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Psychiatric sequelae after SARS-Cov-2 infection: trajectory, predictors and associations in a longitudinal Australian cohort

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Original Article

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Abstract

A relationship between SARS-CoV-2 infection and psychiatric symptoms has been identified but is still being fully investigated. Neuropsychiatric sequalae have been reported for several infectious agents and are not unexpected for SARS-CoV-2 infection. This study follows for 12 months a sample ($N = 144$) of people who have had a confirmed infection of SARS-CoV-2. Medical and neuropsychiatric data and biological specimens are collected at 6 study visits. The 34-item SPHERE questionnaire, the Depression in the Medically Ill instrument, the EQ-5D-5L quality of life instrument and the visual analogue scale of fatigue were administered at multiple timepoints and associations with measures of illness and inflammatory biomarkers were investigated using the generalised estimating equation. Associations between inflammatory biomarkers and mental health measures of various effect sizes were identified. A robust inverse association was found between mental health outcomes and long covid status, but not between mental health outcomes and covid illness severity. This study suggests that long covid may be the strongest predictor of neuropsychiatric symptoms amongst people who have been infected with SARS-CoV-2.

Significant Outcomes

- No association was found between mental health outcomes and COVID illness severity.
- Long COVID may be the strongest predictor of neuropsychiatric symptoms amongst people who have been infected with SARS-CoV-2.
- Changes in immunologic biomarkers were associated with worse outcomes in mental health and quality-of-life measures

Limitations

- Neuropsychiatric outcomes and quality of life were not measured at admission
- History of illness prior to COVID infection was not collected
- No mental health diagnostic interview was administered
- This study used a small, heterogeneous sample. Studies elsewhere have found an association between psychiatric outcomes and measures of illness severity. It is not possible to determine whether findings of no association was due to the study being underpowered, methodological deficiencies that may have failed to detect an association, or whether there is genuinely no association.

Introduction

Prolonged illness, lasting months after the resolution of acute SARS-CoV-2 infection, continues to gain increased attention. This condition, known as post-COVID condition, post-acute sequelae of SARS-CoV-2 (PASC) or 'Long COVID' refers to persistent symptoms usually 3 months from the onset of COVID-19 which generally have an impact on everyday functioning (Soriano *et al.*, 2021). In addition to the commonly described persistent fatigue and dyspnoea,

neuropsychiatric symptoms have also been observed. *De novo* diagnosis of mood or anxiety, stress, or adjustment disorder in patients without previous history may also occur following SARS-CoV-2 infection, and these symptom clusters may lead to decreased quality of life and increased mortality (Diez-Quevedo *et al.*, 2021). Psychotic symptoms have also been reported from 14 to 90 days following acute infection (Gallo *et al.*, 2022). Psychiatric symptoms may develop *de novo* in people with no previous psychiatric history or represent exacerbation of symptoms in people with a history of psychiatric illness, with *de novo* psychiatric symptoms but not relapse of previous psychiatric illness associated with elevated inflammatory biomarkers interleukin-6 and C-reactive protein (CRP) (Iglesias-Gonzalez *et al.*, 2022). Reports vary regarding the prevalence of symptoms and associated risk factors, with a 6-month follow-up of 236,379 patients with COVID-19 finding a neurological or psychiatric diagnosis in 33.62% of the cohort with 12.84% as a first diagnosis and a more severe COVID-19 illness found to be a risk factor (Taquet *et al.*, 2021). Elsewhere, a study of 62,328 COVID-19 patients in China reported rates of stress as 48.1%, depression (26.9%) and anxiety (21.8%) (Bareeqa *et al.*, 2021).

Neuropsychiatric symptoms have long been associated with diverse mild to severe infections. They may be caused by the direct effects of the agent on the nervous system, psychological effects of illness, systemic biological effects including immune system activation, adverse effects of medications or combinations of these factors. The real or perceived threat from the COVID-19 pandemic has resulted in increased stress, anxiety and depression in the general community (Salari *et al.*, 2020), so it is unsurprising that psychological effects of COVID-19 also impact people who are infected. Many viruses like HIV and coronaviruses directly impact the brain (Cheng *et al.*, 2020). Activation of immuno-inflammatory systems, especially raised levels of pro-inflammatory cytokines, have been implicated in several psychiatric disorders including schizophrenia, bipolar disorder, major mood disorders, suicidal behaviour, post-traumatic disorder and autism (Leboyer *et al.*, 2016). Treatment with antiretroviral agents, including oseltamivir (Tamiflu) (Fuyuno, 2007), has been associated with adverse psychiatric effects (Abers *et al.*, 2014). A study of people with comorbid COVID-19 and mental illness found low rates of drug–drug interactions between treatments for the two illnesses resulting in mainly drowsiness (4.3% of cases) and borderline QTc prolongation (1.5% of cases) (Arbelo *et al.*, 2021).

It is difficult to assess the effect of a pandemic that is in progress; however, there is data from previous pandemics of coronaviruses. A study of the severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) pandemics concluded that, while most patients recover without experiencing mental illness, a significant proportion of patients in the acute stage experienced delirium. There was also a possibility of emergence of depression, anxiety, fatigue, post-traumatic stress disorder and rarer neuropsychiatric syndromes in the longer term (Rogers *et al.*, 2020). A similar pattern appears to be emerging for COVID-19.

Neuropsychiatric outcomes and quality of life were investigated in a cross-sectional analysis of 179 people who had been hospitalised for COVID-19 and followed up at 2-month post-discharge. There was moderate impairment of immediate verbal memory and learning (38% of the cohort), delayed verbal memory (11.8%), verbal fluency (34.6%) and working memory (6.1%), as well as neurocognitive impairment in at least one function (58.7%). Rates of anxiety (29.6%), depression (26.8%) and post-traumatic stress disorder (25.1%) were detected using validated screening instruments. Quality of life was assessed using the 12-item Short-Form Health Survey, with low scores for physical and mental components detected in 44.1% and 39.1% of patients, respectively. Delirium and psychiatric morbidity were positively associated with neurocognitive impairment. Female gender was related with increased psychiatric morbidity (Mendez *et al.*, 2021). Elsewhere, 1077 COVID-19 patients were interviewed 2 to 7 months after hospital discharge and administered questionnaires to assess mental health and quality of life. Illness severity was the greatest risk factor for mental health impairments in patients followed up a median of 5.9 months post-discharge (Evans *et al.*, 2021).

More recently, larger studies have confirmed the relationship between SARS-CoV-2 infection and psychiatric symptoms. A study of 236,379 patients found that 33.62% of patients received a neurological or psychiatric diagnosis within 6 months of infection, with 12.84% being a first diagnosis. A more severe COVID-19 illness was the greatest risk factor for a neurological or psychiatric diagnosis (Taquet *et al.*, 2021).

