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Post-acute sequelae of COVID-19 infection

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ABSTRACT

To determine if people infected with SARS-CoV-2 were at higher risk of developing selected medical conditions post-recovery, data were extracted from the database of a large health maintenance organization (HMO) in Israel between March 2020 and May 2021. For each condition, a condition-naïve group prior to COVID-19 (PCR-positive) infection were compared to a condition-naïve, non-COVID-19 infected group, matched by gender, age, socioeconomic status, minority group status and number of months visited primary care physician (PCP) in previous year. Diagnosis and recuperation dates for each COVID-19 infected participant were applied to their matched comparison participant (1:1 ratio). Incidence of each condition was measured between date of recuperation and end of study period for each group and Cox regression models developed to determine hazard ratios by group status, controlling for demographic and health variables.

Crude and adjusted incidence rates were higher for the COVID-19 infected group than those not infected with COVID-19 for treatment for depression/anxiety, sleep disturbance, diagnosis of deep venous thrombosis, lung disease and fibromyalgia. Differences in incidence were no longer observed between the two groups for treatment of sleep disturbance, and diagnosis of lung disease when those hospitalized during the acute-phase of illness (any reason) were excluded. No difference was found by COVID-19 infection status for post-acute incidence of diabetes, cerebrovascular accident, myocardial infarction, acute kidney disease, hypertension and ischemic heart disease.

Patients post-COVID-19 infection should be evaluated for depression, anxiety, sleep disturbance, DVT, lung disease and fibromyalgia.

1. Introduction

Since the start of the pandemic in 2019, over 350 million people world-wide have been infected with SARS-CoV-2 virus. (W H O, 2022) By mid-2020 it was becoming clear that infection with the virus had long term effects for some of those infected. Commonly reported post-infection symptoms include fatigue, dyspnea, chest pain, cognitive disturbances and arthralgia. (Nalbandian et al., 2021). In addition to persisting symptoms after the acute phase of illness, numerous studies have reported an increased incidence of a broad range of conditions among those who had been infected with SARS-CoV-2 virus compared to those not infected. Studies have reported higher incidence of depression and anxiety, (Al-Aly et al., 2021; Huang et al., 2021; Mazza et al., 2020; Deng et al., 2021) sleep disturbance, (Al-Aly et al., 2021; Huang et al., 2021) deep venous thrombosis, (Ho et al., 2021; Clavijo et al., 2021; Zuin et al., 2022; Nopp et al., 2020) myocardial infarction, (Ho et al., 2021) acute kidney infection, (Bruchfeld, 2021; Portolés et al., 20202020) hypertension, (Al-Aly et al., 2021; Tadic et al., 2020) lung disease, (Lund et al., 2021; Townsend et al., 2021) diabetes (Sathish et al., 2021; Ruissen et al., 2021) and neurological conditions, such as cerebrovascular accident and fibromyalgia. (Ho et al., 2021; Nannoni et al., 2021; Collantes et al., 2021) For some of these conditions, such as deep venous thrombosis (DVT), it has been suggested that the higher risk is a sequelae of severe illness in the acute stage of infection (secondary to hospitalization, mechanical ventilation, intensive care unit (ICU) care) (Ho et al., 2021; Roberts et al., 2020) rather than a consequence unique to SARS-CoV-2 infection exposure.

As in other countries, from the end of February 2020 Israel has experienced a number of large waves of SARS-CoV-2 infection. (Rosen et al., 2021; Leshem and Wilder-Smith, 2021) We set out to measure

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post- acute incidence for each of these conditions in a large health maintenance organization (HMO) in Israel, comparing incidence in the infected population to a matched comparison group that were not diagnosed with COVID-19. We also wished to explore the relationship between COVID-19 infection and incidence of conditions by acute-phase hospitalization status, vaccination status and age group.

