Journal of Autoimmunity 135 (2023) 102991

Contents lists available at ScienceDirect

Journal of Autoimmunity

journal homepage: www.elsevier.com/locate/jautimm

Pre-existing conditions associated with post-acute sequelae of COVID-19

Elizabeth T. Jacobs [*,1], Collin J. Catalfamo [1], Paulina M. Colombo, Sana M. Khan, Erika Austhof, Felina Cordova-Marks, Kacey C. Ernst, Leslie V. Farland, Kristen Pogreba-Brown

Mel and Enid Zuckerman College of Public Health, University of Arizona, Tucson, AZ, USA

ARTICLE INFO

Handling Editor: Dr. M.E. Gershwin

Keywords:
COVID-19
SARS-CoV-2
PASC

ABSTRACT

Post-acute sequelae of COVID-19 (PASC) are conditions that occur or remain at least 28 days after SARS-CoV-2 infection. While some risk factors for PASC have been identified, little is known about pre-existing conditions that render one susceptible to developing PASC. Data from participants (n = 1224) in a longitudinal COVID-19 cohort study in Arizona were used to investigate comorbid conditions associated with PASC. After adjustment of the models for age, BMI, gender, race, and smoking, the following pre-existing conditions were statistically significantly associated with the development of PASC: asthma (OR = 1.54; 95% CI = 1.10–2.15); chronic constipation (OR = 4.29; 95% CI = 1.15–16.00); reflux (OR = 1.54; 95% CI = 1.01–2.34); rheumatoid arthritis (OR = 3.69; 95%CI = 1.15–11.82); seasonal allergies (OR = 1.56; 95% CI = 1.22–1.98); and depression/anxiety (OR = 1.72; 95% CI = 1.17–2.52). When grouping conditions together, statistically significant associations with PASC were observed for respiratory (OR = 1.47; 95% CI = 1.06–2.14); gastrointestinal (OR = 1.62; 95% CI = 1.16–2.26), and autoimmune conditions (OR = 4.38; 95% CI = 1.59–12.06). After adjustment for severity of acute SARS-CoV-2 infection and depression/anxiety, seasonal allergies (OR = 1.48; 95% CI 1.15–1.91) and autoimmune disease (OR = 3.78; 95% CI - 1.31-10.91) remained significantly associated with risk for PASC. These findings indicate that numerous pre-existing conditions may be associated with an increased risk for the development of PASC. Patients with these conditions should consider taking extra steps to avoid infection.

1. Introduction

SARS-CoV-2 infection and its associated disease state, COVID-19, have caused unprecedented societal and healthcare challenges worldwide since the first reports were published in early 2020 [1]. Initially, attention on the pandemic focused largely on the acute stage of infection, as it was associated with substantial morbidity and mortality. As vaccines have reduced the severity of acute outcomes [2], research efforts have grown to encompass the associated long-term symptoms and conditions reported following acute infection. These outcomes have been referred to by numerous labels, including post-acute sequelae of COVID-19 (PASC), long-haul COVID, post-COVID conditions, or Long COVID. Currently, the case definition for PASC from the Centers for Disease Control and Prevention includes any new or ongoing symptoms 4 weeks or more after the acute infection [3]. Some conditions commonly reported as PASC include "brain fog" or difficulty with cognition, fatigue, shortness of breath, and gastrointestinal disorders [1,4–16].

In addition to these, there is an increasingly wide range of signs and symptoms that occur after acute infection [17] yet little is known about the characteristics that place individuals at greatest risk for development of PASC. Some risk factors that have been identified include: the presence of severe acute symptoms [4,6,8–11,15,18]; increasing age [8,9,15,18,19], female sex [6,10–12,15,20], and pre-existing comorbidities [7–11,18]. To date, few studies have described associations between specific pre-existing conditions prior to infection with SARS-CoV-2 and post-acute symptoms. Those that have identified diabetes [8], lung disease [8], frailty [21], chronic obstructive pulmonary disease [21], use of medications for autoimmune disorders [22], asthma [23], multiple sclerosis [24], and depression/anxiety [25] as possible risk factors.

There is growing scientific awareness and acceptance that SARS-CoV-2 infection can cause long-term symptoms. The scale of past and ongoing transmission means PASC will have striking impacts on healthcare delivery as well as the individual lives of those affected [26]. It is critically important to seek scientific consensus on the risk factors for PASC. In the present study, we utilized data from the Arizona

* Corresponding author. University of Arizona Cancer Center, 1515 N. Campbell Ave. P.O. Box 245024, Tucson, AZ, 58724, USA.
E-mail address: jacobse@email.arizona.edu (E.T. Jacobs).
[1] These authors have contributed equally to the manuscript and are co-first authors.

https://doi.org/10.1016/j.jaut.2022.102991
Received 14 November 2022; Received in revised form 17 November 2022; Accepted 31 December 2022
Available online 6 January 2023

CoVHORT, a prospective cohort study of COVID-19 launched in May 2020, to ascertain which pre-existing conditions engendered a greater risk for the development of PASC after SARS-CoV-2 infection. The Arizona CoVHORT collected detailed, well-characterized data regarding pre-existing conditions, symptoms, and severity of COVID-19 disease course, basic demographic information, and health behavior variables allowing prospective identification of pre-existing comorbidities that confer the greatest risk for development of PASC.

2. Methods

All participants in the present work were from the Arizona CoVHORT, a prospective cohort study designed to investigate the acute and long-term effects of SARS-CoV-2 infection among Arizona residents and launched in May 2020, as described in detail previously [27]. To date, more than 8500 participants have enrolled in the study. Briefly, several approaches were employed to recruit participants for the study, including collaborations through health department case investigations of COVID-19 [28], early COVID-19 testing efforts, distribution of informational materials at vaccination sites, and postcard mailings throughout the state. All residents of the state were eligible to join the study, irrespective of whether they had been infected with SARS-CoV-2 or not. All participants provided written informed consent, and ethical approval was obtained from the University of Arizona Institutional Review Board (Protocol #2003521636).

