted hazard ratios (dots) and 95% confidence intervals (error bars) are presented, as are estimated excess burden (bars) and 95% confidence intervals (error bars). Burdens are presented per 1000 persons at 6 months of follow-up.

Figure 3

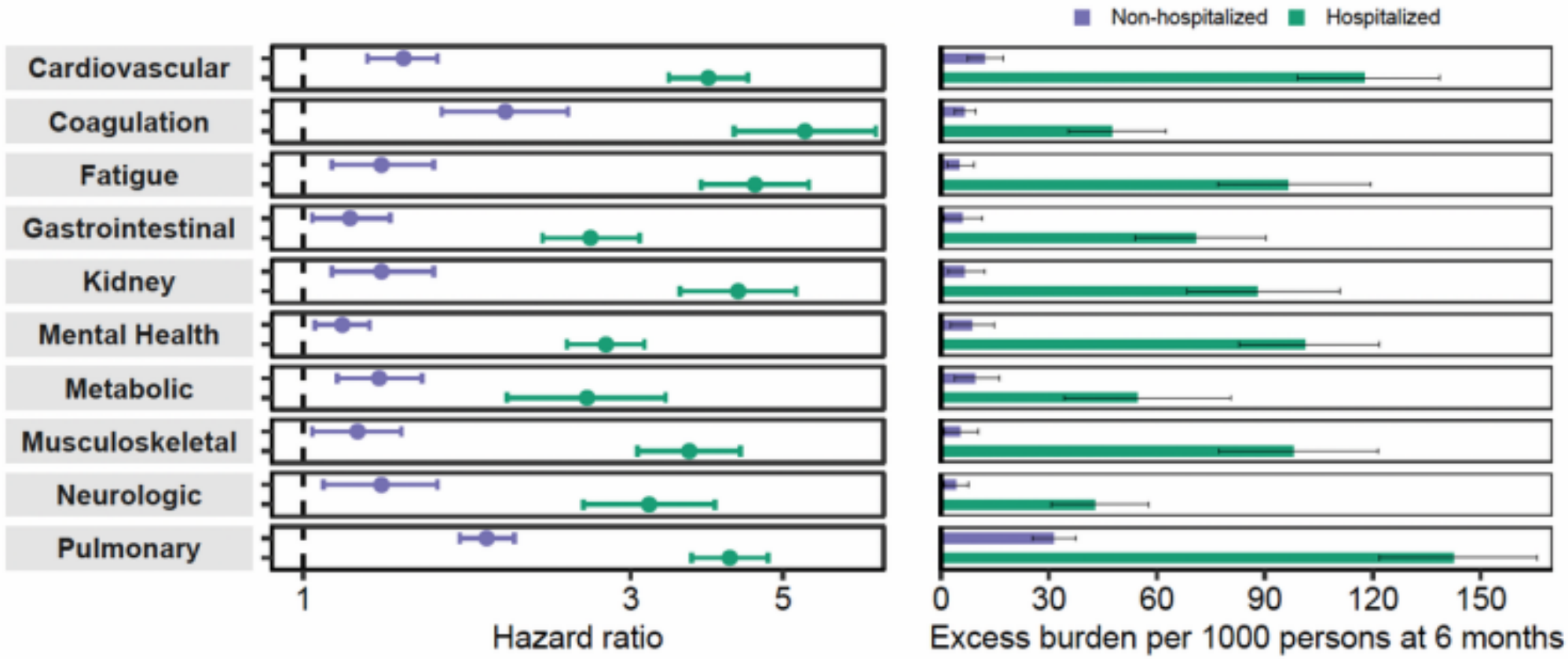


Figure 3

Risk and 6-month excess burden of post-acute sequelae by organ system in those with breakthrough COVID-19 by care setting of the acute phase of the disease. Risk and excess burden were estimated in mutually exclusive groups defined by care setting of breakthrough COVID-19 (not hospitalized and hospitalized) during the acute phase of the disease. Incident outcomes were assessed from 30 days after the positive COVID-19 test to end of follow-up. All results are in comparison to the control group of those with no record of a positive COVID-19 test. Adjusted hazard ratios (dots) and 95% confidence intervals (error bars) are presented, as are estimated excess burden (bars) and 95% confidence intervals (error bars). Burdens are presented per 1000 persons at 6 months of follow-up.

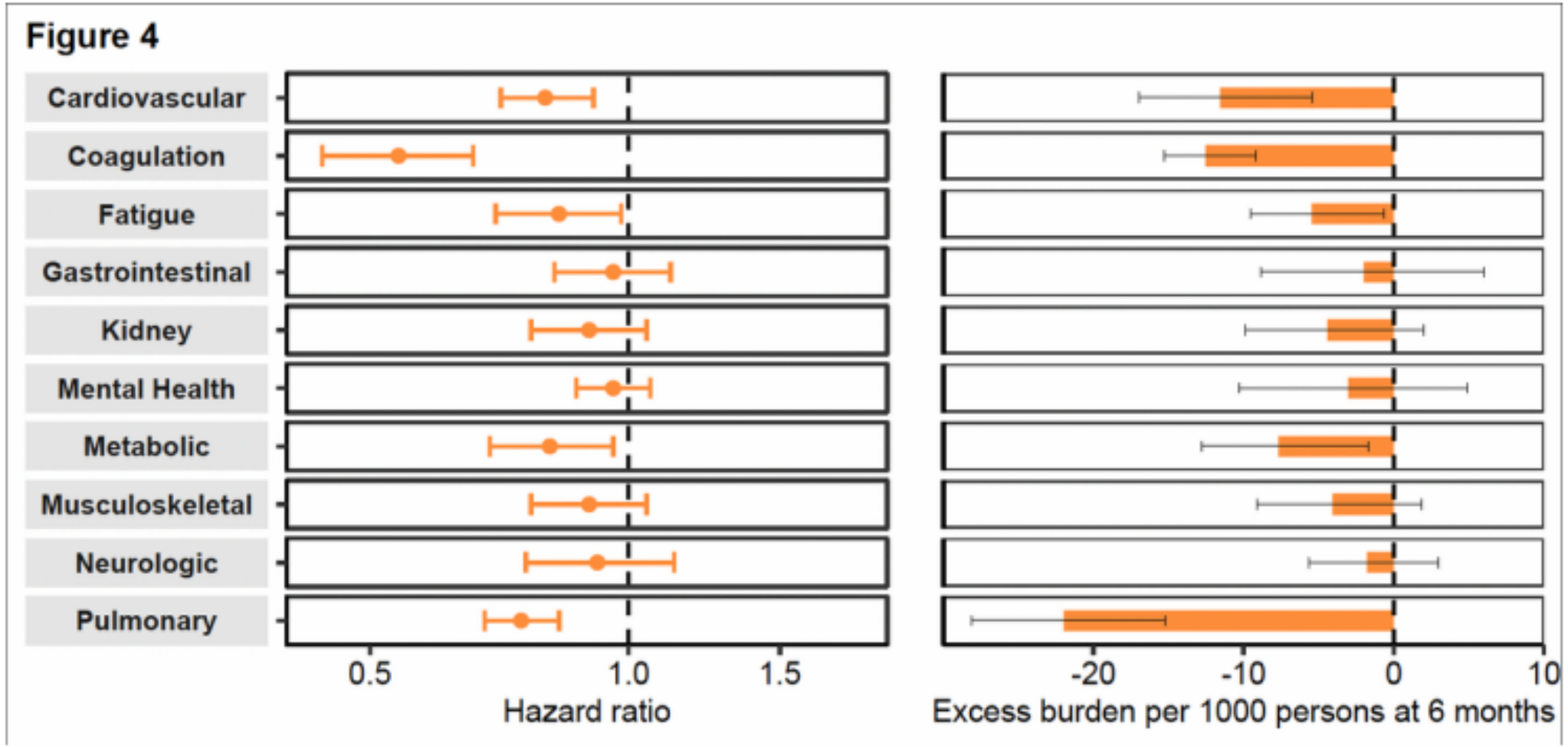
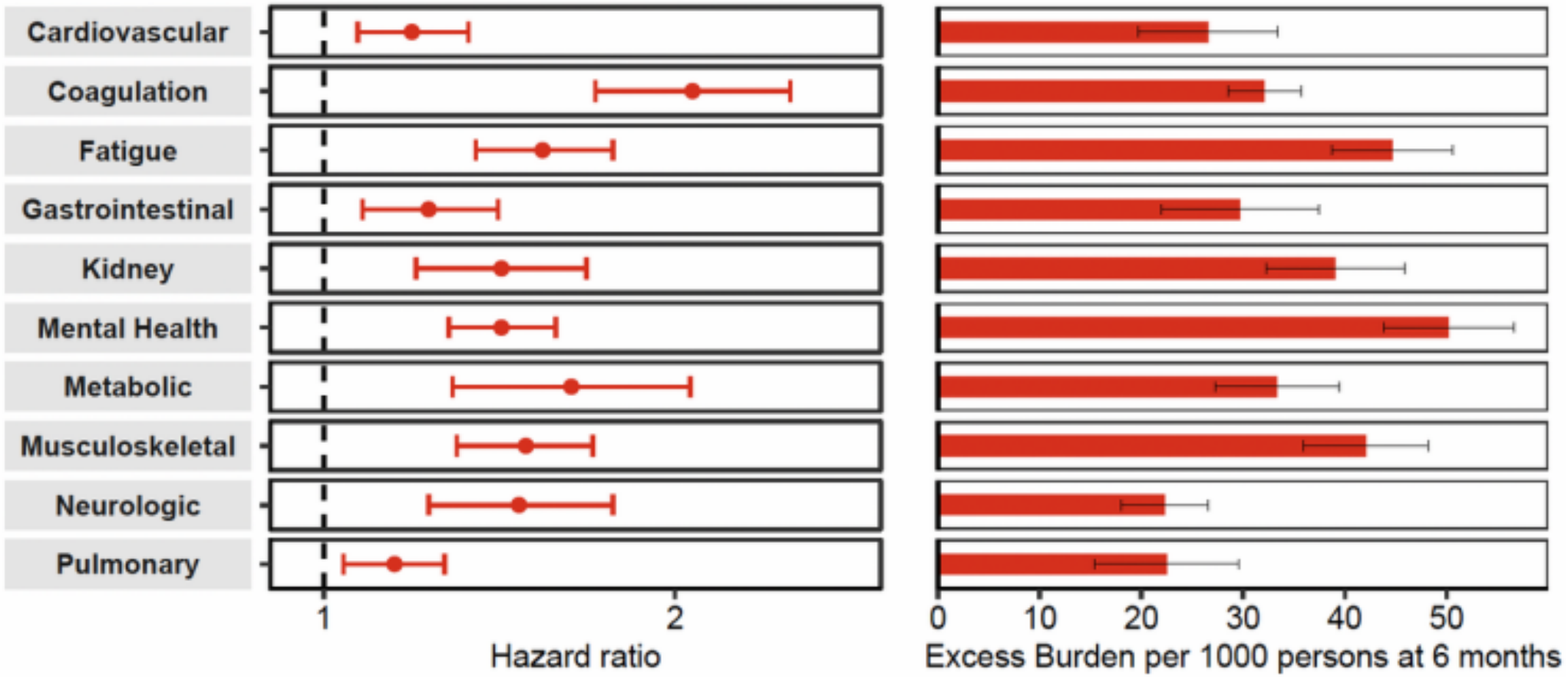