2. Methods

All data for the study were extracted from the Maccabi HealthCare database. Maccabi is the second largest health maintenance organization (HMO) in Israel, providing health care coverage for over a quarter (2.6 million) of the country's population. The database includes demographic data for all members, as well as records for all out-patient and community-based physician/other health profession visits (including diagnoses and height/weight/blood pressure measurements recorded in visit), procedures, hospitalizations, prescription purchases and laboratory tests. All laboratory testing is carried out at Maccabi Central laboratory. The HMO has established illness registries (such as myocardial infarction (MI), cerebrovascular accident (CVA), hypertension (HTN) and diabetes registries).

Polymerase chain reaction (PCR) testing is carried out for all HMO members presenting with symptoms or reporting exposure to a confirmed case, free of charge. The HMO maintains a COVID-19 registry, including all members testing positive for SARS-CoV-2 infection, date of infection (first positive PCR test) and date of recovery. Date of recovery is calculated as ten days from date of infection for those at low-risk of serious illness, and reported date of recovery by the COVID-19 outreach team for all high-risk members. At the time of the study, high-risk members (based on age, chronic illness background and/or hospitalization for COVID-19) were followed up daily by the outreach team.

The study was carried out from March 2020 to May 2021 (inclusive). HMO members with SARS-CoV-2 infection (PCR positive) and a matched comparison group were selected to determine incidence rates for each of the following conditions: use of antidepressants/anxiolytics as an indication of depression/anxiety, use of benzodiazepines as an indication of sleep disturbance, DVT, lung disease, fibromyalgia, diabetes, CVA, MI, ischemic heart disease (IHD) as evidenced by recent percutaneous transluminal coronary angioplasty (PTCA), acute kidney disease (AKI) and HTN. For each condition, any member aged 20 and over with a positive PCR test (first) in the study period and no evidence of each condition prior to COVID-19 diagnosis, comprised the 'COVID-19′ group. For each member in the 'COVID-19′ group, a matched comparison member with no laboratory evidence of prior SARS-CoV-2 infection (no positive PCR or IgG serology test result) was identified. The 'comparison' group was matched for age group, gender, socioeconomic status and population group, such as Orthodox Jew or Arab (based on census and national survey classifications applied to home address). The comparison group was also matched for the number of months in 2019 in which a primary care physician (PCP) was visited at least once. This variable was included as a proxy for general health status and healthcare visit behavior over time to reduce the potential for bias based on differential use of services. Diagnosis and recuperation dates were 'applied' to each matched control member, to avoid bias secondary to temporal changes in use of services (e.g.: during lockdown periods). Comparison group members with evidence of the condition prior to 'diagnosis' were removed. Members who left the HMO or died between Jan 2019 and date of diagnosis were excluded from both COVID-19 and comparison groups. The number of unmatched COVID-19 cases was extremely low (minimum: 3, maximum: 272 cases, median: 33 cases (~0.05 %) for eleven conditions tested) and were excluded from analysis.

For each selected condition, number of new cases between date of recovery and end of study period (herein referred to as the follow-up period) were identified for each group. For some of the conditions, analyses were limited to relevant older age groups. Condition-specific case identification and exclusions were as follows: new cases of depression/anxiety were defined as those with a first purchase of any antidepressant or anxiolytic medication in the follow-up period, where no purchases were made prior to recovery date and up to two years prior to COVID-19 diagnosis. In a similar manner, new cases of sleep disturbance were identified, using benzodiazepine purchases. New cases of DVT, lung disease (pulmonary embolism, chronic obstructive pulmonary disease (COPD), pulmonary hypertension) and fibromyalgia were based on hospital and community-based physician visit diagnoses. Those with a first diagnosis during the follow-up period were considered new cases for the condition, and members with a prior diagnosis (ever) were excluded from the relevant condition analyses. IHD, as evidenced by a first (non-diagnostic) (PTCA during the follow-up period, with those having had a PTCA prior to recovery date and up to two years prior to COVID-19 diagnosis excluded from this analysis. New IHD analyses were limited to those aged 40 +. New AKI was defined as a first abnormal result of eGFR (<60 ml/min/1.73 m^2) or micro-albumin (>30 mg) in the follow-up period. Those with abnormal results prior to recovery date and up to two years prior to COVID-19 diagnosis were excluded from analysis. New AKI analyses were limited to those aged 40+ Finally, new cases of HTN, MI, CVA and diabetes were identified on the basis of date of entry into the respective illness registries. Those members with registry entry dates prior to recovery date were removed from the respective illness analyses. Number of new cases of HTN included all aged 20+, diabetes was limited to all aged 30+, MI to all aged 40+, and CVA to all aged 50+.