Electronic surveys were distributed to collect self-reported information on participant demographics and pre-existing conditions, as well as additional questions on acute symptoms and severity for those who reported an infection. Further data included items regarding health behaviors and COVID-19 test results. Electronic surveys designed using REDCap were administered upon enrollment as well as every 3 months following enrollment and continuing to the present. After a participant reported a SARS-CoV-2 infection either at their baseline enrollment survey or in any subsequent quarterly survey, the individual was emailed links to follow-up symptom surveys every 6 weeks after the reported infection date. These surveys included specific items inquiring about 25 new or recurrent symptoms that they observed in the previous 6 weeks, and included an open text field for collection of information regarding any condition they experienced. For the present work, data were included that were collected between May 28, 2020 and May 27, 2022.

A total of 1224 participants from CoVHORT were included in the present analysis. To be eligible for this analytic sample, participants must have reported 1) a positive SARS-COV-2 test; 2) the date of their positive test; and 3) competed at least one survey regarding symptoms at least 6 months after infection. The primary outcome variable of the study was the presence of PASC, which was defined as self-reported continuing or new symptoms 28 days or more following the test date for the acute infection. Those without PASC reported no symptoms on their follow-up symptom surveys at 6 weeks or more after their acute infection. The primary exposure variables were health conditions that were reported by the participant as having been present prior to infection with SARS-CoV-2.

3. Statistical analyses

Descriptive data for baseline characteristics of CoVHORT participants with and without PASC were calculated using frequencies and percentages for categorical variables, and with means and standard deviations for continuous variables. Frequencies and proportions of pre-existing comorbidities among participants with and without PASC were compared using Pearson's chi-squared test. In order to assess whether severity of acute disease might have driven any associations with the development of PASC; means, standard deviations, and the Student's t-test were used to compare severity of acute infection between those with pre-existing conditions and those without. Severity was assessed using two methods: a self-reported scale developed for CoVHORT, which ranged from 1 to 10, with 1 being lowest and 10 being highest severity, in response to the question, "*On a scale from 1-10, how would you characterize the severity of your illness?*"; and the and the NIH's COVID-19 Treatment Guidelines which defines SARS-CoV-2 infections as asymptomatic if no symptoms are experienced, mild if patients experience symptoms but do not experience dyspnea/shortness of breath or present with abnormal chest imaging, moderate if patients exhibit symptoms of lower respiratory disease (dyspnea/shortness of breath), severe if patients exhibit signs of lower respiratory disease and require oxygen therapy, and critical if patients exhibit signs of acute respiratory distress syndrome and require admission to the intensive care unit [29]. Moderate, severe, and critical infection severities were combined into one group for our analysis because most CoVHORT participants reported mild illnesses. Odds ratios and 95% confidence intervals were generated to examine the association between each pre-existing comorbidity and the development of PASC using unconditional logistic regression modeling, with an α of 0.05 for statistical significance. In addition to presenting individual pre-existing conditions, these were also grouped into categories of diseases for ascertainment of whether specific organ systems or types of illness carried risk in general. Potentially confounding variables were assessed and those that changed the point estimate by 10% or greater were included in the final multivariate logistic regression analyses [30]. Three models were generated to assess the relationship between comorbid conditions and PASC. Model 1 was adjusted for age, BMI, gender, race, and smoking; Model 2 was additionally adjusted for severity of acute infection, defined by NIH criteria [29]. Model 3 was additionally adjusted for depression/anxiety because there are some data indicating that depression/anxiety is both prevalent in those with other comorbid conditions and may be related to the development of PASC [31]. Finally, to clarify whether usual symptoms of pre-existing conditions were driving the reporting of symptoms post-acute infection, we removed common symptoms of these conditions and conducted sensitivity analyses to assess whether the associations were attenuated. We confined these analyses to conditions that were found to be statistically significant in primary analyses, as follows. For asthma, the following symptoms were removed: shortness of breath, chest pain, and cough; for constipation, all GI symptoms such as diarrhea, nausea, vomiting, and constipation; for rheumatoid arthritis, joint pain, fever, and fatigue; for depression/anxiety, insomnia, fatigue, loss of appetite, brain fog, GI symptoms and stress; for allergies, congestion, sore throat, cough, fatigue, conjunctivitis; and for lupus, fatigue, fever, joint pain, shortness of breath, chest pain. All analyses were conducted using STATA statistical software package [version 17.0], Stata Corporation, College Station, TX].

4. Results

Table 1 presents the characteristics of CoVHORT participants who reported a positive test for SARS-CoV-2, by PASC status. A total of 518 (42.3%) reported they had continuing symptoms after acute infection qualifying as PASC. The age median and range were similar between the two groups, but there was a statistically significantly greater proportion of female participants who experienced PASC (45.6% female vs. 34.0% male,; $p = 0.001$). Sparse data were available for non-binary participants ($n = 4$); however, 75% of those reporting non-binary gender also reported having PASC. The highest proportion of PASC was observed among those reporting Asian race (56.0%), followed by White (42.4%), Black or African-American (40.0%), Mixed race (34.0%), and American Indian or Alaska Native (33.3%). Those who preferred not to answer this question on race were three times more likely to report PASC than not. The proportion of those reporting PASC increased with increasing BMI category, with 32.2%, 40.2%, 44.1%, and 49.6% of participants in each of the following BMI categories, respectively, reporting PASC: 18.5–24.9, 25.0–29.9, 30.0–34.9, and $\geq$35.0. No significant difference in PASC development was observed for smoking history. Among the

Table 1
Characteristics of CoVHORT Participants who tested positive for SARS-CoV-2, by PASC Status.

