Long-term clinical outcomes following SARS-CoV-2 infection include persistent symptoms and cardiovascular disease beyond 3 months post-infection

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Background

- Many symptomatic SARS-CoV-2 infections (COVID-19) suffer persistent or chronic consequences ('long COVID')
- Long COVID is potentially highly relevant to military duties and medical readiness
- The Military Health System (MHS) is the DoD single payer health system
  - Serves ~9.6 million beneficiaries - including 1.4 million active duty service members (ADSM)
- We sought to evaluate the impact of COVID-19 on ADSM and adult MHS beneficiary health following infection
  1) Persistent self-reported symptoms
  2) Medical encounters (ICD-10)

DOD VACCINATION ADMINISTRATION TO DOD POPULATION

DOD Vaccine Data	
Total Doses Delivered	Total Doses Administered
4,466,510	4,945,662

DOD COVID-19 CUMULATIVE TOTALS

	Cases	Hospitalized	Recovered	Deaths
Military	230,284	2,065	217,227	40
Civilian	61,577	1,743	51,586	282
Dependent	33,993	447	31,697	18
Contractor	21,750	594	19,335	96
Total	347,604	4,849	319,845	436

https://www.defense.gov/Explore/Spotlight/Coronavirus-DOD-Response/ and https://health.mil/About-MHS ; both accessed 6 Sept 2021

Data updated 0600, September 1, 2021

JAMA Network Open

JAMA Netw Open. 2021 May 3;4(5):e2111417.

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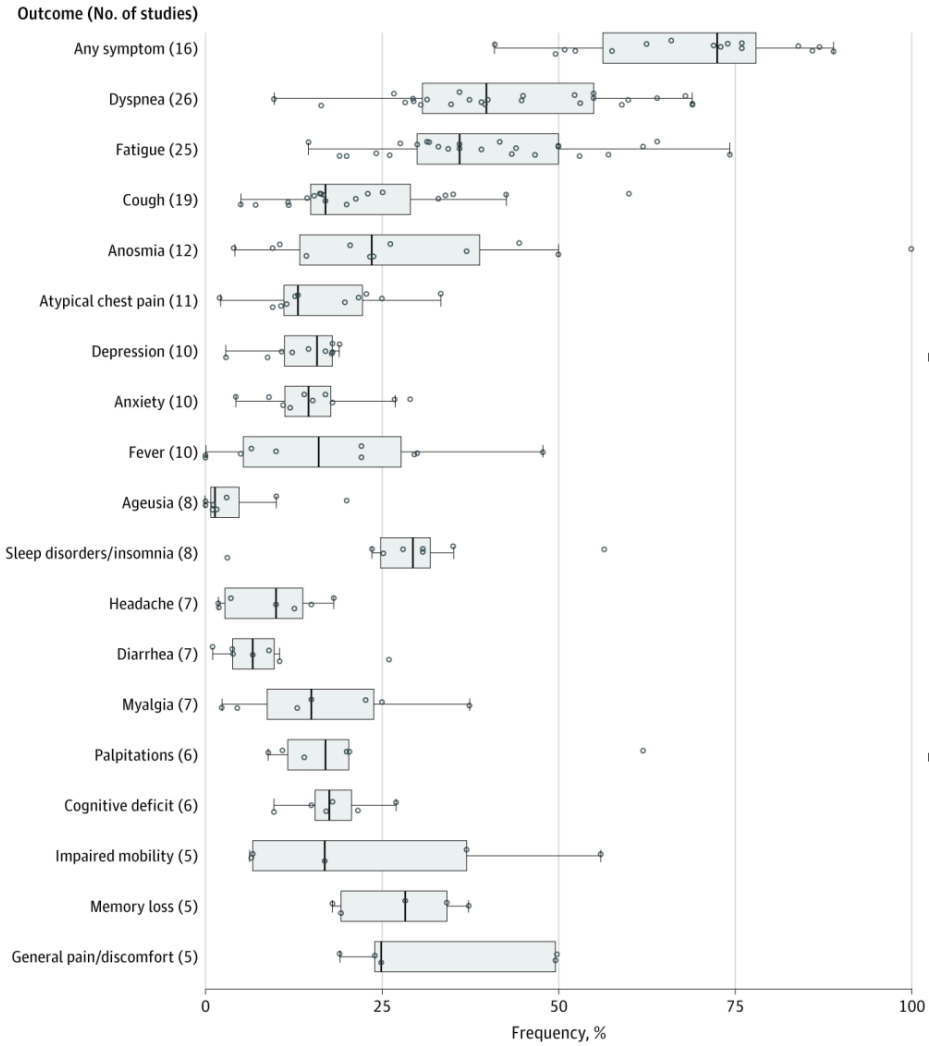
Original Investigation | Infectious Diseases

