Supplementary material

Post-acute COVID-19 neuropsychiatric symptoms are not associated with ongoing nervous system injury

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Supplementary methods

Variables used in the analyses

Here we provide details on how the different variables used in the analyses were measured and encoded.

The following variables were used as markers of COVID-19 severity:

- WHO score: this is a scale defined by the WHO to capture the level of respiratory support needed by patients with COVID-19. It consists of 4 levels: no oxygen required (level 0), supplemental oxygen required (level 1), ventilation required (level 2, which we captured based on either continuous positive airway pressure ventilation, bi-level non-invasive ventilation or high-flow nasal oxygen needed at any point during hospital admission), and lastly invasive ventilation/oxygenation required (level 3, which was captured as either invasive mechanical ventilation or extra-corporeal membrane oxygenation). This was encoded as a continuous variable.
- National Early Warning Scores (NEWS): This scale captures the degree of departure of physical observations (a.k.a. vitals) from their normal range and is used nationally in the National Health Service (NHS) in the UK. It is a score ranging from 0 to 20 which we encoded as a continuous variable. Specifically, the following scoring is applied for the different physical observations and the total score is obtained by summing up the scores for the different items:
    - Respiratory Rate [breaths/min]: ≤ 8 (+2 points), 9-11 (+1 point), 12-20 (0 points), 21-21 (+2 points), ≥ 25 (+ 3 points);
    - Oxygen saturations: ≤ 91% (+3 points), 92-93% (+2 points), 94-95% (+1 point), ≥ 96% (+0 points);
    - Any supplemental oxygen: No (+0 points), Yes (+2 points);

- Temperature: ≤ 35°C (+3 points), 35.1-36°C (+1 point), 36.1-38°C (+0 points), 38.1-39°C (+1 point), ≥ 39.1°C (+2 points);
- Systolic Blood Pressure [mmHg]: ≤ 90 (+3 points), 91-100 (+2 points), 101-110 (+1 point), 111-219 (+0 points), ≥220 (+3 points);
- Heart Rate [beats per minute]: ≤ 40 (+3 points), 41-50 (+1 point), 51-90 (+0 points), 91-110 (+1 point), 111-130 (+2 points), ≥131 (+3 points).

- Recovery clusters: identified in a previous study based on the PHOSP cohort with clusters calculated using patient symptom questionnaires, physical performance, and cognitive assessment data.[1] The four resulting clusters, stratifying patients in terms of the severity of their recovery and the level of subsequent impairment, were categorised as follows:
  - Mild impairment;
  - Moderate impairment with cognitive impairment;
  - Severe impairment;
  - Very severe impairment.

  Recovery cluster variable was encoded categorically with mild impairment used as a reference level.
- Duration of hospital admission: captured from the participant's health record and recorded as a continuous variable
- Diagnosis of pulmonary embolism during hospitalisation: captured from the participant's health record and recorded as a continuous variable
- Admission to intensive care: captured from the participant's health record and recorded as a continuous variable
- Presence of altered consciousness or confusion during admission: captured from the participant's health record and recorded as a continuous variable

The neuropsychiatric outcomes used were the total Montreal Cognitive Assessment (MoCA), the Patient Health Questionnaire (PHQ-9), the Generalized Anxiety Disorder scale (GAD-7), and a cognitive subset of the Patient Symptom Questionnaire (PSQ). The latter is a score ranging from 0 to 7 which we encoded as a continuous variable. The latter was defined as the sum of the following items from PSQ:

- Within the last seven days, have you had any of these symptoms…?
    - Confusion (Yes: +1 point, No: 0 point)
    - Short term memory loss (Yes: +1 point, No: 0 point)
    - Difficulty with concentration (Yes: +1 point, No: 0 point)
    - Difficulty with communication (Yes: +1 point, No: 0 point)
    - Slowing down in your thinking (Yes: +1 point, No: 0 point)
- Do you have difficulty remembering or concentrating?:
    - No: 0 points
    - Yes, some difficulty: + 1/3 point
    - Yes, a lot of difficulty: + 2/3 points
    - Yes, cannot do at all: +1 point
- Do you have difficulty communicating, for example understanding or being understood?
    - No: 0 points
    - Yes, some difficulty: + 1/3 point
    - Yes, a lot of difficulty: + 2/3 points
    - Yes, cannot do at all: +1 point

The different covariates used in the analysis and their measurement were as follows:

- Diagnoses of respiratory condition
- Diagnosis of a rheumatological condition
- Diagnosis of cardiovascular condition
- Diagnosis of gastrointestinal condition
- History of a cerebrovascular accident
- Diagnosis of dementia
- Diagnosis of Parkinson's disease
- Diagnosis of depression or anxiety
- Diagnosis of another chronic condition, specifically chronic fatigue syndrome or chronic pain
- Diagnosis of diabetes
- Diagnosis of hypothyroidism/hyperthyroidism or other chronic metabolic/endocrine disorder
- Diagnosis of chronic kidney disease
- History of cancer
- History of chronic infectious diseases
- Educational level (highest level completed): encoded as a categorical variable with the following 8 categories:
    - None
    - Primary School
    - Secondary School (GCSE level, NVQ level ½ or equivalent, typically at the age of 16)
    - Sixth form college (A-levels, NVQ level 3 or equivalent, typically at the age of 18)
    - Vocational qualification (NVQ level 4 or equivalent)

    - Undergraduate university degree or NVQ level 5 or equivalent
    - Post-graduate qualification
    - Prefer not to say
- Annual Household Income: encoded as a categorical variable with the following categories:
    - < £19,000
    - £19,001- £26,000
    - £26,001-£35,000
    - £35,001-£48,000
    - >£48,001
    - Prefer not to say
- Marital status: encoded with a single binary variable (married vs. not)
- Whether English was a patient's first language, as reported by the patient and encoded as a binary variable.