	PASC Status				
	PASC-(n = 706)		PASC+ (n = 518)		P-value
Age (median, IQR)	47	(33–60)	49	(36–60)	0.147
Gender	n	%	n	%	0.001
Female	464	54.4	389	45.6	
Male	239	66.0	123	34.0	
Non-binary	1	25.0	3	75.0	
Race					0.056
American Indian or Alaska Native	10	66.7	5	33.3	
Asian	11	44.0	14	56.0	
Black or African American	9	60.0	6	40.0	
White	630	57.6	464	42.4	
Mixed Race	33	66.0	17	34.0	
Prefer not to answer	4	25.0	12	75.0	
Ethnicity					0.497
Non-Hispanic	563	56.8	428	43.2	
Hispanic or Latino/a	123	60.3	81	39.7	
Prefer not to answer	5	71.4	2	28.6	
BMI (kg/m^2), category					0.007
18.5–24.9	116	67.8	55	32.2	
25.0–29.9	207	59.8	139	40.2	
30.0–34.9	152	55.9	129	44.1	
≥35.0	118	50.4	116	49.6	
Cigarette smoking					
Never	671	58.1	484	41.9	0.11
Occasionally or Regularly	20	41.9	17	52.5	
At least one pre-existing condition	462	65.4	382	73.7	0.002
Number of pre-existing conditions (median, IQR)	1	(0–2)	2	(0–3)	0.000

As shown in Table 2, the presence of several specific pre-existing conditions was associated with the development of PASC. Significantly increased proportions of PASC vs. no PASC were found for asthma, congestive heart failure, irritable bowel syndrome, chronic constipation, colitis, reflux, systemic lupus erythematosus (SLE), rheumatoid arthritis, seasonal allergies, thyroid disease, and depression/anxiety. To assess whether severity of acute disease was higher among those with these conditions, Supplemental Table 1 presents a comparison of the severity of acute infection by comorbidities. Using the CoVHORT study criteria for severity on a scale of 1–10, statistically significantly greater severity of acute illness was reported for the following conditions: asthma, bronchitis or emphysema, COPD, irritable bowel syndrome, colitis, reflux, diabetes, pre-diabetes, rheumatoid arthritis, seasonal allergies, and depression/anxiety. In addition, participants in the following disease groups also experienced higher self-reported severity: respiratory, gastrointestinal, diabetes, and autoimmune. Using the NIH severity criteria on a scale of 1–3, asthma, COPD, high blood pressure, irritable bowel syndrome, diabetes, chronic constipation, colitis, and rheumatoid arthritis, were associated with higher severity; while the categories for respiratory, gastrointestinal, diabetes, and autoimmune conditions were also associated.

69% of participants who reported at least one pre-existing condition, the majority (73.7%) reported PASC, with the median number of pre-existing conditions in the PASC group being 2, as compared to only 1 in the group without PASC..

Table 3 shows three models for the adjusted odds ratios (aORs) and 95% confidence intervals (CIs) for the association between pre-existing conditions, categories of pre-existing conditions, and the development of PASC. For Model 1, the following pre-existing conditions were statistically significantly associated with the development of PASC: asthma (OR = 1.54; 95% CI = 1.10–2.15); chronic constipation (OR = 4.29; 95% CI = 1.15–16.00); reflux (OR = 1.54; 95% CI = 1.01–2.34); rheumatoid arthritis (OR = 3.69; 95%CI = 1.15–11.82); seasonal allergies (OR = 1.56; 95% CI = 1.22–1.98); and depression/anxiety (OR = 1.72; 95% CI = 1.17–2.52). A point estimate could not be calculated for SLE, as all 5 participants reporting this disease also experienced PASC. After grouping together conditions into disease categories, statistically significant associations with PASC were observed for respiratory (OR = 1.47; 95% CI = 1.06–2.14); gastrointestinal (OR = 1.62; 95% CI = 1.16–2.26), and autoimmune conditions (OR = 4.38; 95% CI = 1.59–12.06). In model 2 where disease severity was included, all results were attenuated, but seasonal allergies and depression/anxiety remained statistically significantly associated with PASC, as did the broad categories for gastrointestinal disease and autoimmune disease. Finally, when depression/anxiety was added to the model, only two comorbid conditions remained statistically significantly related to PASC; these were seasonal allergies (OR = 1.48; 95% CI = 1.15–1.91) and autoimmune disease (OR = 3.78; 95% CI = 1.31–10.91).

Table 2
Pre-existing conditions by PASC Status.

Pre-existing Condition	PASC-(n = 706)		PASC+ (n = 518)		P-value
	n	%	n	%	
Respiratory					
Asthma	83	11.8	90	17.4	0.005
Bronchitis or Emphysema	2	0.3	3	0.6	0.42
COPD	10	1.4	6	1.2	0.69
Cardiovascular					
Myocardial Infarction	3	0.4	3	0.6	0.70
Heart Disease such as Angina	7	1.0	6	1.2	0.78
Congestive Heart Failure	0	0.0	3	0.6	0.04
Stroke	5	0.7	4	0.8	0.90
High Blood Pressure	119	16.9	101	19.5	0.23
High Cholesterol	109	15.4	85	16.4	0.65
Other cardiac/heart disease	22	3.1	18	3.5	0.73
Gastrointestinal					
Liver Disease	3	0.4	5	1.0	0.25
Ulcerative Colitis	2	0.3	3	0.6	0.42
Irritable Bowel Syndrome	31	4.4	39	7.5	0.02
Chronic Diarrhea	4	0.6	5	1.0	0.42
Chronic Constipation	3	0.4	11	2.1	0.006
Colitis	2	0.3	6	1.2	0.06
Reflux	46	6.5	56	10.8	0.007
Diabetes					
Diabetes	32	4.5	29	5.6	0.40
Pre-Diabetes	32	4.5	35	6.8	0.09
Gestational Diabetes	6	0.8	11	2.1	–
Autoimmune					
Systemic lupus erythematosus	0	0.0	5	1.0	0.009
Multiple Sclerosis	1	0.1	2	0.4	0.39
Rheumatoid Arthritis	4	0.6	13	2.5	0.004
Other Conditions					
Kidney Disease	6	0.8	4	0.8	0.88
Seasonal Allergies	244	34.6	238	45.9	0.00
Valley Fever	6	0.8	10	1.9	0.10
Cancer	56	7.9	47	9.1	0.47
Thyroid Disease	70	9.9	76	14.7	0.01
Depression/Anxiety	56	7.9	71	13.7	0.001
Other Arthritis	43	6.1	45	8.7	0.08

