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Full-length Article

Blood-Brain barrier disruption in long COVID and cognitive correlates: A cross-sectional MRI study

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ABSTRACT

Disruption of the blood–brain barrier (BBB) may contribute to neuropsychiatric symptoms observed in Long COVID (LC). Using a non-contrast magnetic resonance imaging (MRI) technique, we investigated BBB permeability in individuals with LC and its relationship to cognitive function. We hypothesized that LC individuals would show greater BBB permeability than recovered individuals, and that higher permeability would correlate with poorer cognition. Ninety-seven participants meeting the 2024 NASEM definition of LC with at least one neuropsychiatric symptom and 31 recovered controls completed an MRI scan and cognitive testing. BBB permeability was assessed using water-extraction-with-phase-contrast-arterial-spin-tagging (WEPCAST) MRI, which estimates the permeability-surface-area product (PS) of arterially labeled water entering the brain. Cognitive performance was summarized into eight factor scores derived from principal components analysis. Compared to controls, the LC group was older (M = 47 vs. 39 years, $P = 0.003$), less educated ($P = 0.02$), more likely female ($P = 0.04$), and had higher hospitalization rates for COVID-19 ($P = 0.02$). PS was significantly elevated in the LC group after adjusting for age and sex (B = 18.59, SE = 6.11, $\beta = 0.28$, $P = 0.003$). No significant group differences were found in cerebral blood flow, extraction fraction (E), or brain volume. Within the LC group, higher PS was associated with poorer motor function, but not with other cognitive domains. These findings indicate subtle but persistent BBB disruption in LC individuals over two years post-infection, with a potential link to motor dysfunction. This supports prior evidence of BBB changes following severe COVID-19 and suggests that BBB integrity may be a long-term biomarker of neuropsychiatric complications in LC.

1. Introduction

Mild-to-moderate SARS-CoV-2 symptoms typically last approximately two weeks, but many individuals develop persistent neurological symptoms including brain fog, which significantly impact daily functioning. This prolonged symptomatology, often referred to as Long COVID (LC), is characterized by health issues that continue or emerge after the acute phase of infection. Understanding the biological mechanisms of these symptoms is critical for developing strategies to prevent and treat LC.

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Disruption of the blood brain barrier (BBB) is common in neurotropic viral infections, including coronaviruses. The BBB, formed by vascular endothelial and other supporting cells, functions to regulate blood–brain exchange of substances and protect the central nervous system (CNS) from peripheral immune response, neurotoxins, and pathogens. (Abbott et al., 2010; Abbott et al., 2006) Acute SARS-CoV-2 infection has been shown in some studies to alter BBB integrity, with elevated albumin serum-to-cerebral spinal fluid (CSF) ratio observed acutely and several weeks post-infection. (Jarius et al., 2022) Neuroimaging studies have extended these findings to individuals with LC, although sample sizes have generally been small and results mixed. For example, one study using dynamic contrast-enhanced (DCE) magnetic resonance imaging (MRI) demonstrated that individuals with LC who reported cognitive complaints (brain fog, n = 11) had greater BBB disruption than those without complaints (n = 11) or recovered controls (n = 10), with imaging conducted approximately 5–7 months post-infection. (Greene et al., 2024) Another DCE-MRI study reported increased BBB disruption in individuals with LC and clinically confirmed cognitive impairment (n = 14) compared to non-COVID-19 controls (n = 10), with disruption most pronounced in the frontal white matter and brainstem three months after infection; no changes were observed over 12 months of follow-up. (Chaganti et al., 2024) A more recent, larger-scale study of older adults with LC reporting cognitive complaints (n = 27), approximately 1.7 years after infection combined DCE-MRI with multi-compartment diffusion imaging to assess both BBB integrity and brain microstructure. (Reas et al., 2025) Compared to cognitively normal SARS-CoV-2-recovered controls (n = 49), individuals with LC exhibited widespread BBB leakage—particularly in frontal and parietal lobe—and subcortical microstructural abnormalities. Notably, BBB disruption was more pronounced among men, and associations between BBB permeability and cognitive function were stronger in individuals with elevated polygenetic hazard scores for Alzheimer's disease (AD). These findings raise critical questions about the intersection of LC, BBB dysfunction, and risk for neurodegenerative disease. In contrast, a study using 99 m Technetium diethylenetriaminepentaacetic acid (99mTc-DTPA) single-photon emission computed tomography (SPECT) found no differences in BBB permeability between individuals with LC and brain fog (n = 14) and controls without COVID-19 or cognitive symptoms (n = 10). (Gupta et al., 2024) These divergent results highlight the need for further investigation into the role of BBB dysfunction in LC, and suggest that differences in methodology, tracer properties, and participant characteristics may contribute to inconsistent findings. Furthermore, current techniques involving CSF sampling and contrast-based imaging are invasive and limited to detecting permeability to larger molecules, which constrains scalability and generalizability.

To address these limitations, we used a noninvasive, validated MRI measure of BBB integrity, the water-extraction-with-phase-contrast-arterial-spin-tagging (WEPCAST) MRI pulse sequence, which uses water as an endogenous tracer to assess permeability. (Lin et al., 2021; Lin et al., 2021; Lin et al., 2018; Wei et al., 2023) Water (18 g/mol) is a smaller molecule than albumin (66,500 g/mol) as measured in CSF, and the molecules assessed by contrast-imaging via MRI (e.g., gadobenate dimegulmine [1058.1 g/mol], gadolinium-diethylenetriamine pentaacetic [513.5 g/mol]) or SPECT (e.g., DTPA [393 g/mol]), allow for more precise permeability estimation. Previous studies in AD revealed that water permeability was associated with amyloid, tau, and cognitive function, whereas albumin permeability was not. (Lin et al., 2021) A small pilot study found increased permeability in intensive care unit (ICU) COVID-19 survivors about three months post-discharge using WEPCAST (Shi et al., 2023), but its application to LC remains unexplored. We aimed to examine BBB permeability in a large sample of individuals with LC who present with at least one neuropsychiatric symptom (e.g., brain fog or headaches). We hypothesized greater BBB permeability in LC compared to individuals who have recovered from acute COVID-19, and that greater permeability in those with LC would be associated with poorer cognitive function.

2. Methods

2.1. Study participants

Participants included individuals meeting the NASEM 2024 published definition of LC (Soriano et al., 2022) who presented with at least one neuropsychiatric symptomand individuals who recovered from acute SARS-CoV-2 (controls). Participants were recruited through multiple channels: (1) MyChart recruitment blasts to eligible individuals within the Johns Hopkins Health System who had agreed to be contacted for research, (2) flyers posted in clinical and community settings, (3) referrals from enrolled participants (e.g., family members), and (4) the Johns Hopkins HOPE Registry—a centralized database of individuals interested in participating in COVID-19-related studies. Eligibility for MyChart outreach was determined using a predefined algorithm developed in collaboration with the institutional recruitment team. This algorithm identified adults aged 18–80 with a documented history of SARS-CoV-2 infection based on either a positive polymerase chain reaction (PCR) or antigen test or an ICD-10 diagnosis code (e.g., U09.9: Post COVID-19 condition, unspecified; Z86.16: Personal history of COVID-19). Only individuals with an active MyChart account who met these preliminary criteria were invited. While both LC and control participants were recruited through these shared channels, most LC participants were drawn from specialized clinics, including the Johns Hopkins Post-Acute COVID-19 Team (PACT) and the Long COVID Myalgic Encephalomyelitis/Chronic Fatigue Syndrome Clinics in Baltimore, MD.

