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Supplemental information

Disentangling the cognitive, physical, and mental health sequelae of COVID-19

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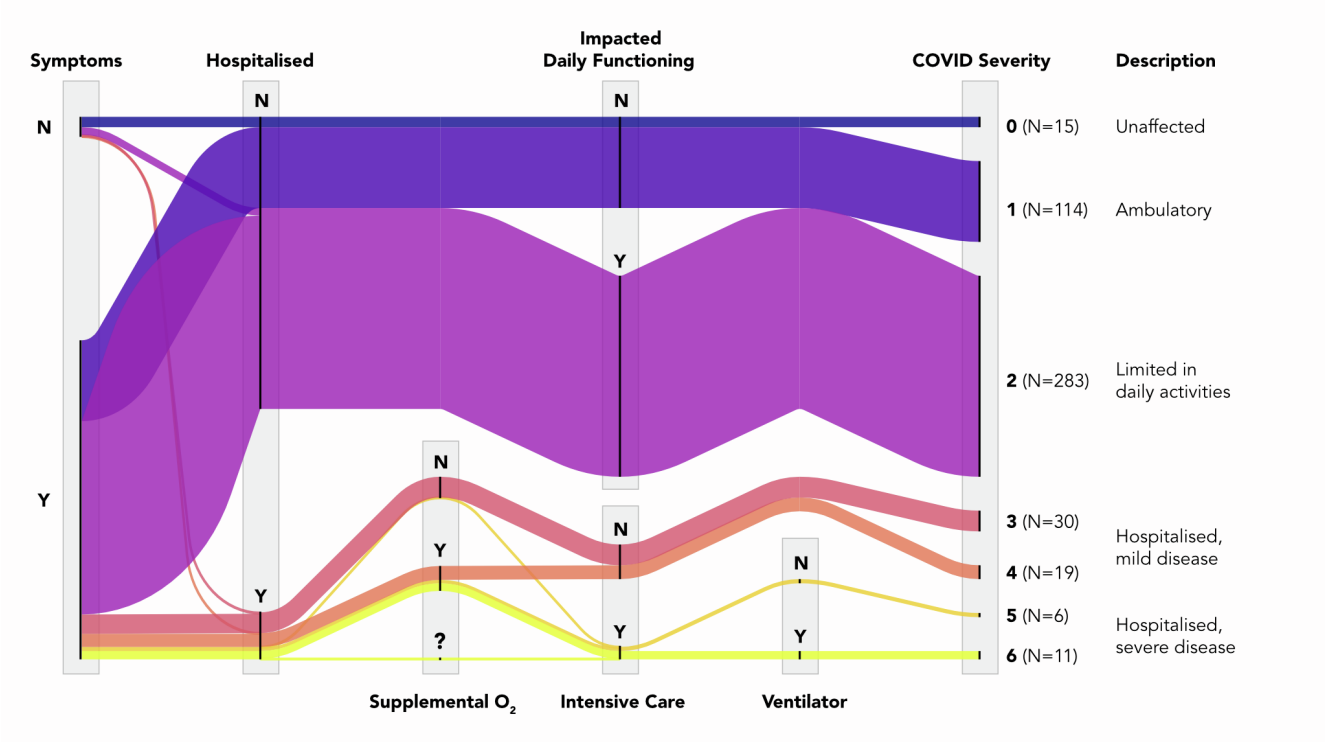
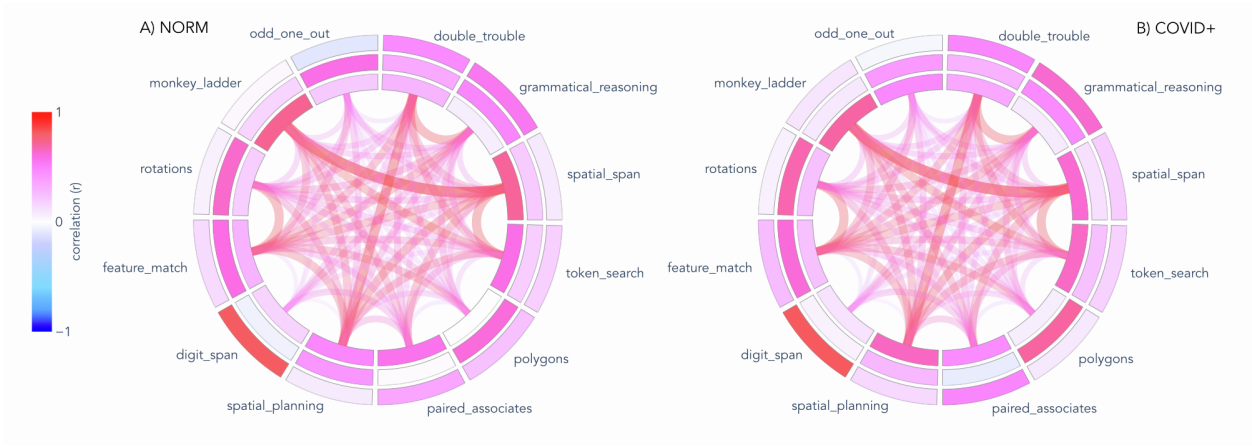
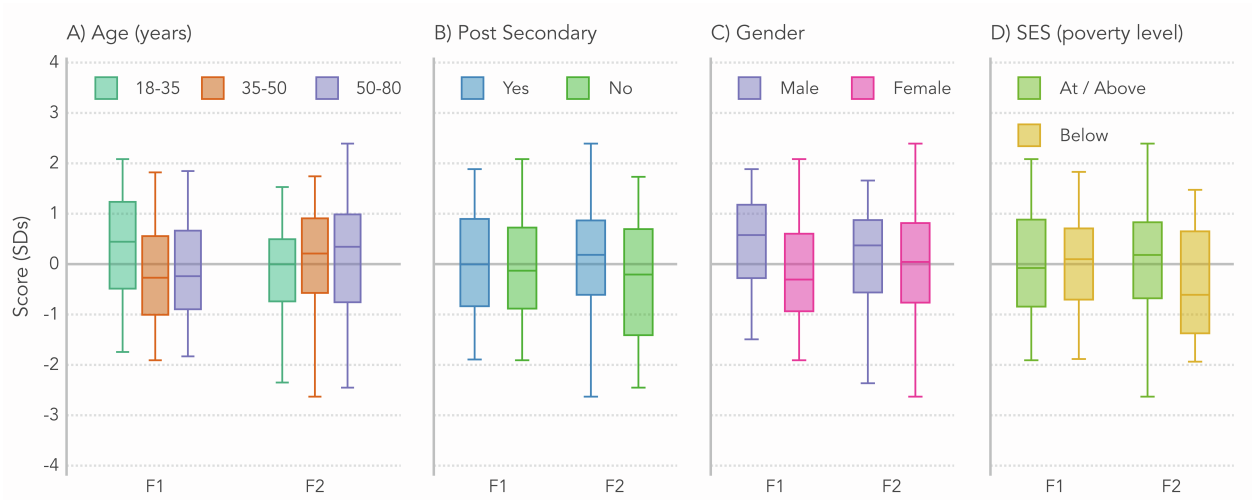
Supplementary Figures