Figure 4

Risk and 6-month excess burden of post-acute sequelae by organ system in people with breakthrough COVID-19 compared to those with COVID-19 without prior vaccination. Incident outcomes were assessed from 30 days after the positive COVID-19 test to end of follow-up. All results are in comparison to those with COVID-19 without prior vaccination. Adjusted hazard ratios (dots) and 95% confidence intervals (error bars) are presented, as are estimated excess burden (bars) and 95% confidence intervals (error bars). Burdens are presented per 1000 persons at 6 months of follow-up.

Figure 5



Risk and 6-month excess burden of post-acute sequelae by organ system in people who were hospitalized during the acute phase of breakthrough COVID-19 compared to those hospitalized with seasonal influenza. Incident outcomes were assessed from 30 days after the positive COVID-19 test to end of follow-up. All results are in comparison to those who were hospitalized with seasonal influenza. Adjusted hazard ratios (dots) and 95% confidence intervals (error bars) are presented, as are estimated excess burden (bars) and 95% confidence intervals (error bars). Burdens are presented per 1000 persons at 6 months of follow-up.

Association between vaccination status and reported incidence of post-acute COVID-19 symptoms in Israel: a cross-sectional study of patients tested between March 2020 and November 2021

Paul Kuodi[1], Yanay Gorelik[1], Hiba Zayyad[1,3], Ofir Wertheim[3], Karine Beiruti Wiegler[2], Kamal Abu Jabal[1,2], Amiel A. Dror[1,4], Saleh Nazzal[3], Daniel Glikman[1,3], Michael Edelstein[1,2]

Methods

- Invited individuals who were PCR positive for SARS-CoV-2 infection at participating hospitals between March 2020 and November 2021 to fill out an online questionnaire

Results

- 951 infected and 2437 uninfected individuals
- Of the infected 637(67%) were vaccinated
- 174 infected individuals were excluded because of not reporting their vaccination status

Table 1. Baseline characteristics of the study population					
	Frequency (n) percent (%)				
Variable**	**All participants**	**Received 1 vaccine dose**	**Received two vaccine doses**	**Unvaccinated**	**p-value**
Demographic characteristics					
Age (n= 951)					**<0.001**
19-35	288 (30.3)	109(32.1)	59 (20.1)	120 (37.9)	
36-60	468 (49.2)	171 (50.3)	135 (45.9)	162 (51.1)	
>60	195 (20.5)	60 (17.6)	100 (34)	35 (11)	
Sex (n=750)					
Male	283 (37.7)	96 (35.4)	100 (42.4)	87 (35.8)	0.206
Female	467 (62.3)	175 (64.6)	136 (57.6)	156 (64.2)	
Ethnic identity (n=469)					
Jewish	325 (69.3)	118 (66.3)	97 (73.5)	110 (69.2)	0.398
Christian/Muslim Arabs/Druze	144 (30.7)	60 (33.7)	35 (26.5)	49 (30.8)	
Residence (n=460)					
City (Over 20,000 inhabitants)	218 (47.4)	76 (43.7)	64 (48.9)	78 (50.3)	0.374
Town (up to 20,000 residents)	67 (14.6)	26 (14.9)	16 (12.2)	25 (16.1)	
Community residence/ Kibbutz*	154 (33.5)	60 (34.5)	48 (36.6)	46 (29.7)	
Others	21 (4.5)	12 (6.9)	3 (2.3)	6 (3.9)	
Education level(n=434)					
Tertiary institution	248 (57.14)	95 (57.23)	78 (62.90)	75 (52.08)	0.563
Vocational Training	81 (18.66)	28 (16.87)	22 (17.74)	31 (21.53)	
High school	93 (21.43)	37 (22.29)	21 (16.94)	35 (24.31)	
Elementary school	12 (2.76)	6 (3.61)	03 (2.42)	03 (2.08)	
Body mass index (n=458)					
Underweight	10 (2.2)	04 (2.3)	02 (1.5)	04 (2.6)	0.585
Normal	165 (36)	63 (36.2)	47 (35.9)	55 (36)	
Overweight	175 (38.2)	58 (33.3)	55 (42)	62 (40.5)	
Obese	108 (23.6)	49 (28.2)	27 (20.6)	32 (20.9)	

Table 1. Baseline characteristics of the study population

	Frequency (n) percent (%)				
Variable**	**All participants**	**Received 1 vaccine dose**	**Received two vaccine doses**	**Unvaccinated**	**p-value**
Demographic characteristics					
Pre-SARS-CoV-2 infection Chronic Conditions (n=951)					
Hypertension	85 (8.9)	28 (8.2)	41 (13.9)	16 (5.1)	0.008
Asthma	34 (3.6)	08 (2.3)	11 (3.7)	15 (4.7)	
Diabetes mellitus	60 (6.3)	24 (7.1)	24 (8.2)	12 (3.8)	
Chronic obstructive pulmonary disease	15 (1.6)	08 (2.3)	01 (0.3)	06 (1.9)	
Hospitalisation (n=951)	85 (8.9)	35 (10.3)	21 (7.1)	29 (9.1)	0.277
COVID-19 symptomatic at SARS-CoV-2 infection (n=951)	636 (66.9)	252 (74.1)	167 (56.8)	217 (68.4)	**<0.001**
Time from beginning of symptoms to responding to the survey (Days)	302 (296)[†]	348.00 (166)[†]	114.50 (340)[†]	246.50 (189)[†]	**0.031**