Data for each condition were stratified for further analysis by acute-phase hospitalization (between diagnosis and date of recuperation: yes/no) and age group (<40/40+). Data was also collected for each population group regarding prior vaccination against SARS-CoV-2 virus (yes/no) and number of doses received. It should be noted that the national vaccination campaign, using BNT1626 vaccine commenced six months into the follow-up period, initially targeting those aged sixty and over or with low-immunity.

2.1. Statistical analysis

For each condition, the proportion of new cases in each group was compared, using chi square analysis. This process was repeated, stratifying separately by acute-phase hospitalization and age group (±40). Chi Square analysis was also used to assess any association between vaccination status, COVID-19 status and each outcome condition. The number of days from recovery date to diagnosis date of the condition, death, left the HMO or end of study period was calculated for each study participant for each condition. Cox regression models were developed for each condition in order to calculate hazards ratios by group status (COVID-19 yes/no), controlling for the demographic and health variables: gender, age, socioeconomic status, population group, number months visited PCP in 2019, BMI, vaccination prior to recovery and presence of HTN, heart disease, diabetes, cancer and COPD. Analyses were carried out using SPSS, version 24 (IBM©).

The study was carried out with the prior approval of the Maccabi internal review board and the Maccabi Helsinki committee (MHS-0174-20). Informed consent was waived by the Helsinki committee, given the database source and the aggregated presentation of findings, ensuring member anonymity.

3. Results

For each condition-specific study population, persons having recovered from COVID-19 were more likely to be obese, with a greater proportion having diabetes and a lower proportion having cancer (Table 1). The distribution of all matched variables remained consistent across study populations, with the exception of the diabetes study population. Compared to all other condition-specific populations, the proportion of aged 60+ was higher in the diabetes study population, as

Table 1
Demographic & health characteristics (%) of study population by group (COVID-19 & comparison) for each selected condition, Maccabi HealthCare Services, Israel, March 2020-May 2021 * $p < 0.05$.