Table 4 presents similar results to Table 3, but with common symptoms of each pre-existing condition removed from the definition of PASC, to ascertain whether these usual symptoms were driving the classification of PASC. In these analyses, modest attenuation of the association was observed for asthma, rheumatoid arthritis, allergies, and depression/anxiety; however, all but rheumatoid arthritis remained statistically significant, as did the results for each disease group. These analyses also allowed for the calculation of a point estimate for SLE, because one participant was categorized as not having PASC once common SLE symptoms were removed from the classification. The results for SLE were not statistically significant, likely due to the small sample size (n = 5).

5. Discussion

The results of this prospective study show that specific pre-existing conditions are associated with an increased risk of PASC following acute infection with SARS-CoV-2. Individuals reporting having asthma, chronic constipation, gastrointestinal reflux, rheumatoid arthritis seasonal allergies, or depression/anxiety were at significantly increased

Table 3
Adjusted ORs (95% CIs) for the development of PASC by pre-existing condition.

Pre-existing condition	n PASC/ Total	Adjusted OR[a] (95% CI)	Adjusted OR[b] (95% CI)	Adjusted OR[c] (95% CI)
Respiratory		*1.47 (1.06–2.14)*	*1.33 (0.94–1.87)*	*1.25 (0.88–1.78)*
Asthma	90/173	1.54 (1.10–2.15)	1.40 (0.98–1.99)	1.33 (0.93–1.90)
Bronchitis or Emphysema	3/5	2.72 (0.44–16.90)	1.66 (0.26–10.44)	1.33 (0.21–8.29)
COPD	6/10	0.67 (0.24–1.91)	0.42 (0.14–1.26)	0.43 (0.14–1.26)
Cardiovascular		*0.99 (0.75–1.32)*	*0.94 (0.70–1.27)*	*0.89 (0.66–1.21)*
Myocardial Infarction	3/6	1.33 (0.26–6.81)	1.51 (0.26–8.79)	1.41 (0.24–8.18)
Heart Disease such as Angina	6/13	1.31 (0.41–4.14)	1.22 (0.36–2.08)	1.03 (0.30–3.49)
Stroke	4/9	1.09 (0.29–4.43)	0.98 (0.22–4.38)	0.83 (0.19–3.74)
High Blood Pressure	101/ 220	1.10 (0.47–1.52)	1.00 (0.71–1.40)	0.98 (0.70–1.38)
High Cholesterol	85/194	0.95 (0.68–1.33)	0.93 (0.66–1.32)	0.86 (0.60–1.22)
Other cardiac/ heart disease	18/40	1.10 (0.56–2.18)	0.91 (0.45–1.87)	0.87 (0.42–1.80)
Gastrointestinal		*1.62 (1.16–2.26)*	*1.47 (1.04–2.09)*	*1.32 (0.92–1.90)*
Liver Disease	5/8	2.44 (0.56–10.67)	2.38 (0.53–10.77)	2.31 (0.52–10.25)
Ulcerative Colitis	3/5	2.31 (0.38–14.20)	2.29 (0.33–16.12)	1.97 (0.29–13.25)
Irritable Bowel Syndrome	39/70	1.59 (0.97–2.63)	1.40 (0.83–2.38)	1.25 (0.73–2.13)
Chronic Diarrhea	5/9	1.01 (0.25–4.16)	0.93 (0.22–3.96)	0.95 (0.22–4.12)
Chronic Constipation	11/14	4.29 (1.15–16.00)	3.12 (0.83–11.64)	2.65 (0.70–10.10)
Colitis	6/8	3.20 (0.63–16.1)	1.74 (0.34–9.00)	1.61 (0.31–8.23)
Reflux	56/102	1.54 (1.01–2.34)	1.49 (0.95–2.31)	1.33 (0.84–2.09)
Diabetes		*1.31 (0.89–1.92)*	*1.22 (0.82–1.82)*	*1.10 (0.73–1.65)*
Diabetes	29/61	1.15 (0.66–2.01)	0.98 (0.55–1.75)	0.87 (0.49–1.57)
Pre-Diabetes	35/67	1.25 (0.75–2.09)	1.20 (0.70–2.04)	1.06 (0.62–1.83)
Gestational Diabetes	11/17	2.14 (0.78–5.91)	2.31 (0.83–6.37)	2.23 (0.80–6.20)
Autoimmune		*4.38 (1.59–12.06)*	*4.29 (1.49–12.39)*	*3.78 (1.31–10.91)*
Systemic lupus erythematosus	5/5	N/A	N/A	N/A
Multiple Sclerosis	2/3	2.23 (0.20–24.48)	1.42 (0.12–16.77)	1.29 (0.10–16.10)
Rheumatoid Arthritis	13/17	3.69 (1.15–11.82)	3.20 (0.96–10.74)	2.97 (0.88–10.00)
Other Conditions				
Seasonal Allergies	238/ 482	1.56 (1.22–1.98)	1.55 (1.20–1.99)	1.48 (1.15–1.91)
Valley Fever	10/16	2.33 (0.83–6.56)	2.20 (0.75–6.47)	2.14 (0.72–6.40)
Cancer	47/103	1.04 (0.67–1.61)	1.14 (0.72–1.81)	1.11 (0.70–1.76)
Kidney Disease	4/10	0.78 (0.21–2.84)	0.75 (0.20–2.84)	0.71 (0.19–2.70)
Thyroid Disease	76/146	1.34 (0.93–1.93)	1.35 (0.92–1.97)	1.30 (0.89–1.91)
Depression/ Anxiety	71/127	1.72 (1.17–2.52)	1.83 (1.22–2.74)	N/A