The ADAPT study is a prospective cohort of adults with confirmed SARS-CoV-2 infection confirmed in Sydney, Australia. Findings from 16- to 32-week follow-ups have been reported elsewhere (Darley *et al.*, 2021; Darley *et al.*, 2021; Phetsouphanh *et al.*, 2022). The aim of the current APADT substudy was to investigate neuropsychiatric outcomes and quality of life in a cohort of patients recovering after SARS-CoV-2 infection including both those managed in hospital and in the community for acute infection. We aim to describe the prevalence, severity and trajectory of persistent psychiatric symptoms. Secondary aims of the study were to identify predictors of mental illness and to investigate the relationship between immunological biomarkers in collected biospecimens and mental illness.

Method

Cohort

In March 2020, a cohort of adults after SARS-CoV-2 infection, confirmed by polymerase chain reaction and who could be contacted, were invited to participate in the ADAPT study. The study was approved by the St Vincent's Hospital Research Ethics Committee (2020/ETH00964). This cohort includes patients who were diagnosed through both St Vincent's hospital testing clinics (internal) and patients referred from external testing clinics (external). The cohort was recruited from confirmed COVID-19 cases. Medical history, including psychiatric history, was not a consideration for study inclusion. All patients were followed longitudinally under a defined schedule of assessments at commencing at baseline screening with follow-up (fu_1 to fu_6) visits scheduled at 1, 2, 4, 16, 32 and 48 weeks after the date of positive confirmation of SARS-CoV-2 demonstrated using the polymerase chain reaction (PCR) test, allowing for flexibility between scheduled and actual assessment dates for pragmatic reasons. Baseline demographics and symptoms from the period of acute infection were recalled retrospectively at the enrolment visit. The current analysis uses data up to 48 weeks of follow-up post-baseline. For this substudy, we included patients recruited between March 2020 and March 2021 with a minimum of 5.9 ± 3.5 months follow-up (fu_4 to fu_6).

Measures

Demographic data, comorbidities, symptoms at acute infection and confirmation of COVID-19 diagnosis were collected at

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baseline for all participants. At each assessment visit from the week 2 follow-up onwards, recovery symptoms were collected and psychiatric outcome scales and screens were performed including: Depression in the Medically Ill 10 item scale where a score of ≥ 9 suggested probable or definite depression (Parker *et al.*, 2002), SPHERE screening tool for mental disorders (Hickie *et al.*, 2001) and the EQ-5D-5L quality-of-life instrument (EuroQol Research Foundation, 2019). The visual analogue scale of fatigue (Lee *et al.*, 1991) was collected at the 8- and 12-month time points. At each assessment visit, blood for CRP was collected and biobanked for serologic and immunologic research. All data were stored on REDCAP.

Definitions

We defined Long COVID as the presence of persistent fatigue, or shortness of breath, or chest tightness > 4 months after initial infection. Any patients with abnormal mental health measures were offered either 'This Way Up' an online mental health tool (Andrews, 2020), or formal review by a hospital psychiatrist.

Statistical analyses

Longitudinal associations between with mental health self-report measures across follow-ups and potential predictive measures, including symptom severity, Long COVID status, pre-existing comorbidities or psychological conditions at baseline and CRP level, were investigated using the generalised estimating equation (GEE) models for continuous outcomes with Gaussian distribution, or dichotomised outcomes with logistic link. Models were adjusted for age, gender and smoking status. We used an unstructured covariance structure in employed GEE models to account for with-subject autocorrelation due to multiple measurements across the follow-ups.

Results

Demographics

A total of 144 patients completed assessment visits between 6 and 48 weeks and were included for analysis. The demographic and clinical characteristics of participants are described in Table 1. Participants included 84 (58.33%) males and 60 (41.67%) females, with a mean age of 46.9 ± 14.7 years and mean body mass index (BMI) 25.1 ± 4.0. Twelve (8.3%) patients reported a history of psychiatric illness and 95 (66.7%) reported at least one medical comorbidity. Hundred and fourteen (79.2%) patients had achieved higher technical education.

Clinical outcomes and trajectories

Long COVID was present in a similar proportion of patients at follow-up visit 4 (fu_4), 16 weeks post-baseline (n = 38, 26.4%) compared with the follow-up 5 (fu_5), 32 weeks post-baseline (n = 40, 27.8%), reducing to *n* = 16 (11.1%) at follow-up 6 (fu_6), 48 weeks post-baseline, suggesting that there was little recovery between 16 and 32 weeks, that only reduced as the cohort size decreased with participants lost to follow-up at 48 weeks. The burden of mental illness for the cohort is summarised in Table 2, which shows that by follow-up 3 (fu_3) at 4 weeks post-baseline, measures of quality of life, somatic distress and psychological distress have mean values within the normal range; however, a large subgroup of the cohort has significant impairment. Over 60% of the cohort have significant scores for somatic distress and over 64% for psychological distress at 4, 16 and 32 weeks.

Table 1. Sociodemographic characteristics of participants at baseline

Baseline characteristics	*n*	%
Gender		
Female	60	41.67
Male	84	58.33
Employment		
Full-time employment	80	55.56
Part-time/casual employment	20	13.89
Other	44	30.55
Education		
Completed high school up to year 10	6	4.16
Completed high school up to year 12	24	16.67
Completed higher technical education (TAFE, College, University degree)	114	79.17
Current smoker		
No	84	58.33
Yes	56	38.89
Unknown	4	2.78
Pre-existing psychological conditions		
No	132	91.67
Yes	12	8.33
Comorbidities (e.g., cardiac disease, asthma)		
No	92	63.89
Yes	52	36.11

Associations with mental health outcomes: clinical and inflammatory markers

Associations between baseline clinical characteristics at the time of acute infection and the presence of Long COVID were assessed using GEE models. The results are summarised in Table 3. The results for an analysis of predictors of psychological conditions suggest that Long COVID status is the most important predictor of mental impairment.

A stronger association was found between Long COVID and all mental health measures, where Long COVID was designated to participants who still had respiratory symptoms, malaise or fatigue at fu_4. No statistically significant association was found between severity of medical symptom of COVID and any of the psychiatric measures.

Associations with mental health outcomes: immunologic biomarkers

A battery of 27 immunologic biomarkers was measured from blood specimens collected at 62 participants at fu_4 (16 weeks) and from 20 participants at fu_5 (32 weeks) and tested for associations with mental health and quality-of-life measures (DMI/SPHERE/EQ-5D-5L/VAS) were investigated using GEE models. This demonstrated several significant associations of various effect sizes (Table 4), where a small effect is < 0.01, medium is