Details on statistical and robustness analyses

In this paper, we addressed two objectives:

- Objective 1: seeking association between markers of nervous system injury and post-acute neuropsychiatric outcomes
- Objective 2: seeking associations between markers of severity of the acute COVID-19 illness and markers of nervous system injury

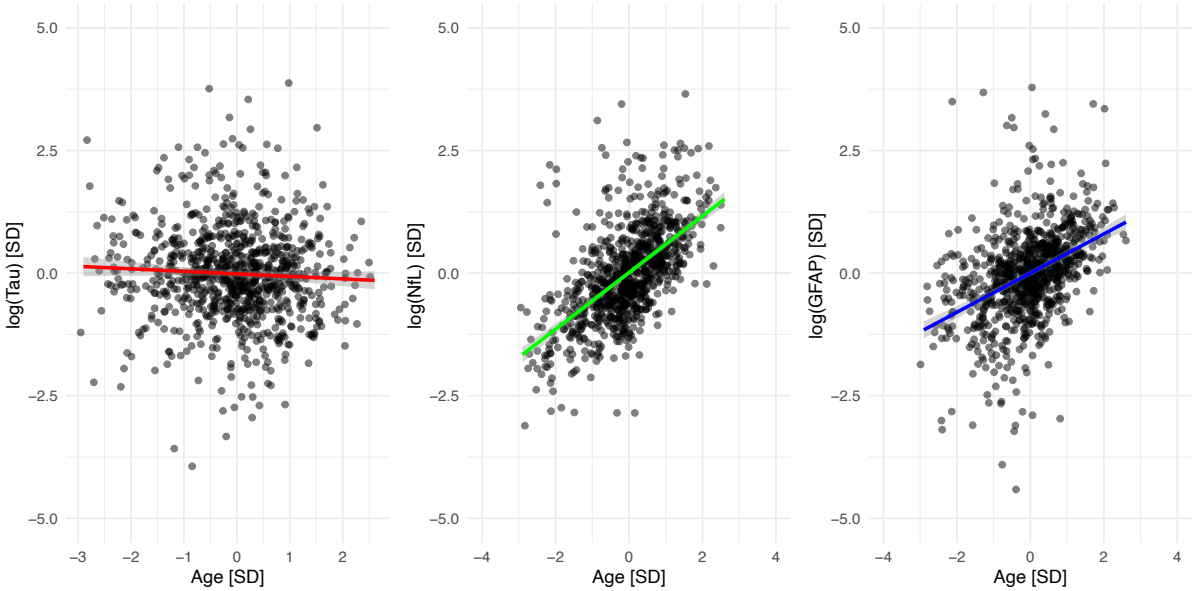
In the primary analysis, only complete data was used (any participant with missing data on any of the exposure, outcome, or covariate data was discarded) and 3x8 separate regression models were estimated for Objective 1 (one for each marker of nervous system injury and

each neuropsychiatric outcome) and 7x3 separate regression models were estimated for Objective 2 (one for each marker of COVID-19 severity and each marker of nervous system injury, where each model returned one coefficient except for the model related to recovery clusters which returned 3 coefficients, one for each level of the categorical variable).

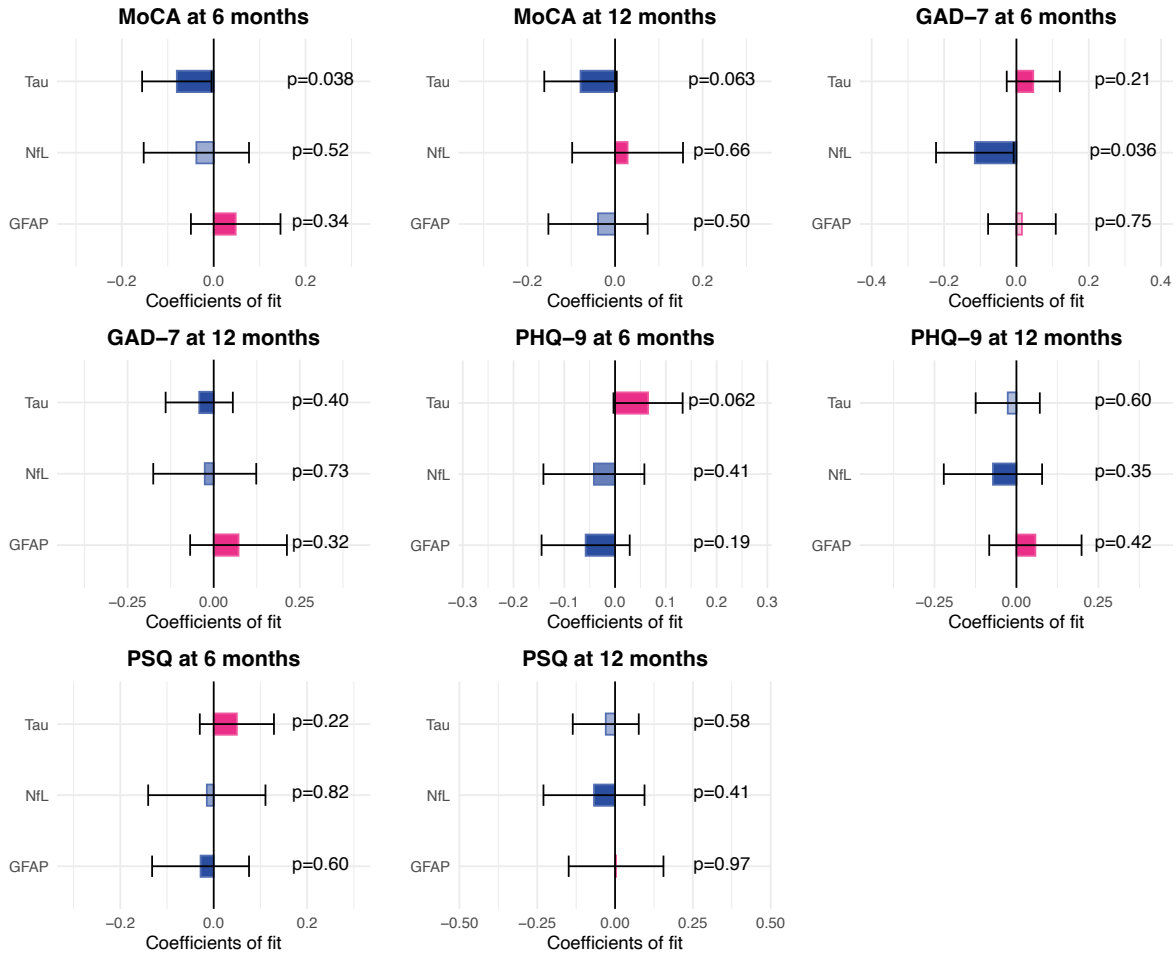
For both Objectives 1 and 2, we then ran 2 robustness analysis:

1) Using a single model incorporating all independent variables: for Objective 1, this meant that all three markers of nervous system injury were incorporated as independent variable in the regression model and only 8 separate regressions (rather than 24) were estimated (one for each neuropsychiatric outcome). For Objective 2, this meant that all seven markers of COVID-19 severity were incorporated as independent variables in the regression model and only three separate regressions (rather than 21) were estimated (one for each marker of nervous system injury).
2) Imputing missing data: Missing data on markers of COVID-19 severity, post-acute neuropsychiatric outcomes (i.e. GAD-7, PHQ-9, MoCA, and C-PSQ) or confounders were imputed (markers of nervous system injury were not imputed and only participants with complete data on these biomarkers were included). Variables used to predict aforementioned missing data were demographics, COVID-19 severity markers and markers of nervous system injury. The imputation was achieved using multiple imputation by chain equation model with 20 chains and 5 iterations, using the mice package (version 3.14.0). To maximise the information available in the imputation, the whole PHOSP-COVID cohort (not just those with markers of nervous system injury) was used to impute the missing data.

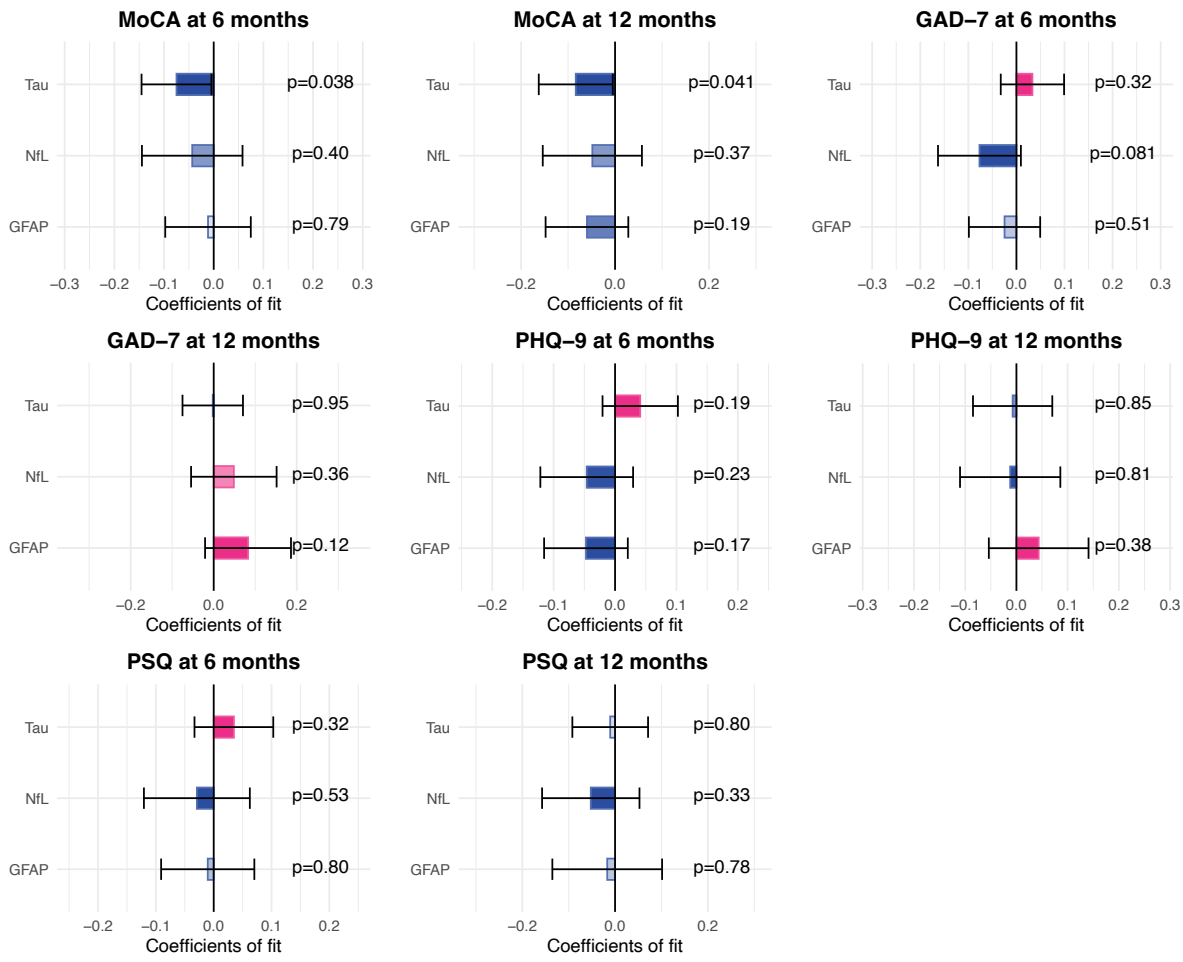
Supplementary figures



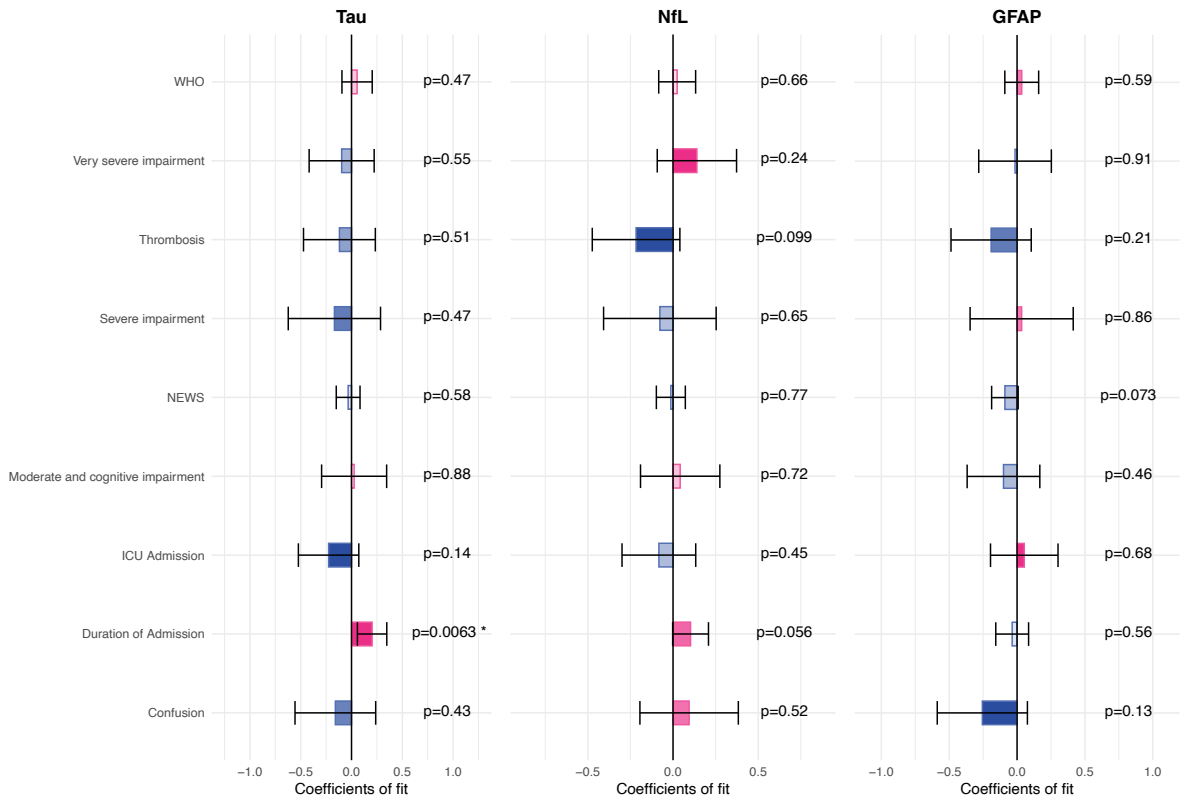
Supplementary Figure 1: Distributions of standardised markers of nervous system injury in logarithmic scale as functions of standardised age at hospitalisation admission. Pearson's correlation with standardised age is as follows; r (p-value): log(Tau) r = -0.05 (0.13); log(NfL) r = 0.57 (< 0.001); log(GFAP) r = 0.38 (< 0.001).



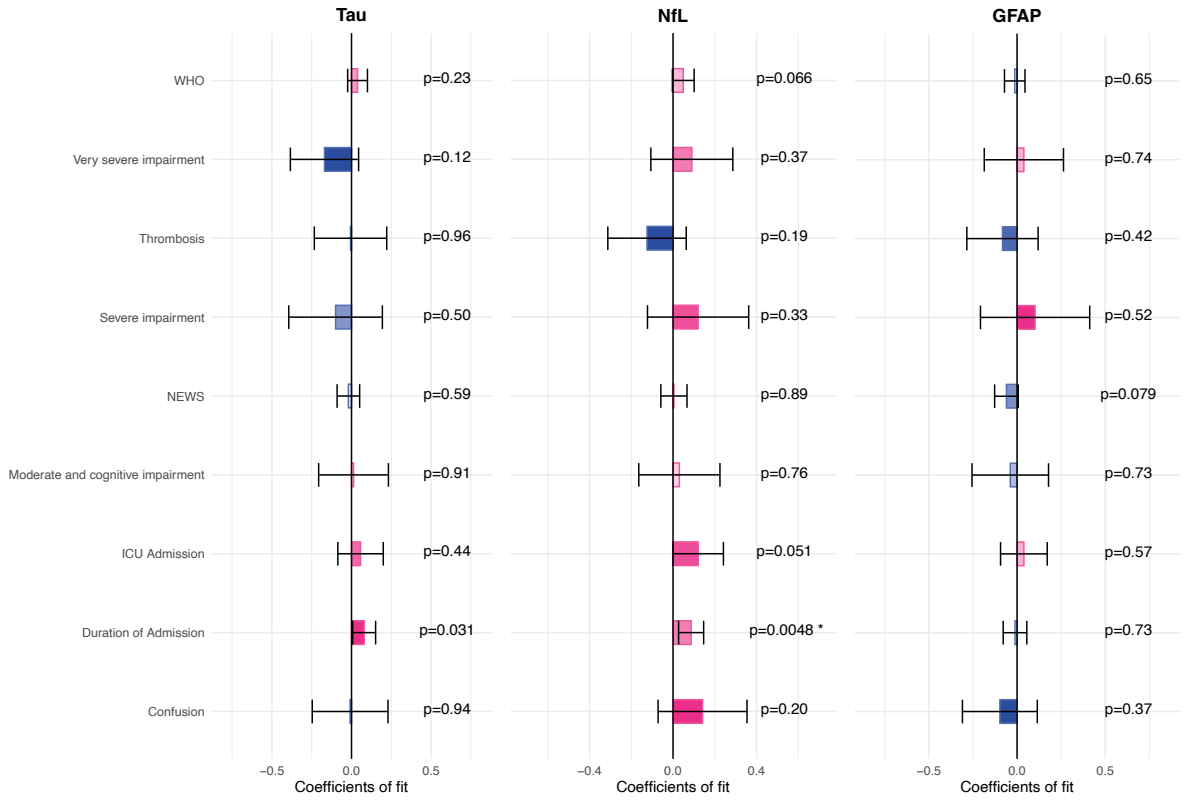
Supplementary Figure 2: Same as Figure 1 of the main manuscript but based on a model wherein all three markers of nervous system injury are included as independent variables in a single regression model. Uncorrected p-values are reported next to each bar and Bonferroni-corrected p-values meeting statistical significance thresholds are flagged as follows: * <0.05, **<0.01, ***<0.001