[a] Model adjusted for age (continuous), BMI (categorical; 18.5–24.9; 25.0–29.9; 30.0–39.9; ≥ 40.0); gender (ref: female; 1 = male; 2 = nonbinary); race (ref: 1 = white, 2 = Asian; 3 = AI/AN; 4 = AA; 5 = Mixed race; smoking (ref = never smoker; 1 = current smoker).

[b] Model adjusted for age (continuous), BMI (categorical; 18.5–24.9; 25.0–29.9; 30.0–39.9; ≥ 40.0); gender (ref: female; 1 = male; 2 = nonbinary); race (ref: 1 = white, 2 = Asian; 3 = AI/AN; 4 = AA; 5 = Mixed race; smoking (ref = never smoker; 1 = current smoker), and severity (NIH criteria).

[c] Model adjusted for age (continuous), BMI (categorical; 18.5–24.9; 25.0–29.9; 30.0–39.9; ≥ 40.0); gender (ref: female; 1 = male; 2 = nonbinary); race (ref: 1 = white, 2 = Asian; 3 = AI/AN; 4 = AA; 5 = Mixed race; smoking (ref = never smoker; 1 = current smoker), and severity (NIH criteria), and depression/anxiety.

Table 4
Sensitivity analysis of statistically significant associations between pre-existing conditions and development of PASC, with common symptoms of pre-existing conditions removed.

Pre-existing condition	PASC/Total	Adjusted OR [1] (95% CI)
Respiratory		
Asthma	86/170	1.48 (1.06–2.08)
Bronchitis or Emphysema	3/5	2.72 (0.44–16.90)
COPD	6/10	0.67 (0.24–1.91)
Total Disease Category		*1.42 (1.02–1.98)*
Gastrointestinal		
Liver Disease	5/8	2.44 (0.56–10.67)
Ulcerative Colitis	3/5	2.31 (0.38–14.20)
Irritable Bowel Syndrome	39/70	1.59 (0.97–2.63)
Chronic Diarrhea	5/9	1.01 (0.25–4.16)
Chronic Constipation	11/14	4.60 (1.23–17.18)
Colitis	1/1	3.20 (0.63–16.1)
Reflux	5/8	1.54 (1.01–2.34)
Total Disease Category		*1.62 (1.16–2.26)*
Autoimmune		
Systemic lupus erythematosus	4/5	4.52 (0.50–41.1)
Multiple Sclerosis	2/3	2.23 (0.20–24.48)
Rheumatoid Arthritis	11/17	2.12 (0.75–6.04)
Total Disease Category		*3.42 (1.32–8.89)*
Other Conditions		
Seasonal Allergies	218/474	1.39 (1.09–1.78)
Depression/Anxiety	61/125	1.53 (1.04–2.25)

risk for the later development of PASC. While a point estimate could not be generated for SLE, 100% ofindividuals in our study who reported this condition and experienced a SARS-CoV-2 infection also reported having experienced PASC. Finally, when grouping conditions together, we observed that respiratory, gastrointestinal, and autoimmune conditions were all statistically significantly associated with PASC. When adding severity of acute SARS-CoV-2 infection and depression/anxiety to the model, only the presence of an autoimmune condition and seasonal allergies remained statistically significantly associated with PASC.

Previous investigations have shown that the presence of comorbid conditions is related to a significantly increased risk for PASC development [7–11,18]; however, to date, there is a dearth of studies identifying the specific conditions that may have the strongest associations. Data are particularly sparse for understanding if autoimmune disease renders individuals more susceptible to PASC [22]. However, a recent review of evidence described various autoimmune disorders that SARS-CoV-2 infection may initiate, including Guillain-Barre syndrome, SLE, neuromyelitis optica, myasthenia gravis, and vasculitis [32]. Additionally, in a study conducted by Dreyer et al. [22], it was found that individuals who reported medication use for an autoimmune condition were significantly more likely to still be experiencing fatigue and shortness of breath 30 days after their initial SARS-CoV-2 infection. Further, multiple sclerosis is known to be caused, at least in part, by infection with Epstein-Barr virus (EBV) [33], and SARS-CoV-2 has been shown to have the potential to reactivate EBV [34]. A prospective study from the UK showed that 57% of those with multiple sclerosis experienced an exacerbation of symptoms after COVID-19, including new or worsening symptoms [24]. This leads to the possibility that SARS-CoV-2 could interact with latent viruses to re-initiate inflammation and autoimmunity [35]. Given this information, it is possible that infection with SARS-CoV-2 may also

aggravate symptoms among those who already have an autoimmune condition, particularly among those using immunosuppressive medications to control their disease [22].

Next, results for the relationship between pre-existing allergies and risk for PASC have been equivocal. In a prior publication by our own research group, a significant association was observed between 127 participants reporting seasonal allergies [36] and risk of PASC, consistent with the expanded findings herein among 482 participants with allergies. Even after adjustment for acute severity and depression/anxiety, the results remained statistically significant. A prospective study conducted in Russia in a pediatric population also reported that allergic disease was significantly related to persistent symptoms following infection, possibly through the activation of mast cells [37]. However, due to the complexity of allergies, further work on specific allergic phenotypes is necessary.