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Table 2. Mental health measures at each follow-up

	n†	Follow-up 3	Follow-up 4	Follow-up 5	Follow-up 6
EQ-5D-5L					
Mobility	142	1.09 ± 0.38(98)	1.12 ± 0.43(124)	1.09 ± 0.40(103)	1.19 ± 0.56(75)
Personal care	142	1.04 ± 0.28(98)	1.02 ± 0.20(124)	1.02 ± 0.20(103)	1.01 ± 0.12(75)
Usual activities	142	1.41 ± 0.87(98)	1.28 ± 0.64(124)	1.27 ± 0.63(103)	1.29 ± 0.71(75)
Pain/discomfort	143	1.43 ± 0.69(97)	1.42 ± 0.69(124)	1.42 ± 0.73(103)	1.51 ± 0.72(75)
Depression/anxiety	143	1.58 ± 0.78(96)	1.56 ± 0.75(122)	1.59 ± 0.75(103)	1.67 ± 0.79(75)
SPHERE					
Total	142	8.47 ± 9.41(116)	7.90 ± 9.82(122)	7.84 ± 9.07(102)	7.27 ± 8.64(74)
Somatic distress	142	2.72 ± 3.00(120)	2.38 ± 2.93(124)	2.50 ± 2.92(103)	2.16 ± 2.65(74)
Somatic distress ≥ 3	143	60.66%(74)	64.52%(80)	61.17%(63)	64.86%(48)
Psychological distress	142	1.56 ± 2.53(122)	1.60 ± 2.56(124)	1.17 ± 1.97(103)	1.20 ± 1.78(74)
Psychological distress ≥ 2	143	67.21%(82)	68.55%(85)	73.79%(76)	64.86%(48)
VAS Your health today	88	81.44 ± 12.45(99)	82.42 ± 11.19(125)	82.11 ± 11.89(103)	82.87 ± 12.09(75)
DMI10*	93	5.74 ± 6.61(120)	5.16 ± 6.04(104)		4.54 ± 5.31(63)
VAS fatigue**	77			2.76 ± 2.63(103)	3.19 ± 2.60(75)

For each measure at each follow-up, *n* is presented in parentheses.
†Number of participants who completed measure at least once.
*DMI10 was not administered in Wave 5.
**The fatigue VAS was not administered at Wave 3 and Wave 4.

Table 3. GEE models for investigating associations between pre-existing comorbidities or psychological conditions baseline, C-reactive protein level, symptom severity and Long COVID status, with mental health self-report measures across follow-ups, adjusted for age, gender and smoking status

Predictor	β	95% CI	*z*	*p*
EQ – 5D – 5L: Mobility				
Comorbidity	0.02	−0.11, 0.16	0.32	0.752
Psychological condition	0.04	−0.17, 0.24	0.36	0.721
CRP	0.005	−0.0002, 0.01	1.85	0.065
Symptom severity	−0.01	−0.14, 0.11	−0.22	0.826
Long COVID	0.23	0.09, 0.36	3.31	0.001
EQ – 5D – 5L: Personal care				
Comorbidity	0.03	−0.03, 0.10	0.97	0.334
Psychological condition	0.05	−0.04, 0.15	1.41	0.160
CRP	0.001	−0.001, 0.004	1.24	0.215
Symptom severity	−0.005	−0.06, 0.05	−0.16	0.871
Long COVID	0.07	0.004, 0.13	2.08	0.038
EQ – 5D – 5L: Usual activities				
Comorbidity	0.02	−0.18, 0.21	0.18	0.858
Psychological condition	0.21	−0.08, 0.50	1.44	0.151
CRP	0.004	−0.004, 0.01	0.99	0.323
Symptom severity	−0.009	−0.18, 0.16	−0.10	0.917
Long COVID	0.68	0.49, 0.88	6.98	< 0.001
EQ – 5D – 5L: Pain/discomfort				
Comorbidity	0.14	−0.06, 0.35	1.36	0.173
Psychological condition	0.19	−0.12, 0.49	1.19	0.236

(*Continued*)

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Table 3. (*Continued*)

Predictor	β	95% CI	*z*	*p*
CRP	−0.002	−0.01, 0.01	−0.58	0.564
Symptom severity	0.03	−0.15, 0.21	0.31	0.755
Long COVID	0.40	0.20, 0.61	3.90	<0.001
EQ – 5D – 5L: Depression/anxiety				
Comorbidity	0.08	−0.15, 0.31	0.70	0.486
Psychological condition	0.44	0.11, 0.77	2.59	0.010
CRP	−0.01	−0.01, 0.003	−1.24	0.215
Symptom severity	−0.04	−0.24, 0.16	−0.36	0.719
Long COVID	0.31	0.09, 0.53	2.76	0.006
SPHERE: Total				
Comorbidity	0.69	−2.12, 3.50	0.48	0.682
Psychological condition	3.90	−0.37, 8.17	1.79	0.073
CRP	0.02	−0.08, 0.12	0.38	0.700
Symptom severity	0.32	−2.20, 2.84	0.25	0.802
Long COVID	7.01	4.22, 9.80	4.93	<0.001
SPHERE: Somatic distress				
Comorbidity	−0.10	−0.95, 0.75	−0.23	0.818
Psychological condition	0.64	−0.64, 1.92	0.98	0.328
CRP	0.004	−0.03, 0.03	0.25	0.799
Symptom severity	−0.20	−0.97, 0.56	−0.52	0.602
Long COVID	2.767	1.93, 3.61	6.43	<0.001
SPHERE: Psychological distress				
Comorbidity	0.14	−0.55, 0.83	0.41	0.685
Psychological condition	1.66	0.65, 2.68	3.23	0.001
CRP	−0.008	−0.03, 0.02	−0.61	0.542
Symptom severity	−0.004	−0.61, 0.60	−0.01	0.988
Long COVID	0.79	0.12, 1.45	2.33	0.020
Your health today (VAS)				
Comorbidity	0.97	−2.52, 4.47	0.55	0.585
Psychological condition	−4.26	−9.51, 0.99	−1.59	0.112
CRP	−0.19	−0.33, −0.06	−2.87	0.004
Symptom severity	−0.66	−3.91, 2.48	−0.41	0.679
Long COVID	−8.03	−11.50, −4.56	1.77	<0.001
DMI – 10				
Comorbidity	−0.87	−2.75, 1.00	−0.91	0.362
Psychological condition	3.89	1.08, 6.70	2.72	0.007
CRP	0.004	−0.08, 0.08	0.11	0.916
Symptom severity	0.90	−0.79, 2.260	1.04	0.297
Long COVID	3.76	1.88, 5.64	3.92	<0.001
Fatigue (VAS)				
Comorbidity	0.23	−0.81, 1.28	0.43	0.665
Psychological condition	−0.23	−1.76, 0.08	−0.29	0.771
CRP	0.04	−0.002, 0.08	1.85	0.064

(*Continued*)

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Table 3. (*Continued*)

Predictor	β	95% CI	*z*	*p*
Symptom severity	−0.51	−1.42, 0.41	−1.09	0.276
Long COVID	2.53	1.51, 3.54	4.89	<0.001
Predictor	**OR**	**95% CI**	***z***	***p***
SPHERE: Somatic distress ≥ 3*				
Comorbidity	1.08	0.56, 2.10	0.23	0.818
Psychological condition	1.24	0.46, 3.37	0.42	0.675
CRP	1.00	0.98, 1.02	−0.10	0.922
Symptom severity	1.20	0.69, 2.10	0.65	0.513
Long COVID	4.37	2.40, 7.95	4.83	<0.001
SPHERE: Psychological distress ≥ 2*				
Comorbidity	0.92	0.44, 1.93	−0.22	0.830
Psychological condition	2.31	0.80, 6.63	1.55	0.121
CRP	0.98	0.96, 1.01	−1.31	0.189
Symptom severity	1.92	1.03, 3.57	2.05	0.041
Long COVID	2.09	1.10, 3.98	2.25	0.024

Comorbidity (yes), psych comorbid (yes), Symptom severity (severe), Long COVID (yes).
*Odds ratio and 95% CI are reported.