Characteristic (N)	Depression/Anxiety		Sleep Disturbance		DVT		Lung Disease		Fibromyalgia		Diabetes	
	Covid-19 N = 95,462	Comparison N = 95,462	Covid-19 N = 94,211	Comparison N = 94,211	Covid-19 N = 109,208	Comparison N = 109,208	Covid-19 N = 109,097	Comparison N = 109,097	Covid-19 N = 108,765	Comparison N = 108,765	Covid-19 N = 71,683	Comparison N = 71,683
Gender (% males)	49.9	49.9	50.0	50.0	48.7	48.7	48.6	48.6	49.0	49.0	47.8	47.8
Age group (%)												
20–29	28.9	28.9	29.7	29.7	27.1	27.1	27.1	27.1	27.1	27.1		
30–39	20.6	20.6	21.2	21.2	19.9	19.9	20.0	20.0	19.9	19.9	30.1	30.1
40–49	20.3	20.3	20.6	20.6	20.4	20.4	20.5	20.5	20.3	20.3	29.9	29.9
50–59	16.8	16.8	16.6	16.6	17.3	17.3	17.3	17.3	17.1	17.1	23.3	23.3
60+	13.4	13.4	11.9	12.0	15.4	15.4	15.1	15.1	15.5	15.5	16.7	16.7
Socioeconomic status												
Low	37.9	37.9	38.1	38.1	37.1	37.1	37.1	37.1	37.2	37.2	32.9	32.9
Medium	45.8	45.8	45.6	45.6	46.2	46.2	46.2	46.2	46.2	46.2	48.3	48.3
High	16.3	16.3	16.3	16.3	16.7	16.7	16.7	16.7	16.7	16.7	18.8	18.8
Population group (%)												
General	65.2	65.2	64.9	64.9	66.4	66.4	66.4	66.4	66.3	66.3	70.8	70.8
Orthodox Jew	25.0	25.0	25.3	25.3	24.3	24.3	24.3	24.3	24.4	24.4	20.6	20.6
Arab	9.8	9.8	9.8	9.8	9.7	9.7	9.7	9.7	9.3	9.3	8.5	8.5
No. of months (%)[1]												
0	12.3	12.3	12.5	12.5	11.5	11.5	11.5	11.5	11.6	11.6	11.2	11.2
1–2	47.7	47.7	48.2	48.2	45.1	45.1	45.2	45.2	45.3	45.3	45.0	45.0
3+	40.0	40.0	39.3	39.3	43.4	43.4	43.3	43.3	43.1	43.1	43.8	43.8
BMI												
None in last 3 years	31.5*	34.0*	31.9*	34.4*	30.2*	32.6*	30.3*	32.6*	30.3*	32.7*	31.4*	33.4*
<30	48.7*	48.9*	38.5*	38.6*	49.1*	49.4*	49.0*	49.3*	49.0*	49.4*	37.2*	48.3*
30+	19.8*	17.1*	19.6*	17.0*	20.7*	18.0*	20.7*	18.1*	20.7*	18.0*	21.5*	19.9*
% in registry												
HTN	13.1*	13.6*	11.9	12.2	15.1	15.3	14.9	15.1	15.2*	15.5*	15.8	16.1
Heart disease	5.5*	5.7*	4.9	5.1	6.4	6.4	6.2	6.2	6.5	6.5	6.0	6.2
Diabetes	6.8*	6.4*	6.5*	6.2*	8.0*	7.3*	7.8	7.3	8.0*	7.4*		
Cancer	3.6*	4.2*	3.3*	3.7*	4.2*	5.0*	4.2*	4.9*	4.3*	5.0*	4.9*	5.7*
COPD	0.8*	1.0*	0.7*	0.8*	1.1*	1.2*	0.9*	1.0*	1.1*	1.2*	1.1*	1.2*

was the proportion of participants from a higher socioeconomic bracket. Minority groups were under-represented in the diabetes study population, compared to other components of the study.

We found small, but significantly higher crude incidence rates for depression/anxiety, sleep disturbance, DVT, lung disease, fibromyalgia and diabetes among persons who had recuperated from COVID-19 compared to those who had never been diagnosed (Table 2). However, no difference in the proportion of new cases for AKI, MI, HTN, CVA or IHD was found between those that had recovered from COVID-19 and those who had never been diagnosed with COVID-19. For every condition tested, 91 % of all hospitalizations during the acute phase of the illness (from diagnosis to discharge) were amongst the COVID-19 group. When crude incidence rates were stratified by acute-phase hospitalization, among those not hospitalized, the difference between the COVID-19 group and comparison group was no longer evident for crude incidence rates for sleep disturbance, DVT or diabetes (Table 2). No differences were found for any condition between the two groups among those hospitalized.

When adjusted for demographic and health factors (Table 3), the COVID-19 group remained more likely than the comparison group to be at risk of post-acute depression/anxiety, sleep disturbance, DVT, lung disease and fibromyalgia but not for diabetes. When adjustment was repeated excluding those that had an acute-phase hospitalization, the association between COVID-19 status and outcome was no longer evident for sleep disturbance or lung disease (Table 4).

3.1. Age group

When results were stratified by age, no difference in crude incidence was found for any of the conditions between COVID-19 status and outcome for those under the age of 40, with the exception of lung disease (0.035 vs 0.016, p =.050). However, for those aged 40 and over, incidence rates were consistently higher among the COVID-19 group than the comparison group for depression/anxiety (1.7 vs 1.4, p =.003), sleep disturbance (2.2 vs 1.9, p =.006) and DVT (0.17 vs 0.09, p =.003) but not for lung disease (0.14 vs 0.09, p = 0.063) or fibromyalgia (0.44 vs 0.37, p = 0.11).