To ensure accurate cohort assignment (LC vs. control), all participants completed a structured, clinician-administered LC Symptom Screener (see Supplemental Materials). This tool assessed new-onset or worsened post-COVID symptoms across multiple domains, including fatigue, post-exertional malaise (PEM), unrefreshing sleep, cognitive dysfunction (e.g., brain fog, memory, and concentration problems), orthostatic intolerance, pain, and sensory hypersensitivities. Additional items screened for features of dysautonomia and mast cell activation (e.g., vasomotor instability, secretomotor symptoms, dermatologic reactions, and food-triggered GI symptoms). Participants were assigned to the LC group if they met the 2024 NASEM LC criteria (Soriano et al., 2022) and endorsed one or more persistent symptoms consistent with these domains. Individuals were assigned to the recovered control group only if they reported full resolution of all acute COVID-19 symptoms and denied any ongoing or recurrent post-acute symptoms—including neuropsychiatric complaints such as brain fog or headaches.

Inclusion criteria included: 1) aged 18–80 years (we included a wide age span given the prevalence of neuropsychiatric symptoms from COVID-19 in younger and older individuals), 2) ability to give informed consent and travel to the study site, 3) individuals $>$ 8 weeks after acute COVID-19, either with post-acute sequela of COVID-19 and report $\geq$ 1 neuropsychiatric symptom (e.g., brain fog, headaches, etc; LC participants) or who had recovered from acute COVID-19; at minimum COVID-19 was based on self-reported positivity of an home test. Exclusion criteria included: 1) lack of English proficiency, 2) recent or active substance misuse (within 3 months) as determined through clinical interview and toxicology testing (nicotine/cannabis was permitted), 3) primary psychotic symptoms, and 4) MRI contraindications.

2.2. Standard protocol Approvals, Registrations, and Patient Consents

The study protocol received approval from the Johns Hopkins Institutional Review Board.

2.3. Procedures

This cross-sectional study involved a two-visit protocol conducted between July 2023 and January 2025. Participants were initially screened by phone to assess interest and preliminary eligibility. Those

who qualified attended an in-person screening visit at Johns Hopkins, during which they provided written informed consent, completed the Structured Clinical Interview for DSM Disorders (SCID) IV interview, underwent urine toxicology, had their vital signs measured, and completed questionnaires related to COVID-19 history, cognition and mental health (see below for details). A blood draw was performed to obtain a complete metabolic panel and complete blood count with differential, D-Dimer, and high sensitivity C-reactive protein. Eligible participants returned for a second visit to complete a brain MRI, a comprehensive cognitive test battery, and a follow-up blood draw.

2.3.1. Clinical assessments and questionnaires during study enrollment

RADx® Underserved Populations (RADx-UP) Tier 1 and 2 assessments, along with the Yale COVID-19 Review of Systems (Yale CRS)-version 10 were used to characterize participants in terms of pre-existing conditions, acute and LC symptomatology, vaccination status (based on the RADx-UP item: "*Have you received a COVID-19 vaccine?*"), COVID-19 variant (based on the date of initial infection), complications (including hospitalization), and self-reported disability. To improve classification of acute COVID-19 severity, we used a RADx-UP item that asked participants to report the highest level of care received for any COVID-19 infection. Responses were categorized into six mutually exclusive levels: (1) hospital intensive care unit, (2) hospital inpatient, (3) hospital emergency department, (4) urgent care/walk-in clinic, (5) primary doctor or healthcare center, and (6) stayed home or did not seek treatment. Participants reporting multiple levels of care were assigned to the highest level endorsed. This variable was used to create a binary hospitalization indicator, with hospitalization defined as any report of ICU care or inpatient stay, in line with WHO COVID-19 severity classification guidelines.

To enable comparisons between our sample and other LC studies, including the National Institutes of Health (NIH) Researching COVID to Enhance Recovery (RECOVER) study (Thaweethai et al., 2023), we computed a post-acute sequelae of SARS-CoV-2 infection (PASC) score and determined PASC categorization (PASC + or intermediate) based on a combination of validated questionnaires and single-item symptom questions adapted from RECOVER. These included the Quality of Life in Neurological Disorders SF v2.0 short form (Cella et al., 2012), Seattle Angina Questionnaire (Spertus et al., 1995), and the Patient-Reported Outcomes Measurement Information System (PROMIS) SF v1.0-Fatigue 13a. (Cella et al., 2007) In addition, participants responded to ten single-item symptom questions designed to capture LC symptomatology consistent with RECOVER. (Thaweethai et al., 2023) These items were: 1) loss of/change in smell or taste, 2) PEM/worsening of symptoms after even minor physical or mental effort, 3) persistent, chronic cough, 4) excessive thirst, 5) palpitations, racing heart, arrhythmia, skipped beats, 6) changes in desire for/comfort with/capacity for sex, 7) gastrointestinal ([GI]stomach) symptoms (feeling full, vomiting after eating, diarrhea, constipation), 8) abnormal movements, 9) hair loss, and 10) feeling faint, dizzy, "goofy", or having difficulty thinking soon after standing up from a sitting or lying position. These items were used to characterize the range and prevalence of LC-related symptoms in a manner consistent with RECOVER, allowing our sample to be contextualized alongside other national cohorts.

In addition to the SCID-IV, mental health risk factors and symptoms were assessed with the following: Patient Health Questionnaire-9, Generalized Anxiety Disorder Screener-7, PTSD Civilian Checklist, and the Childhood Trauma Questionnaire.

2.3.2. Cognitive test battery

The test battery included standard neuropsychological tests as well as tablet-based assessments using the Brainbaseline platform (Clinical ink) and questionnaires. The standard assessments included the Hopkins Verbal Learning Test-revised (Shapiro et al., 1999; Woods et al., 2005), Grooved Pegboard (Merker et al., 2011), and the Global Neuropsychological Assessment (GNA). (Olson et al., 2022) The GNA includes story learning and memory, fluency, digit and spatial span forward and backwards. The tablet-based assessments included Stroop-color and interference, Symbol substitution, Trail Making Test-Part 1 and 2, and Finger Tapping. (Lee et al., 2012; Rubin et al., 2021) Self-reported cognitive complaints were assessed with the Cognitive Failures Questionnaire (Broadbent et al., 1982; Rast et al., 2009) and the Behavior Rating Inventory of Executive Function-Adult Version. (Roth, 2005) To reduce the number of outcomes, we used exploratory factor analysis with varimax rotation. The 35 test scores reduced to eight factor scores, reflecting self-reported cognitive complaints (Factor 1), psychomotor speed (Factor 2), motor function (Factor 3), category-cued fluency (Factor 4), verbal episodic memory (Factor 5), letter-cued fluency (Factor 6), verbal semantic memory (Factor 7), and attention and working memory (Factor 8), see **Supplemental Materials**, **Table S1**.