Table 2. Post COVID-19 symptoms among vaccinated and unvaccinated participants				
	Number and proportion experiencing post COVID symptoms, (n (%))			
Post COVID symptoms	**All participants (n=951)**	**Received 1 vaccine dose (n=340)**	**Received two vaccine doses (n=294)**	**Unvaccinated (n=317)**
Fatigue	208 (21.87)	93 (27.35)	33 (11.22)	82 (25.87)
Headache	190 (19.98)	80 (23.53)	41 (13.95)	69 (21.77)
Weakness in arms or legs	128 (13.46)	57 (16.76)	20 (6.08)	51 (16.09)
Persistent muscle pain	98 (10.30)	45 (13.24)	17 (5.78)	36 (11.36)
Loss of concentration	90 (9.46)	44 (12.94)	13 (4.42)	33 (10.41)
Hair loss	88 (9.25)	43 (12.65)	09 (3.06)	36 (11.36)
Problem sleeping	85 (8.94)	42 (12.35)	14 (4.76)	29 (09.15)
Dizziness	74 (7.78)	30 (8.82)	12 (4.08)	32 (10.09)
Persistent cough	70 (7.36)	26 (7.65)	20 (6.80)	24 (7.57)
Shortness of breath	68 (7.15)	29 (8.53)	14 (4.76)	25 (7.89)
Loss of taste	63 (6.62)	20 (5.88)	15 (5.10)	28 (8.83)
Chest pains	61 (6.41)	24 (7.06)	14 (4.76)	23 (7.26)
Pins and needles	60 (6.31)	31 (9.12)	06 (2.04)	23 (7.26)
Palpitations	57 (5.99)	26 (7.65)	12 (4.08)	19 (5.99)
Depression and anxiety	55 (5.78)	19 (5.59)	17 (5.78)	19 (5.99)
Abdominal pain	54 (5.68)	24 (7.06)	08 (2.72)	22 (6.94)
Problems with balance	52 (5.47)	24 (7.06)	07 (2.38)	21 (6.62)
Inability to control body movement	49 (5.15)	22 (6.47)	09 (3.06)	18 (5.68)
Joint pain or swelling	47 (4.94)	22 (6.47)	05 (1.70)	20 (6.31)
Loss of smell	41 (4.31)	09 (2.65)	09 (3.06)	23 (7.26)
Loss of appetite	40 (4.21)	11 (3.24)	12 (4.08)	17 (5.36)
Pain on breathing	40 (4.21)	16 (4.71)	08 (2.72)	16 (5.05)
Nausea and vomiting	37 (3.89)	11 (3.24)	07 (2.38)	19 (5.99)
Constipation	34 (3.58)	12 (3.53)	08 (2.72)	14 (4.42)
Erectile dysfunction	32 (3.36)	12 (3.53)	08 (2.72)	12 (3.79)
Diarrhoea	31 (3.26)	11 (3.24)	05 (1.70)	15 (4.73)
Double vision	29 (3.05)	17 (5.00)	03 (1.02)	09 (2.84)

Table 2. Post COVID-19 symptoms among vaccinated and unvaccinated participants				
	Number and proportion experiencing post COVID symptoms, (n (%))			
Post COVID symptoms	**All participants (n=951)**	**Received 1 vaccine dose (n=340)**	**Received two vaccine doses (n=294)**	**Unvaccinated (n=317)**
Problems speaking or communicating	28 (2.94)	15 (4.41)	03 (1.02)	10 (3.15)
Weight loss	28 (2.94)	06 (1.76)	08 (2.72)	14 (4.42)
Tremor / shakiness	27 (2.84)	11 (3.24)	08 (2.72)	08 (2.52)
Problems passing urine	16 (1.68)	06 (1.76)	02 (0.68)	08 (2.52)
Loss of sensation, one side of the body	15 (1.58)	07 (2.06)	02 (0.68)	06 (1.89)
Skin lumps or rashes	13 (1.37)	05 (1.47)	02 (0.68)	06 (1.89)
Problems swallowing or chewing	12 (1.26)	05 (1.47)	03 (1.02)	04 (1.26)
Blood clots in veins	12 (1.26)	05 (1.47)	03 (1.02)	04 (1.26)
Kidney problems	12 (1.26)	05 (1.47)	02 (0.68)	05 (1.58)
Fainting / blackouts	10 (1.05)	04 (1.18)	04 (1.36)	02 (0.63)
Seizures / fits	10 (1.05)	04 (1.18)	03 (1.02)	03 (0.95)
Heart attack & stroke	03 (0.32)	02 (1.87)	01 (1.27)	00 (0.00)

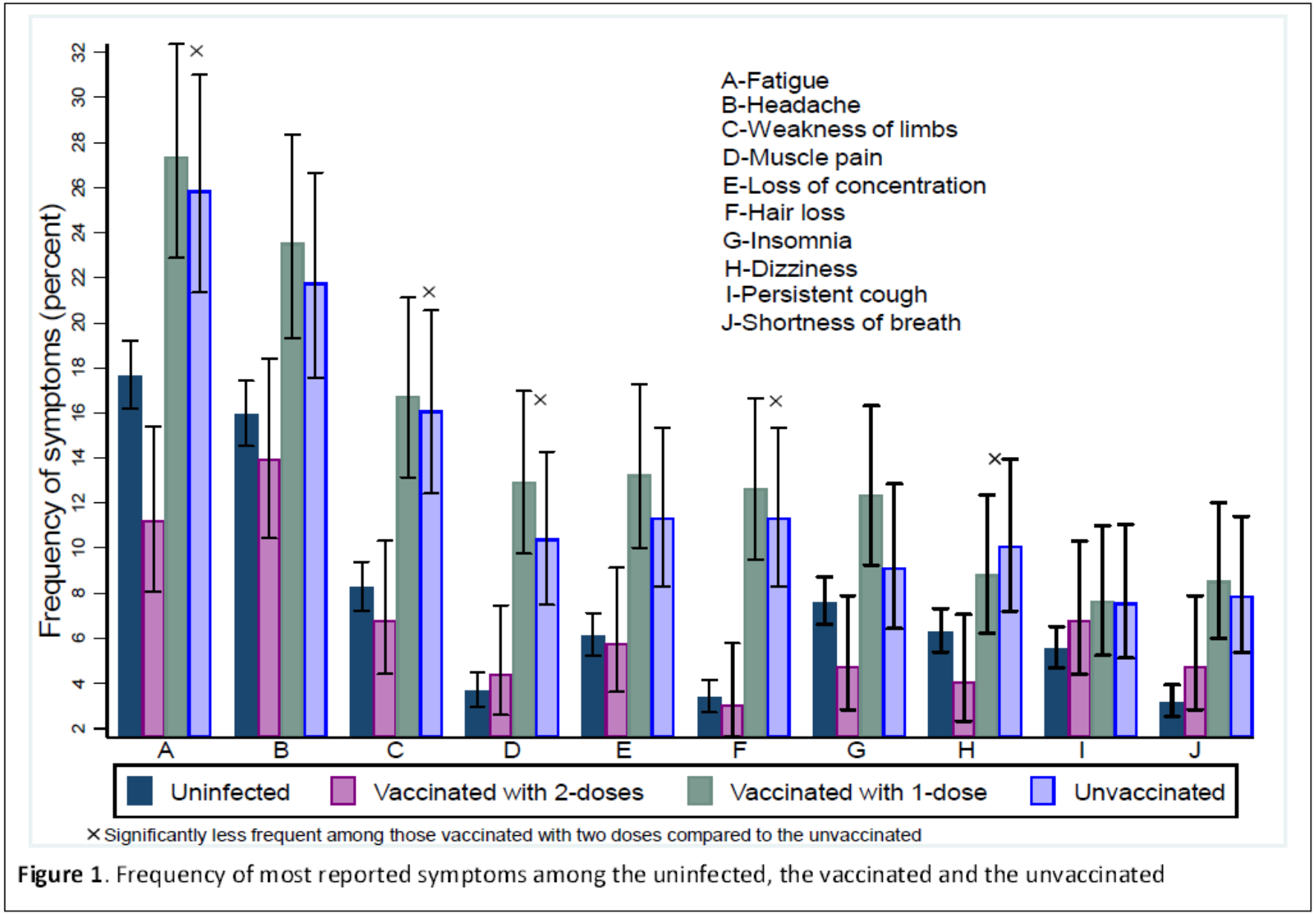


Figure 1. Frequency of most reported symptoms among the uninfected, the vaccinated and the unvaccinated

UK Health Security Agency

The effectiveness of vaccination against long COVID

A rapid evidence briefing

Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study

Michela Antonelli, Rose S Penfold, Jordi Merino, Carole H Sudre, Erika Molteni, Sarah Berry, Liane S Canas, Mark S Graham, Kerstin Klaser, Marc Modat, Benjamin Murray, Eric Kerfoot, Liyuan Chen, Jie Deng, Marc F Österdahl, Nathan J Cheetham, David A Drew, Long H Nguyen, Joan Capdevila Pujol, Christina Hu, Somesh Selvachandran, Lorenzo Polidori, Anna May, Jonathan Wolf, Andrew T Chan, Alexander Hammers, Emma L Duncan, Tim D Spector, Sebastien Ourselin, Claire J Steves**

Findings

Fully vaccinated participants were about half as likely to have symptoms lasting ≥28 days than unvaccinated participants (odds ratio [OR] = 0.51, 95% CI: 0.32 to 0.82, p=0.005), whereas partially vaccinated participants were about as likely to have symptoms lasting ≥28 days than unvaccinated participants (OR = 1.04, 95% CI: 0.86 to 1.25, p=0.69).

Fully vaccinated younger adults (18 to 59 years) were much less likely to have symptoms lasting ≥28 days than younger unvaccinated adults (OR = 0.21, 95% CI: 0.08 to 0.59, p=0.003).

Prevalence, characteristics, and predictors of Long COVID among diagnosed cases of COVID-19

M. C. Arjun, Arvind Kumar Singh, Debkumar Pal, Kajal Das, Alekhya Gajjala, Mahalingam Venkateshan, Baijayantimala Mishra, Binod Kumar Patro, Prasanta Raghab Mohapatra, Sonu Hangma Subba

doi: https://doi.org/10.1101/2022.01.04.21268536

Findings

- Note: subjects were vaccinated with Covaxin
- Fully vaccinated participants were more likely to have long COVID symptoms 4weeks from the date of diagnosis than unvaccinated participants (OR = 2.32,95% CI: 1.17 to 4.58, p=0.01).
- These results are in the opposite direction to all other studies

COVID-19 Vaccine (Whole Virion Inactivated Corona Virus vaccine), BBV152, COVAXIN®

EUL holder: Bharat Biotech International Limited

The COVID-19 Vaccine COVAXIN® (BBV152) is a whole virion inactivated SARS-CoV-2 based vaccine against coronavirus disease 2019 (COVID-19). It stimulates the body's immune system without risk of causing disease: once inactivated viruses get presented to the body's immune system, they stimulate the production of antibodies and make the body ready to respond to an infection with live SARS-CoV-2. This vaccine contains aluminum-based adjuvant to enhance the response of the immune system, and the preservative 2-phenoxyethanol to secure microbial stability of the vaccine.