The results of the present study for asthma are consistent with two others [23,38], but differ from another [39]. In a study conducted among 4500 participants with asthma from the UK, it was reported that approximately 56% had PASC; these individuals indicated that their breathing was worse since their SARS-CoV-2 infection, that inhaler use increased, and that the overall management of their disease was worse than prior to having COVID-19 [38]. Another large, prospective cohort study including more than 4000 participants from the UK, US, and Sweden showed that of asthma, lung disease, diabetes, heart disease, and kidney disease, asthma was the only pre-existing condition that was associated with the presence of symptoms at 28 days or more following acute SARS-CoV-2 infection [23]. In contrast, a prospective US study of approximately 35 asthmatic patients and 76 non-asthmatic patients who had tested positive for SARS-CoV-2 reported similar rates of symptoms at 30-, 60-, and 90- days post-infection [39]. In addition, a prior publication from our group using data from early in the pandemic showed that asthma was not significantly associated with the development of PASC [36]. At the time of publication, data from only 48 participants with asthma were available for the previous analysis, as compared to 173 participants for the present work. These findings suggest that the impact of pre-existing asthma on PASC may require comparatively large study populations to detect. Nonetheless, given that an estimated 25 million Americans are living with asthma [40], even modest effects could have a large impact on overall public health. While there have been equivocal findings regarding the relationship between different types of asthma and COVID-19 severity, heterogenous cytokine pathways may explain some of the variation in results [41]. Further, when severity of acute disease was added to the model, the results were no longer statistically significant, indicating that any relationship between pre-existing asthma and risk for PASC is related to the severity of the initial infection. As such, this is an area that requires further research with special attention to asthma phenotypes.

Prior work from our group within this population has shown that individuals who experienced gastrointestinal (GI) symptoms during acute infection were more likely than those who did not to report having persistent GI symptoms $\geq$45 days, with irritable bowel syndrome having been diagnosed in 3.0% of those with GI-related PASC [16]. However, work regarding the relationship between pre-existing GI conditions and PASC is sparse. We found that chronic constipation and reflux were both associated with an increased risk for PASC. There is increasing understanding of the role of the gut microbiota in immunity and response to infection by pathogens in general [42]. Because SARS-CoV-2 binds to angiotensin-converting enzyme-2 (ACE2) and transmembrane protease serine-2 (TMPRSS2), and both are expressed in the GI tract, there is a potential pathway for pathological disruption [43]. Recent work has shown that the gut microbiome is altered during SARS-CoV-2 infection, with some commensal bacteria known to have a role in immune protection being observed in lower proportions among those infected [44]; differences in the distribution of these commensals was also found to be related to disease severity. Hence, dysregulation within the GI tract prior to infection may lead to long-term effects arising from SARS-CoV-2 itself.

Depression/anxiety was the final pre-existing condition which we found to be associated with the development of PASC, and its inclusion in the final models for each pre-existing condition attenuated all point estimates toward the null with the exception of seasonal allergies and autoimmune conditions. Prior work has indicated that pre-existing anxiety and depression are associated with an increased risk of experiencing post-acute symptoms [25]. It is possible that anxiety and depression may render an individual more likely to be attuned to changes in physical health and hence more likely to report symptoms of PASC. In a study by Noviello et al. [31], it was found that both gastrointestinal symptoms and somatoform conditions were observed among patients who had been infected with SARS-CoV-2. While we were unable to directly assess somatoform disorders within this study, it is possible that extant depression or anxiety are so intertwined with the comorbidities under study that their impact cannot be separated with a comparatively small number of cases. Thus, adjusting for depression/anxiety may potentially be overfitting the models and as such may falsely attenuate the point estimates. In addition, there are also potential biological mechanisms that may also explain the observed relationship. While the role of psychological stress in immune system function is complex [45], prior work has demonstrated that depression and anxiety are intricately interwoven with inflammatory pathways that themselves are related to immune response [46]. Further, psychological interventions, particularly cognitive-behavioral therapy, significantly improve several physiological parameters related to immune function [47]. These findings indicate that developing therapies specifically for those who suffer from PASC would have beneficial effects on overall health and is an urgent area of attention.

Increasing severity of acute SARS-CoV-2 infection has been shown to be associated with a greater risk for developing PASC, though less severe initial infections have also been linked to a lesser extent [48]. In the present study, several comorbid conditions were associated with severity of acute infection, but not with PASC, including COPD and high blood pressure. These findings provide further evidence that while severity is a major contributor to risk for PASC, it does not appear to contribute in a homogeneous manner. Instead, it exhibits heterogeneity of effect based on the type of comorbidity and the presence of other factors, such as autoimmune disease. Further research into the biological mechanisms through which severity of acute disease contributes to PASC development are urgently needed.

Several strengths of this paper are noteworthy. The Arizona CoVHORT is a prospective study of more than 8500 participants, with well-characterized data regarding demographics, pre-existing conditions, and infection with SARS-CoV-2 with extensive data available regarding post-acute effects of COVID-19. However, limitations of the work must be addressed. First, while we queried participants specifically about whether symptoms arose following COVID-19 infection, it is possible that some data may capture usual symptoms related to pre-existing disease processes. To further examine this possibility, we conducted analyses whereby commonly-reported symptoms for each type of illness were removed, and saw similar results. Next, we largely relied on self-reports of COVID-19, though many participants were recruited via case investigations conducted by our research team, and we specifically ask for self-reported laboratory confirmed diagnoses of SARS-CoV-2. Although participants can self-report a COVID-19-like illness, these do not reflect most Arizona CoVHORT participants, and none of those participants are included in the present analysis. Next, an ideal study would include a broader, more diverse study. It has been demonstrated repeatedly that the pandemic has been experienced differently by individuals from different racial and ethnic groups, and further work must address whether risk factors for PASC differ by these characteristics.