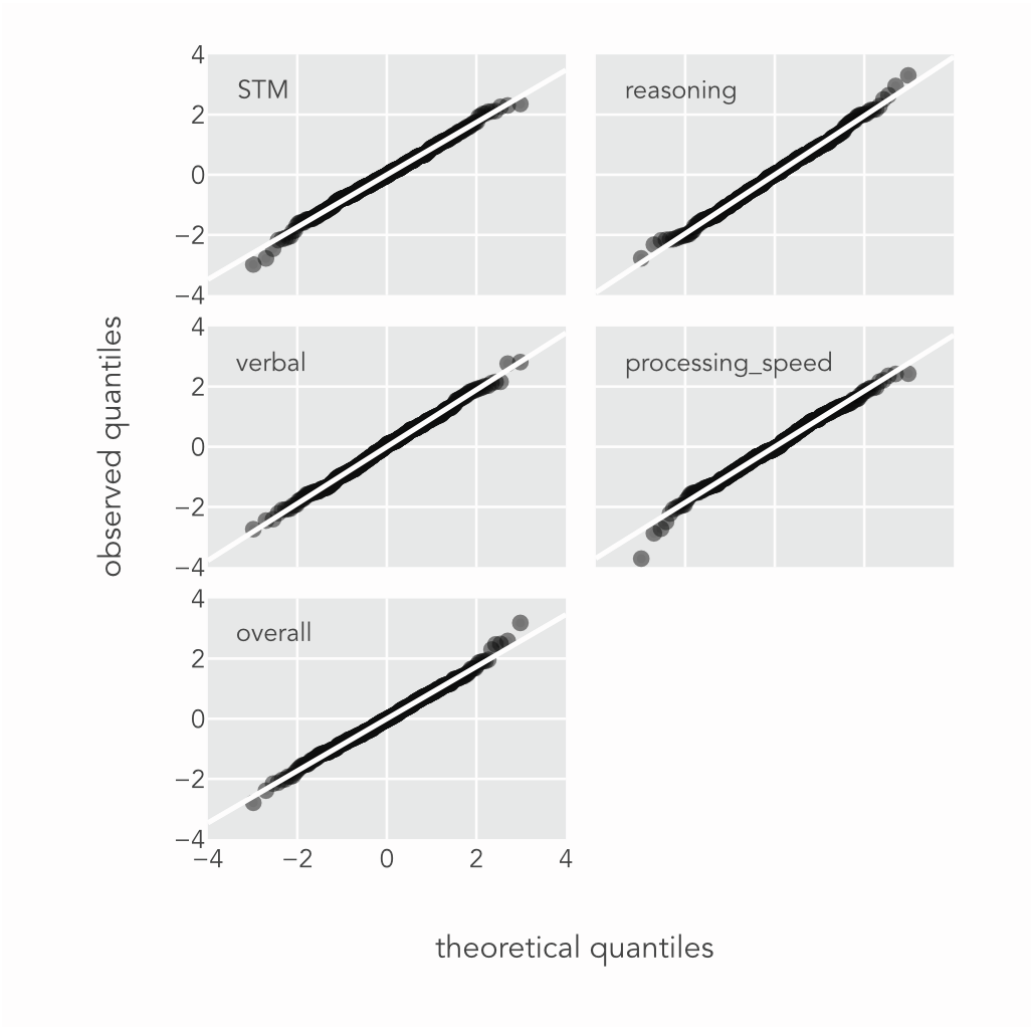
Supplementary Figure 1. COVID-19 questionnaire responses. Related to Table 2. The response rate to each COVID-related item on the questionnaire, where the number of participants that responded *"Yes"* (Y), "*No"* (N), or *"I don't know"* (?) is proportional to the height of the response node (i.e., the vertical black line). Coloured bands correspond to groups of participants that were assigned the same WHO COVID severity score (0-6) according to their responses to these questions, which can be observed by following each coloured band through the response nodes. The figure also depicts the sequence of questions that each group was asked; for example, the unaffected group (score = 0, dark blue band) selected none of the listed symptoms, were not hospitalised (and therefore not asked about ICU, etc.) and were not impacted in their daily functioning.