3.2. Vaccination

For all conditions, the COVID-19 group were less likely to have been vaccinated than the comparison group, with typically around 26 % of the COVID-19 having been vaccinated prior to recovery compared to 49 % in the comparison group. Small but significant differences in incidence rate of new illness by vaccine status were found for some conditions. For example, 1.6 % of those not vaccinated were diagnosed with depression/anxiety compared to 1.04 % for those vaccinated (p <.001). Similar findings were found for sleep disturbance (1.85 % vs 1.24 %, p < 0.001) and diabetes (0.33 % vs 0.15 %, p <.001). However, vaccination status was strongly related to age and socioeconomic status for all conditions, and when included in each model, did not impact the relationship between COVID-19 status and condition outcome (Table 3).

Table 2
Proportion of new cases for selected conditions among recuperated COVID-19 persons and matched persons without COVID-19, stratified by hospitalization status in acute phase of illness, Maccabi HealthCare Services, Israel, March 2020-May 2021.

Condition	Group	Total			Excluding Hospitalized			Hospitalized Only		
		N	% new cases	p value	N	% new cases	p value	N	% new cases	p value
Depression/anxiety	COVID-19	95,462	1.7	<0.001	91,283	1.5	0.017	4179	5.3	0.542
	Comparison	95,462	1.4		95,072	1.4		390	4.6	
Sleep disturbance	COVID-19	94,211	1.9	<0.001	90,348	1.7	0.269	3863	6.0	0.344
	Comparison	94,271	1.6		93,896	1.6		375	4.8	
DVT	COVID-19	109,208	0.15	0.002	103,815	0.13	0.113	5393	0.67	0.747
	Comparison	109,208	0.10		108,702	0.10		506	0.79	
Lung disease	COVID-19	109,097	0.19	0.049	103,805	0.11	0.021	5292	1.72	0.954
	Comparison	109,097	0.15		108,563	0.15		534	1.69	
Fibromyalgia	COVID-19	108,765	0.29	0.010	103,327	0.28	0.034	5438	0.52	0.939
	Comparison	108,765	0.24		108,211	0.24		554	0.54	
Diabetes	COVID-19	71,683	0.33	0.028	68,097	0.28	0.33	3586	1.17	0.168
	Comparison	71,683	0.26		71,339	0.25		344	2.03	
CVA	COVID-19	35,465	0.11	0.340						
	Comparison	35,465	0.14							
MI	COVID-19	57,413	0.04	0.555						
	Comparison	57,413	0.04							
IHD (PTCA)	COVID-19	57,931	0.14	0.451						
	Comparison	57,931	0.16							
AKI	COVID-19	50,303	1.43	0.469						
	Comparison	50,303	1.38							
HTN	COVID-19	92,962	0.49	0.087						
	Comparison	92,962	0.44							

Table 3
Hazards ratios (95 % CI) of Cox regression models for each Illness/condition, Maccabi HealthCare Services, Israel, Mar 2020-May 2021.

