Brain, Behavior, & Immunity - Health 48 (2025) 101093

Contents lists available at ScienceDirect

Brain, Behavior, & Immunity - Health

journal homepage: www.editorialmanager.com/bbih/default.aspx

Neurocognitive trajectories in long COVID: Evidence from longitudinal analyses

Jacqueline H. Becker [a,*], Jia Li [b], Jenny J. Lin [a], Alex Federman [a], Emilia Bagiella [c], Minal S. Kale [a], Daniel Fierer [d], Logan Bartram [d], Juan P. Wisnivesky [a,e]

[a] Division of General Internal Medicine, Department of Medicine, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, New York, NY, 10029, USA
[b] Graduate School of Biomedical Sciences, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, New York, NY, 10029, USA
[c] Center for Biostatistics, Department of Population Health Science & Policy, Icahn school of Medicine at Mount Sinai, One Gustave L. Levy Place, New York, NY, 10029, USA
[d] Division of Infectious Diseases, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, New York, NY, 10029, USA
[e] Division of Pulmonary and Critical Care Medicine, Icahn School of Medicine at Mount Sinai, One Gustave L. Levy Place, New York, NY, 10029, USA

ARTICLE INFO

Keywords:
COVID-19
Cognitive impairment
Long COVID

ABSTRACT

Background: Patients frequently report symptoms of cognitive impairment or "brain fog" after acute COVID-19 infection, but the trajectory of these symptoms over time has yet to be determined. We assessed cognitive function over a 42-month period after acute SARS-CoV-2 infection and identified factors associated with the trajectory of cognitive function over this period.

Methods: We analyzed data from participants in the Mount Sinai Health System Post-COVID-19 Registry in New York City, a prospective cohort study of adults followed after acute SARS-CoV-2 infection of any severity. Participants were identified from a list of all patients with COVID-19 who received care at an MSHS facility in New York, recruited beginning April 2020 and followed through January 2024. Cognition was assessed using well-validated in-person measures of attention, working memory, processing speed, executive functioning, language, and memory. We used linear mixed models to investigate the relationships between cognitive scores and time. We also assessed factors (including race, ethnicity, site of acute COVID-19 care, fatigue, depression, anxiety, body mass index, medical comorbidities, and COVID-19 vaccination) that may influence changes in cognitive scores over time.

Findings: We analyzed data from 1553 participants (median age 53 years, 63 % female, 17 % Black, 21 % Hispanic). In adjusted analyses, scores from cognitive measures of attention, working memory, processing speed, executive functions, and verbal learning and memory improved progressively through 42 months post-COVID. However, despite the improvements, on average, measures of processing speed and executive functioning remained $\geq$1 standard deviation below the normative mean. Having a body mass index of <25 kg/m^2 was predictive of a greater improvement in cognitive scores.

Interpretation: While cognitive impairment occurring after COVID-19 improved over time in most domains, processing speed and executive functioning remained below the normal range. The cognitive health burden of Long COVID is therefore significant and lasting. Future studies should examine interventions to support rapid recovery, as well as dynamic risk prediction models to determine factors that may impact cognitive recovery longer term.

1. Introduction

While most people recover from coronavirus-19 (COVID-19) without complications, millions of individuals experience post-acute sequelae of SARS-CoV-2, also known as Long COVID (LC), resulting in an unprecedented public health burden (National Academies of Sciences E and and Medicine, 2024). Among the constellation of LC symptoms, "brain fog" is commonly reported, referring to self-perception of slowness,

This article is part of a special issue entitled: Post-COVID19 condition published in Brain, Behavior, & Immunity - Health.

* Corresponding author. One Gustave L. Levy Place, New York, NY, 10029, USA.
E-mail address: jacqueline.becker@mountsinai.org (J.H. Becker).

https://doi.org/10.1016/j.bbih.2025.101093
Received 28 May 2025; Received in revised form 25 July 2025; Accepted 16 August 2025
Available online 19 August 2025
2666-3546/© 2025 The Authors. Published by Elsevier Inc. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

difficulties concentrating, and forgetfulness that are often reflective of a wide range of neuropsychiatric symptoms, including cognitive dysfunction (Becker et al., 2021; Becker et al., 2023). Importantly, these cognitive challenges can significantly impair functioning, particularly among younger adults who comprise a large proportion of those affected by LC (Kim et al., 2023).