EFFECT OF FULL VACCINATION AND POST-COVID OLFACTORY DYSFUNCTION IN RECOVERED COVID-19 PATIENT. A RETROSPECTIVE LONGITUDINAL STUDY WITH PROPENSITY MATCHING.

Bumi Herman[1,2], Pramon Viwattanakulvanid[1], Azhar Dzulhadj[3], Aye Chan Oo[1], Karina Patricia[4], Sathirakorn Pongpanich[1]

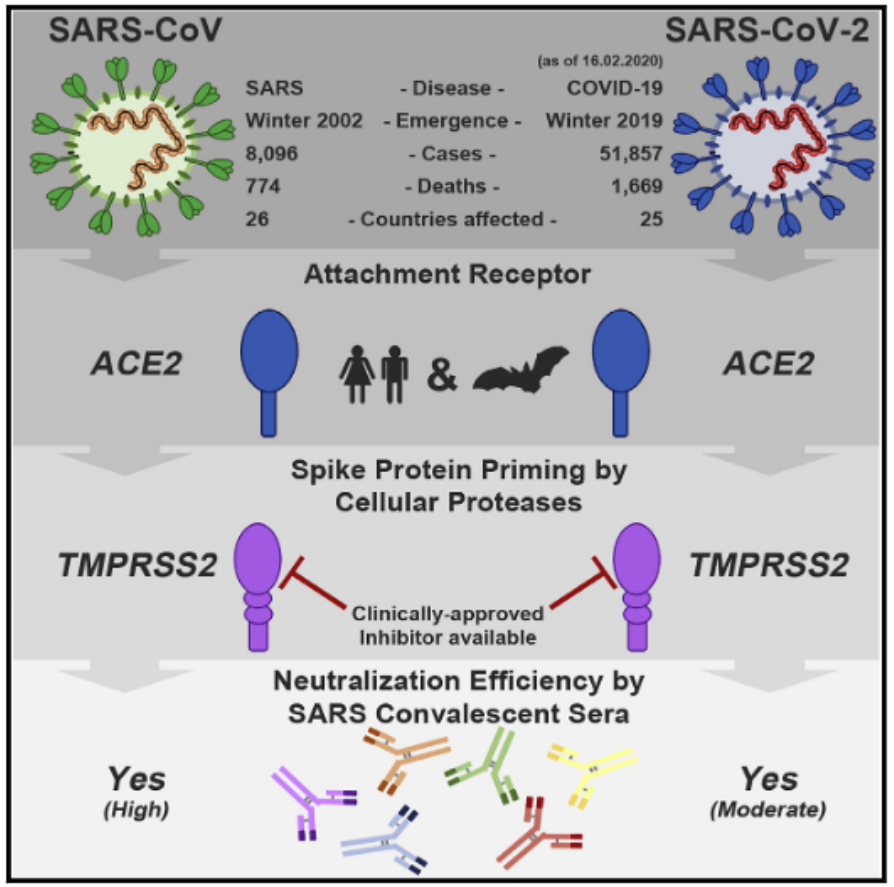
Findings

- While fully vaccinated participants were less likely to develop olfactory dysfunction after infection than unvaccinated participants (OR = 0.31, 95% CI:0.10 to 0.94), there was little evidence for an association between full vaccination and olfactory dysfunction 4 weeks after the end of infection (p=0.59)

Pathophysiology of Long COVID

SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor

Graphical Abstract



Authors

Markus Hoffmann, Hannah Kleine-Weber, Simon Schroeder, ..., Marcel A. Müller, Christian Drosten, Stefan Pöhlmann

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In Brief

The emerging SARS-coronavirus 2 (SARS-CoV-2) threatens public health. Hoffmann and coworkers show that SARS-CoV-2 infection depends on the host cell factors ACE2 and TMPRSS2 and can be blocked by a clinically proven protease inhibitor. These findings might help to establish options for prevention and treatment.

SARS-CoV-2: Olfaction, Brain Infection, and the Urgent Need for Clinical Samples Allowing Earlier Virus Detection

Rafal Butowt* and Katarzyna Bilinska

Cite this: *ACS Chem. Neurosci.* 2020, 11, 9, 1200–1203
Publication Date: April 13, 2020
https://doi.org/10.1021/acschemneuro.0c00172

Figure 1

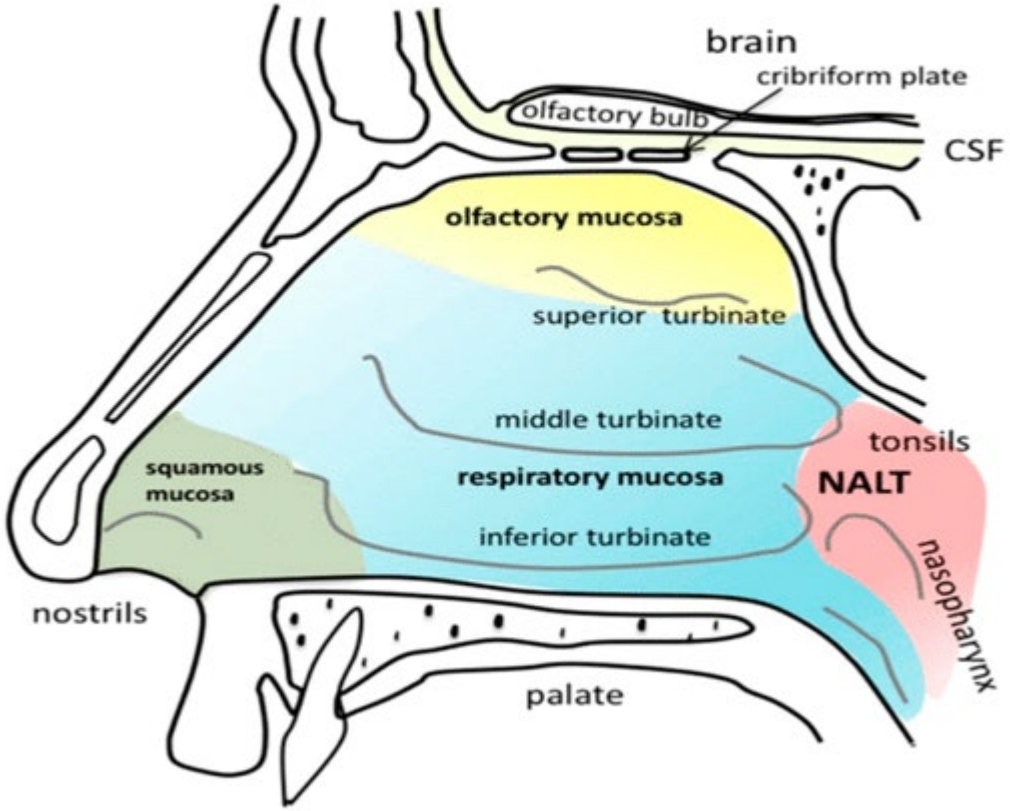


Table 1. ACE2 and TMPRSS2 Expression in Human and Mouse Nasal Cavity Epithelia[a]

nasal cavity	hACE2	hTMPRSS2	mACE2	mTMPRSS2	database
respiratory epithelium	+	+	+	ND	Bgee, GEO
olfactory epithelium	+	ND	+	+	Bgee, GEO
olfactory receptor neurons	ND	ND	− or low	+	Bgee, GEO

[a]Data based on Affymetrix and RNAseq. hACE2, human ACE2; hTMPRSS2, human TMPRSS2; mACE2, mouse ACE2; mTMPRSS2, mouse TMPRSS2. +, positive expression; ND, no data available. Note that olfactory receptor neurons are major part of OE; however, OE also contains several types of non-neuronal cells.