Assessment of the Frequency and Variety of Persistent Symptoms Among Patients With COVID-19

A Systematic Review

Tahmina Nasserie, MPH; Michael Hittle, BS; Steven N. Goodman, MD, MHS, PhD



1974 records identified
1247 article titles/abstracts screened
92 full-text articles assessed for eligibility
47 studies deemed eligible
45 studies included (9751 total participants)

- >1 persistent symptom 72.5% (55.0-80.0%)
  - Shortness of breath/dyspnea 36.0% (27.6-50.0%)
  - Fatigue or exhaustion 40.0% (31.0-57.0%)
  - Sleep disorders or insomnia 29.4% (24.4-33.0%)
  - Cognitive deficits 17.6% (15.0-21.6%)
- **Limitation**: Only 12/45 included outpatients

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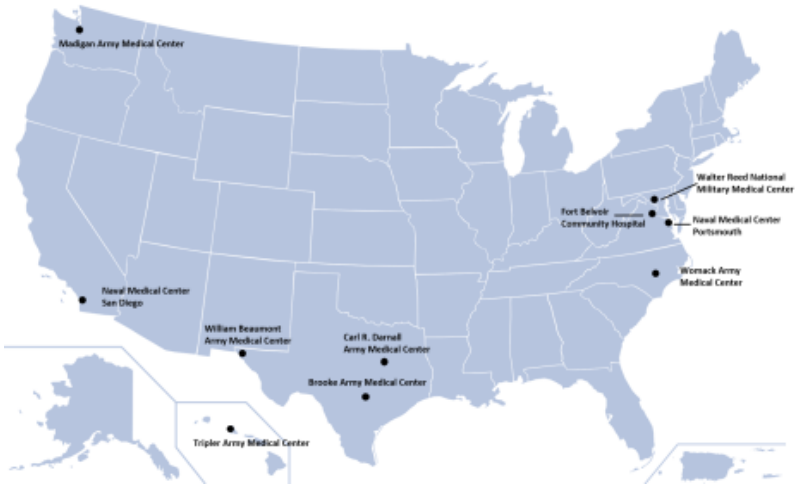
Epidemiology, Immunology, and Clinical Characteristics of Emerging Infectious Diseases with Pandemic Potential (EPICC) COVID-19 Cohort Study

- **Overall Study Objective:** To fill critical gaps in understanding SARS-CoV-2 infection among active duty and MHS beneficiaries and to inform and support development of diagnostic, treatment and prevention strategies toward improving force health protection
  - Long COVID presents a significant threat → key focus area
- **Study Design:** Prospective, longitudinal observational cohort study of COVID-19; participation via in-person or remote/online pathways
  - 12-month prospective follow-up with CRF, questionnaires; 5-year EMR follow-up
    - Self-administered questionnaires: 0, 1, 3, 6, 9, 12 months
  - Repeated specimens collected for virological and host response analysis
- **Population: DoD active duty & MHS beneficiaries (in/outpatients; adults/children; online ≥18 y/o)**
  - Laboratory confirmed SARS-CoV-2 infection, OR
  - Meets criteria for SARS-CoV-2 testing, OR
  - Received SARS-CoV-2 vaccine
- **Enrollment open:** March 2020 (vaccinees 2021)
  - 10 sites + online; N = 5086 to date



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Methods – Analysis Plan

- Inclusion: SARS-CoV-2+ adult subjects
  - Enrolled March 2020 - April 2021
  - With questionnaire data ≥28 days post symptom onset (dpso)
    - Self-reported online questionnaires initiated late 2020 (adults only)
  - Descriptive statistics
- Healthcare encounters from MHS Data Repository (MDR)
  - Including ICD-10 codes used here
  - Calculated odds of organ-system clinical diagnoses pre-/post-symptom onset
    - Generalized linear models adjusted for prior healthcare use and age