Supplementary Figure 3: Same as Figure 1 of the main manuscript but based on a dataset wherein missing data for covariates were imputed using multiple imputations and results pooled across imputations using Rubin's rule. Uncorrected p-values are reported next to each bar and Bonferroni-corrected p-values meeting statistical significance thresholds are flagged as follows: * <0.05, **<0.01, ***<0.001



Supplementary Figure 4: Same as Figure 2 of the main manuscript but based on a model wherein all markers of severity of the acute COVID-19 illness are included as independent variables in a single regression model. Uncorrected p-values are reported next to each bar and Bonferroni-corrected p-values meeting statistical significance thresholds are flagged as follows: * <0.05, **<0.01, ***<0.001



Supplementary Figure 5: Same as Figure 2 of the main manuscript but based on a dataset wherein missing data for covariates were imputed using multiple imputations and results pooled across imputations using Rubin's rule. Uncorrected p-values are reported next to each bar and Bonferroni-corrected p-values meeting statistical significance thresholds are flagged as follows: * <0.05, **<0.01, ***<0.001

Supplementary tables

Supplementary Table 1. Baseline characteristics for the cohort used in this study and for all other PHOSP-COVID participants.

Cohort	PHOSP-COVID participants with neural injury markers	All other PHOSP-COVID participants
COHORT SIZE	891	1806
SOCIODEMOGRAPHIC FACTORS		
Age; mean (SD)	57.3 (12.5)	58.2 (12.8)
Sex; n (%)		
Female	312 (35.0)	637 (35.3)
Male	535 (60.0)	958 (53.0)
Unknown	44 (4.9)	211 (11.7)
Race; n (%)		
White	668 (75.0)	1199 (66.4)
Asian	122 (13.7)	188 (10.4)
Black	47 (5.3)	130 (7.2)
Mixed	14 (1.6)	37 (2.0)
Other	24 (2.7)	75 (4.2)
Unknown	16 (1.8)	177 (9.8)
Educational level; n (%)		
Primary school	16 (1.8)	41 (2.3)
Secondary school	271 (30.4)	488 (27.0)
Sixth form college	105 (11.8)	212 (11.7)
Vocational Qualification	97 (10.9)	192 (10.6)
Undergraduate university degree	157 (17.6)	279 (15.4)
Post-graduate qualification	113 (12.7)	232 (12.8)
None	23 (2.6)	45 (2.5)
Prefer not to say	29 (3.3)	57 (3.2)
Unknown	80 (9.0)	260 (14.4)
Household income; n (%)		
< £19,000	104 (11.7)	275 (15.2)
£19,001 – £26,000	100 (11.2)	195 (10.8)
£26,001 – £35,000	104 (11.7)	180 (10.0)

£35,001 – £48,000	105 (11.8)	180 (10.0)
>£48,001	210 (23.6)	366 (20.3)
Prefer not to say	189 (21.2)	346 (19.2)
Unknown	79 (8.9)	264 (14.6)
Marital status; n (%)		
Married	500 (56.1)	895 (49.6)
Unmarried	322 (36.1)	662 (36.7)
Unknown	69 (7.7)	249 (13.8)
English as a first language; n (%)		
Yes	691 (77.6)	1298 (71.9)
No	135 (15.2)	271 (15.0)
Unknown	65 (7.3)	237 (13.1)
COMORBIDITIES; n (%)		
Cancer	61 (6.8)	122 (6.8)
Cardiovascular condition	372 (41.8)	791 (43.8)
ME/CFS/Fibromyalgia/Chronic pain	40 (4.5)	91 (5.0)
Chronic kidney disease	33 (3.7)	73 (4.0)
Cerebrovascular accident	33 (3.7)	70 (3.9)
Dementia	< 10	< 10
Diabetes	166 (18.6)	351 (19.4)
Metabolic/endocrine disorder	65 (7.3)	152 (8.4)
Gastrointestinal condition	179 (20.1)	371 (20.5)
Infectious disease	21 (2.4)	49 (2.7)
Parkinson’s disease	< 10	< 10
Depression or anxiety	151 (16.9)	308 (17.1)
Respiratory condition	254 (28.5)	457 (25.3)
Rheumatological condition	121 (13.6)	273 (15.1)

Supplementary Table 2: Baseline characteristics of the cohort with a 12-month follow-up

Cohort	
COHORT SIZE	507
SOCIODEMOGRAPHIC FACTORS	
Age; mean (SD)	58.8 (12.0)
Sex; n (%)	
Female	170 (33.5)
Male	320 (63.1)
Unknown	17 (3.4)
Ethnicity; n (%)	
White	396 (78.1)
Asian	66 (13.0)
Black	22 (4.3)
Mixed	8 (1.6)
Other	12 (2.4)
Unknown	3 (0.6)
Educational level; n (%)	
Primary school	6 (1.2)
Secondary school	154 (30.4)
Sixth form college	61 (12.0)
Vocational qualification	61 (12.0)
Undergraduate university degree	92 (18.1)
Post-graduate qualification	67 (13.2)
None	15 (3.0)
Prefer not to say	13 (2.6)
Unknown	38 (7.5)
Household income; n (%)	
< £19,000	58 (11.4)
£19,001 – £26,000	57 (11.2)
£26,001 – £35,000	66 (13.0)
£35,001 – £48,000	60 (11.8)
>£48,001	118 (23.3)
Prefer not to say	112 (22.1)
Unknown	36 (7.1)
Marital status; n (%)	
Married	298 (58.8)
Unmarried	179 (35.3)
Unknown	30 (5.9)
English as a first language; n (%)	
Yes	407 (80.3)
No	75 (14.8)
Unknown	25 (4.9)
COMORBIDITIES; n (%)	
Cancer	34 (6.7)
Cardiovascular condition	230 (45.4)
ME/CFS/Fibromyalgia/Chronic pain	22 (4.3)
Chronic kidney disease	17 (3.4)