Despite the substantial clinical and public health implications, the persistence of cognitive deficits post-COVID-19 remain poorly understood. Longitudinal studies examining cognitive outcomes after COVID-19 have yielded inconsistent findings, primarily due to differences in study design, measurement methods, and populations studied. Some investigations have demonstrated persistent dysfunction up to one year post-COVID (Rass et al., 2022), while others suggest partial recovery in a subset within this time frame (Frontera et al., 2022). However, few studies have assessed cognitive outcomes beyond one year, and fewer still have utilized validated, comprehensive neuropsychological assessments (Becker et al., 2023).

Hampshire et al. (2024) examined cognition after COVID-19 in a sample of 800,000 adults in England using an online survey, finding modest deficits in patients post-COVID relative to non-infected controls, which persisted for ≥1 year. However, the study was limited by a lack of validated neuropsychological measures, overrepresentation of White participants, potential survey response bias, and a single timepoint, limiting the assessment of cognitive change. Another study of 1593 older adults (mean age 61.5) hospitalized for COVID-19 documented gradual improvement in self-reported cognitive symptoms over three years (Fernández-de-Las-Peñas et al., 2022). However, this study did not quantify deficits using objective measures, and focused on a hospitalized, older cohort, limiting its generalizability to the broader population of younger, non-hospitalized individuals with LC.

Now, over five years since the onset of the pandemic, critical gaps remain in understanding whether and over what amount of time patients may recover from post-COVID cognitive dysfunction. The aim of this longitudinal study was to characterize multiple aspects of cognition using validated neuropsychological assessments among participants with differing levels of COVID-19 severity over 42-months. We also investigated factors associated with cognitive change over time, hypothesizing that COVID-19 severity will have the greatest influence on cognitive trajectories.

2. Methods

2.1. Study design and participants

We analyzed data from the Mount Sinai Health System's (MSHS) Post-COVID-19 Registry, a prospective cohort of ethnoculturally diverse COVID-19 patients treated in outpatient, emergency department (ED), or inpatient hospital settings (Wisnivesky et al., 2021, 2022). Participants were identified from a list including all patients with SARS-CoV-2 infection who received care at an MSHS facility in New York, recruited beginning April 2020 and followed through January 2024, regardless of reported symptoms. Eligible participants were ≥18 years of age, fluent in English or Spanish, and had laboratory-confirmed SARS-CoV-2 infection (i.e., positive test, serum antibody positive against spike protein if unvaccinated, or N-capsid peptide if vaccinated). Participants were assessed at baseline (which occurred at varying times since their initial acute COVID-19 episode, mean time 8.4 months) and annually thereafter, for up to three follow-ups. Each visit consisted of sociodemographic questionnaires, surveys, and neuropsychological tests. The study was approved by the Institutional Review Board, and informed consent was obtained from all participants.

2.2. Study variables

Sociodemographic characteristics were collected using the National Health Interview Survey (NHIS). (National Center of Health Statistics) Pre-COVID health, COVID vaccinations, and acute COVID-19 presentation and treatment were collected via self-report using the PhenX COVID-19 toolkit (Krzyzanowski et al., 2021). Site of acute COVID-19 care was categorized as outpatient, ED, or inpatient hospitalization and used as a proxy for COVID-19 severity. Time since COVID-19 was assessed via self-report and/or medical records. Body mass index (BMI) was calculated based on measured height and weight. Medical comorbidities were based on participants' report of a physician diagnosis. (National Center of Health Statistics) Fatigue was assessed using the PROMIS-29 v2.1 Fatigue Subscale (Hays et al., 2018). Depression was assessed using the Patient Health Questionnaire (PHQ-8) (Kroenke et al., 2001), with a score of ≥10 representing clinically significant depression symptoms (Kroenke et al., 2001). Anxiety was assessed using the General Anxiety Disorder (GAD-7) questionnaire, with a score of ≥10 representing clinically significant anxiety symptoms (Spitzer et al., 2006).