Results – Study Population

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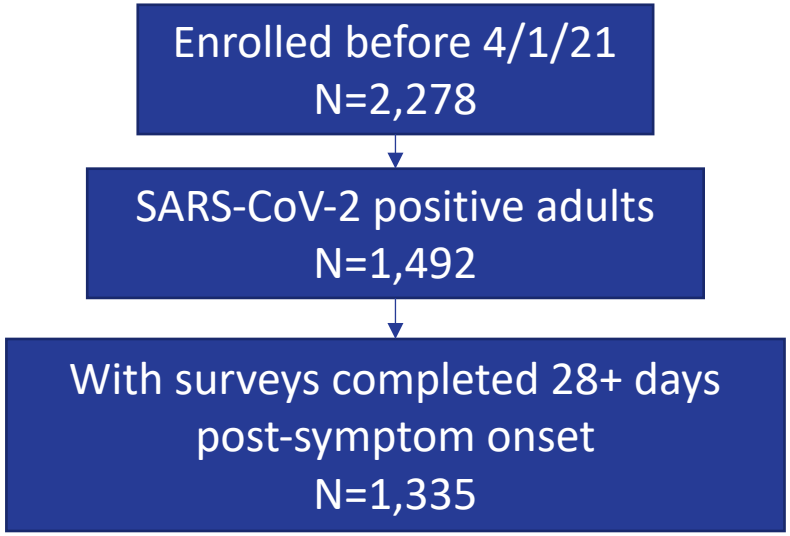
- 1335 participants included who were SARS-CoV-2+, symptomatic, and had survey ≥28 days
- Majority 18-44 y/o, male, white, and active duty
- ~20% were inpatients during acute illness
- ~1/3 participated through the online pathway



	N=1335
Age group	
<18	0 (0.0%)
18-44	871 (65.2%)
45-64	370 (27.7%)
65+	94 (7.0%)
Male	
Female	561 (42.0%)
Male	774 (58.0%)
Race/ethnicity	
Asian	59 (4.4%)
Black	145 (10.9%)
Hispanic or Latino	299 (22.4%)
Other	88 (6.6%)
White	744 (55.7%)
Military status	
Active duty	779 (58.4%)
Dependent	303 (22.7%)
Retired military	253 (19.0%)
Participation	
Online pathway	466 (34.9%)

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Results – Persistent/Chronic Symptoms

- Among COVID+ adults, nearly 70% had resolved illness at time of follow-up survey
- Median duration of illness overall 15 days
  - 45% acute, 19% persistent, 36% chronic
- Among N=410 with ongoing illness, median duration of illness 179 days
- Among 1285 with chronic symptoms data
  - 25.2% reported any chronic symptoms
    - 75.3% (244/324) ≥1 mod-severe

Time periods shown are in days	**N=1335**
Illness status at survey	
Ongoing	410 (30.7%)
Resolved	925 (69.3%)
Duration of illness (all)	
Median (Q1, Q3)	15 (7, 37)
Illness duration group	
<28	602 (45.1%)
28-84	249 (18.7%)
85+	484 (36.2%)
Dur. ongoing illness (N=410)	
Median (Q1, Q3)	179 (100, 257)
Any chronic symptoms reported	
No	961 (74.8%)
Yes	324 (25.2%)
Missing	50
Any ≥ moderate chronic symptoms reported	
No	1,041 (81.0%)
Yes	244 (19.0%)
Missing	50
Maximum symptom severity reported in survey (ever)	
Mild	354 (27.4%)
Moderate	597 (46.2%)
Severe	340 (26.3%)
Missing	44

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Results – Mod./Severe Symptoms

- 9.6% had not resumed normal activities by one month
- Most frequent symptoms >28 days: dyspnea, loss of smell/taste, fatigue, and exercise intolerance