Table 4. GEE models for investigating associations between biomarkers and mental health self-report measures across follow-ups, adjusted for age, gender and smoking status

Predictor	B[95% CI]	*p*	Effect size (η_p^2)
EQ − 5D − 5L: Mobility			
MPOB2	−6.38e − 06[− 0.000019, 5.77e − 06]	0.300	0.0022
ICAM1B4	−0.000025[− 0.000053, 3.48e − 06]	0.085	0.018
GMCSFB5	−0.00052[− 0.0010, 1.19e − 06]	0.051	0.00074
IFNα2B3	0.011[− 0.00021, 0.021]	0.054	0.15
IFNβB6	−0.000095[− 0.00018, −0.000013]	0.024	0.0032
IFNγB9	−0.00012[− 0.00026, 0.000023]	0.099	0.0010
IFNλ1A8	0.0017[− 0.0016, 0.0051]	0.305	0.012
IFNλ23B4	0.0021[0.0010, 0.0032]	< 0.001	0.21
IL1βA4	0.026[− 0.024, 0.076]	0.299	0.030
IL5B9	−9.76e − 06[− 0.000017, −2.62e − 06]	0.008	0.0013
IL6A5	0.0052[− 0.0084, 0.019]	0.454	0.0070
IL8A10	0.00041[− 0.0030, 0.0039]	0.813	0.00015
IL9A8	−0.000063[− 0.00012, −7.74e − 06]	0.026	0.0038
IL10B7	0.0034[− 0.0063, 0.013]	0.494	0.0044
IL12p70B2	−0.00033[− 0.0017, 0.0010]	0.636	0.00012
IL13A5	−0.000033[− 0.000063, −1.92e − 06]	0.037	0.00090
IL33B3	−3.73e − 06[− 8.66e − 06, 1.19e − 06]	0.136	0.0046
IP10A7	0.0014[− 0.00076, 0.0035]	0.203	0.014
MCP1A10	−0.000073[− 0.00021, 0.000065]	0.295	0.0020
PD1B5	−0.000029[− 0.000055, −3.67e − 06]	0.025	0.0025
PECAM1B3	−0.000040[− 0.000077, −3.65e − 06]	0.031	0.0095
PTX3A7	1.00e − 05[− 0.000026, 0.000046]	0.586	0.0018

(*Continued*)

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Table 4. (*Continued*)

Predictor	B[95% CI]	*p*	Effect size (η_p^2)
sCD25A4	−0.000035[− 0.000095, 0.000025]	0.248	0.0040
TGFb1A3	−0.000025[− 0.000045, −4.87e − 06]	0.016	0.0024
TIM3B6	7.57e − 06[− 0.000023, 0.000038]	0.623	0.0033
TNFαA6	0.0012[− 0.0016, 0.0040]	0.406	0.014
VCAM1B5	−0.000041[− 0.000087, 5.02e − 06]	0.080	0.058
EQ − 5D − 5L: Personal care			
MPOB2	−4.44e − 07[− 2.54e − 06, 1.65e − 06]	0.675	0.00003
ICAM1B4	−0.000020[− 0.000047, 7.83e − 06]	0.159	0.033
GMCSFB5	0.000071[− 0.00032, 0.00046]	0.719	0.000039
IFNα2B3	0.011[0.00058, 0.022]	0.039	0.49
IFNβB6	−4.21e − 06[− 0.000027, 0.000019]	0.720	0.000018
IFNγB9	0.000045[− 0.000084, 0.00017]	0.493	0.00039
IFNλ1A8	0.0019[− 0.00094, 0.0047]	0.189	0.039
IFNλ23B4	0.0023[0.0013, 0.0033]	< 0.001	0.72
IL1βA4	0.036[− 0.014, 0.087]	0.158	0.16
IL5B9	−2.82e − 06[− 6.80e − 06, 1.16e − 06]	0.164	0.00030
IL6A5	0.00021[− 0.0010, 0.0014]	0.729	0.000034
IL8A10	0.0014[− 0.0011, 0.0039]	0.260	0.0052
IL9A8	−0.000023[− 0.000057, 0.000010]	0.172	0.0015
IL10B7	0.0051[− 0.0051, 0.0152]	0.323	0.029
IL12p70B2	0.00048[− 0.00080, 0.0018]	0.459	0.00073
IL13A5	−0.000016[− 0.000041, 7.70e − 06]	0.180	0.00065
IL33B3	−1.82e − 06[− 4.66e − 06, 1.02e − 06]	0.207	0.0029
IP10A7	0.0013[− 0.00054, 0.0031]	0.166	0.033
MCP1A10	−3.73e − 06[− 0.000028, 0.000020]	0.760	0.000015
PD1B5	−0.000011[− 0.000026, 5.20e − 06]	0.188	0.00089
PECAM1B3	−9.88e − 06[− 0.000024, 4.56e − 06]	0.178	0.0016
PTX3A7	−1.55e − 06[− 5.25e − 06, 2.15e − 06]	0.408	0.00012
sCD25A4	−5.97e − 06[− 0.000017, 4.55e − 06]	0.263	0.00033
TGFb1A3	−7.76e − 06[− 0.000019, 3.66e − 06]	0.181	0.00065
TIM3B6	0.000019[− 9.57e − 06, 0.000048]	0.189	0.060
TNFαA6	0.0015[− 0.0014, 0.0044]	0.298	0.066
VCAM1B5	−0.000032[− 0.000074, 0.000011]	0.144	0.099
EQ − 5D − 5L: Usual activities			
MPOB2	−0.000015[− 0.000047, 0.000017]	0.346	0.0042
ICAM1B4	−0.000013[− 0.000075, 0.000049]	0.685	0.0016
GMCSFB5	0.0068[− 0.0050, 0.019]	0.257	0.042
IFNα2B3	0.022 [0.0087, 0.036]	0.002	0.23
IFNβB6	0.00016[− 0.00032, 0.00064]	0.501	0.0032
IFNγB9	0.0012[− 0.0010, 0.0035]	0.283	0.036
IFNλ1A8	0.0051[− 0.0021, 0.012]	0.162	0.034
IFNλ23B4	0.0034[0.0020, 0.0048]	< 0.001	0.19
IL1βA4	0.032[− 0.042, 0.11]	0.394	0.017

(*Continued*)

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Table 4. (*Continued*)