In conclusion, this work identified numerous pre-existing conditions that may be related to increased risk for PASC. These findings will facilitate the development of public health efforts targeting high risk groups to prevent infection via vaccinations and boosters, masking,

ventilation and air filtration, and workplace accommodations.

Funding information

This research received no specific grant from any funding agency, commercial or not-for-profit sectors.

Declaration of competing interest

The authors report there are no competing interests to declare.

Data availability

Data will be made available on request.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaut.2022.102991.

References

[1] N. Zhu, D. Zhang, W. Wang, et al., A novel coronavirus from patients with pneumonia in China, 2019, N. Engl. J. Med. 382 (8) (2020) 727–733.
[2] I.D. Plumb, L.R. Feldstein, E. Barkley, et al., Effectiveness of COVID-19 mRNA vaccination in preventing COVID-19-associated hospitalization among adults with previous SARS-CoV-2 infection - United States, june 2021-february 2022, MMWR Morb. Mortal. Wkly. Rep. 71 (15) (2022) 549–555.
[3] Prevention CfDCa, Post-COVID conditions: overview for healthcare providers, Published, https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/post-covid-conditions.html, 2022. Accessed 10/11/2022.
[4] C. Fernandez-de-Las-Penas, D. Palacios-Cena, V. Gomez-Mayordomo, et al., Prevalence of post-COVID-19 symptoms in hospitalized and non-hospitalized COVID-19 survivors: a systematic review and meta-analysis, Eur. J. Intern. Med. 92 (2021) 55–70.
[5] M. Michelen, L. Manoharan, N. Elkheir, et al., Characterising long COVID: a living systematic review, BMJ Global Health 6 (9) (2021), e005427.
[6] A.A. Asadi-Pooya, A. Akbari, A. Emami, et al., Long COVID syndrome-associated brain fog, J. Med. Virol. (2021).
[7] M.L. Bell, C.J. Catalfamo, L.V. Farland, et al., Post-acute sequelae of COVID-19 in a non-hospitalized cohort: results from the Arizona CoVHORT, PLoS One 16 (8) (2021), e0254347.
[8] M.A. Hossain, K.M.A. Hossain, K. Saunders, et al., Prevalence of long COVID symptoms in Bangladesh: a prospective inception cohort study of COVID-19 survivors, BMJ Glob Health 6 (12) (2021).
[9] B. Kayaaslan, F. Eser, A.K. Kalem, et al., Post-COVID syndrome: a single-center questionnaire study on 1007 participants recovered from COVID-19, J. Med. Virol. 93 (12) (2021) 6566–6574.
[10] C. Fumagalli, C. Zocchi, L. Tassetti, et al., Factors associated with persistence of symptoms 1 year after COVID-19: a longitudinal, prospective phone-based interview follow-up cohort study, Eur. J. Intern. Med. (2021).
[11] D. Menges, T. Ballouz, A. Anagnostopoulos, et al., Burden of post-COVID-19 syndrome and implications for healthcare service planning: a population-based cohort study, PLoS One 16 (7) (2021), e0254523.
[12] D.R.T. Knight, B. Munipalli, Logvinov II, et al., Perception, Prevalence, and Prediction of Severe Infection and Post-acute Sequelae of COVID-19, The American Journal of the Medical Sciences, 2022.
[13] R. Kozak, S.M. Armstrong, E. Salvant, et al., Recognition of long-COVID-19 patients in a Canadian tertiary hospital setting: a retrospective analysis of their clinical and laboratory characteristics, Pathogens 10 (10) (2021).
[14] C.H. Sudre, B. Murray, T. Varsavsky, et al., Attributes and predictors of long COVID, Nat. Med. 27 (4) (2021) 626–631.
[15] Y. Kim, S.-W. Kim, H.-H. Chang, K.T. Kwon, S. Bae, S. Hwang, Significance and associated factors of long-term sequelae in patients after acute COVID-19 infection in korea, Infect Chemother 53 (3) (2021) 463–476.
[16] E. Austhof, M.L. Bell, M.S. Riddle, et al., Persisting gastrointestinal symptoms and post-infectious irritable bowel syndrome following SARS-CoV-2 infection: results from the Arizona CoVHORT, Epidemiol. Infect. 150 (2022) e136.
[17] S.M. Khan, L.V. Farland, C.J. Catalfamo, et al., Elucidating symptoms of COVID-19 illness in the Arizona CoVHORT: a longitudinal cohort study, BMJ Open 12 (1) (2022), e053403.
[18] D.J. Pinato, J. Tabernero, M. Bower, et al., Prevalence and impact of COVID-19 sequelae on treatment and survival of patients with cancer who recovered from SARS-CoV-2 infection: evidence from the OnCovid retrospective, multicentre registry study, Lancet Oncol. 22 (12) (2021) 1669–1680.
[19] E. Westerlind, A. Palstam, K.S. Sunnerhagen, H.C. Persson, Patterns and predictors of sick leave after Covid-19 and long Covid in a national Swedish cohort, BMC Publ. Health 21 (1) (2021) 1023.
[20] I.M. Tleyjeh, B. Saddik, N. AlSwaidan, et al., Prevalence and predictors of Post-Acute COVID-19 Syndrome (PACS) after hospital discharge: a cohort study with 4 months median follow-up, PLoS One 16 (12) (2021), e0260568.
[21] C. Fumagalli, C. Zocchi, L. Tassetti, et al., Factors associated with persistence of symptoms 1 year after COVID-19: a longitudinal, prospective phone-based interview follow-up cohort study, Eur. J. Intern. Med. (2021).