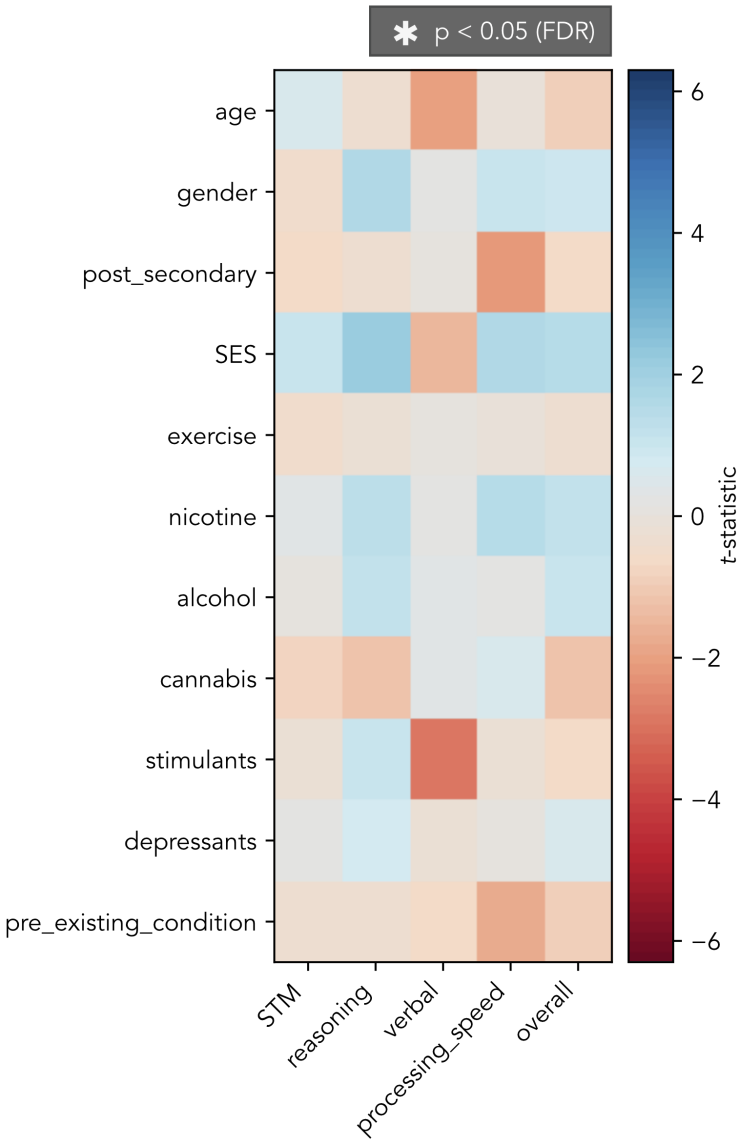
Supplementary Figure 2. Similarity of cognitive factor structures in NORM and COVID+ groups. Related to Figure 1A. Principal components analysis of cognitive tests scores in the two groups produced qualitatively similar factor solutions, with similar groupings of tests on each of the three factors. A) Normative (NORM) group (N=7,832) and B) COVID+ group (N=478).