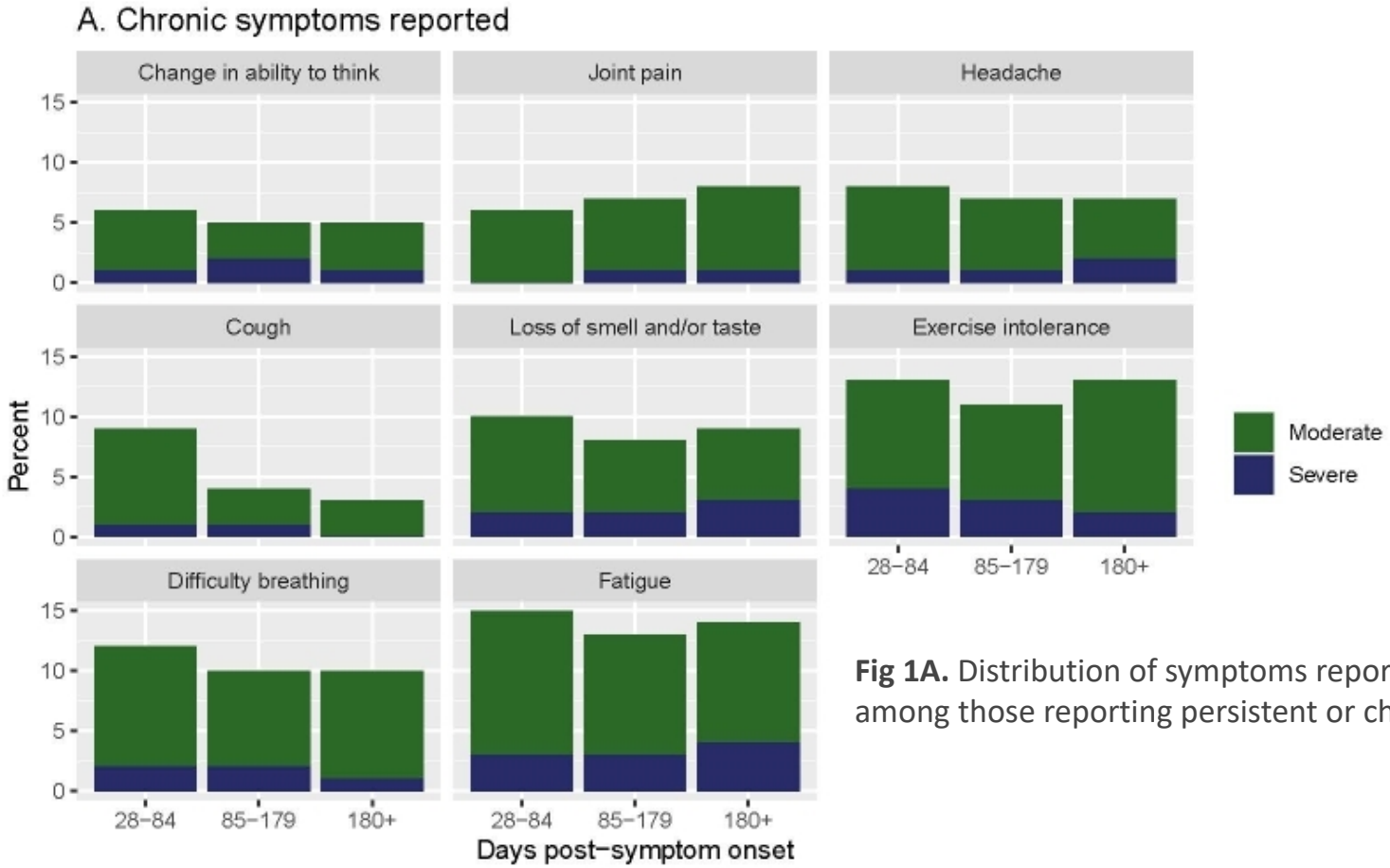


Fig 1A. Distribution of symptoms reported in surveys among those reporting persistent or chronic symptoms