[22] N. Dreyer, N. Petruski-Ivleva, L. Albert, et al., Identification of a vulnerable group for post-acute sequelae of SARS-CoV-2 (PASC): people with autoimmune diseases recover more slowly from COVID-19, Int. J. Gen. Med. 14 (2021) 3941–3949.
[23] C.H. Sudre, B. Murray, T. Varsavsky, et al., Attributes and predictors of long COVID, Nat. Med. 27 (4) (2021) 626–631.
[24] A. Garjani, R.M. Middleton, R. Hunter, et al., COVID-19 is associated with new symptoms of multiple sclerosis that are prevented by disease modifying therapies, Mult Scler Relat Disord 52 (2021), 102939.
[25] D.R.T. Knight, B. Munipalli, Logvinov II, et al., Perception, prevalence, and prediction of severe infection and post-acute sequelae of COVID-19, Am. J. Med. Sci. (2022).
[26] D. Blumenthal, E.J. Fowler, M. Abrams, S.R. Collins, Covid-19 — implications for the health care system, N. Engl. J. Med. 383 (15) (2020) 1483–1488.
[27] C.J. Catalfamo, K.M. Heslin, A. Shilen, et al., Design of the Arizona CoVHORT: a population-based COVID-19 cohort, Front. Public Health 9 (21) (2021).
[28] K. Pogreba Brown, E. Austhof, A.M. Rosa Hernández, et al., Training and incorporating students in SARS-CoV-2 case investigations and contact tracing, Publ. Health Rep. 136 (2) (2020) 154–160.
[29] Health Nio, COVID-19 Treatment Guidelines Panel. Coronavirus Disease 2019 (COVID-19) Treatment Guidelines, National Institutes of Health, 2022. Published, https://www.covid19treatmentguidelines.nih.gov/. Accessed 10/18/2022, 2022.
[30] R.M. Mickey, S. Greenland, The impact of confounder selection criteria on effect estimation, Am. J. Epidemiol. 129 (1) (1989) 125–137.
[31] D. Noviello, A. Costantino, A. Muscatello, et al., Functional gastrointestinal and somatoform symptoms five months after SARS-CoV-2 infection: a controlled cohort study, Neuro Gastroenterol. Motil. 34 (2) (2022), e14187.
[32] H. Zacharias, S. Dubey, G. Koduri, D. D'Cruz, Rheumatological complications of covid 19, Autoimmun. Rev. 20 (9) (2021), 102883.
[33] K. Bjornevik, M. Cortese, B.C. Healy, et al., Longitudinal analysis reveals high prevalence of Epstein-Barr virus associated with multiple sclerosis, Science 375 (6578) (2022) 296–301.
[34] T. Chen, J. Song, H. Liu, H. Zheng, C. Chen, Positive Epstein-Barr virus detection in coronavirus disease 2019 (COVID-19) patients, Sci. Rep. 11 (1) (2021), 10902.
[35] G. Bellucci, V. Rinaldi, M.C. Buscarinu, et al., Multiple sclerosis and SARS-CoV-2: has the interplay started? Front. Immunol. 12 (2021), 755333.
[36] C.J. Bell MBC, L.V. Farland, K.C. Ernst, E.T. Jacobs, Y.C. Klimentidis, M. Jehn, K. Pogreba-Brown, Post-acute sequelae of COVID-19 in a non-hospitalized cohort: results from the Arizona CoVHORT, medRxiv (2021), 2021032921254588.
[37] I.M. Osmanov, E. Spiridonova, P. Bobkova, et al., Risk factors for post-COVID-19 condition in previously hospitalised children using the ISARIC Global follow-up protocol: a prospective cohort study, Eur. Respir. J. 59 (2) (2022).
[38] K.E.J. Philip, S. Buttery, P. Williams, et al., Impact of COVID-19 on people with asthma: a mixed methods analysis from a UK wide survey, BMJ Open Respir Res 9 (1) (2022).
[39] L.E. Eggert, Z. He, W. Collins, et al., Asthma phenotypes, associated comorbidities, and long-term symptoms in COVID-19, Allergy 77 (1) (2022) 173–185.
[40] Prevention CfDCa, National Health Interview Survey Data, U.S. Department of Health & Human Services, 2019. Published 2020, https://www.cdc.gov/asthma/nhis/2019/data.htm. (Accessed 23 September 2022). Accessed.
[41] A. Ludwig, C.E. Brehm, C. Fung, et al., Asthma and coronavirus disease 2019-related outcomes in hospitalized patients: a single-center experience, Ann. Allergy Asthma Immunol. 129 (1) (2022) 79–87 e76.
[42] Y. Belkaid, T.W. Hand, Role of the microbiota in immunity and inflammation, Cell 157 (1) (2014) 121–141.
[43] B. Wang, L. Zhang, Y. Wang, et al., Alterations in microbiota of patients with COVID-19: potential mechanisms and therapeutic interventions, Signal Transduct. Targeted Ther. 7 (1) (2022) 143.
[44] Y.K. Yeoh, T. Zuo, G.C. Lui, et al., Gut microbiota composition reflects disease severity and dysfunctional immune responses in patients with COVID-19, Gut 70 (4) (2021) 698–706.
[45] S.C. Segerstrom, G.E. Miller, Psychological stress and the human immune system: a meta-analytic study of 30 years of inquiry, Psychol. Bull. 130 (4) (2004) 601–630.
[46] C.H. Lee, F. Giuliani, The role of inflammation in depression and fatigue, Front. Immunol. 10 (2019) 1696.
[47] G.S. Shields, C.M. Spahr, G.M. Slavich, Psychosocial interventions and immune system function, JAMA Psychiatr. 77 (10) (2020) 1031.
[48] Y. Xie, B. Bowe, Z. Al-Aly, Burdens of post-acute sequelae of COVID-19 by severity of acute infection, demographics and health status, Nat. Commun. 12 (1) (2021) 6571.