Supplementary Figure 3. Dissociable health factors associated with COVID-19 infection. Related to Figure 1B. Factor scores F1 (overall physical health, including COVID severity) and F2 (mental health & wellness) – as a function of: **A)** age (in three arbitrary bins), **B)** completion of post-secondary education, **C)** gender, and **D)** socio-economic status (relative to poverty level) while growing up. Boxes span from the 1st to 3rd quartiles, horizontal lines within a box indicate the median, and whiskers span 1.5 times the interquartile range (limited to min/max of the sample).



Supplementary Figure 4. Are the residuals from linear regression models normally distributed? Related to STAR Methods (Statistical Analysis) and Table 3. Quantile-quantile plots of the residuals from linear regression models that predict each composite cognitive scores from the two health factors – physical (F1) and mental (F2) health – in the COVID+ sample (N=478).



Supplementary Figure 5. Exploratory pairwise comparisons between cognitive scores and socio-demographic and health-related variables. Related to STAR Methods (Statistical Analysis). Each cell represents the regression coefficient from a general linear model with one predictor (the variable indicated by that row) and one dependent variable (the column; cognitive score). Each predictor is considered in isolation from the others. The cell colour indicates the *t*-statistic of the parameter estimate (blue indicates a positive relationship, whereas red indicates the converse). Stars indicate significant effects, $p < 0.05$, corrected for multiple comparisons using the False Discovery Rate (FDR) across all *t*-tests in the panel (N=55 statistical tests).