Characteristic	Depression/Anxiety	Sleep Disturbance	DVT	Lung Disease	Fibromyalgia	Diabetes
Group						
Covid-19	1.214 (1.127–1.307)	1.143 (1.067–1.225)	1.455 (1.143–1.851)	1.321 (1.075–1.623)	1.270 (1.076–1.499)	1.137 (0.937–1.379)
Comparison	–	–	–	–	–	–
Gender						
Male	–	–	–	–	–	–
Female	1.250 (1.159–1.348)	1.302 (1.212–1.398)	1.063(0.835–1.354)	0.968 (0.786–1.193)	4.620 (3.654–5.841)	0.578 (0.474–0.705)
Age (years)	1.008 (1.005–1.010)	1.018 (1.015–1.021)	1.026 (1.017–1.036)	1.054 (1.046–1.063)	1.003 (0.997–1.009)	1.027 (1.019–1.036)
Socioeconomic status						
Low	–	–	–	–	–	–
Medium	1.198 (1.075–1.336)	1.064 (0.962–1.176)	1.110 (0.795–1.559)	0.984 (0.657–1.474)	1.080 (0.859–1.359)	1.006 (0.776–1.322)
High	1.240 (1.084–1.419)	1.143 (1.009–1.296)	0.995 (0.637–1.553)	0.893 (0.614–1.299)	0.613 (0.442–0.850)	1.003 (0.702–1.434)
Population group (%)						
General	1.491 (1.272–1.747)	1.789 (1.533–2.088)	1.248 (0.766–2.034)	0.984 (0.657–1.474)	1.238 (0.926–1.654)	0.629 (0.446–0.886)
Orthodox Jew	1.065 (0.910–1.246)	1.565 (1.347–1.818)	1.275 (0.794–2.047)	1.045 (0.696–1.568)	0.465 (0.335–0.644)	0.552 (0.393–0.775)
Arab	–	–	–	–	–	–
No. months visited PCP in 2019	1.127 (1.111–1.143)	1.122 (1.107–1.137)	1.109 (1.063–1.157)	1.054 (1.018–1.091)	1.254 (1.218–1.291)	1.019 (0.983–1.055)
BMI						
No measurement in last 3 years	–	–	–	–	–	–
<30	1.498 (1.357–1.654)	1.388 (1.265–1.522)	1.626 (1.092–2.421)	1.864 (1.245–2.792)	1.954 (1.497–2.551)	2.618 (1.759–3.897)
30+	1.255 (1.110–1.419)	1.341 (1.199–1.499)	3.023 (1.995–4.582)	2.237 (1.463–3.421)	2.316 (1.726–3.109)	9.269 (6.270–13.701)
HTN registry						
No	–	–	–	–	–	–
Yes	1.101 (0.985–1.219)	1.101 (0.995–1.219)	1.128 (0.825–1.543)	1.349 (1.037–1.756)	0.580 (0.449–0.750)	1.405 (1.110–1.780)
Heart disease						
No	–	–	–	–	–	–
Yes	1.239 (1.090–1.409)	1.118 (0.987–1.266)	0.985 (0.686–1.414)	2.157 (1.692–2.750)	0.877 (0.631–1.220)	1.184 (0.885–1.584)
Diabetes						
No	–	–	–	–	–	
Yes	0.987 (0.869–1.121)	0.975 (0.867–1.096)	0.927 (0.664–1.293)	0.989 (0.776–1.259)	0.843 (0.633–1.122)	
Cancer						
No	–	–	–	–	–	–
Yes	1.142 (0.989–1.319)	1.109 (0.966–1.272)	1.042 (0.698–1.554)	1.227 (0.938–1.605)	1.092 (0.800–1.491)	0.669 (0.446–1.002)
COPD						
No	–	–	–	–	–	–
Yes	1.392 (1.100–1.761)	1.134 (0.887–1.451)	1.039 (0.853–1.736)	3.641 (2.708–4.897)	0.880 (0.478–1.621)	1.157 (0.658–2.037)
Vaccinated before recovery						
No	–	–	–	–	–	–
Yes	1.032 (0.918–1.160)	0.974 (0.874–1.086)	1.217 (0.853–1.736)	1.044 (0.790–1.380)	2.224 (1.738–2.846)	0.627 (0.457–0.860)

4. Discussion

This large observational study allowed us to compare incidence rates for eleven different conditions between over 90,000 COVID-19 cases and matched comparison controls that were condition-naïve prior to COVID-19 diagnosis. Follow-up data, both hospital and community-based, was available for up to fourteen months. We found that infection with COVID-19 increased the likelihood of post-acute incidence for depression/anxiety, sleep disturbance, DVT, lung disease and fibromyalgia. Acute-phase hospitalization accounted for the difference between the COVID-19 infected and non-infected group for sleep disturbance, and lung disease. Depression/anxiety, DVT and fibromyalgia, independent of hospitalization status, were still more likely to occur among those with COVID-19 than those without COVID-19. We did not find evidence of increased risk for post-acute diabetes, CVA, MI, IHD (based on PTCA), AKI or HTN.