2.3.3. MRI protocol and analysis

MRI was performed on a research-dedicated 3 Tesla MR system (Philips Healthcare, Best, the Netherlands). All MRI data was processed using in-house MATLAB scripts (version R2021b, Mathworks, Natick, MA), blinded to group identity. The WEPCAST MRI sequence, processing scripts, and associated instructions are available for request and download through the Siemens Teamplay platform. WEPCAST MRI was performed to estimate BBB permeability to water. Technical details of WEPCAST have been previously published (Lin et al., 2021; Lin et al., 2018; Shi et al., 2025). Briefly, water molecules are selectively labeled in the arteries that enter the brain and the proportion of water that remains in the vessels compared to the amount that diffuses into the brain tissue at the capillary-tissue interface is measured, thereby quantifying an estimate of the water extraction fraction (E). This measurement is conducted in the major cerebral veins, typically the superior sagittal sinus (SSS), providing a whole-brain estimate of E. During MRI data processing, a pair of flow-encoded MR images in the control and label conditions are collected and their subtraction yields the WEPCAST image which demonstrates the arterially labeled blood in the SSS. A kinetic signal model is then used to obtain E based on the control and label signal intensity in the posterior SSS (Shi et al., 2025; Lin et al., 2021) with a blood T1 value calculated from the individual hematocrit level (Li et al., 2016). The following imaging parameters were used for the WEPCAST MRI: single-slice sagittal plane, labeling duration = 4 s, post-labeling delay = 3 s, single-shot gradient-echo-planar-imaging-readout, velocity encoding (VENC) = 20 cm/s, field-of-view (FOV) = $200 \times 200 \times 10$ mm^3, voxel size = $3.1 \times 3.1 \times 10$ mm^3, repetition time (TR) = 9200 ms, echo time (TE) = 9.5 ms, SENSE factor = 3, number of control/label pair = 10, scan duration = 6:17 min. Another M_0 scan with identical acquisition but a TR of 10 s was performed for signal normalization.

Phase-contrast (PC) velocity-encoded MRI was conducted at the four feeding arteries (right/left internal carotid arteries and right/left vertebral arteries) of the brain to measure the total blood flux (Peng et al., 2015), with the following imaging protocol: single slice, FOV = $200 \times 200 \times 5$ mm^3, voxel size = $0.5 \times 0.5 \times 5$ mm^3, TR = 18 ms, TE = 9 ms, flip angle = 15°, VENC = 40 cm/s, scan duration = 14.8 s. Whole-brain volume was obtained from a high-resolution 1 mm^3 isotropic T1-weighted magnetization-prepared rapid gradient echo (MPRAGE) scan using the Computational Anatomy Toolbox (CAT) (Gaser et al., 2024). Global cerebral blood flow (CBF) f can then be calculated by normalizing the total flux with the whole-brain volume. Lastly, the BBB permeability index, known as the permeability-surface-area product (PS), is determined based on the Renkin–Crone model (Crone, 1963): $PS = -\ln(1-E)\cdot f$.

2.4. Statistical analyses

Group differences (LC vs. controls) in PS, CBF, E, and brain volume were examined using linear regressions and conducted in IBM SPSS Statistics (Version 29; IBM Corp. 2023). Group was the primary factor of

interest and age and sex were included as covariates. Several other variables differed between groups—such as hospitalization for COVID-19, mental health risk factors and symptoms, and medical comorbidities—but were not included in the models as they were either not significantly associated with PS (Fig. S1) or were considered *organismic confounders* (i.e., features intrinsically linked to the pathophysiology of LC rather than independent sources of bias, Fig. S2). Additional regressions were conducted to examine associations between PS and cognitive outcomes adjusting for age, sex, race, and education. Within the LC group, we explored predictors of higher PS, adjusting for age and sex. Given the exploratory, hypothesis-generating nature of these analyses in a novel clinical population, correction for multiple comparisons (e.g., false discovery rate) was not applied. Analyses were conducted in R version 4.4.0 and SciDataReportR v7.13.0. Significance was set at $P < 0.05$.

3. Results

3.1. Study population

Fig. 1 shows how the analytic sample was derived. Ninety-seven LC and 31 controls, aged 19–74 years, were included in the analysis (Table 1). For the LC group, the average time since the index infection was 34.6 months (SD = 11.6), while for the control group, the average time since the first infection was 30.1 months (SD = 13.7). On average, the LC group was older (M[mean] = 47 years, standard deviation [SD] = 13; range 19–74 years) compared to the control group (M = 39 years, SD = 13; range 23–68 years; $P = 0.003$). The LC group was more likely to be female (76 % vs. 55 %, $P = 0.04$) and less educated (17 vs. 18 years, $P = 0.02$), although both groups, on average, had completed at least a college degree. The LC group reported more current mental health symptoms and higher lifetime rates of depressive, trauma- and panic-related symptoms/disorders as well as emotional abuse and neglect compared to the control group. They also reported higher rates of several pre-existing medical comorbidities (e.g., autoimmune disease, asthma, hypertension) compared to controls.

During acute COVID-19, symptoms were somewhat more severe in the LC group compared to controls, with individuals in the LC group reporting more frequent headaches (83 % vs. 65 %, $P = 0.02$), confusion (44 % vs. 11 %, $P < 0.001$), and a greater loss or change in their sense of taste (51 % vs. 19 %, $P = 0.002$). The majority of participants (96 %) received a COVID-19 vaccine. Among the LC group, the most commonly reported PASC symptoms included PEM (82 %), GI issues (82 %), brain fog (67 %), fatigue (66 %), palpitations (66 %), and chest pain (62 %). Fifteen percent of the LC group were hospitalized due to COVID-19, however, the majority did not experience severe complications (e.g., required intubation). Additionally, 45 % self-reported disability, and among those with disability, 81 % reported difficulty concentrating, remembering, or making decisions; 73 % had serious difficulty walking or climbing stairs; 73 % had difficulty performing errands alone; and 45 % had difficulty dressing or bathing.

With respect to clinical laboratory values, the LC group had higher CRP levels (M = 2.6 vs. 1.8, $P = 0.03$) and erythrocyte sedimentation rate (M = 13 vs. 7, $P = 0.003$), but lower creatinine (M = 0.84 vs. 0.89, $P = 0.03$), total protein (M = 6.9 vs. 7.0, $P = 0.03$), total bilirubin (M = 0.44 vs. 0.53, $P = 0.006$), red blood cell count (M = 4.6 vs. 4.8, $P = 0.04$) compared to controls (Table S2). Additionally, the LC group had a higher percentage of neutrophils (59 % vs. 56 %, $P = 0.04$) and immature granulocytes (28 % vs. 16 %, $P = 0.001$), but lower absolute immature granulocytes (0.09 vs. 0.16, $P = 0.04$).

As expected, based on inclusion criteria, the LC group reported more self-reported cognitive complaints (Factor 1) compared to controls ($P < 0.001$). No statistically significant differences were observed between groups on the other cognitive factors, including verbal episodic memory (Factor 5; $P = 0.075$). See Table 1 for full results.