Theories on Anosmia Pathogenesis

- Nasal obstruction through congestion and rhinorrhea
  - Many patients do not have rhinorrhea
  - No significant mucosal swelling of the nasal cleft on imaging
- Direct infection of olfactory receptor neurons leading to cell death
  - Time course of cellular regeneration not consistent
  - No expression of viral entry proteins on ON
  - Absence of virus in ON in vitro

Theories on Anosmia Continued

- Viral infiltration the brain, causing damage to the olfactory center (olfactory bulb and cortex)?
  - No viral replication noted in the olfactory receptor neuros or olfactory bulb neurons
  - No evidence the virus can reach the brain through the olfactory route
- Does the virus damage support cells in the olfactory epithelium?
  - Prevailing theory

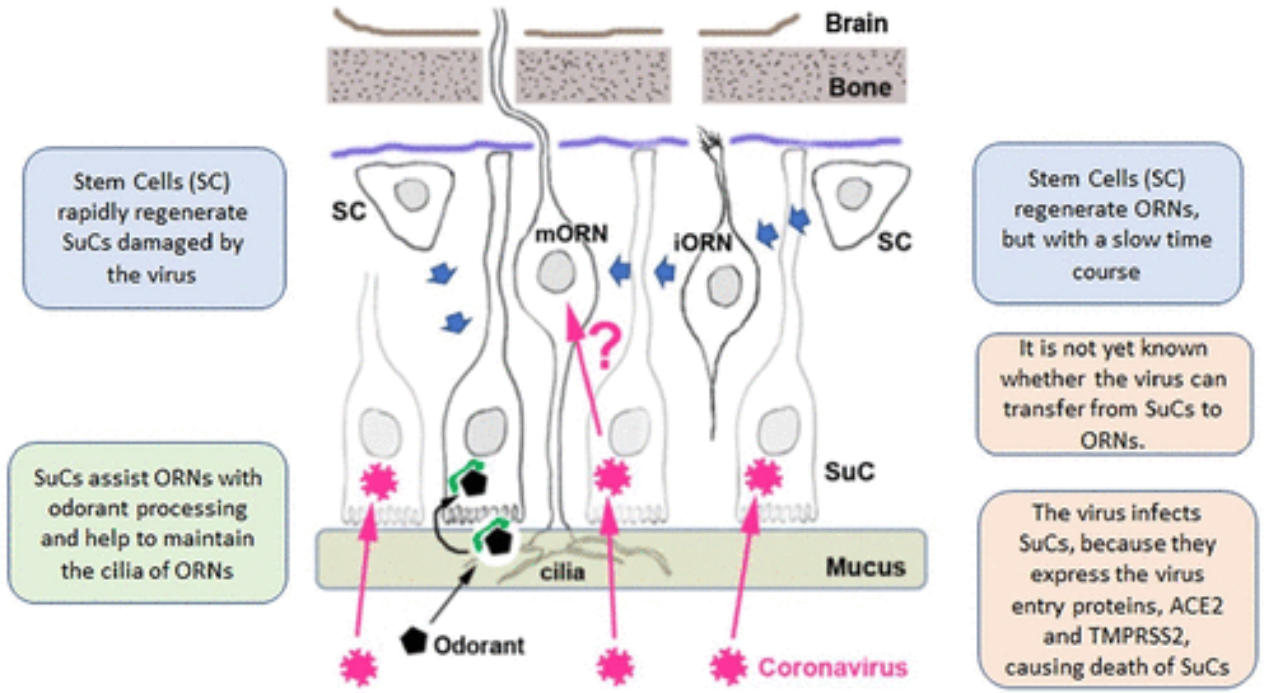


Figure 4. Entry of the SARS-CoV-2 virus in the olfactory epithelium and the virus' predicted effects that may explain the anosmia in COVID-19 patients. Coronavirus enters (pink arrows) and accumulates in the sustentacular cells (SuC) which abundantly express ACE2 and TMPRSS2 proteins, the entry proteins of the virus. SuCs normally partake in the processing of the odorants by endocytosing the odorant-binding protein complex (green-black symbol), by detoxifying, by maintaining the cilia of mature olfactory receptor neurons (mORN), and by maintaining epithelial integrity. Olfactory sensation is impaired when these essential SuC functions are disrupted. It is unknown whether the virus may transfer from SuC to mature olfactory receptor neurons (mORN) which lack ACE2 and TMPRSS2 proteins (Table 2), but have axons extending to the brain. Both the SuC and mORN can be replaced by stem cells (SC —blue arrows), although SuC replacement is much faster than replacement of mORN where SC first generates immature ORN (iORN) whose axons have to grow through the bone to the brain.

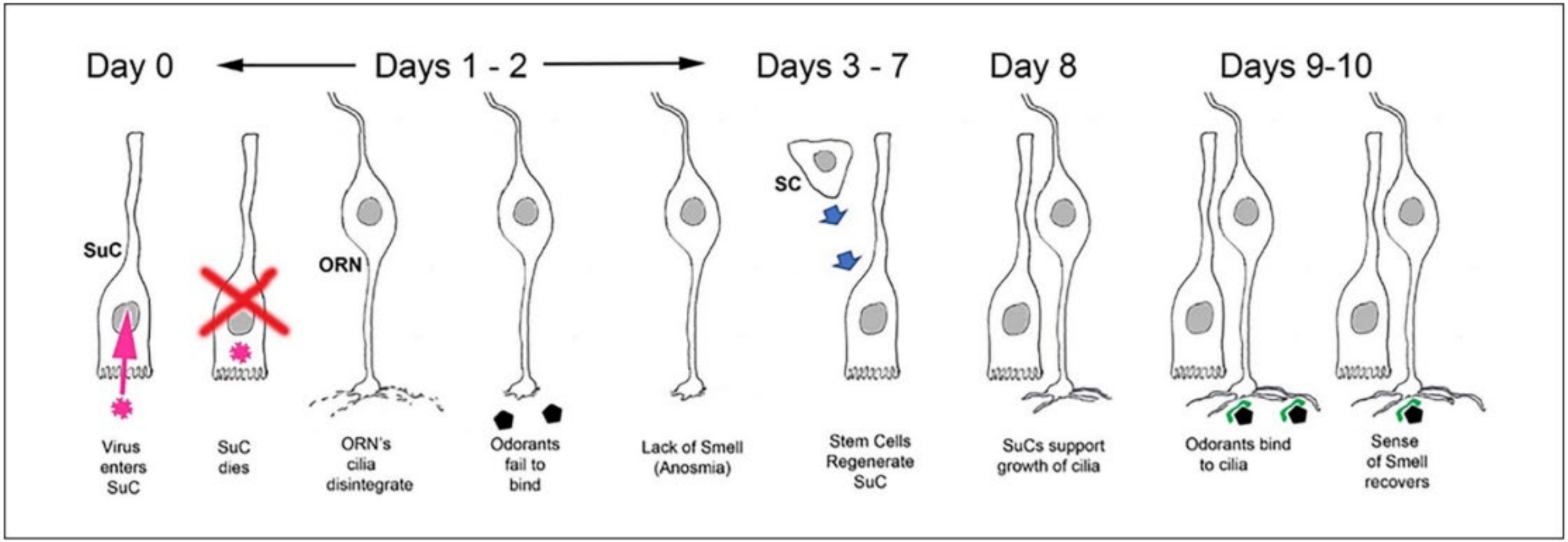


Figure 5. Time course of cellular events that may cause loss of smell and its recovery in COVID-19 patients. Day 0 = day of infection. Symbols and abbreviations are the same as explained in Figures 3 and 4. SuC, sustentacular cell; ORN, olfactory receptor neuron; SC, stem cell.