4.1. Increased incidence conditions

Other studies have also found increased incidence of depression/anxiety, (Al-Aly et al., 2021; Deng et al., 2021) sleep disturbance, (Al-Aly et al., 2021) DVT (Zuin et al., 2022; Roberts et al., 2020; Cai et al., 2020; Kerbikov et al., 2021) and lung disease (Al-Aly et al., 2021; Townsend et al., 2021) among those with a prior COVID-19 infection. In contrast, Lund et al (Lund et al., 2021) compared incidence of a large number of illnesses and conditions in a non-hospitalized population in Denmark. Using a similar methodology to the present study but with a shorter follow-up period (two weeks to six months), no difference was found for antidepressant or benzodiazepine use (new or renewed after a 12-month gap) between COVID-19 patients and matched controls. It is difficult to know why Lund et al's findings (2021) (Lund et al., 2021) are different from the present study: whether due to differences in study methodology, such as follow-up time, medications incorporated or

Table 4
Cox Hazard Models*, including/excluding patients hospitalized during the acute phase of infection, for selected conditions among recuperated COVID-19 persons and matched persons without COVID-19, Maccabi HealthCare Services Israel, March 2020-May 2021.

Condition	Group	Including Hospitalized	Excluding Hospitalized
Depression/ anxiety	COVID-19	1.214 (1.127–1.307)	1.130 (1.047–1.220)
	Comparison		
Sleep disturbance	COVID-19	1.143 (1.067–1.225)	1.070 (0.996–1.150)
	Comparison		
DVT	COVID-19	1.455 (1.143–1.851)	1.312 (1.015–1.696)
	Comparison		
Lung disease	COVID-19	1.321 (1.075–1.623)	0.921 (0.722–1.175)
	Comparison		
Fibromyalgia	COVID-19	1.270 (1.076–1.499)	1.265 (1.067–1.499)
	Comparison		
Diabetes	COVID-19	1.137 (0.937–1.379)	1.060 (0.864–1.300)
	Comparison		

* Measures included in the model: COVID-19 status, gender, age, socioeconomic status, population group, number months visited PCP in 2019, BMI, vaccination prior to recovery and presence of HTN, heart disease, diabetes, cancer and COPD.

matching variables used (age, gender and diagnosis week only were used in the Lund et al [14] study[14]) or broader population differences relating to propensity to present to a physician for depression/anxiety or sleep disturbance or treatment prescription between Israel and Denmark.

A number of studies have described the potential for exacerbation of illness for patients with fibromyalgia that become infected with COVID-19. (Salaffi et al., 2021; Mohabbat et al., 2020) In this study we were able to demonstrate an increased incidence of newly diagnosed fibromyalgia for COVID-19 infected patients. Fibromyalgia incidence was higher among the COVID-19 population group, irrespective of whether they had been hospitalized. Given the increased risk for women, it is important to make PCPs aware of this increased risk.

4.2. Impact of hospitalization on condition incidence

The increased risk for DVT among hospitalized patients is well documented. About 19 % of hospitalized patients develop a DVT and another 4 % will develop a DVT post-discharge, (Nopp et al., 2020) with the likelihood of developing a DVT being higher after surgical intervention and/or prolonged immobility. Some of the DVT studies described above focused exclusively hospitalized COVID-19 patients. (Zuin et al., 2022; Roberts et al., 2020) Other studies demonstrated lower risk for venous thromboembolism (DVT and pulmonary embolism combined) among non-hospitalized compared to hospitalized patients. (Clavijo et al., 2021; Nopp et al., 2020; Xie et al., 2022) Our findings suggest that the risk of post-acute DVT and lung disease for COVID-19 patients was not limited to those hospitalized. We suggest that while prolonged immobility, and ICU/mechanical ventilation during hospitalization contribute to higher DVT incidence, inflammatory response to COVID-19 infection may also increase risk.