3.2. BBB permeability and cognitive correlates in LC

We hypothesized that people with LC would have greater BBB disruption compared to those who recovered from acute COVID-19. We observed that PS was significantly higher in the LC group compared to controls after adjusting for age and sex (B[unstandardized beta coefficient] = 18.59, SE = 6.11, β[standardized beta] = 0.28, $P = 0.003$; Fig. 2**a**). Although these variables may function as organismic confounders, supplemental models adjusting for COVID-19 hospitalization alone (B = 16.47, SE = 6.21, β = 0.244, $P = 0.009$), or hospitalization plus acute symptoms (nausea, loss or alteration of taste, confusion; B = 13.86, SE = 6.51, β = 0.206, $P = 0.035$), did not account for the

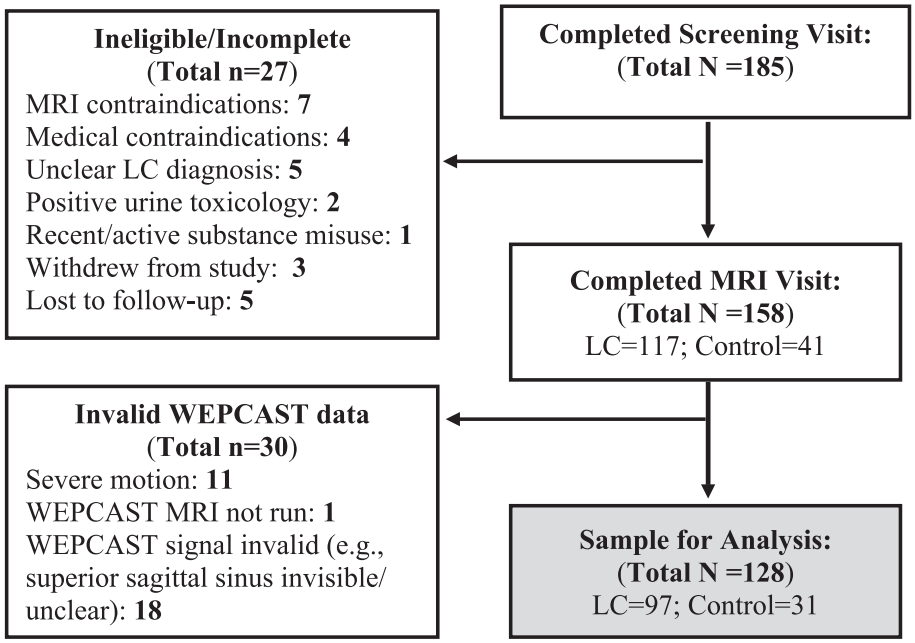

Fig. 1. Flow chart illustrating the selection process for Long COVID (LC, NASEM 2024) and SARS-CoV-2 infected, fully recovered controls. Colored boxes indicate participants included in the final analytic sample for the present study.

Table 1
Characteristics of patients with Long COVID (LC, NASEM 2024) versus controls (SARS-CoV-2 infected, fully recovered).

	N	LC (n = 97) n (%)	Controls (n = 31) n (%)	*P*-value
Demographics				
Age, M (SD)	128	47.3 (12.8)	39.3 (12.7)	0.003
Years of education, M (SD)	128	16.7 (2.5)	18.0 (2.8)	0.023
Education	128			0.114
High school diploma or equivalent		3 (3.1)	0 (0)	
Bachelor's degree (4-year college)		48 (49.5)	10 (32.3)	
Post-baccalaureate education (e.g., graduate/professional training)		46 (47.4)	21 (67.7)	
Female sex	128	74 (76)	17 (55)	0.039
Race	128			0.264
White		79 (81)	21 (68)	
Black		11 (11)	5 (16)	
Asian		5 (5.2)	3 (10)	
Other		2 (2.1)	2 (6)	
Ethnicity	128			0.690
Hispanic or Latino		6 (6)	3 (10)	
Not Hispanic or Latino		90 (94)	28 (90)	
Unknown		1 (1)	0 (0)	
Employment status	128			<0.001
Currently employed full-time		43 (44.3)	27 (93.1)	
Currently employed part-time		4 (4.1)	1 (3.4)	
Not currently employed, but employed in past year		2 (2.1)	0 (0)	
Disabled		21 (21.6)	0 (0)	
Unemployment supported by savings/other or retired		27 (28.9)	1 (3.4)	
Mental Health and Substance Use				
Lifetime SCID diagnosis				
Post-traumatic stress disorder	128	32 (33)	4 (13)	0.030
Major depressive disorder	128	51 (53)	10 (32)	0.049
Bipolar disorder	128	3 (1)	0 (0)	0.322
Generalized anxiety disorder	128	27 (28)	5 (16)	0.190
Panic disorder	128	14 (14)	0 (0)	0.021
Alcohol use disorder	128	14 (14)	4 (13)	0.831
Nicotine use	128			0.20
Never		66 (68)	26 (84)	
Past		23 (24)	3 (10)	
Active in past year		8 (8)	2 (6)	
Any Childhood Trauma via CTQ				
Emotional abuse	126	49 (52)	8 (26)	0.012
Physical abuse	126	26 (27)	8 (26)	0.865
Sexual abuse	126	28 (29)	4 (13)	0.066
Emotional neglect	126	46 (48)	7 (23)	0.011
Physical neglect	126	23 (24)	4 (13)	0.183
Patient Health Questionnaire (PHQ)-9 total score	126	12.2 (7.1)	2.9 (5.4)	<0.001
Generalized Anxiety Disorder (GAD)-7 total score	127	7.8 (5.8)	2.6 (7.8)	<0.001
PTSD Civilian Scale (PCLC) total score	126	39.8 (14.7)	22.8 (10.3)	<0.001
Vitals, M (SD)				
Diastolic	128	70.9 (10.3)	71.2 (11.5)	0.993
Systolic	128	125 (16.2)	122 (13.8)	0.448
Body mass index	128	29.2 (6.6)	27.4 (4.6)	0.242
RADx® Underserved Populations (RADx-UP)				
Pre-existing conditions				
Immunocompromised condition	127	18 (19)	1 (3)	0.042
Autoimmune disease	127	23 (24)	2 (6)	0.033
Hypertension	128	31 (32)	2 (6)	0.005
Diabetes	128	7 (7)	2 (6)	>0.999
Chronic kidney disease	128	4 (4)	0 (0)	0.572
Cancer diagnosis and/or treatment in the past 12 months	127	4 (4)	0 (0)	0.571
Cardiovascular disease	128	3 (3)	0 (0)	>0.999
Asthma	128	30 (31)	1 (3)	0.002
Chronic obstructive pulmonary disease	128	3 (3)	0 (0)	>0.999
Other chronic lung disease	128	4 (4)	0 (0)	0.572
Sickle cell anemia	128	0 (0)	0 (0)	>0.999
Self-reported disability and of those with disability,	124	42 (45)	2 (7)	<0.001
Difficulty concentrating, remembering, or making decisions	43	33 (81)	1 (50)	0.379
Serious difficulty walking or climbing stairs	43	30 (73)	0 (0)	0.086
Difficulty dressing or bathing	44	19 (45)	0 (0)	0.498
Difficulty doing errands alone (i.e., shopping)	43	30 (73)	0 (0)	0.086
Ever received a COVID-19 vaccine	128	93 (96)	30 (97)	>0.999
COVID-19 variant	128			0.002
Pre-delta		32 (33)	3 (10)	
Delta		28 (28.9)	6 (19)	
Omicron		31 (32)	14 (45)	
Post-Omicron		6 (6.2)	8 (26)	
Months since first COVID infection	127	34.6 (11.6)	30.1 (13.7)	0.145
Months since index COVID infection	127	33.9 (12.3)	30.1 (13.7)	0.218
COVID-19 Care: Highest level of care for <u>any</u> COVID-19 infection?	125			<0.001
Hospital intensive care unit (ICU)		4 (4.3)	0 (0)	
Hospital inpatient		10 (10.6)	0 (0)	
Outpatient/Acute Care		51 (54.3)	6 (19.4)	
Home-based or no care		29 (30.9)	25 (80.6)	
Hospitalization from COVID-19 (ICU or inpatient)	125	14 (14.9)	0 (0)	0.020
Yale COVID-19 Review of Symptoms-version 10				
Symptoms during acute COVID-19				
Fever	128	69 (71)	22 (71)	0.986
Cough or shortness of breath	128	76 (78)	21 (68)	0.230
Upper respiratory (sore throat, congestion)	128	78 (80)	21 (68)	0.142
Nausea or vomiting	128	32 (33)	7 (23)	0.273
Diarrhea	128	30 (31)	6 (19)	0.212
Loss or altered sense of smell	128	45 (46)	9 (29)	0.088
Loss or altered sense of taste	128	50 (51)	6 (19)	0.002
Seizure	128	1 (1)	0 (0)	>0.999
Headache	128	81 (83)	20 (65)	0.024
Confusion	128	42 (43)	3 (10)	<0.001
Any COVID-19 complications				
Required NC 02	125	4 (4)	0 (0)	0.571
Required NIV	125	2 (2)	0 (0)	>0.999
Required intubation	125	1 (1)	0 (0)	>0.999
Co-morbid infection	125	4 (4)	0 (0)	0.571
Thrombosis	125	3 (3)	0 (0)	0.574
Bleeding	125	1 (1)	0 (0)	>0.999
Stroke	125	1 (1)	0 (0)	>0.999
Extracorporeal Membrane Oxygenation (ECMO)	125	1 (1)	0 (0)	>0.999
PASC score items				
Smell/taste	128	38 (39)	1 (3)	<0.001
Postexertional malaise	128	80 (82)	1 (3)	<0.001
Chronic cough	128	22 (23)	1 (3)	0.014
Brain fog[a]	128	65 (67)	0 (0)	<0.001
Thirst	128	40 (41)	1 (3)	<0.001
Palpitations	128	64 (66)	2 (6)	<0.001
Chest pain[a]	128	60 (62)	6 (19)	<0.001
Fatigue[a]	128	64 (66)	3 (10)	<0.001
Sexual desire or capacity	128	44 (45)	2 (6)	<0.001