Cerebrovascular accident	21 (4.1)
Dementia	< 10
Diabetes	107 (21.1)
Metabolic/endocrine disorder	40 (7.9)
Gastrointestinal condition	98 (19.3)
Infectious disease	11 (2.2)
Parkinson's disease	< 10
Depression or anxiety	83 (16.4)
Respiratory condition	143 (28.2)
Rheumatological condition	63 (12.4)
COVID-19 SEVERITY MARKERS	
WHO; mean (SD)	2.53 (1.09)
NEWS; mean (SD)	3.76 (2.44)
Duration of hospital admission; mean (SD)	16.5 (20.9)
Pulmonary embolism; n (%)	52 (10.3)
Altered consciousness/confusion; n (%)	48 (9.5)
COVID-19 Recovery clusters; n (%)	
Mild impairment	69 (13.6)
Moderate and cognitive impairment	111 (21.9)
Severe impairment	49 (9.7)
Very severe impairment	177 (34.9)
Unknown	101 (19.9)
CLINICAL SCALES AT 6 MONTHS; mean (SD)	
MoCA	26.4 (3.21)
GAD-7	5.02 (5.83)
PHQ-9	6.34 (6.62)
PSQ	2.05 (2.11)
NEURAL INJURY MARKERS; mean (SD)	
GFAP	4.30 (0.85)
Tau protein	1.72 (0.79)
NfL	2.29 (0.69)

Supplementary Table 3: Regression coefficients and 95% confidence intervals for the variables (covariates and neural injury markers) used in the regression model wherein clinical scales measured at 6 months in each column are dependent variables.

	Dependent variables			
	MoCA at 6 months	**GAD-7 at 6 months**	**PHQ-9 at 6 months**	**C-PSQ at 6 months**
Covariates				
Cardiovascular condition	0.083 (-0.084 - 0.25)	0.22 (0.058 - 0.38)	0.16 (0.013 - 0.31)	0.05 (-0.13 – 0.23)
Cerebrovascular accident	-0.41 (-0.79 - -0.026)	-0.11 (-0.45 - 0.24)	-0.029 (-0.35 - 0.29)	0.065 (-0.32 – 0.45)
Dementia	1.13 (-0.71 - 2.96)	0.55 (-1.31 - 2.41)	0.13 (-1.60 - 1.86)	0.71 (-1.16 – 2.59)
Parkinson's disease	0.31 (-1.47 - 2.09)	0.20 (-1.09 - 1.50)	0.62 (-0.58 - 1.82)	-0.55 (-2.39 – 1.29)
Depression or anxiety	-0.12 (-0.33 - 0.084)	0.67 (0.47 - 0.87)	0.62 (0.44 - 0.81)	0.39 (0.17 – 0.61)
ME/CFS/Fibromyalgia/Chronic pain	-0.48 (-0.84 - -0.12)	0.66 (0.31 - 1.01)	0.57 (0.25 - 0.89)	0.49 (0.13 – 0.85)
Diabetes	-0.14 (-0.33 - 0.053)	0.12 (-0.065 - 0.31)	0.058 (-0.12 - 0.23)	0.045 (-0.17 – 0.26)
Respiratory condition	-0.0093 (-0.17 - 0.15)	0.14 (-0.019 - 0.29)	0.083 (-0.059 - 0.23)	-0.0079 (-0.18 – 0.16)
Rheumatological condition	0.18 (-0.039 - 0.40)	0.094 (-0.12 - 0.30)	0.21 (0.012 - 0.40)	0.068 (-0.16 – 0.29)
Gastrointestinal condition	0.012 (-0.17 - 0.19)	0.021 (-0.15 - 0.19)	0.089 (-0.072 - 0.25)	-0.081 (-0.27 – 0.11)
Metabolic/endocrine disorder	-0.036 (-0.31 - 0.24)	0.04 (-0.22 - 0.30)	-0.044 (-0.29 - 0.20)	0.14 (-0.14 – 0.41)
Chronic kidney disease	-0.13 (-0.50 - 0.24)	-0.072 (-0.43 - 0.28)	-0.013 (-0.34 - 0.32)	0.059 (-0.33 – 0.45)
Cancer	-0.17 (-0.44 - 0.11)	0.17 (-0.10 - 0.44)	0.14 (-0.11 - 0.39)	-0.076 (-0.33 – 0.45)
Chronis infectious disease	0.11 (-0.40 - 0.62)	-0.50 (-0.95 - -0.06)	-0.26 (-0.67 - 0.15)	-0.12 (-0.62 – 0.39)
Age	-0.22 (-0.33 - -0.12)	-0.097 (-0.20 - 0.0021)	-0.14 (-0.23 - -0.049)	-0.10 (-0.21 – 0.013)
Sex (female)	-0.06 (-0.22 - 0.097)	0.12 (-0.031 - 0.27)	0.16 (0.023 - 0.31)	0.055 (-0.12 – 0.23)
Race (reference: White)				
Mixed	-0.40 (-1.01 - 0.21)	0.078 (-0.51 - 0.67)	-0.29 (-0.84 - 0.26)	-0.063 (-0.66 – 0.54)
Asian	-0.064 (-0.34 - 0.21)	-0.21 (-0.48 - 0.063)	-0.15 (-0.40 - 0.094)	-0.24 (-0.54 – 0.063)
Black	-0.64 (-0.97 - -0.31)	0.012 (-0.32 - 0.34)	-0.14 (-0.45 - 0.17)	-0.18 (-0.57 – 0.21)
Other	-0.17 (-0.67 - 0.34)	-0.081 (-0.58 - 0.42)	-0.0092 (-0.47 - 0.45)	-0.32 (-0.84 – 0.19)
Educational level (reference: None)				
Primary school	-0.67 (-1.37 - 0.027)	-0.19 (-0.85 - 0.47)	-0.36 (-0.97 - 0.26)	-0.37 (-1.07 – 0.33)
Secondary school	0.50 (0.03 - 0.97)	-0.16 (-0.62 - 0.31)	-0.049 (-0.48 - 0.38)	-0.03 (-0.55 – 0.49)
Sixth form college	0.65 (0.16 - 1.15)	-0.11 (-0.61 - 0.38)	-0.057 (-0.51 - 0.40)	-0.083 (-0.63 – 0.46)
Vocational qualification	0.71 (0.21 - 1.21)	0.017 (-0.47 - 0.51)	0.099 (-0.36 - 0.55)	0.24 (-0.30 – 0.46)
Undergraduate university degree	0.65 (0.15 - 1.14)	-0.18 (-0.67 - 0.30)	-0.20 (-0.65 - 0.24)	0.10 (-0.43 – 0.64)
Post-graduate qualification	0.99 (0.48 - 1.50)	-0.26 (-0.76 - 0.24)	-0.14 (-0.61 - 0.32)	-0.008 (-0.57 – 0.55)
Prefer not to say	0.72 (0.13 - 1.31)	0.11 (-0.46 - 0.68)	0.10 (-0.42 - 0.63)	0.70 (0.048 – 1.36)
Income (reference: < £19,000)				
£19,001 – £26,000	-0.024 (-0.32 - 0.27)	-0.45 (-0.74 - -0.17)	-0.53 (-0.79 - -0.26)	-0.18 (-0.49 – 0.12)
£26,001 – £35,000	0.18 (-0.11 - 0.47)	-0.66 (-0.94 - -0.39)	-0.68 (-0.94 - -0.42)	-0.39 (-0.69 - -0.087)
£35,001 – £48,000	0.12 (-0.18 - 0.42)	-0.44 (-0.73 - -0.15)	-0.52 (-0.79 - -0.25)	-0.38 (-0.71 - -0.06)
>£48,001	0.30 (0.022 - 0.57)	-0.49 (-0.75 - -0.22)	-0.56 (-0.80 - -0.31)	-0.32 (-0.60 - -0.026)