For several other conditions studied here, much or all of the increased incidence could be attributed to being hospitalized. We suggest that the hospitalization experience - isolation, fear and residual health impact – may explain the higher use benzodiazepines in this group.

4.3. No increased incidence conditions

We did not find evidence of higher risk of diabetes, CVA, MI, IHD, AKI or HTN for COVID-19 patients. While diabetes is clearly a risk factor for COVID-19 infection, severity of disease and mortality, (Zhou et al., 2021) it is less clear whether new-onset diabetes after COVID-19 infection is a risk. Sathish et al. (2021) reported a pooled proportion of 14.4 % of new-onset diabetes in COVID-19 patients based on eight studies with high heterogeneity. Requena et al. (2020) reported higher rates of CVA for COVID-19 patients (1.2 %) but stated that for most, the etiology of these cases (N = 26) were unrelated to COVID-19. Ho et al. (2021), in a study of all COVID-19 patients in Scotland reported incidence rates for MI and CVA within the first 56 days of infection. However, no control group was employed for comparison. Xie et al. (2022) found higher incidence for a number of cardiac conditions, including CVA, IHD and thrombotic disorders. This study was based on veteran's affairs database, that included largely a white, male and older population group.

As for diabetes, CKD and HTN are risk factors for COVID-19. Bruchfeld (2021), Tadic et al. (2020), Ng et al. (2021) in a study including 10,000 hospitalized COVID-19 patients in NY, calculated mortality incidence of 10.8/1000 patient-days for acute kidney disease (AKI), 37.5/1000 patient-days for AKI dialysis and 31.1/1000 patient-days for AKI without dialysis. Again, no control group was reported.

Given the 'newness' of the disease, and the many unknowns regarding prognosis and recovery, COVID-19 patients are perhaps exposed to more detailed medical scrutiny. It is possible that for some of these conditions, testing revealed pre-existing conditions that were simply not diagnosed prior to COVID-19 exposure.

4.4. Impact of age

For almost all of the conditions, age was a significant contributor to outcome. Physicians should be more vigilant in screening for the above factors for those aged forty and over.

Study limitations: While the comparison group was matched for a broad range of factors, we cannot exclude the possibility that behavioral and other factors, for which data is unavailable, were not included. Some of the outcome measures were based on date of diagnosis after COVID-19 recovery. It is possible that conditions were diagnosed during the hospitalization period, but only recorded after discharge by the family physician, thereby inflating the differences between the two groups for those conditions (eg: DVT). An unknown percentage of the control group may also have had COVID-19 (not diagnosed/asymptomatic), minimizing the differences between the two groups. Data was based on one HMO and, although large, generalization of the results to all Israel or beyond, should be carried out with caution. While a broad range of conditions was included here, other conditions (for which data was not available) may have increased incidence post-infection with SARS-CoV-2 virus.

5. Conclusions

Depression/anxiety and fibromyalgia are rare but significant sequelae for the COVID-19 infected population, as are DVT, lung disease and sleep disturbance. Physicians should be aware of the increased risks, screen their post-acute COVID-19 patients for these sequelae and treat accordingly.

CRediT authorship contribution statement

Kertes Jennifer: Conceptualization, Methodology, Investigation, Data curation, Formal analysis. **Shapiro Ben David Shirley:** Methodology, Validation. **Porath Avi:** Methodology, Validation. **Rahamim-Cohen Daniella:** Methodology. **Shamir Stein Naama:** Conceptualization, Methodology, Project administration. **Ekka Zohar Anat:** Conceptualization, Methodology. **Mizrahi-Reuveni Miri:** .

Declaration of Competing Interest

The authors declare that they have no known competing financial

interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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