Supplementary Tables

Supplementary Table 1. Classification criteria and counts of WHO COVID-19 severity scores. Related to Table 2. Percentages (of participants in each WHO category) are relative to the entire COVID+ sample. Y/N indicates the response "Yes" or "No". Green indicates the option associated with better health, whereas red indicates the response associated with poorer health.

Description	Question	Yes / No	WHO Score	Count
Unaffected	Symptoms	N	0	15 (3.1%)
	Hospital	N		
Ambulatory	Symptoms	Y	1	114 (23.8%)
	Daily Routine	Y		
	Hospital	N		
Limited in activities	Symptoms	Y	2	283 (59.2%)
	Daily Routine	N		
	Hospital	N		
Hospitalised, mild disease	Hospital	Y	3	30 (6.3%)
	Supplemental O_2	N		
	Intensive Care	N		
	Hospital	Y	4	19 (4.0%)
	Supplemental O_2	Y		
	Intensive Care	N		
Hospitalised, severe disease	Hospital	Y	5	6 (1.3%)
	Intensive Care	Y		
	Ventilator	N		
	Hospital	Y	6	11 (2.3%)
	Intensive Care	Y		
	Ventilator	Y		

Supplementary Table 2. Health-related questionnaire scales. Related to Figure 1B.

Summary statistics (mean and standard deviation; *M, SD*) of individual health-related scales, and their loadings on the two health factors (F1 & F2), in COVID+ participants (N = 478).

			Factor	
variable	***M***	***SD***	**F1**	**F2**
SF36_physical_functioning	69.48	29.13	0.84	0.01
SF36_role_limitations_physical	37.08	43.03	0.78	0.11
SF36_role_limitations_emotional	56.35	43.23	0.25	0.61
SF36_energy_fatigue	33.91	23.98	0.78	0.30
SF36_pain	66.74	26.07	0.69	0.15
GAD2	2.11	1.95	0.20	0.75
PHQ2	2.00	1.86	0.37	0.73
"How would you rate your memory? (0-5)	2.28	1.01	0.58	0.23
"*…back to your baseline level of cognitive functioning?"*	*32.23% "Yes"*		0.616	0.609
WHO COVID severity	1.97	1.03	-0.47	-0.02
(approximate) days since most recent test	93.39	67.88	-0.02	0.03
eigenvalue			4.67	1.48
% variance explained			32.53	15.49

Extraction method: Factor analysis with Varimax rotation.

Supplementary Table 3. Cognitive test scores. Related to Figure 1A. Summary statistics (mean and standard deviation; *M, SD*) for the individual (uncorrected) cognitive test scores, along with their factor loadings on the three factors (STM, reasoning, verbal). Figure 1A shows a visual representation of the factor solution derived from the normative (NORM) dataset.

	NORM (N = 7,832)					**COVID+** (N = 478)				
			Factor					**Factor**		
Test	***M***	***SD***	**STM**	**Reasoning**	**Verbal**	***M***	***SD***	**STM**	**Reasoning**	**Verbal**
SS	5.66	1.06	0.71	0.20	0.08	5.62	0.99	0.63	0.12	0.20
GR	17.93	5.19	0.07	0.49	0.55	17.04	5.43	0.08	0.47	0.63
DT	25.46	15.10	0.29	0.34	0.47	19.29	15.49	0.35	0.30	0.49
OOO	15.89	2.07	0.2	0.59	-0.1	15.78	1.99	0.48	0.41	-0.04
ML	7.70	1.16	0.72	0.16	0.03	7.49	1.16	0.70	0.09	0.10
RO	76.35	34.99	0.19	0.63	0.05	73.31	35.44	0.24	0.68	0.06
FM	114.38	29.47	0.3	0.60	0.14	110.18	32.00	0.24	0.61	0.26
DS	6.67	1.40	0.17	-0.06	0.81	6.65	1.27	0.10	0.05	0.82
SP	19.15	9.82	0.49	0.42	0.08	18.87	8.31	0.65	0.28	0.15
PA	4.67	0.99	0.57	0.02	0.36	4.50	0.93	0.46	-0.08	0.49
PO	41.48	21.86	0	0.61	0.24	37.55	22.11	0.07	0.70	0.08
TS	7.23	2.12	0.59	0.19	0.18	7.84	1.73	0.65	0.24	0.17
		eigenvalue	3.76	1.06	0.98			4.05	1.05	1.02
		% variance explained	18.48	17.69	12.09			20.12	16.44	14.37