Prefer not to say	0.12 (-0.14 - 0.37)	-0.26 (-0.52 - -0.014)	-0.41 (-0.64 - -0.17)	-0.29 (-0.56 - -0.019)
Is Married	0.11 (-0.046 - 0.26)	-0.15 (-0.30 - -0.0043)	-0.19 (-0.33 - -0.053)	-0.067 (-0.23 – 0.099)
English as a first language	0.54 (0.27 - 0.81)	-0.35 (-0.60 - -0.091)	-0.064 (-0.30 - 0.17)	0.11 (-0.17 – 0.40)
Neural injury markers				
Tau	-0.08 (-0.16 - -0.0047)	0.047 (-0.027 - 0.12)	0.065 (-0.0031 - 0.13)	0.05 (-0.03 – 0.13)
NfL	-0.038 (-0.15 - 0.077)	-0.12 (-0.22 - -0.0076)	-0.042 (-0.14 - 0.058)	-0.015 (-0.14 – 0.11)
GFAP	0.048 (-0.05 - 0.15)	0.015 (-0.079 - 0.11)	-0.058 (-0.15 - 0.029)	-0.028 (-0.13 – 0.0076)

Supplementary Table 4: Regression coefficients and 95% confidence intervals for the variables (covariates and neural injury markers) used in the regression model wherein clinical scales measured at 12 months in each column are dependent variables.

	Dependent variables			
	MoCA at 12 months	**GAD-7 at 12 months**	**PHQ-9 at 12 months**	**C-PSQ at 12 months**
Covariates				
Cardiovascular condition	0.03 (-0.16 - 0.22)	0.25 (0.023 - 0.47)	0.13 (-0.096 - 0.36)	0.22 (-0.03 – 0.46)
Cerebrovascular accident	-0.17 (-0.55 - 0.21)	-0.26 (-0.72 - 0.20)	-0.13 (-0.60 - 0.35)	0.086 (-0.43 – 0.61)
Dementia	0.76 (-0.85 - 2.38)	1.21 (-0.75 - 3.18)	0.33 (-1.65 - 2.30)	0.67 (-1.37 – 2.71)
Parkinson's disease	0.42 (-0.68 - 1.51)	0.95 (-0.39 - 2.29)	0.36 (-0.98 - 1.70)	0.45 (-0.94 – 1.83)
Depression or anxiety	-0.11 (-0.35 - 0.13)	0.65 (0.36 - 0.93)	0.64 (0.36 - 0.92)	0.54 (0.24 – 0.84)
ME/CFS/Fibromyalgia/ Chronic pain	-0.57 (-1.00 - -0.14)	0.63 (0.11 - 1.15)	0.68 (0.16 - 1.20)	0.84 (0.26 – 1.42)
Diabetes	-0.29 (-0.50 - -0.079)	0.02 (-0.23 - 0.27)	0.067 (-0.19 - 0.32)	0.17 (-0.11 – 0.45)
Respiratory condition	0.10 (-0.073 - 0.28)	-0.074 (-0.29 - 0.14)	-0.08 (-0.29 - 0.13)	-0.046 (-0.28 – 0.19)
Rheumatological condition	0.00068 (-0.25 - 0.25)	-0.036 (-0.34 - 0.27)	0.10 (-0.20 - 0.41)	-0.058 (-0.38 – 0.26)
Gastrointestinal condition	0.15 (-0.059 - 0.36)	0.067 (-0.19 - 0.32)	0.068 (-0.19 - 0.33)	-0.092 (-0.37 – 0.18)
Metabolic/endocrine disorder	-0.13 (-0.45 - 0.20)	0.03 (-0.33 - 0.39)	0.026 (-0.34 - 0.39)	0.051 (-0.36 – 0.46)
Chronic kidney disease	0.065 (-0.34 - 0.47)	0.15 (-0.35 - 0.64)	-0.041 (-0.54 - 0.46)	0.055 (-0.50 – 0.61)
Cancer	0.0057 (-0.32 - 0.33)	0.087 (-0.31 - 0.49)	-0.06 (-0.46 - 0.34)	0.11 (-0.32 – 0.55)
Chronic infectious disease	-0.73 (-1.32 - -0.13)	-0.086 (-0.69 - 0.51)	-0.16 (-0.76 - 0.44)	-0.069 (-0.69 – 0.55)
Age	-0.25 (-0.37 - -0.12)	-0.21 (-0.36 - -0.068)	-0.17 (-0.32 - -0.024)	-0.18 (-0.34 - -0.016)
Sex (female)	0.097 (-0.081 - 0.27)	0.15 (-0.061 - 0.35)	0.10 (-0.11 - 0.31)	0.032 (-0.20 – 0.26)
Race (Reference: White)				
Mixed	-1.30 (-2.08 - -0.52)	0.031 (-0.76 - 0.82)	-0.20 (-0.99 - 0.59)	0.056 (-0.76 – 0.87)
Asian	-0.038 (-0.37 - 0.29)	0.21 (-0.16 - 0.58)	0.14 (-0.23 - 0.51)	-0.12 (-0.53 – 0.29)
Black	-0.67 (-1.10 - -0.24)	0.087 (-0.42 - 0.59)	-0.087 (-0.60 - 0.42)	-0.24 (-0.75 – 0.27)
Other	0.011 (-0.59 - 0.61)	-0.016 (-0.68 - 0.65)	-0.0099 (-0.68 - 0.66)	-0.14 (-0.90 – 0.61)
Educational level (reference: None)				
Primary school	-0.93 (-1.86 - -0.0063)	-0.27 (-1.35 - 0.82)	-0.38 (-1.47 - 0.71)	-0.62 (-1.93 – 0.68)
Secondary school	-0.0023 (-0.54 - 0.53)	-0.0093 (-0.68 - 0.66)	0.089 (-0.58 - 0.76)	-0.20 (-1.09 – 0.69)
Sixth form college	0.14 (-0.42 - 0.71)	-0.14 (-0.85 - 0.56)	-0.074 (-0.78 - 0.63)	-0.27 (-1.19 – 0.65)
Vocational qualification	0.15 (-0.42 - 0.71)	0.007 (-0.70 - 0.71)	0.16 (-0.55 - 0.87)	-0.047 (-0.97 – 0.87)
Undergraduate university degree	0.23 (-0.33 - 0.79)	-0.14 (-0.84 - 0.57)	0.041 (-0.66 - 0.74)	-0.15 (-1.07 – 0.76)
Post-graduate qualification	0.42 (-0.15 - 0.99)	-0.24 (-0.96 - 0.48)	-0.01 (-0.74 - 0.72)	-0.30 (-1.22 – 0.63)
Prefer not to say	-0.28 (-0.99 - 0.43)	0.16 (-0.68 - 0.99)	0.12 (-0.72 - 0.96)	0.15 (-0.89 – 1.18)
Income (Reference: < £19,000)				
£19,001 – £26,000	0.36 (0.019 - 0.70)	-0.31 (-0.71 - 0.094)	-0.32 (-0.73 - 0.085)	-0.24 (-0.70 – 0.23)
£26,001 – £35,000	0.52 (0.20 - 0.85)	-0.42 (-0.81 - -0.028)	-0.59 (-0.98 - -0.19)	-0.20 (-0.64 – 0.24)
£35,001 – £48,000	0.29 (-0.054 - 0.63)	-0.23 (-0.64 - 0.19)	-0.44 (-0.86 - -0.026)	-0.11 (-0.60 – 0.37)
>£48,001	0.58 (0.26 - 0.90)	-0.47 (-0.85 - -0.088)	-0.60 (-0.98 - -0.22)	-0.16 (-0.60 – 0.28)