Predictor	B[95% CI]	*p*	Effect size (η_p^2)
IL5B9	−0.000033[− 0.000046, −0.000021]	< 0.001	0.0050
IL6A5	0.026[− 0.012, 0.064]	0.182	0.060
IL8A10	0.0073[− 0.0099, 0.024]	0.404	0.016
IL9A8	−0.00023[− 0.00033, −0.00013]	< 0.001	0.017
IL10B7	0.023[− 0.0097, 0.055]	0.168	0.069
IL12p70B2	0.011[− 0.0077, 0.029]	0.252	0.043
IL13A5	−0.00015[− 0.00021, −0.000084]	< 0.001	0.0064
IL33B3	−0.000012[− 0.000021, −2.76e − 06]	0.011	0.014
IP10A7	0.0019[− 0.0019, 0.0057]	0.330	0.0085
MCP1A10	−0.00049[− 0.00086, −0.00012]	0.010	0.031
PD1B5	−0.000091[− 0.00014, −0.000046]	< 0.001	0.0074
PECAM1B3	−0.000024[− 0.000097, 0.000048]	0.507	0.0012
PTX3A7	0.000040[− 0.000038, 0.00012]	0.311	0.0094
sCD25A4	−0.00019[− 0.00030, −0.000080]	0.001	0.041
TGFb1A3	−0.000069[− 0.000099, −0.000038]	< 0.001	0.0061
TIM3B6	1.10e − 06 [− 0.000046, 0.000048]	0.963	0.000023
TNFαA6	0.0053[− 0.0015, 0.012]	0.127	0.093
VCAM1B5	−0.000043[− 0.00011, 0.000022]	0.190	0.022
EQ − 5D − 5L: Pain/discomfort			
MPOB2	−3.91e − 06 [− 0.000038, 0.000031]	0.822	0.00029
ICAM1B4	−0.000048[− 0.000099, 3.12e − 06]	0.065	0.024
GMCSFB5	0.00041[− 0.0034, 0.0042]	0.832	0.00016
IFNα2B3	0.016[0.0017, 0.030]	0.029	0.12
IFNβB6	−0.00020[− 0.00050, 0.000093]	0.177	0.0053
IFNγB9	−0.000054[− 0.00084, 0.00073]	0.892	0.000070
IFNλ1A8	0.0025[− 0.0036, 0.0086]	0.417	0.0087
IFNλ23B4	0.0029[0.0014, 0.0044]	< 0.001	0.14
IL1βA4	0.012[− 0.060, 0.085]	0.738	0.0024
IL5B9	−0.00031[− 0.00063, 4.55e − 06]	0.053	0.0016
IL6A5	0.0089[− 0.0098, 0.028]	0.348	0.0074
IL8A10	−0.0012[− 0.0091, 0.0066]	0.760	0.00047
IL9A8	−0.000071[− 0.00029, 0.00015]	0.518	0.0017
IL10B7	0.023[− 0.0097, 0.055]	0.422	0.0055
IL12p70B2	0.00078[− 0.0052, 0.0068]	0.798	0.00024
IL13A5	−0.00015[− 0.00020, −0.000087]	< 0.001	0.0063
IL33B3	−6.71e − 06[− 0.000015, 1.78e − 06]	0.120	0.0049
IP10A7	0.0022[− 0.0016, 0.0061]	0.254	0.013
MCP1A10	0.00012[− 0.00028, 0.00052]	0.548	0.0049
PD1B5	−0.000064[− 0.00012, −4.98e − 06]	0.034	0.0067
PECAM1B3	−0.000091[− 0.00016, −0.000025]	0.007	0.017
PTX3A7	0.000070[− 6.19e − 07, 0.00014]	0.052	0.030
sCD25A4	−0.00011[− 0.00023, 0.000019]	0.095	0.013
TGFb1A3	−0.000075[− 0.00011, −0.000045]	< 0.001	0.0077

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Table 4. (*Continued*)

Predictor	B[95% CI]	*p*	Effect size (η_p^2)
TIM3B6	0.000019[− 0.000026, 0.000063]	0.409	0.0071
TNFαA6	0.0020[− 0.0020, 0.0061]	0.326	0.014
VCAM1B5	−0.000051[− 0.00012, 0.000015]	0.132	0.031
EQ − 5D − 5L: Depression/anxiety			
MPOB2	0.00045[− 0.00009, 0.00098]	0.102	0.013
ICAM1B4	0.00049[− 0.00047, 0.0014]	0.319	0.0085
GMCSFB5	−0.027[− 0.087, 0.033]	0.376	0.0024
IFNα2B3	0.0010[− 0.0096, 0.012]	0.850	0.00045
IFNβB6	0.0010[− 0.0096, 0.012]	0.850	0.00045
IFNγB9	−0.0043[− 0.017, 0.0084]	0.507	0.0015
IFNλ1A8	−0.035[− 0.17, 0.096]	0.596	0.0059
IFNλ23B4	−0.040[− 0.063, −0.017]	0.001	0.093
IL1βA4	−0.18[− 1.32, 0.96]	0.758	0.0017
IL5B9	−0.00031[− 0.00063, 4.55e − 06]	0.053	0.0016
IL6A5	−0.11[− 0.31, 0.091]	0.287	0.0037
IL8A10	0.094[− 0.065, 0.25]	0.245	0.0098
IL9A8	−0.00032[− 0.0028, 0.0021]	0.796	0.00012
IL10B7	−0.15[− 0.38, 0.083]	0.207	0.010
IL12p70B2	−0.047[− 0.14, 0.048]	0.332	0.0030
IL13A5	−.00094[− 0.0024, 0.00053]	0.208	0.00091
IL33B3	0.000034[− 0.00015, 0.00022]	0.723	0.00043
IP10A7	0.0041[− 0.060, 0.069]	0.899	0.00015
MCP1A10	0.00018[− 0.0062, 0.0066]	0.957	0.000014
PD1B5	−0.00063[− 0.0015, 0.00023]	0.150	0.0013
PECAM1B3	0.00076[− 0.00048, 0.0020]	0.226	0.0041
PTX3A7	−0.00097[− 0.0024, 0.00043]	0.173	0.020
sCD25A4	0.0023[− 0.00041, 0.0049]	0.097	0.020
TGFb1A3	−0.00064[− 0.0013, 0.000032]	0.062	0.0019
TIM3B6	0.00022[− 0.00048, 0.00093]	0.533	0.0034
TNFαA6	−0.039[− 0.097, 0.019]	0.187	0.018
VCAM1B5	0.00078[− 0.00031, 0.0019]	0.159	0.026
SPHERE: Total			
MPOB2	−0.00029[− 0.00086, 0.00028]	0.316	0.019
ICAM1B4	−0.00091[− 0.0016, −0.00020]	0.013	0.042
GMCSFB5	−0.24 [− 0.43, −0.054]	0.012	0.094
IFNα2B3	0.17[− 0.0093, 0.34]	0.063	0.075
IFNβB6	0.00069[− 0.0027, 0.0041]	0.691	0.00029
IFNγB9	−0.0037[− 0.011, 0.0040]	0.343	0.0016
IFNλ1A8	0.041[− 0.058, 0.14]	0.417	0.011
IFNλ23B4	0.031[0.012, 0.050]	0.002	0.078
IL1βA4	0.37[− 0.64, 1.38]	0.467	0.011
IL5B9	−0.00034[− 0.00087, 0.00019]	0.205	0.0027
IL6A5	−0.015[− 0.16, 0.13]	0.832	0.00011