Extraction method: Principal Component Analysis (PCA) with Varimax rotation.

STM – Short-Term Memory; SS – Spatial Span; GR – Grammatical Reasoning; DT – Double Trouble; OOO – Odd One Out; ML – Monkey Ladder; RO – Rotations; FM – Feature Match; DS – Digit Span; SP – Spatial Planning; PA – Paired Associates; PO – Polygons; TS – Token Search

Supplementary Table 4: Associations between health factors and demographic variables. Related to Figure 1B and Supplementary Figure 3. Results from linear regression analyses modelling the relationship between demographic variables and physical (F1) and mental (F2) health factor scores. *P*-values and confidence intervals are Bonferroni-corrected (N=8). Bold entries indicate significant effects ($p_{adj} < 0.05$).

DV	IV	β	*t*	*df*	p_{adj}	CI	ΔR^2	f^2
F1	**age**	**-0.01**	**-3.20**	**473**	**0.012**	**(-0.020, -0.002)**	**0.020**	**0.022**
	male	**0.57**	**5.91**	**473**	**< 0.001**	**(0.304, 0.832)**	**0.067**	**0.074**
	post_secondary	0.1	0.91	473	1.000	(-0.212, 0.422)	0.002	0.002
	SES	0.06	0.36	473	1.000	(-0.403, 0.523)	0.000	0.000
F2	**age**	**0.01**	**2.82**	**473**	**0.040**	**(0.000, 0.019)**	**0.016**	**0.017**
	male	0.15	1.52	473	1.000	(-0.120, 0.418)	0.005	0.005
	post_secondary	**0.4**	**3.36**	**473**	**0.007**	**(0.072, 0.719)**	**0.023**	**0.024**
	SES	-0.37	-2.17	473	0.242	(-0.846, 0.099)	0.009	0.010

DV – dependent variable, IV – independent variable, β - estimated coefficient; t - t-statistic; df – degrees of freedom; p_{adj} - adjusted p-value; CI - confidence intervals; f^2 - Cohen's f

Supplementary Table 5. Comparisons of COVID+ F1-subgroups against normative baseline. Related to Figure 2. Two-sample *t*-test results comparing COVID+ participants, grouped into tercile bins based on F1, against the normative sample; "worse", "average", and "better" correspond to the 0%-33%, 33%-66%, and 66%-100% percentile bins (higher F1 associated with better physical health). P-values and confidence intervals are Bonferroni corrected (N=15), and bold entries indicate significant effects ($p_{adj} < 0.05$).

F1_bin	score	difference	*t*	*df*	p_{adj}	CI
worse	STM	0.01	0.09	164.26	1.000	(-0.214, 0.228)
	reasoning	**-0.35**	**-4.06**	**162.69**	**0.001**	**(-0.614, -0.095)**
	verbal	**-0.34**	**-4.57**	**165.24**	**< 0.001**	**(-0.566, -0.120)**
	processing_speed	**-0.51**	**-6.31**	**162.81**	**< 0.001**	**(-0.745, -0.267)**
	overall	**-0.36**	**-4.80**	**163.11**	**< 0.001**	**(-0.589, -0.138)**
average	STM	0.07	1.04	164.70	1.000	(-0.139, 0.289)
	reasoning	-0.12	-1.55	164.14	1.000	(-0.346, 0.109)
	verbal	-0.19	-2.48	165.29	0.210	(-0.408, 0.037)
	processing_speed	**-0.24**	**-3.23**	**163.87**	**0.022**	**(-0.452, -0.019)**
	overall	-0.10	-1.60	164.95	1.000	(-0.298, 0.090)
better	STM	0.09	1.42	168.38	1.000	(-0.095, 0.269)
	reasoning	-0.12	-1.68	166.18	1.000	(-0.331, 0.092)
	verbal	-0.03	-0.32	165.51	1.000	(-0.261, 0.210)
	processing_speed	-0.14	-2.03	165.68	0.657	(-0.343, 0.065)
	overall	-0.02	-0.31	165.89	1.000	(-0.216, 0.175)