Prefer not to say	0.54 (0.24 - 0.85)	0.0019 (-0.36 - 0.37)	-0.23 (-0.60 - 0.14)	-0.055 (-0.47 – 0.36)
Is Married	0.092 (-0.082 - 0.27)	-0.09 (-0.30 - 0.12)	-0.20 (-0.40 - 0.011)	-0.19 (-0.42 – 0.035)
English as a first language	0.64 (0.33 - 0.95)	0.11 (-0.24 - 0.46)	0.19 (-0.16 - 0.54)	0.11 (-0.27 – 0.49)
Neural injury markers				
Tau	-0.079 (-0.16 - 0.0039)	-0.042 (-0.14 - 0.056)	-0.026 (-0.12 - 0.071)	-0.03 (-0.14 – 0.076)
NfL	0.029 (-0.098 - 0.16)	-0.026 (-0.18 - 0.12)	-0.072 (-0.22 - 0.078)	-0.068 (-0.23 – 0.094)
GFAP	-0.039 (-0.15 - 0.074)	0.072 (-0.068 - 0.21)	0.058 (-0.083 - 0.20)	0.0025 (-0.15 – 0.15)

Supplementary Table 5: Results of the analysis of individual cognitive domains. Regression coefficients and 95% confidence intervals for the association between neural injury markers (independent variables) and individual domains of the Montreal Cognitive Assessment (MoCA; dependent variables) recorded at 6 months post-COVID-19.

	Neural injury markers					
	GFAP		**Tau**		**NfL**	
Cognitive domain	**Coefficient (95% CI)**	**P-value**	**Coefficient (95% CI)**	**P-value**	**Coefficient (95% CI)**	**P-value**
MoCA (visuospatial)	-0.068 (-0.15 - 0.017)	0.12	-0.066 (-0.14 - 0.0092)	0.086	-0.057 (-0.15 - 0.04)	0.25
MoCA (naming)	0.017 (-0.068 - 0.10)	0.7	-0.032 (-0.11 - 0.043)	0.4	-0.036 (-0.13 - 0.06)	0.47
MoCA (attention)	0.053 (-0.04 - 0.15)	0.26	-0.037 (-0.12 - 0.046)	0.38	0.033 (-0.073 - 0.14)	0.55
MoCA (language)	0.012 (-0.073 - 0.096)	0.79	-0.036 (-0.11 - 0.039)	0.35	-0.037 (-0.13 - 0.06)	0.45
MoCA (abstract)	-0.0089 (-0.099 - 0.081)	0.85	-0.036 (-0.12 - 0.044)	0.38	-0.021 (-0.12 - 0.081)	0.69
MoCA (recall)	-0.00051 (-0.085 - 0.084)	0.99	-0.066 (-0.14 - 0.0096)	0.088	-0.055 (-0.15 - 0.041)	0.26
MoCA (orientation)	0.059 (-0.033 - 0.15)	0.21	-0.024 (-0.11 - 0.058)	0.57	0.039 (-0.065 - 0.14)	0.47

References

1. Evans RA, McAuley H, Harrison EM, et al. Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. *Lancet Respir Med*. 2021;9(11):1275-1287.