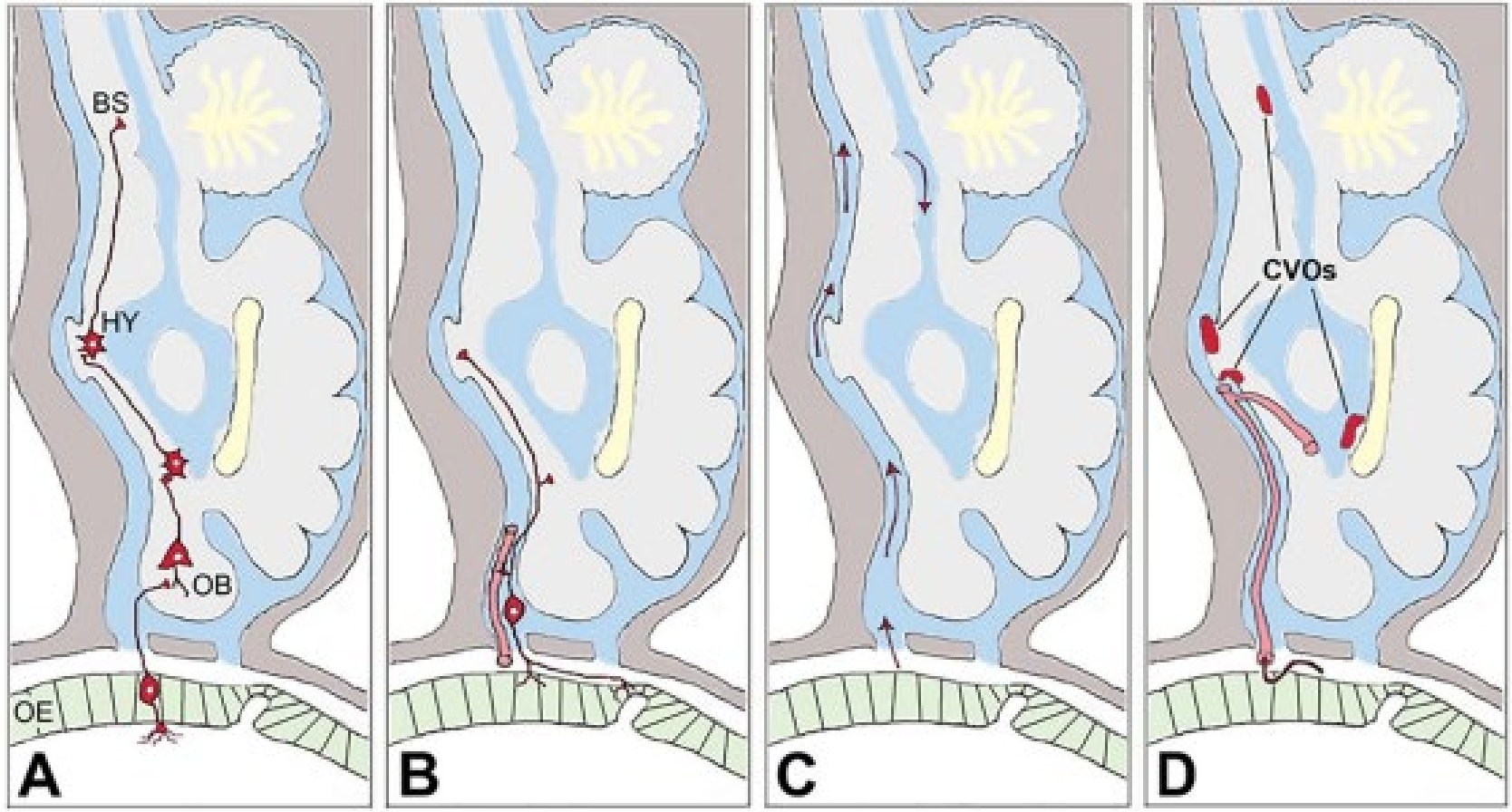
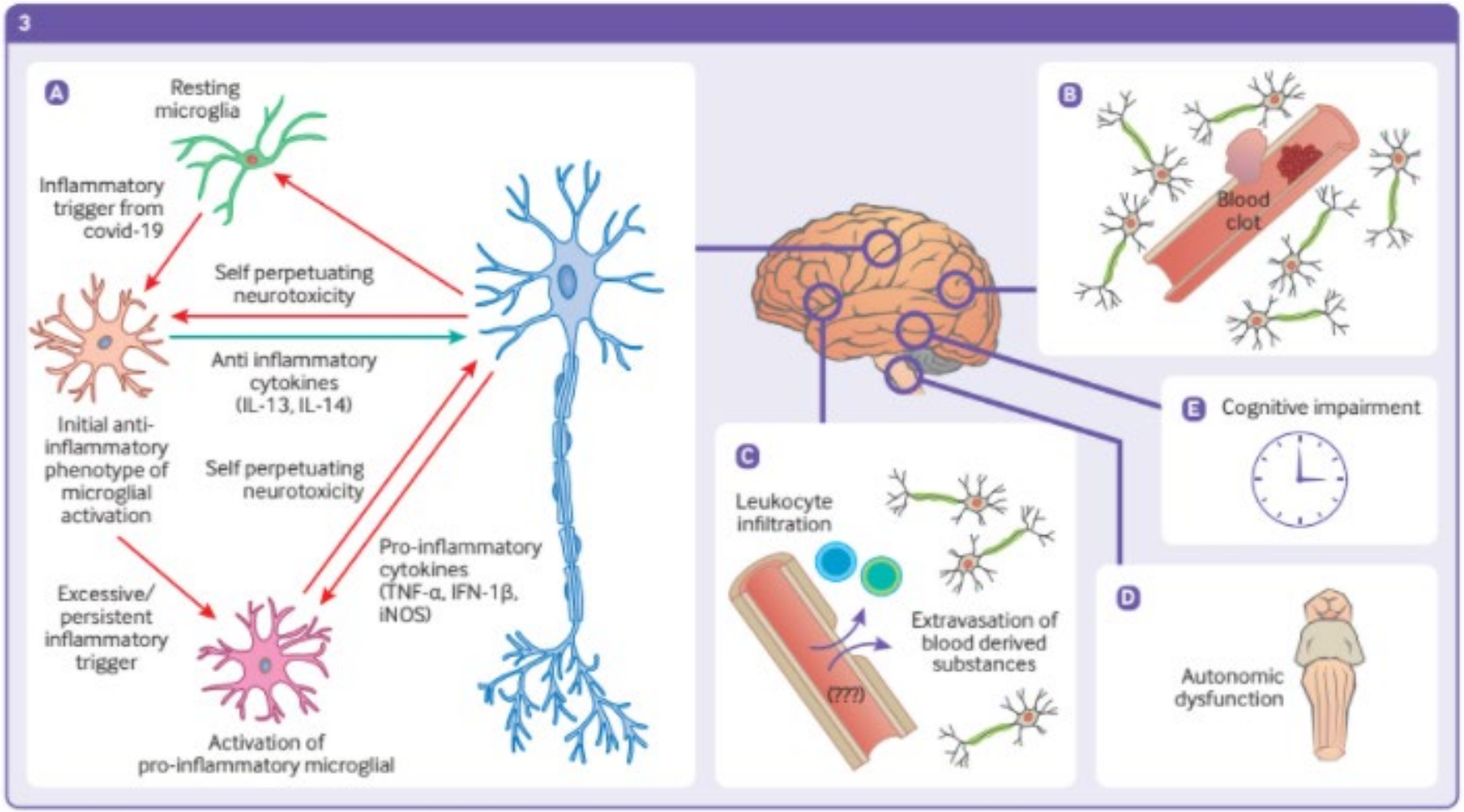
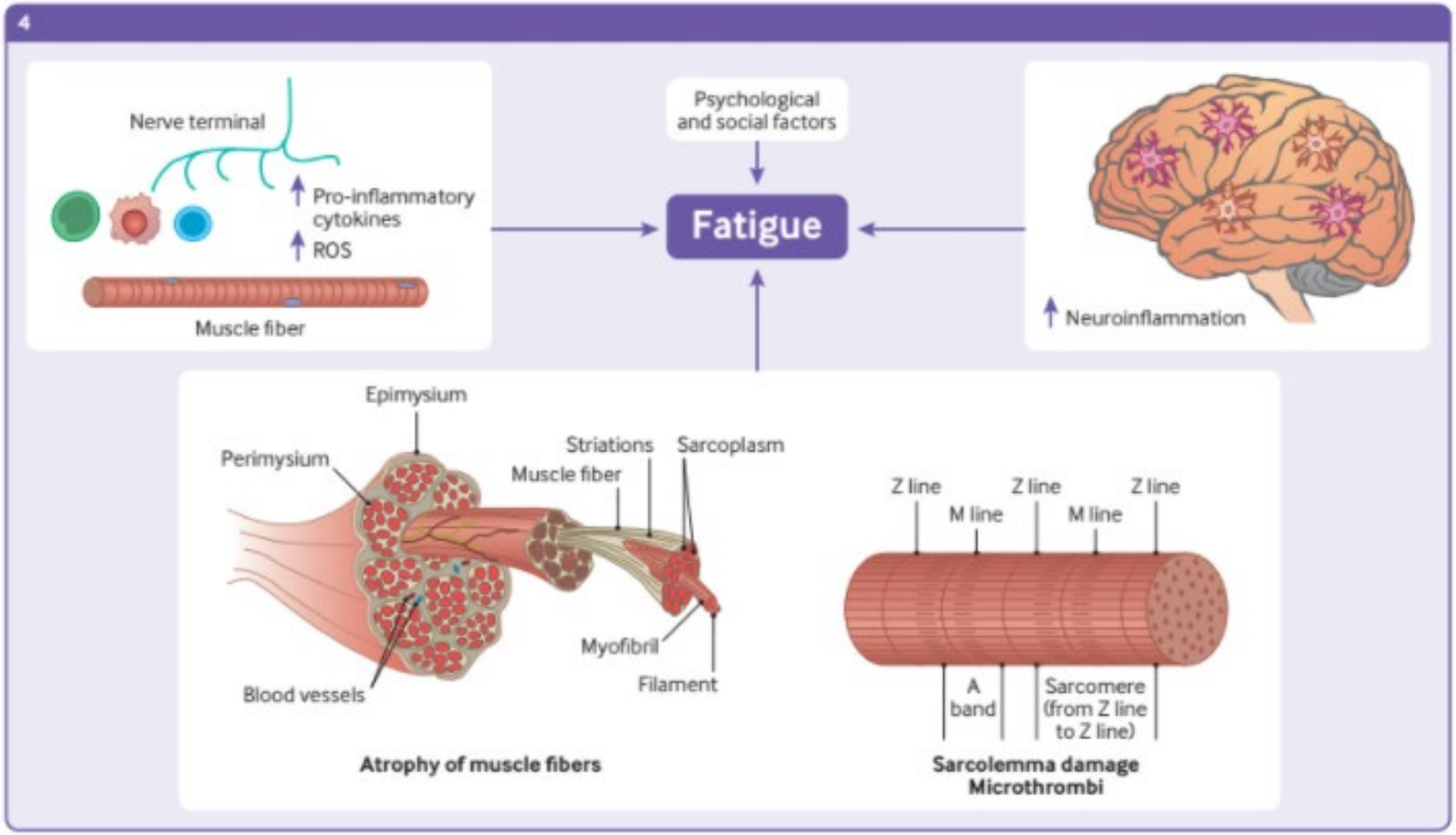


Figure 6. Four potential routes of SARS-CoV-2 virus from the nose to the brain through the cribriform plate. (A) Olfactory circuits. (B) Nervus terminalis. (C) Cerebrospinal fluid. (D) Vasculature. BS, brainstem; CVOs, circumventricular organs; HY, hypothalamus; OB, olfactory bulb; OE, olfactory epithelium.