t - t-statistic; df – degrees of freedom; p_{adj} - adjusted p-value; CI - confidence intervals

Supplementary Table 6: Results of linear regression models including additional covariates. Related to Table 4. Linear regression parameters modelling the relationship between cognitive scores and physical (F1) and mental (F2) health factor scores. *P*-values and confidence intervals are Bonferroni-corrected for 15 comparisons, and bold entries indicate significant effects ($p_{adj} < 0.05$). Nuisance variables were included as covariates of no interest.

DV	IV	β	*t*	*df*	p_{adj}	CI	ΔR^2	f^2
STM	F1	0.04	0.87	464	1.000	(-0.089, 0.163)	0.002	0.002
	F2	0.01	0.31	464	1.000	(-0.109, 0.135)	0.000	0.000
reasoning	F1	0.07	1.38	464	1.000	(-0.075, 0.208)	0.004	0.004
	F2	0.06	1.29	464	1.000	(-0.077, 0.197)	0.003	0.004
verbal	**F1**	**0.15**	**3.24**	**464**	**0.020**	**(0.013, 0.286)**	**0.021**	**0.023**
	F2	-0.01	-0.25	464	1.000	(-0.143, 0.121)	0.000	0.000
processing_speed	**F1**	**0.14**	**3.12**	**464**	**0.029**	**(0.008, 0.275)**	**0.020**	**0.021**
	F2	-0.05	-1.10	464	1.000	(-0.177, 0.081)	0.002	0.003
overall	**F1**	**0.13**	**3.11**	**464**	**0.030**	**(0.007, 0.257)**	**0.020**	**0.021**
	F2	0.04	1.01	464	1.000	(-0.080, 0.162)	0.002	0.002

Covariates of no interest: *1) age; 2) gender; 3) post-secondary education; 4) SES; 5) a pre-existing medical condition (diabetes, obesity, hypertension, stroke, heart attack, or memory problems); 6) weekly exercise; consumption of 7) nicotine, 8) alcohol, 9) cannabis, 10) other stimulants, 11) other depressants*

DV – dependent variable, IV – independent variable, β - estimated regression coefficient; t – t-statistic; df – degrees of freedom; p_{adj} – adjusted p-value; CI – confidence intervals; f^2 – Cohen's f

Supplementary Table 7. Two-sample *t*-tests comparing non-hospitalised and hospitalised COVID+ subgroups. Related to Figure 3. Positive differences indicate higher scores for the non-hospitalised group. Confidence intervals and p-values are Bonferroni corrected (N=7), and bold entries indicate significant effects ($p_{adj} < 0.05$).

score	difference	*t*	*df*	p_{adj}	CI
F1	**0.50**	**3.92**	**88.55**	**0.001**	**(0.149, 0.855)**
F2	-0.03	-0.21	84.41	1.000	(-0.412, 0.354)
STM	-0.18	-1.57	86.14	0.847	(-0.502, 0.138)
reasoning	0.33	2.44	85.62	0.116	(-0.042, 0.693)
verbal	0.13	1.10	93.73	1.000	(-0.192, 0.448)
processing_speed	0.29	2.13	82.47	0.251	(-0.084, 0.656)
overall	0.14	1.10	82.10	1.000	(-0.210, 0.488)

t - t-statistic; df - degrees of freedom; p_{adj} - adjusted p-value; CI - confidence intervals

Supplementary Table 8: Two-sample *t*-tests comparing non-hospitalised and hospitalised groups to the normative baseline. Related to Figure 3. *p*-values and confidence intervals are Bonferroni corrected (N=10), and bold entries indicate significant effects ($p_{adj} < 0.05$).