(*continued on next page*)

Table 1 (*continued*)

	N	LC (n = 97) n (%)	Controls (n = 31) n (%)	*P*-value
Dizziness	128	33 (34)	12 (39)	0.634
Gastrointestinal	128	80 (82)	10 (32)	<0.001
Abnormal movements	128	29 (30)	1 (3)	<0.001
Hair loss	128	42 (43)	1 (3)	<0.001
PASC total score, M (SD)	128	18.2 (8.1)	2.1 (3)	<0.001
PASC+	128	76 (78)	1 (3)	<0.001
Cognitive factor scores, M (SD)				
Factor 1: Self-reported cognitive complaints†	125	0.35 (0.91)	-0.96 (0.61)	<0.001
Factor 2: Psychomotor speed	125	0.03 (1.08)	0.21 (0.77)	0.399
Factor 3: Motor function	125	-0.04 (1.02)	0.19 (0.92)	0.277
Factor 4: Category-cued verbal fluency	125	-0.03 (1.04)	0.13 (0.94)	0.481
Factor 5: Verbal episodic memory	125	-0.11 (0.92)	0.24 (0.93)	0.075
Factor 6: Letter-cued verbal fluency	125	0.01 (1.03)	-0.16 (0.87)	0.445
Factor 7: Verbal semantic memory	125	-0.01 (1.02)	-0.05 (0.98)	0.836
Factor 8: Attention and working memory	125	-0.04 (1.03)	0.13 (1.04)	0.428

Childhood Trauma=Childhood Trauma Questionnaire.
Outpatient/Acute Care= Hospital emergency department, urgent care/walk-in clinic, primary doctor, health care center.
PASC score is calculated by adding up the scores for each symptom an individual has (Table 2 in RECOVER[15]). Score < 12=PASC-intermediate; ≥12=PASC+; [a] Additional severity criteria required (see eTables 1 and 2 in Supplemental 3 in RECOVER).
SCID-V=Structured Clinical Interview for making diagnoses according to the American Psychiatric Association's Diagnostic and Statistical Manual for Mental Disorders (DSM).
Group differences were conducted using Independent T-tests/Mann-Whitney *U* test for continuous variables and Chi-square/Fisher's Exact Test for categorical variables.
† higher = more self-reported cognitive complaints.

observed group difference in PS. Notably, neither hospitalization nor these acute symptoms were significantly associated with PS in the full sample (*P*'s > 0.05). In contrast to PS, there were no significant group differences in whole-brain CBF (β = 0.06, *P* = 0.51; Fig. 2**b**), *E* (β = 0.14, *P* = 0.12; Fig. 2**c**), or brain volume (β = -0.09, *P* = 0.23; Fig. 2**d**). Fig. 3 shows the representative WEPCAST data from a control (68 year old, White, female, 18 years of education) and a LC participant (66 year old, Black, female, 24 years of education). Lower signals can be observed in the posterior SSS of WEPCAST images from the LC patient compared to the control due to more labeled water molecules extracted into the brain, suggesting a more permeable BBB. Due to sample size constraints, we only assessed PS and cognition in the LC group and observed that higher PS was associated with poorer motor function after adjusting for age, sex, race, and education (Fig. 4). BBB permeability was not associated with any additional cognitive domains in the LC group.

3.3. Exploration of predictors of increased BBB permeability in LC

Given that PS was higher among the LC group, we examined factors related to increased permeability (Fig. 5). After adjusting for age and sex, PEM, aspartate aminotransferase (AST), and alanine aminotransferase (ALT), were positively associated with PS (ie. higher values = higher PS), while AST/ALT ratio and dizziness were negatively associated with PS (ie. higher values = lower PS). Mental health and substance use were not associated with PS (**Fig. S3**).