Neurocognitive Long COVID




4
Nerve terminal
Pro-inflammatory cytokines
ROS
Muscle fiber
Psychological and social factors
Fatigue
Neuroinflammation
Epimysium
Perimysium
Striations
Sarcoplasm
Muscle fiber
Myofibril
Filament
Blood vessels
Atrophy of muscle fibers
Z line
M line
Z line
M line
Z line
A band
Sarcomere (from Z line to Z line)
Sarcolemma damage
Microthrombi

Confounding Factors

- Critical illness, ARDS, and long term vent support are known to have detrimental effects on long term cognition
- Psychosocial factors and prolonged isolation due to infection control precautions may also be exacerbating symptoms

Long COVID and DM2

COVID-19 and diabetes mellitus: from pathophysiology to clinical management

Soo Lim[1,5]✉, Jae Hyun Bae[2,5], Hyuk-Sang Kwon[3] and Michael A. Nauck[4]✉

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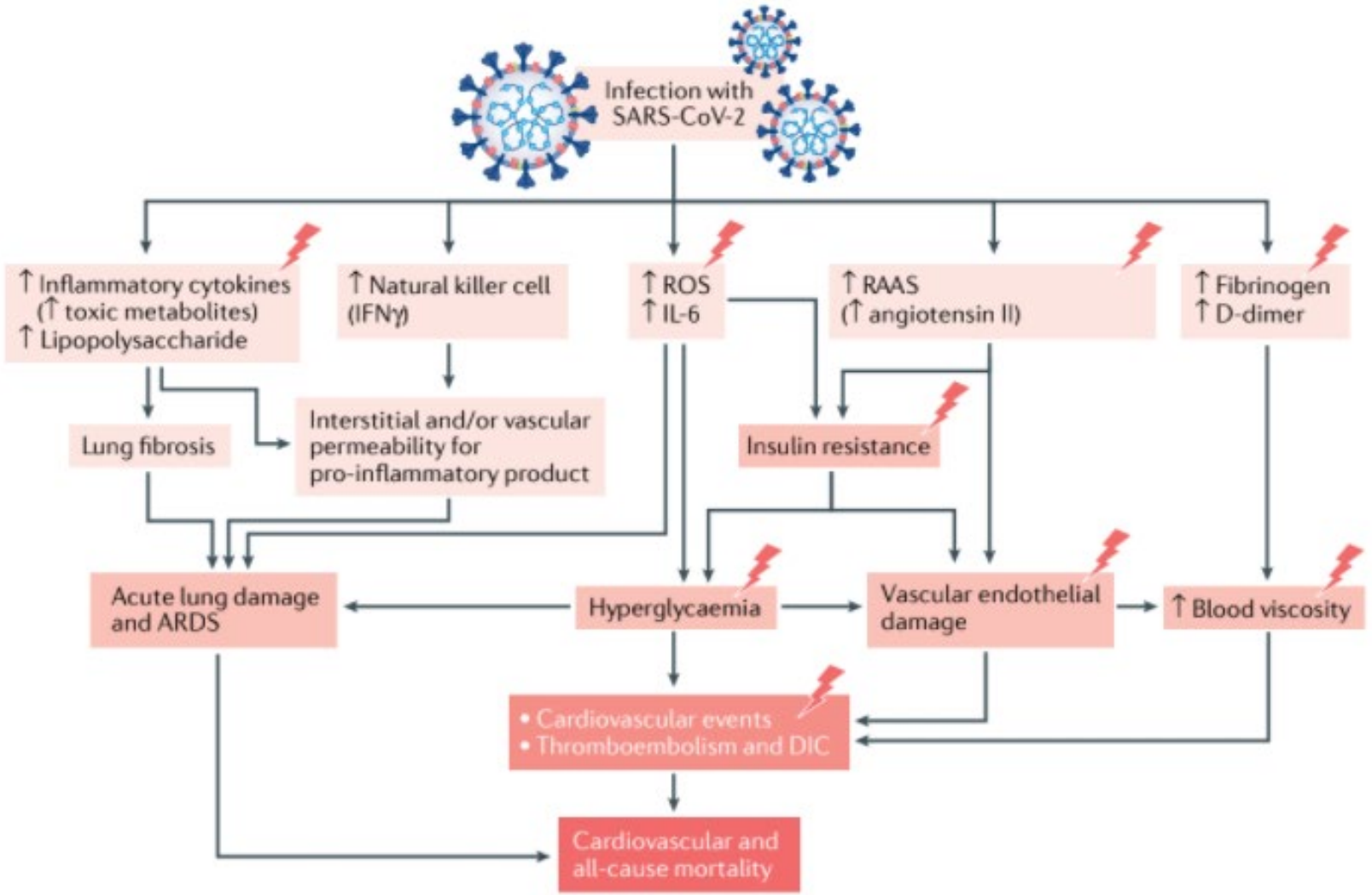
https://doi.org/10.1038/s41574-020-00435-4

Key Points

- Presence of Diabetes Mellitus and degree of hyperglycemia are associated with more severe disease from SARS-CoV-2
- Typical complications of diabetes mellitus (CVD, heart failure and chronic kidney disease) increases COVID-19 mortality


Infection with SARS-CoV-2
↑ Inflammatory cytokines (↑ toxic metabolites) ↑ Lipopolysaccharide
↑ Natural killer cell (IFNγ)
↑ ROS ↑ IL-6
↑ RAAS (↑ angiotensin II)
↑ Fibrinogen ↑ D-dimer
Lung fibrosis
Interstitial and/or vascular permeability for pro-inflammatory product
Insulin resistance
Acute lung damage and ARDS
Hyperglycaemia
Vascular endothelial damage
↑ Blood viscosity
• Cardiovascular events • Thromboembolism and DIC
Cardiovascular and all-cause mortality