Results – Healthcare Encounters

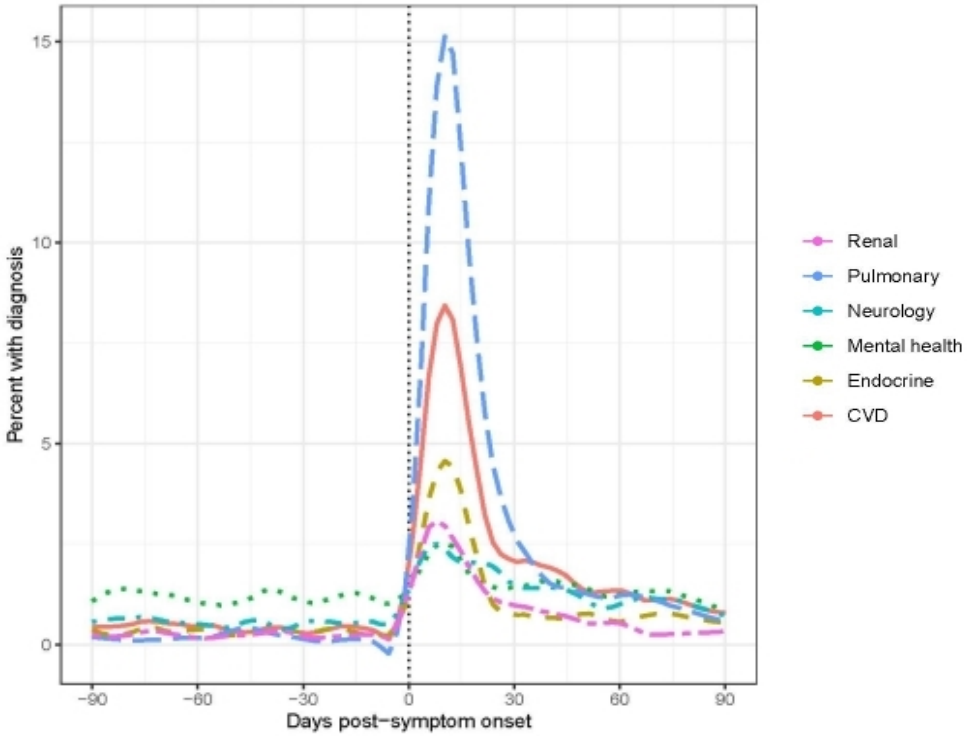


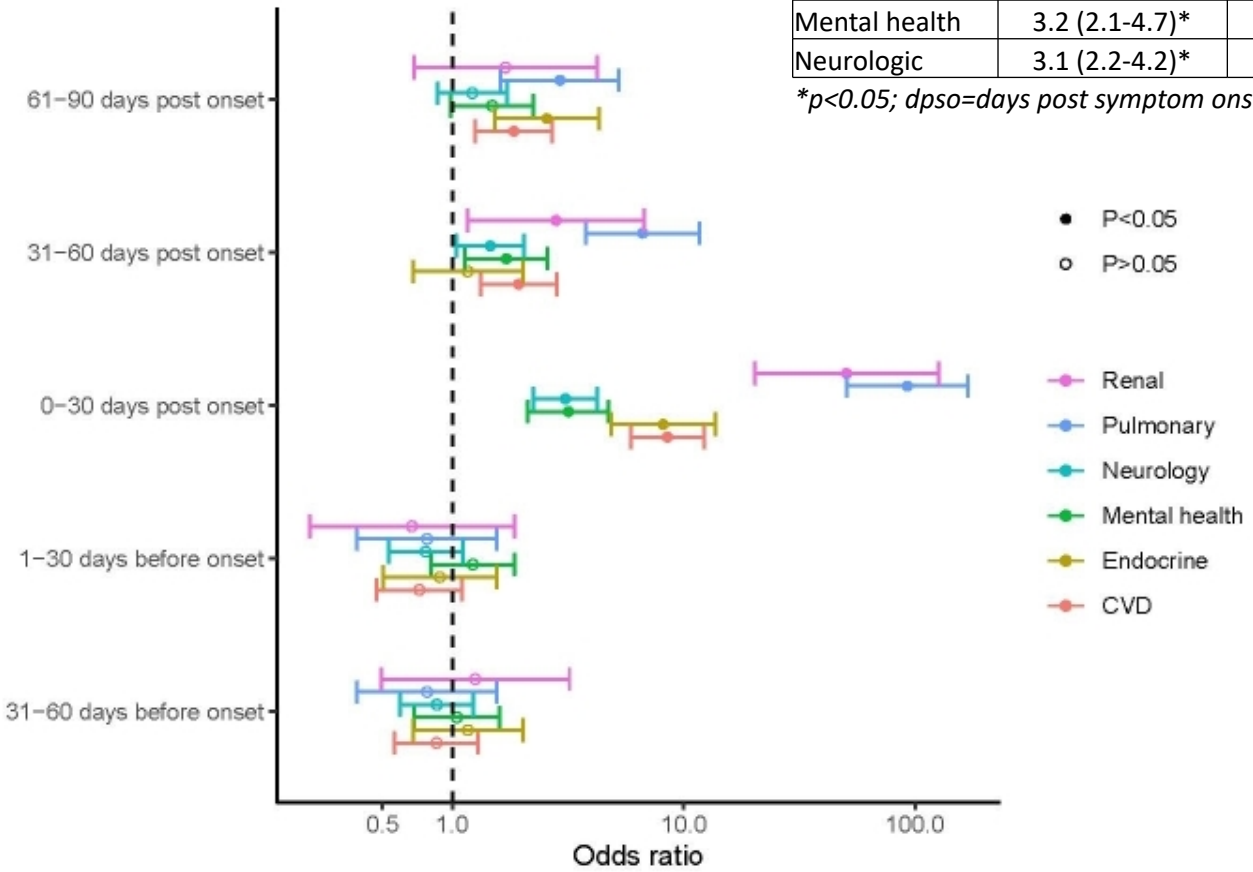
Fig 1B. Healthcare encounters for curated diagnoses (ICD-10): CVD, endocrine, pulmonary, liver, mental health, neurology, and renal.
Day 0 = COVID-19 symptom onset