4. Discussion

The present study examined BBB disruption using WEPCAST MRI in individuals with LC reporting one or more neuropsychiatric symptoms at approximately 34 months after index infection as well as cognitive correlates of BBB disruption. We observed evidence supporting breakdown of the BBB in individuals with LC, consistent with earlier small-sample studies using more invasive techniques (CSF analysis and contrast-enhanced MRI[3-7]). Importantly, this difference in BBB permeability was not accounted for by initial infection severity. This finding, combined with previous research showing greater BBB permeability using WEPCAST in COVID-19 ICU survivors approximately four months after acute infection (Shi et al., 2023), supports the notion that BBB alterations may persist long after acute illness and are detectable in a broader LC population. These findings underscore the utility of

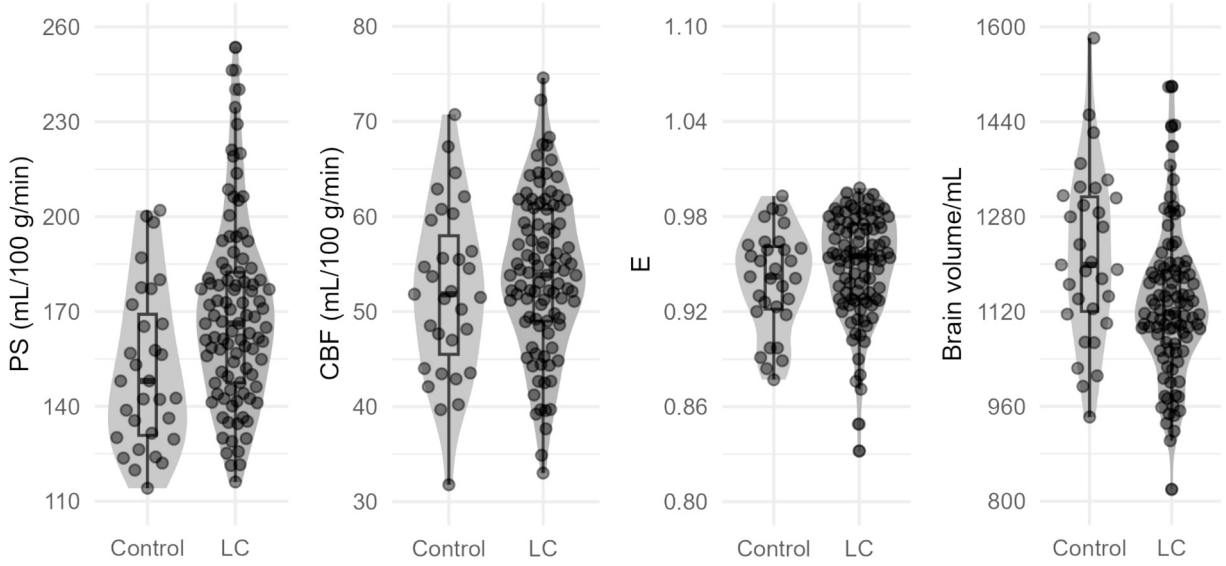

Fig. 2. Group comparisons between individuals with long COVID (LC) and recovered controls for (A) blood–brain barrier permeability (permeability-surface area product, PS), (B) cerebral blood flow (CBF), and (C) water extraction fraction (*E*), and (D) brain volume. All outcomes were adjusted for age and sex using linear regression. Abbreviations: CBF, cerebral blood flow; E, water extraction fraction; PS, permeability-surface area product.

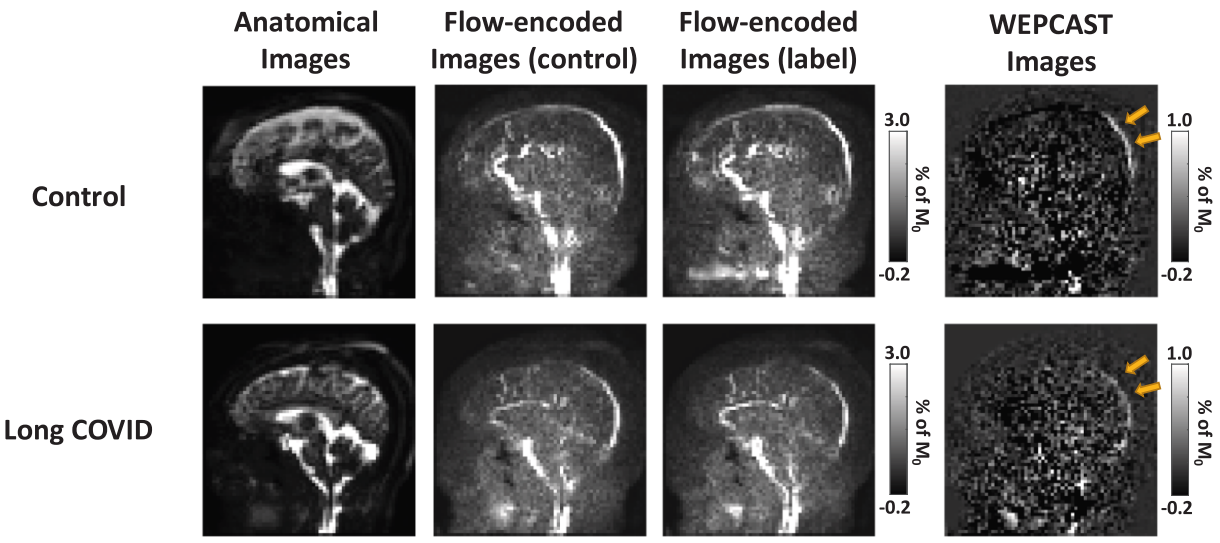

Fig. 3. Representative anatomical, flow-encoded images in the control and label conditions and the corresponding WEPCAST images from a control (68 year old, White, female, 18 years of education) and Long COVID participant (66 year old, Black, female, 24 years of education). Yellow arrows indicate the superior sagittal sinus. WEPCAST = water-extraction-with-phase-contrast-arterial-spin-tagging.

WEPCAST MRI as a non-invasive method for detecting chronic BBB dysfunction in LC.

When examining the neurological correlates of BBB permeability in LC, we observed that greater permeability was associated with poorer motor function, but not other objective cognitive domains (including in closely related functions such as psychomotor speed) or self-reported cognitive dysfunction, despite the centrality of cognitive complaints such as brain fog to LC diagnostic criteria. The only other study to explore correlations between BBB alterations (via DCE-MRI) and cognitive function did not find significant associations. (Chaganti et al., 2024) However, these associations were examined in a small sample (n = 7 with LC) and objective cognitive function was assessed on a limited battery (i.e., CogState Brief Battery) while motor functioning and subjective cognitive concerns were not examined. Aside from this study, most reports have focused on BBB in relation to self-reported cognitive difficulties, particularly brain fog. (Greene et al., 2024; Reas et al., 2025; Gupta et al., 2024) While those studies did not examine BBB differences on other self-reported cognitive or motor issues, we found that increased permeability was specifically associated with motor function, rather than memory or verbal fluency, both of which are common complaints and measurable deficits among individuals with LC. (Serrano Del Pueblo et al., 2024; Panagea et al., 2025) Several factors may explain the absence of broader cognitive associations. First, we did not observe significant differences in objective cognitive performance in the LC cohort compared to controls, limiting variability that might reveal associations with BBB permeability. Second, the current version of WEPCAST MRI provides a global estimate of BBB breakdown derived from signal changes in the SSS (Lin et al., 2021; Lin et al., 2018; Shi et al., 2025), which drains cortical regions such as motor cortex, but not deeper structures such as the medial temporal lobe, which supports memory encoding, or prefrontal regions critical for executive function. Future adaptations using WEPCAST, such as signal acquisition near the prefrontal cortex, may offer region-specific estimates of BBB permeability that better align with cognitive function. Additionally, contrast-MRI may offer greater regional specificity that captures BBB alterations relevant to cognitive domains. (Reas et al., 2025) Finally, cohort characteristics—particularly age—may have influenced the findings. Previous studies demonstrating associations between BBB permeability (via WEPCAST or contrast-MRI) and cognitive outcomes have typically been conducted in older adults (Reas et al., 2025) or individuals with established cognitive impairment (Lin et al., 2021); whereas our LC cohort was relatively young and cognitively intact. Despite the absence of observed associations with cognition in this study, prior literature supports a link between BBB dysfunction and cognitive function (Nation et al., 2019; Knox et al., 2022), underscoring the need for future studies with greater anatomical specificity and sample diversity.