(*Continued*)

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Table 4. (*Continued*)

Predictor	B[95% CI]	*p*	Effect size (η_p^2)
IL8A10	−0.052[− 0.17, 0.070]	0.402	0.0042
IL9A8	0.00022[− 0.0036, 0.0040]	0.909	0.000080
IL10B7	0.017[− 0.15, 0.18]	0.840	0.00020
IL12p70B2	−0.021[− 0.077, 0.035]	0.454	0.00088
IL13A5	−0.0014[− 0.0035, 0.00078]	0.211	0.0027
IL33B3	−0.000099[− 0.00025, 0.000050]	0.189	0.0053
IP10A7	0.017[− 0.035, 0.069]	0.514	0.0036
MCP1A10	0.0010[− 0.0061, 0.0082]	0.776	0.00070
PD1B5	−0.00051[− 0.0019, 0.00088]	0.469	0.0012
PECAM1B3	−0.0018[− 0.0028, −0.00086]	< 0.001	0.034
PTX3A7	0.00061[− 0.00062, 0.0018]	0.326	0.011
sCD25A4	−0.0021[− 0.0039, −0.00032]	0.021	0.025
TGFb1A3	−0.00086[− 0.0019, 0.00019]	0.109	0.0049
TIM3B6	0.00045[− 0.000085, 0.00098]	0.099	0.0020
TNFαA6	0.011[− 0.034, 0.057]	0.617	0.0023
VCAM1B5	−0.00055[− 0.0014, 0.00026]	0.180	0.010
SPHERE: Somatic distress			
MPOB2	−0.000054[− 0.00023, 0.00012]	0.536	0.0027
ICAM1B4	−0.00021[− 0.00044, 0.000032]	0.090	0.022
GMCSFB5	−0.0067[− 0.019, 0.0054]	0.274	0.0022
IFNα2B3	0.050[− 0.0065, 0.11]	0.082	0.058
IFNβB6	0.0010[− 0.00051, 0.0025]	0.190	0.0080
IFNγB9	−0.0016[− 0.0041, 0.0010]	0.225	0.0030
IFNλ1A8	0.016[− 0.014, 0.045]	0.293	0.017
IFNλ23B4	0.0093[0.0033, 0.015]	0.003	0.072
IL1βA4	0.1086802[− 0.20, 0.41]	0.483	0.0092
IL5B9	−0.00016[− 0.00028, −0.000052]	0.005	0.0063
IL6A5	−0.0074[− 0.058, 0.043]	0.772	0.00025
IL8A10	−0.016[− 0.049, 0.018]	0.349	0.0040
IL9A8	−0.00028 [− 0.0013, 0.00077]	0.593	0.0014
IL10B7	−0.0015[− 0.054,0.051]	0.956	0.000015
IL12p70B2	−0.010[− 0.029, 0.0092]	0.302	0.0020
IL13A5	−0.00071[− 0.0012, −0.00024]	0.004	0.0076
IL33B3	−0.000051[− 0.000093, −8.97e − 06]	0.018	0.014
IP10A7	0.0045[− 0.011, 0.020]	0.580	0.0025
MCP1A10	−0.0011[− 0.0032, 0.00099]	0.296	0.0083
PD1B5	−0.00032[− 0.00064, −4.09e − 06]	0.047	0.0048
PECAM1B3	−0.00039[− 0.00070, −0.000092]	0.011	0.016
PTX3A7	0.00021[− 0.00019, 0.00061]	0.301	0.014
sCD25A4	−0.0011[− 0.0016, −0.00050]	< 0.001	0.064
TGFb1A3	−0.00041[− 0.00067, −0.00015]	0.002	0.011
TIM3B6	0.000097[− 0.000063, 0.00026]	0.232	0.0095
TNFαA6	0.0022[− 0.012, 0.016]	0.756	0.00086
VCAM1B5	−0.000064[− 0.00020, 0.000070]	0.347	0.0047

(*Continued*)

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Table 4. (*Continued*)

Predictor	B[95% CI]	*p*	Effect size (η_p^2)
SPHERE: Somatic distress ≥ 3*			
MPOB2	1.00[1.00, 1.00]	0.677	
ICAM1B4	1.00[1.00, 1.00]	0.781	
GMCSFB5	1.00[0.98, 1.02]	0.986	
IFNα2B3	1.01 [0.98, 1.05]	0.335	
IFNβB6	1.00[1.00, 1.01]	0.214	
IFNγB9	1.00[1.00, 1.00]	0.811	
IFNλ1A8	0.99[0.98, 1.01]	0.400	
IFNλ23B4	1.00[1.00, 1.01]	0.571	
IL1βA4	0.98[0.84, 1.14]	0.788	
IL5B9	1.00[1.00, 1.00]	0.600	
IL6A5	1.01[0.95, 1.08]	0.736	
IL8A10	1.00[0.96, 1.03]	0.245	
IL9A8	1.00[1.00, 1.00]	0.825	
IL10B7	1.00[0.96, 1.06]	0.867	
IL12p70B2	1.00[0.97, 1.03]	0.966	
IL13A5	1.00[0.99, 1.00]	0.531	
IL33B3	1.00[1.00,1.00]	0.226	
IP10A7	1.00[0.99, 1.01]	0.806	
MCP1A10	1.00[1.00, 1.00]	0.463	
PD1B5	1.00[1.00, 1.00]	0.445	
PECAM1B3	1.00[1.00, 1.00]	0.238	
PTX3A7	1.00[1.00, 1.00]	0.247	
sCD25A4	1.00[1.00, 1.00]	0.013	
TGFb1A3	0.99[0.99, 1.00]	0.116	
TIM3B6	1.00005[1.00, 1.00]	0.459	
TNFαA6	1.00[0.99, 1.01]	0.696	
VCAM1B5	1.00[1.00, 1.00]	0.967	
SPHERE: Psychological distress			
MPOB2	−0.000084 [− 0.00022, 0.000047]	0.205	0.050
ICAM1B4	−0.00022[− 0.00036, −0.000083]	0.002	0.084
GMCSFB5	−0.0073[− 0.013, −0.0018]	0.010	0.042
IFNα2B3	0.0080[− 0.016, 0.032]	0.511	0.0029
IFNβB6	−0.00077[− 0.0014, −0.00018]	0.011	0.044
IFNγB9	−0.0013[− 0.0028, 0.00013]	0.075	0.0041
IFNλ1A8	0.0079[− 0.013, 0.029]	0.460	0.0081
IFNλ23B4	0.0019[− 0.0013, 0.0051]	0.248	0.0056
IL1βA4	0.041[− 0.11, 0.19]	0.584	0.0025
IL5B9	0.000071[− 0.00017, 0.00031]	0.553	0.0023
IL6A5	−0.030[− 0.048, −0.013]	0.001	0.0080
IL8A10	−0.034[− 0.055, −0.012]	0.003	0.034
IL9A8	−0.000063[− 0.00085, 0.00072]	0.874	0.00013
IL10B7	−0.015[− 0.036, 0.0051]	0.139	0.0032