Healthcare encounters increased significantly in the month following COVID-19 and some categories remained elevated through 3 months

	-3 months	-2 months	-1 month	+1 month	+2 months	+3 months
Any outpatient encounters	243 (18.6%)	221 (16.9%)	224 (17.1%)	403 (30.8%)	307 (23.5%)	288 (22.0%)
Any ER visits	16 (1.2%)	13 (1.0%)	15 (1.1%)	153 (11.7%)	21 (1.6%)	9 (0.7%)
Any inpatient encounters	8 (0.6%)	10 (0.8%)	4 (0.3%)	252 (19.3%)	29 (2.2%)	11 (0.8%)

Results – Healthcare Encounters

Fig 1C. Odds of healthcare encounter for organ-specific diagnosis, by time period. GLM also includes age group and a random effect for participant



Odds Ratios (95% CI) for Diagnoses Post-COVID-19

Diagnosis Grp	0-30 dpso	31-60 dpso	61-90 dpso
Pulmonary	92.5 (50.8-168.4)*	6.6 (3.8-11.7)*	2.9 (1.6-5.3)*
Renal	50.6 (20.3-126.2)*	2.8 (1.2-6.8)*	1.7 (0.7-4.2)
CVD	8.5 (5.9-12.3)*	1.9 (1.3-2.8)*	1.8 (1.3-2.7)*
Endocrine	8.2 (4.9-13.7)*	1.2 (0.7-2)	2.6 (1.5-4.3)*
Mental health	3.2 (2.1-4.7)*	1.7 (1.1-2.6)*	1.5 (1-2.2)
Neurologic	3.1 (2.2-4.2)*	1.5 (1-2)*	1.2 (0.9-1.7)