We identified PEM as a self-reported symptom associated with increased BBB permeability in the LC group. PEM was assessed using a single-item question adapted from RECOVER, which asked participants whether they experienced a “worsening of symptoms after even minor physical or mental effort.” (Thaweethai et al., 2023) This definition is consistent with how PEM is characterized in other LC and Myalgic Encephalomyelitis/Chronic Fatigue Syndrome research. Clinically, PEM refers to a disproportionate flare of fatigue, cognitive difficulties, and neuromuscular symptoms following activity that would not have previously caused such effects. (Stussman et al., 2020) While the exact pathophysiologic mechanism of PEM is not fully understood, vascular dysregulation driven by autonomic dysfunction and mitochondrial dysfunction are suspected to play a central role. (Wirth and Scheibenbogen, 2021; Joseph et al., 2022) In support of this, a recent study found that when compared to healthy adults, people with LC and PEM exhibited an acute exercise-induced reduction in skeletal muscle mitochondrial enzyme activity, increased accumulation of amyloid-containing deposits in skeletal muscle, and a blunted exercise-induced T-cell response in skeletal muscle. (Appelman et al., 2024) These findings suggest that PEM may signal broader immune-metabolic and vascular alterations. The associated release of vasoactive or inflammatory mediators may, in turn, contribute to increased BBB permeability observed in this subgroup of individuals with LC.

Higher values of AST and ALT were found to be predictors for increased BBB permeability; however, this has limited clinical significance as the liver enzyme values in our cohort were well within the normal range (AST M = 22, SD = 7; ALT M = 24, SD = 15) indicating absence of liver pathology. Others have described an elevation of liver enzymes in the LC population (de Lima et al., 2019), but this was linked to the increased severity of acute illness, which was not the case in our cohort as most people in our LC cohort had a mild acute illness. A higher AST/ALT ratio was associated with lower BBB permeability in our LC group, but this finding is clinically insubstantial in the context of normal liver enzyme levels.

Reporting symptoms of dizziness, defined as feeling faint, dizzy, or “goofy, ” was associated with decreased BBB permeability. Dizziness is thought of as a symptom of orthostatic intolerance; we would expect its presence to be associated with a decrease in cerebral blood flow and,

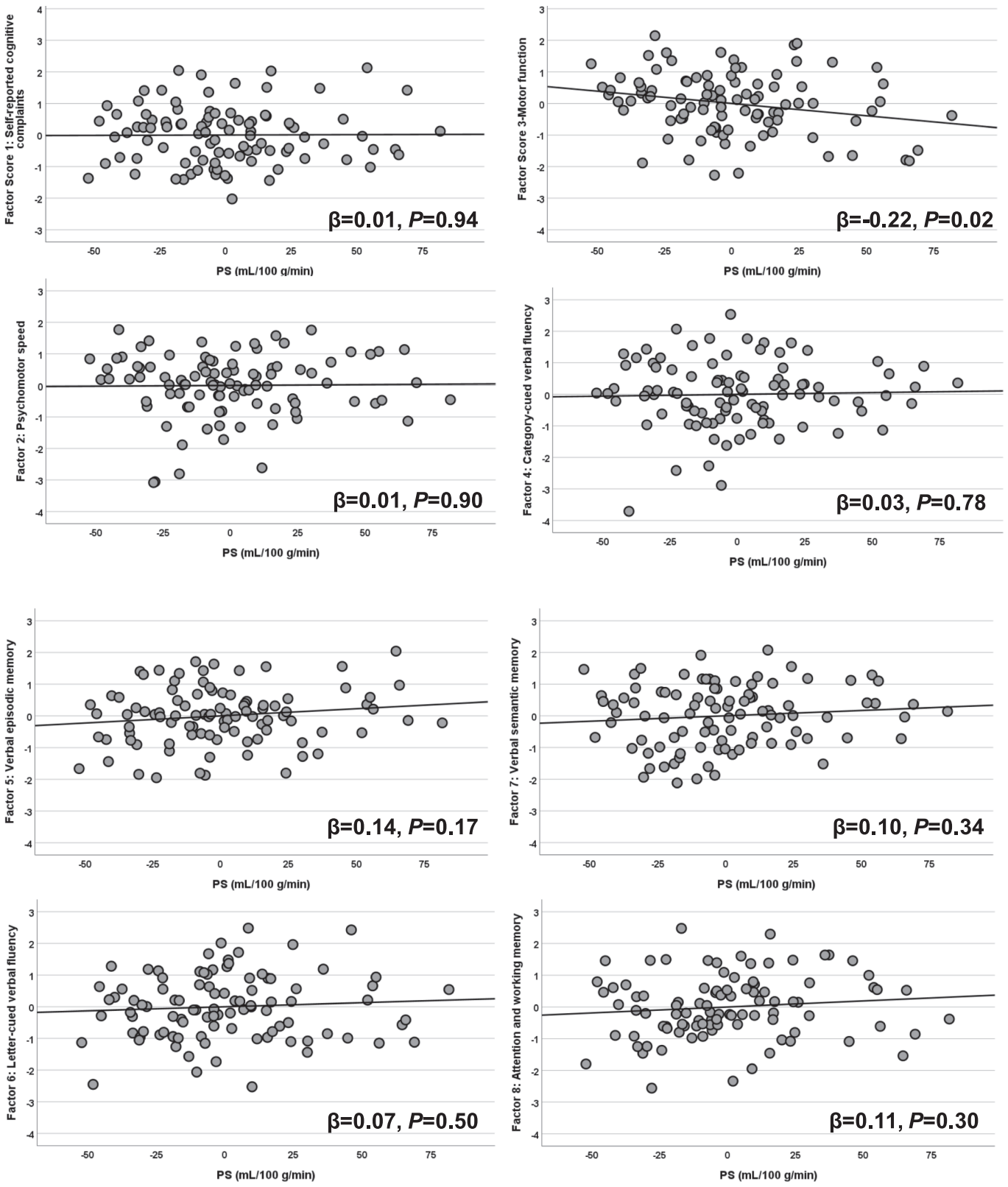

Fig. 4. Associations between blood–brain barrier permeability (permeability-surface area product, PS) and cognitive function among individuals with Long COVID (LC), after adjusting for age, sex, race, and education. PS = permeability-surface area product.

thus, an increase in BBB permeability. (Almutairi et al., 2016) Perhaps decreased CBF is not the primary driver of the observed BBB disruption and other factors, including metabolic changes associated with PEM have a more prominent role. Further understanding the neurobiological underpinnings of the PEM response could provide unique insight into the mechanism of neuropsychiatric sequela of SARS-CoV-2 infection and the development of LC.