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Table 4. (*Continued*)

Predictor	B[95% CI]	*p*	Effect size (η_p^2)
IL12p70B2	−0.012[− 0.020, −0.0039]	0.004	0.0056
IL13A5	0.00025[− 0.00069, 0.0012]	0.597	0.0018
IL33B3	3.40e − 06[− 0.000048, 0.000055]	0.895	0.00012
IP10A7	0.0055[− 0.0052, 0.016]	0.310	0.0073
MCP1A10	−0.00022[− 0.00043, −2.73e − 06]	0.047	0.037
PD1B5	0.00011[− 0.00042, 0.00064]	0.687	0.0010
PECAM1B3	−0.00036[− 0.00059, −0.00014]	0.002	0.026
PTX3A7	−8.38e − 06[− 0.00026, 0.00024]	0.947	0.000042
sCD25A4	−0.000076[− 0.00057, 0.00042]	0.763	0.00063
TGFb1A3	0.00011[− 0.00034, 0.00055]	0.633	0.0015
TIM3B6	−0.000025[− 0.00011, 0.000063]	0.577	0.0012
TNFαA6	−0.0028[− 0.0076, 0.0020]	0.243	0.0027
VCAM1B5	−0.00022[− 0.00043, −2.73e − 06]	0.047	0.037
SPHERE: Psychological distress ≥ 2*			
MPOB2	1.00[1.00, 1.00]	0.160	
ICAM1B4	1.00[1.00, 1.00]	0.083	
GMCSFB5	0.98[0.92, 1.05]	0.563	
IFNα2B3	1.01[0.98, 1.04]	0.615	
IFNβB6	1.00[1.00, 1.00]	0.687	
IFNγB9	1.00[0.98, 1.01]	0.450	
IFNλ1A8	1.00[0.98, 1.02]	0.973	
IFNλ23B4	1.00[1.00, 1.01]	0.544	
IL1βA4	1.01[0.86, 1.19]	0.880	
IL5B9	1.00[1.00, 1.00]	0.708	
IL6A5	0.93[0.75, 1.16]	0.519	
IL8A10	0.96[0.91, 1.02]	0.177	
IL9A8	1.00[1.00, 1.00]	0.834	
IL10B7	0.97[0.89, 1.06]	0.540	
IL12p70B2	0.97[0.86, 1.08]	0.566	
IL13A5	1.00[1.00, 1.00]	0.710	
IL33B3	1.00[1.00,1.00]	0.759	
IP10A7	1.01[0.99, 1.02]	0.282	
MCP1A10	1.00[1.00, 1.00]	0.746	
PD1B5	1.00[1.00, 1.00]	0.735	
PECAM1B3	1.00[1.00, 1.00]	0.130	
PTX3A7	1.00[1.00, 1.00]	0.758	
sCD25A4	1.00[1.00, 1.00]	0.694	
TGFb1A3	1.00[1.00, 1.00]	0.744	
TIM3B6	1.00[1.00, 1.00]	0.975	
TNFαA6	1.00[0.98, 1.01]	0.633	
VCAM1B5	1.00[1.00, 1.00]	0.261	

(*Continued*)

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Table 4. (*Continued*)

Predictor	B[95% CI]	*p*	Effect size (η_p^2)
Your health today (VAS)			
MPOB2	−0.000026[− 0.000060, 6.99e − 06]	0.120	0.53
ICAM1B4	−0.000045[− 0.000085, −4.80e − 06]	0.028	0.49
GMCSFB5	−0.0012[− 0.0041, 0.0018]	0.439	0.0016
IFNα2B3	0.00061[− 0.0063, 0.0075]	0.863	0.048
IFNβB6	−0.00018[− 0.00042, 0.000055]	0.131	0.000012
IFNγB9	−0.00036[− 0.00098, 0.00026]	0.256	0.0036
IFNλ1A8	−0.0010[− 0.0048, 0.0028]	0.594	0.075
IFNλ23B4	0.00012[− 0.0012, 0.0015]	0.861	0.086
IL1βA4	−0.00083[− 0.0023, 0.0012]	0.416	0.00019
IL5B9	0.000048[0.000011, 0.000085]	0.011	0.0020
IL6A5	−0.0032[− 0.013, 0.0064]	0.510	0.0050
IL8A10	−0.0074[− 0.014, −0.00053]	0.035	0.0026
IL9A8	0.00019[0.000046, 0.00034]	0.010	0.00020
IL10B7	−0.0026[− 0.011, 0.0056]	0.526	0.0078
IL12p70B2	−0.0021[− 0.0067, 0.0026]	0.380	0.0028
IL13A5	0.00022[0.000067, 0.00027]	0.005	0.0026
IL33B3	0.000013[3.93e − 06, 0.000022]	0.005	0.0052
IP10A7	−0.0014[− 0.0042, 0.0013]	0.309	0.0024
MCP1A10	0.00027[− 0.00015, 0.00069]	0.212	0.020
PD1B5	0.00013[0.000041, 0.00021]	0.004	0.0011
PECAM1B3	−0.00016[− 0.00022, −0.000093]	< 0.001	0.14
PTX3A7	0.000032[− 0.000017, 0.000081]	0.194	0.087
sCD25A4	5.06e − 06[− 0.00012, 0.00013]	0.934	0.057
TGFb1A3	0.000089[0.000019, 0.00016]	0.013	0.00080
TIM3B6	−5.43e − 08[− 0.000028, 0.000028]	0.997	0.025
TNFαA6	−0.00035[− 0.0021, 0.0014]	0.687	0.0052
VCAM1B5	−0.000029[− 0.000066, 8.30e − 06]	0.128	0.0033
DMI − 10			
MPOB2	−0.00023[− 0.00050, 0.000046]	0.103	0.014
ICAM1B4	−0.00040[− 0.00074, −0.000057]	0.022	0.025
GMCSFB5	−0.000067[− 0.017, 0.017]	0.994	7.47e − 08
IFNα2B3	0.092[0.019, 0.17]	0.014	0.069
IFNβB6	−0.0018[− 0.0030, −0.00059]	0.004	0.010
IFNγB9	−0.00074[− 0.0044, 0.0029]	0.691	0.00023
IFNλ1A8	0.011[− 0.027, 0.049]	0.560	0.0033
IFNλ23B4	0.018[0.0095, 0.027]	< 0.001	0.091
IL1βA4	−0.0018[− 0.013, 0.0093]	0.748	0.00012
IL5B9	0.00039[− 0.00022, 0.0010]	0.204	0.013
IL6A5	−0.0063[− 0.060, 0.047]	0.815	0.000065
IL8A10	−0.053[− 0.10, −0.0015]	0.044	0.015

(*Continued*)

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Table 4. (*Continued*)