Preview

SARS-CoV-2 infection of islet β cells: Evidence and implications

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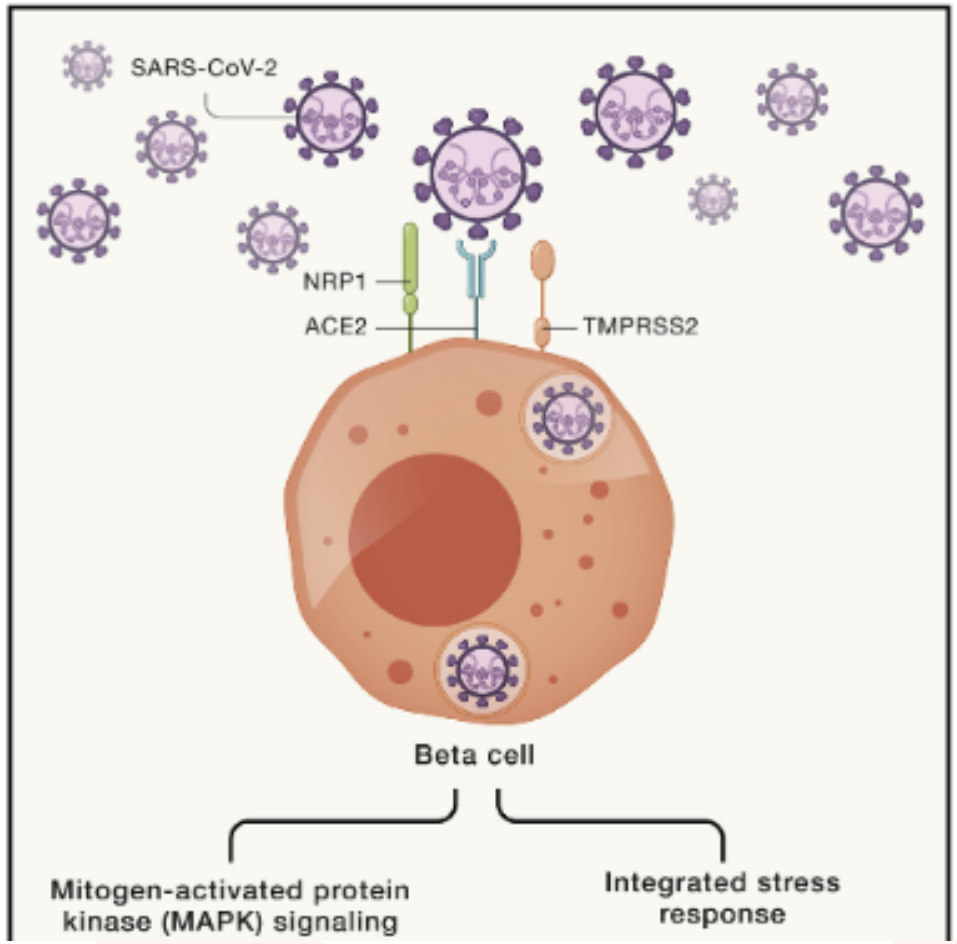
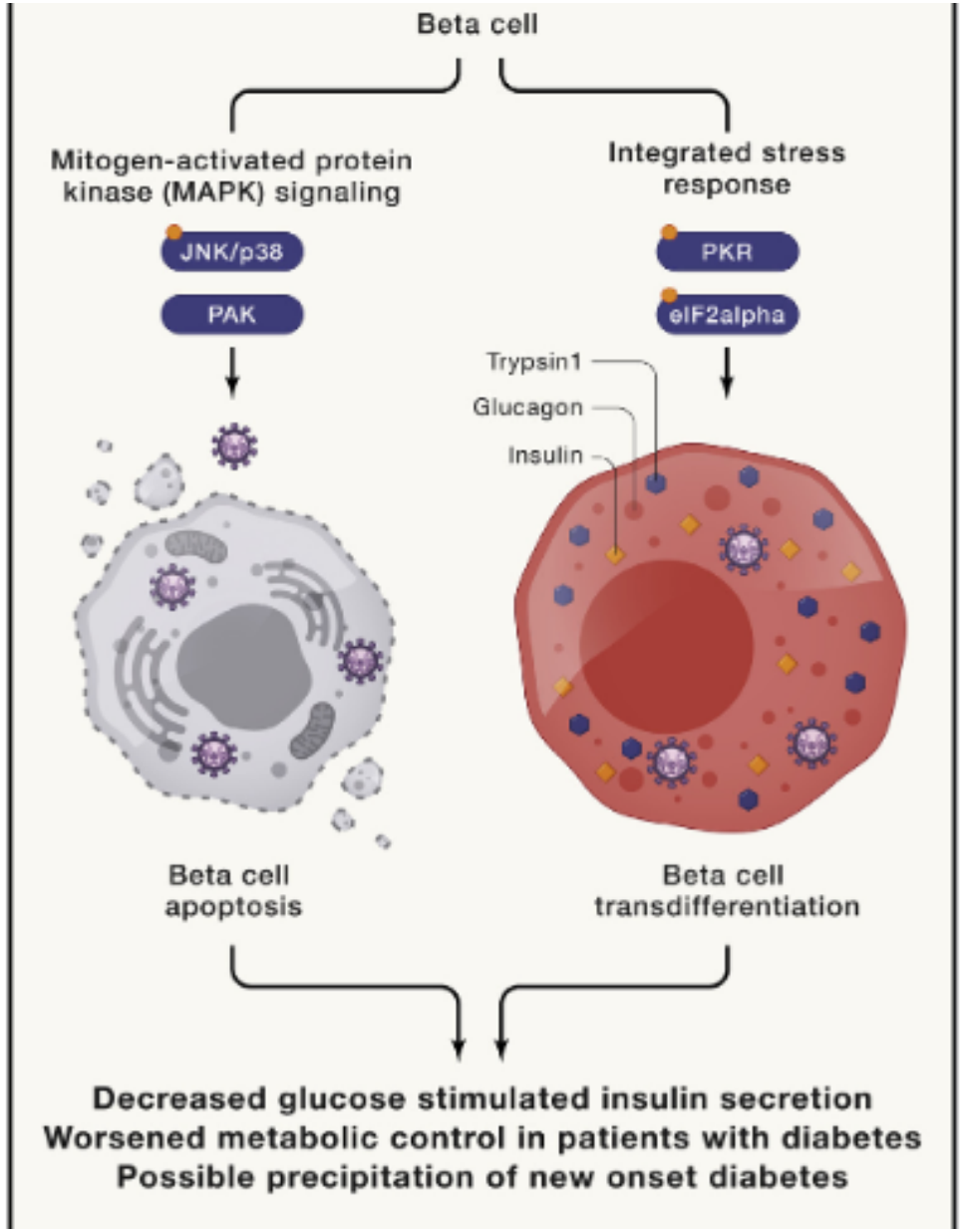
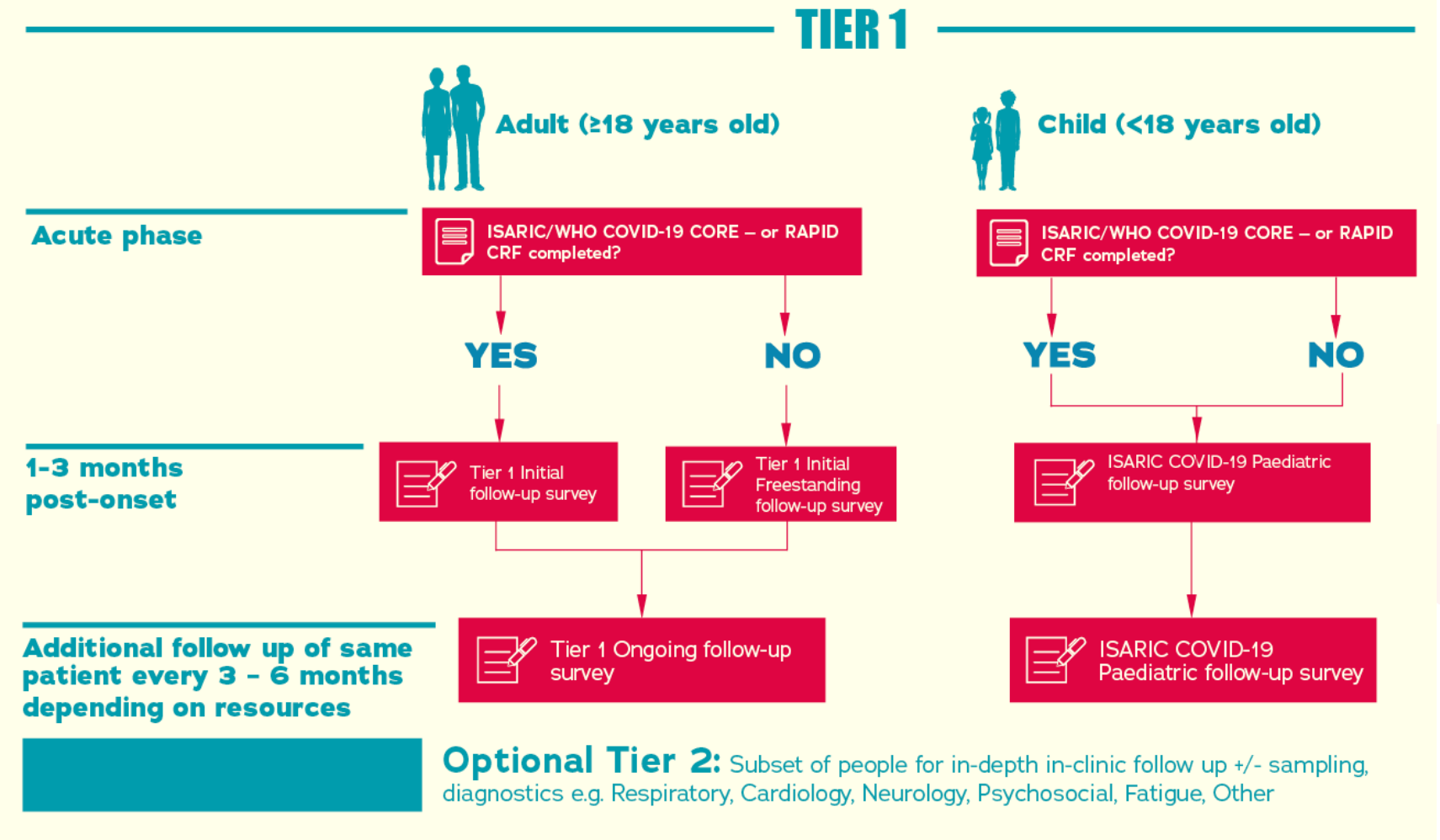

SARS-CoV-2
NRP1
ACE2
TMPRSS2
Beta cell
Mitogen-activated protein kinase (MAPK) signaling
Integrated stress response


Beta cell
Mitogen-activated protein kinase (MAPK) signaling
Integrated stress response
JNK/p38
PAK
PKR
eIF2alpha
Trypsin1
Glucagon
Insulin
Beta cell apoptosis
Beta cell transdifferentiation
Decreased glucose stimulated insulin secretion
Worsened metabolic control in patients with diabetes
Possible precipitation of new onset diabetes

Clinical Trials and Ongoing Research

International Severe Acute Respiratory and emerging Infection Consortium

Clinical Trials and Ongoing Research



National Institute of Allergy and Infectious Diseases

Volunteer for COVID-19 Clinical Trials

We made history with safe and effective vaccines and we'll keep working as long as there are people to protect, variants emerging, and research answers needed to keep us all safe. That means we still need you!

NIAID is conducting and supporting clinical trials evaluating therapies and vaccine candidates against severe acute respiratory syndrome coronavirus type 2 (SARS-CoV-2), the virus that causes coronavirus disease 2019 (COVID-19), as well as studies of people who have recovered from infection.

https://www.niaid.nih.gov/clinical-trials/covid-19-clinical-trials

https://openredcap.nyumc.org/apps/redcap/surveys/?s=TYCLM7PE97

Thank you!

Questions?