There are several limitations to this study. First, the cross-sectional

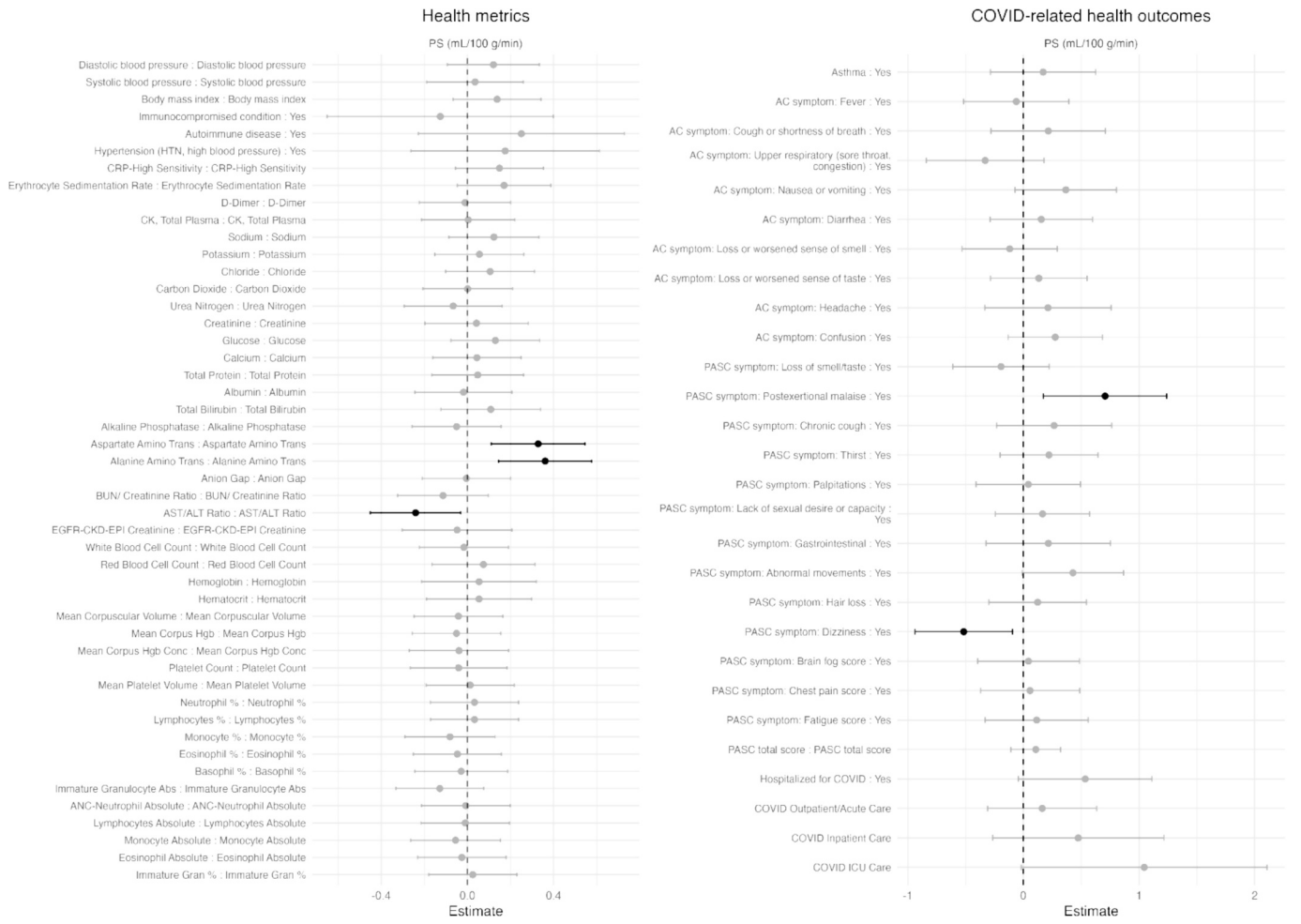

Fig. 5. Forest plots showing associations between health metrics and COVID-related health outcomes and blood brain barrier permeability (measured by permeability-surface area product, PS) among individuals with Long COVID, adjusting for age and sex. PS = permeability-surface area product.

design limits the ability to infer causality. A longitudinal study examining BBB breakdown in LC and its relationship to cognition would provide more definitive insights. Second, we used convenience sampling, which may introduce selection bias, as the sample may not be representative of the broader population of LC. Third, the WEPCAST MRI sequence used in the current study only yields a global measure of BBB permeability, lacking regional specificity. A region-specific WEPCAST method is under development and will enable the measurement of BBB permeability in both the cortical and deep brain regions (Shi et al., 2025) in future studies. Fourth, although we adjusted for age in all models, the broad age range (19–74 years) may introduce heterogeneity in symptom expression and brain physiology that could obscure more age-specific effects, particularly those related to neuroinflammatory or vascular vulnerability. Future studies with larger samples should consider age-stratified analyses to evaluate whether BBB permeability and its clinical correlates vary across the lifespan, particularly in older adults who may exhibit more pronounced effects. (Reas et al., 2025) Fifth, although COVID-19 vaccination status was recorded, we did not collect detailed information on vaccine dose number or timing, which limits the ability to evaluate its impact on BBB integrity. Sixth, while preliminary analyses identified an association between BBB permeability and motor function, no associations were observed with other cognitive domains. This may reflect limited statistical power, the specificity of the BBB signal captured by WEPCAST, or clinical heterogeneity within LC. Seventh, given the exploratory nature of these analyses and the decision not to apply a multiple comparisons correction, findings should be interpreted with caution. Importantly, data collection is ongoing, and this interim analysis may be underpowered to detect more subtle associations. We chose to report these early findings given the robust and replicable group differences in BBB permeability observed with continued enrollment, which we believe warrant early dissemination. Finally, eighth, although education and acute illness severity indictors (e.g., hospitalization) differed between groups, these variables were not included as covariates in our primary models because they were not significantly associated with PS in the full sample (as with education) or were considered organismic confounders—that is, characteristics potentially intrinsic to the LC disease process rather than external sources of bias. This modeling decision may limit generalizability but was made to preserve sensitivity to disease-related effects.

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CRediT authorship contribution statement

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& editing, Visualization, Formal analysis, Data curation. **Raha M. Dastgheyb:** Writing – review & editing, Visualization, Supervision, Formal analysis, Data curation. **Jiani Wu:** Writing – review & editing, Data curation. **Christina Della Penna:** Writing – review & editing, Investigation, Data curation. **Hannah Parker:** Writing – review & editing, Investigation, Data curation. **Isabel Santiuste:** Writing – review & editing, Investigation, Data curation. **Ana Ehrenspeck:** Writing – review & editing, Supervision, Investigation, Data curation. **Jennifer M. Coughlin:** Writing – review & editing, Investigation, Data curation. **Tracy D. Vannorsdall:** Writing – review & editing, Investigation. **Hanzhang Lu:** Writing – review & editing, Writing – original draft, Supervision, Resources, Methodology, Investigation, Formal analysis, Data curation, Conceptualization. **Rebecca Veenhuis:** Writing – review & editing, Writing – original draft, Project administration, Investigation, Funding acquisition, Conceptualization.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2025.07.024.

Data availability

Data will be made available on request.

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