Predictor	B[95% CI]	*p*	Effect size (η_p^2)
IL9A8	0.00055[– 0.0015, 0.0026]	0.605	0.0017
IL10B7	0.032[– 0.042, 0.11]	0.394	0.0025
IL12p70B2	–0.0021[– 0.028, 0.024]	0.871	0.0080
IL13A5	0.0015[– 0.00093, 0.0039]	0.227	0.011
IL33B3	0.000075[– 0.000050, 0.00020]	0.238	0.010
IP10A7	0.0014[– 0.023, 0.026]	0.913	0.0081
MCP1A10	0.0013[– 0.0025, 0.0052]	0.490	0.0032
PD1B5	0.00085[– 0.00050, 0.0022]	0.218	0.012
PECAM1B3	–0.00096[– 0.0015, –0.00039]	0.001	0.024
PTX3A7	0.00033[– 0.000090, 0.00075]	0.122	0.011
sCD25A4	1.46e – 06[– 0.0012, 0.0012]	0.998	3.94e – 08
TGFb1A3	0.00069[– 0.00044, 0.0018]	0.229	0.011
TIM3B6	–0.000094[– 0.00036, 0.00017]	0.490	0.0029
TNFαA6	0.0099[– 0.0094, 0.029]	0.311	0.0060
VCAM1B5	–0.00028[– 0.00066, 0.000098]	0.145	0.016
Fatigue (VAS)			
MPOB2	–0.000068[– 0.00028, 0.00014]	0.518	0.0062
ICAM1B4	–0.000078[– 0.00034, 0.00018]	0.554	0.0044
GMCSFB5	–0.018[– 0.023, –0.013]	< 0.001	0.024
IFNα2B3	0.00051[– 0.050, 0.051]	0.984	9.42e – 06
IFNβB6	0.0036[0.002052, 0.0052]	< 0.001	0.056
IFNγB9	–0.0037[– 0.0053, –0.0021]	< 0.001	0.025
IFNλ1A8	–0.011[– 0.043, 0.020]	0.474	0.010
IFNλ23B4	0.00036[– 0.0072, 0.0079]	0.924	0.00017
IL1βA4	0.063[– 0.26, 0.39]	0.700	0.0045
IL5B9	0.000067[1.60e – 06, 0.00013]	0.045	0.0016
IL6A5	–0.038[– 0.095, 0.019]	0.187	0.010
IL8A10	–0.018[– 0.082, 0.046]	0.577	0.0075
IL9A8	0.00094[– 0.00043, 0.0023]	0.175	0.023
IL10B7	–0.041[– 0.069 – 0.013]	0.005	0.018
IL12p70B2	–0.026[– 0.036, –0.016]	< 0.001	0.021
IL13A5	0.00041[7.99e – 06, 0.00081]	0.046	0.0039
IL33B3	8.08e – 06[– 0.000043, 0.000059]	0.750	0.00055
IP10A7	–0.0044[– 0.027, 0.018]	0.693	0.0037
MCP1A10	–0.00053[– 0.0032, 0.0021]	0.693	0.0028
PD1B5	0.00028[– 0.00015, 0.00071]	0.194	0.0058
PECAM1B3	–0.00054[– 0.00093, –0.00015]	0.008	0.045
PTX3A7	0.000087[– 0.00028, 0.00045]	0.638	0.0031
sCD25A4	–0.00050[– 0.0013, 0.00031]	0.219	0.022
TGFb1A3	0.000090[– 0.000069, 0.00025]	0.260	0.00085
TIM3B6	0.000048[– 0.00024, 0.00033]	0.738	0.0033
TNFαA6	–0.0071[– 0.015, 0.0010]	0.086	0.014
VCAM1B5	0.00078[– 0.00031, 0.0019]	0.159	0.026

Comorbidity (yes), psych comorbid (yes), Symptom severity (severe), Long COVID (yes).
*Odds ratio and 95% CI are reported.

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0.06 and > 0.14 is a large effect. A significant association was found between raised levels of CRP and VAS your health today score ($p = 0.004$). A trend towards significance was found for the VAS fatigue score ($p = 0.064$).

Discussion

Our findings suggests that a designation of Long COVID is the study variable of greatest concern for an increased risk of psychiatric symptoms following SARS-CoV-2 infection. Long COVID appears to be associated with diverse symptoms, including depression, fatigue and reduced quality of life and may be consistent with an emerging chronic fatigue like syndrome.

No association was detected between severity of medical symptom of SARS-CoV-2 infection, such as ventilator use or intensive care unit (ICU) admission and psychiatric outcomes.

A weak association was demonstrated between increased CRP and mental health measures. CRP was only measured at follow-up (fu3 onwards), and measures were generally low. At fu3, there was one person with CRP 58.9, one who scored 15.7 and a third who scored 10.8. All others scored<10. CRP scores at other follow-ups were even lower. This leaves open the possibility that a stronger association between CRP and mental health measures was not detected because of the small sample size and missing the peak for CRP that may have occurred earlier in the illness.

Conclusion

SARS-CoV-2 infection is associated with some psychiatric comorbidity, significantly in people with Long COVID. Further prospective follow-ups are required to determine the duration and characteristics of psychiatric sequaelae of Long COVID. Studies of larger populations are required to fully characterise the association between SARS-CoV-2 infection and psychiatric comorbidity. This study suggests that Long COVID may be the strongest predictor of neuropsychiatric symptoms amongst people who have been infected with SARS-CoV-2.

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Author contribution. SD, JO'D and MB are mental health researchers who prepared the first draft of the manuscript. MM conducted statistical analyses. GM and DRD are involved in COVID treatment and research and collected the data for this study. All authors approved the final manuscript.

Competing interests. **SD** has received grant support from the Stanley Medical Research Institute, NHMRC, Beyond Blue, ARHRF, Simons Foundation, Geelong Medical Research Foundation, Harry Windsor Foundation, Fondation FondaMental, Eli Lilly, Glaxo SmithKline, Organon, Mayne Pharma and Servier, speaker's fees from Eli Lilly, advisory board fees from Eli Lilly and Novartis, and conference travel support from Servier. **MB** has received Grant/Research Support from the NIH, Cooperative Research Centre, Simons Autism Foundation, Cancer Council of Victoria, Stanley Medical Research Foundation, Medical Benefits Fund, National Health and Medical Research Council, Medical Research Futures Fund, Beyond Blue, Rotary Health, A2 milk company, Meat and Livestock Board, Woolworths, Avant and the Harry Windsor Foundation, has been a speaker for Abbot, Astra Zeneca, Janssen and Janssen, Lundbeck and Merck and served as a consultant to Allergan, Astra Zeneca, Bioadvantex, Bionomics, Collaborative Medicinal Development, Janssen and Janssen, Lundbeck Merck, Pfizer and Servier – all unrelated to this work. **MM, JO'D, GM** and **DRD** have no conflicts of interest.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national and institutional committees on human experimentation and with the Helsinki Declaration of 1975, as revised in 2008. The study was approved by the St Vincent's Hospital Research Ethics Committee (2020/ETH00964).

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