Hospitalised	score	difference	*t*	*df*	p_{adj}	CI
	STM	0.03	0.71	460.89	1.000	(-0.092, 0.154)
	reasoning	**-0.15**	**-3.09**	**451.14**	**0.021**	**(-0.291, -0.013)**
No	**verbal**	**-0.17**	**-3.38**	**456.54**	**0.008**	**(-0.305, -0.028)**
	processing_speed	**-0.25**	**-5.49**	**450.44**	**< 0.001**	**(-0.384, -0.123)**
	overall	**-0.14**	**-3.31**	**453.74**	**0.010**	**(-0.265, -0.021)**
	STM	0.21	1.96	66.18	0.541	(-0.103, 0.529)
	reasoning	**-0.48**	**-3.83**	**65.93**	**0.003**	**(-0.840, -0.116)**
Yes	verbal	-0.29	-2.77	66.45	0.073	(-0.604, 0.015)
	processing_speed	**-0.54**	**-4.26**	**65.78**	**< 0.001**	**(-0.908, -0.172)**
	overall	-0.28	-2.36	65.83	0.212	(-0.630, 0.065)

t - t-statistic; df - degrees of freedom; p_{adj} - adjusted p-value; CI - confidence intervals

Supplementary Table 9. Results of linear regression analyses when controlling for hospitalisation stats. Related to Table 4. Linear regression models that predict cognitive scores from: physical (F1) and mental (F2) health factor scores while controlling for hospitalisation status (1 = hospitalised group). *P*-values and confidence intervals are Bonferroni corrected for 15 comparisons, and bold entries indicate significant effects ($p_{adj} < 0.05$).

DV	IV	β	*t*	*df*	p_{adj}	CI	ΔR^2	f^2
	F1	0.04	1.02	474	1.000	(-0.078, 0.160)	0.002	0.002
STM	F2	0.01	0.15	474	1.000	(-0.111, 0.123)	0.000	0.000
	Hospital	0.20	1.74	474	1.000	(-0.141, 0.545)	0.006	0.006
	F1	0.07	1.50	474	1.000	(-0.066, 0.203)	0.005	0.005
reasoning	F2	0.05	1.06	474	1.000	(-0.085, 0.180)	0.002	0.002
	Hospital	-0.29	-2.22	474	0.403	(-0.682, 0.096)	0.010	0.010
	F1	**0.14**	**3.09**	**474**	**0.031**	**(0.006, 0.268)**	**0.020**	**0.020**
verbal	F2	-0.01	-0.34	474	1.000	(-0.144, 0.114)	0.000	0.000
	Hospital	-0.06	-0.46	474	1.000	(-0.437, 0.319)	0.000	0.000
	F1	**0.13**	**3.13**	**474**	**0.028**	**(0.008, 0.262)**	**0.020**	**0.021**
processing_speed	F2	-0.06	-1.37	474	1.000	(-0.183, 0.067)	0.004	0.004
	Hospital	-0.22	-1.74	474	1.000	(-0.584, 0.150)	0.006	0.006
	F1	**0.13**	**3.26**	**474**	**0.018**	**(0.013, 0.250)**	**0.022**	**0.022**
overall	F2	0.03	0.70	474	1.000	(-0.089, 0.145)	0.001	0.001
	Hospital	-0.07	-0.64	474	1.000	(-0.417, 0.269)	0.001	0.001

DV - dependent variable, IV - independent variable, β - estimated coefficient; t - t-statistic; df - t-statistic degrees of freedom; p_{adj} - adjusted p-value; CI - confidence intervals; f^2 - Cohen's f