**p<0.05; dpso=days post symptom onset*

Results – 90 day CVD Encounters

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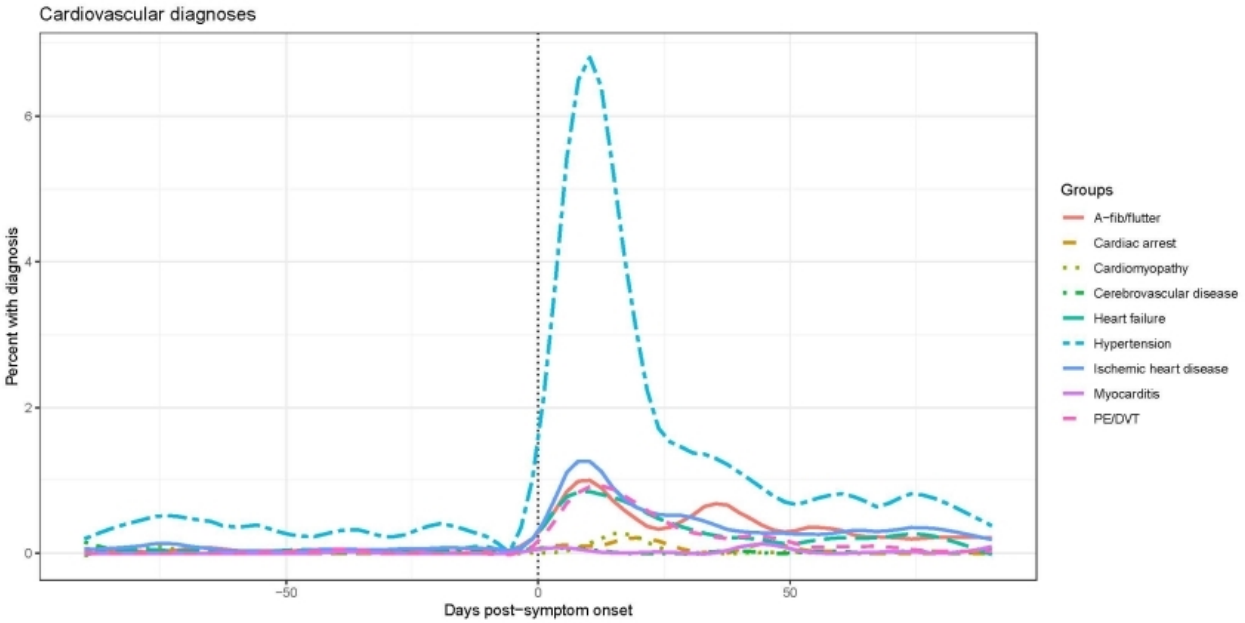
- Cardiovascular encounters increased post-COVID-19 (aOR = 7, 95% CI 5-11)
- Hypertension, ischemic HD, A-fib/flutter, heart failure more frequent post-COVID
- Few myocarditis diagnoses, but may be increased compared with pre-COVID



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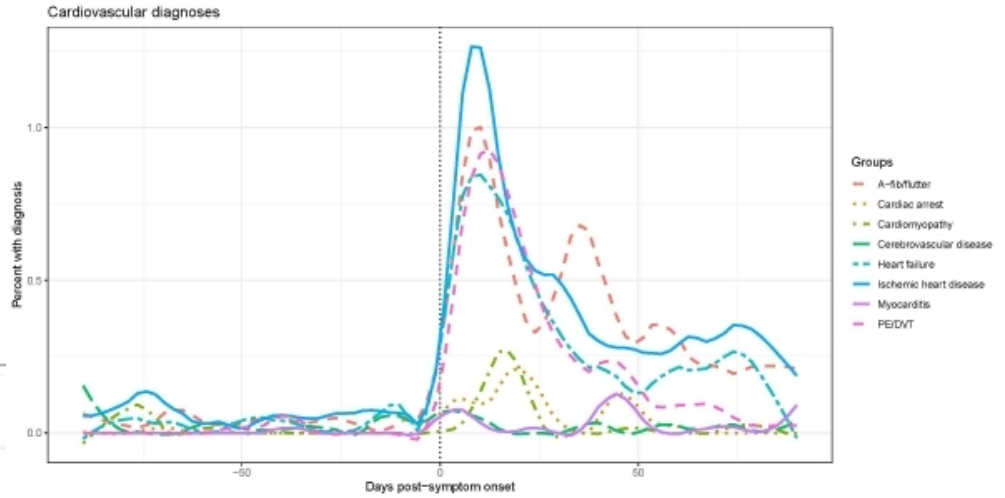

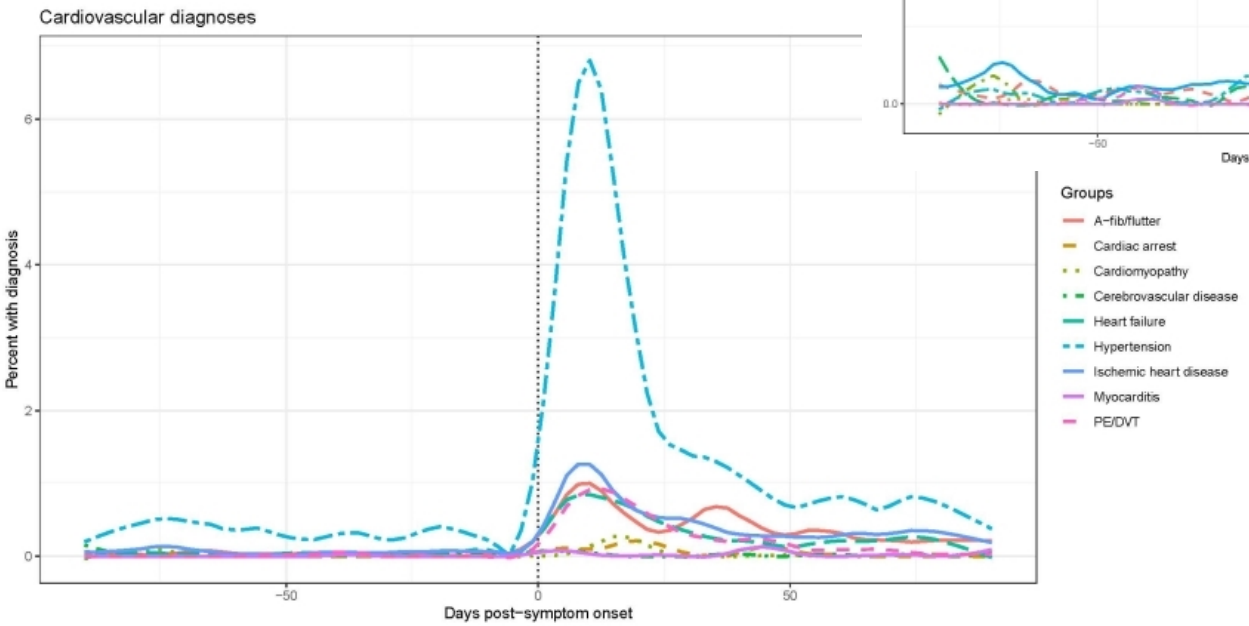

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Discussion – Persistent Symptoms

- In this MHS cohort of relatively young and healthy racially diverse subjects,

  1/4 of adult subjects with COVID-19 had persistent symptoms ≥1 month post-onset

  - >3/4 of these had ≥1 moderate or severe symptom

- Dyspnea, fatigue, exercise intolerance, and loss of smell/taste most common symptoms
  - Some symptoms may directly impact active duty readiness, similar to impact on working age US adults
- Modeling efforts underway - risk factors and predictors of long COVID in this population
  - Including demographics, underlying comorbidities, severity of acute illness, treatments/ medications, and biomarkers of immune response
- Prospective evaluation of pulmonary, cardiac, and neurocognitive effects in process

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Discussion – Healthcare Encounters

- Encounters increased following COVID-19, some dx groups up to 90 days
  - Odds of encounters for pulmonary diagnoses were elevated post-COVID, declining over 3 months
  - Odds of CVD diagnoses were lower than pulmonary, but persisted 3 months post-onset
    - Hypertension, ischemic HD, A-fib/flutter, HF, and myocarditis increased post-COVID
  - Further investigation beyond 90 days and substudies to characterize cardiopulmonary disease are ongoing; neurocognitive symptoms/disease may also be increased and are being evaluated
- Pulmonary, cardiac, and neurologic symptoms/diagnoses are potentially highly relevant to job duties and everyday function → even small proportions affected can present significant concern for certain jobs and when considered across large populations

Conclusions

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- In this MHS cohort, a significant proportion of adult participants had persistent illness up to three months after COVID-19 onset
  - Two lines of evidence: self-reported symptoms and administrative encounters
- Persistent symptoms and increased post-COVID diagnoses may be highly relevant to job duties and everyday function
  - Symptoms including dyspnea, fatigue, and exercise intolerance
  - Diagnoses including pulmonary, cardiac, and neurocognitive
- These findings emphasize the long-term morbidity of COVID-19 and the importance of mitigating SARS-CoV-2 infections, including through vaccination
- Further investigation of measures to identify risk for and preventive measures against long COVID among those infected with SARS-CoV-2 is needed

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