2.3. Cognitive functioning

Cognition was assessed annually using well-validated, in-person neuropsychological measures across several domains. Measures were administered in participants' primary language (English or Spanish) and normative data was sourced from published references suitable for each measure and language (Díaz-Santos et al., 2021). Alternate forms were used for applicable measures to mitigate practice effects. Attention and working memory were assessed using the Number Span (NS) from the National Alzheimer's Coordinating Center battery (Weintraub et al., 2018). Processing speed and executive functioning (EF) were assessed using the Trail Making Test (TMT) (Tombaugh, 2004) parts A and B, respectively. Language and initiation/fluency was assessed through verbal semantic and phonemic fluency tasks (Weintraub et al., 2018). The Hopkins Verbal Learning Test-Revised (HVLT-R) (Benedict et al., 1998) measured verbal learning (HVLT-R Immediate), memory (HVLT-R Delayed recall), and memory retention (HVLT-R Recognition). Finally, the Wide Range Achievement Test, 4th ed. (WRAT-4) (Wilkinson and Robertson, 2006) is a single-word reading test that correlates with estimated premorbid intellectual ability; it is also among the most valid estimates of quality of education among multiethnic, English-speaking samples (Wilkinson and Robertson, 2006). The Word Accentuation Test- Chicago (WAT-C) (Krueger et al., 2006) is an equivalent measure in Spanish (Cosentino et al., 2007). We also calculated Reliable Digits (Sawyer et al., 2017; Rickards et al., 2018) and HVLT-R recognition (Bailey et al., 2017) as validated, embedded indicators of performance validity; participants who did not meet the threshold for optimal validity were excluded from analyses. Raw scores were transformed into demographically corrected *z*-scores using age-, sex- and education-adjusted normative data for English (Heaton, 2004; Sachs et al., 2020) and Spanish speakers (Sáez-Atxukarro et al., 2021; Marquine et al., 2023). Mean *z*-scores were calculated to derive a cognitive composite score (Malek-Ahmadi et al., 2018/09; Andrade, 2021). A *z*-score of ≥1.0 standard deviations (SD) below the normative mean is considered an optimal cutoff to classify cognitive impairment in non-dementia populations (Busse et al., 2006) and in patients post-COVID-19 (Matias-Guiu et al., 2023).

2.4. Statistical analysis

Descriptive statistics assessed sociodemographic distributions. Linear mixed models assessed the trajectory of cognitive functioning over time. Time (months) represented the period from acute COVID-19 to cognitive testing date and was categorized in six-month intervals (<6, 6–12, 12–18, 18–24, 24–30, 30–36, and 36–42 months) to avoid assuming a linear trajectory of cognitive function over time. We fitted models for each cognitive measure and the composite score. A random patient intercept was included to incorporate clustering from repeated assessments; random slopes were omitted as they did not enhance model fit. Models were adjusted for race, ethnicity, site of acute COVID-19 care,

BMI, comorbidities (i.e., depression, anxiety, hypertension, diabetes, cerebrovascular disease, congestive heart failure, chronic obstructive pulmonary disease, and coronary artery disease), fatigue, COVID-19 vaccination status, and premorbid functioning based on the WRAT-4 (or WAT-C for Spanish speakers); age, sex, and education were accounted for by normative data. In exploratory analyses, we included interactions between predictors and time to assess factors that may modify the trajectory of cognitive changes. We used multiple imputation for missing predictor variables. Analyses were conducted using SAS statistical software (SAS Institute, Cary, NC) using two-sided 0.05 significance value.

3. Results

Among 1788 post-COVID participants in the Registry, 64 (4 %) were excluded due to incomplete baseline data, 147 (8 %) were excluded due to prior diagnosis or self-reported pre-COVID history of cognitive problems, and 24 (<2 %) were excluded due to below threshold scores on embedded performance validity indices, resulting in a cohort of 1553 participants. Importantly, our sample included all participants with SARS-CoV-2 infection, regardless of whether they reported LC symptoms. The median (IQR) age at baseline was 53 (40–62) years; 63 % were women, 17 % self-reported as Black, 21 % as Latinx/Hispanic, and 12 % as multiracial. The median (IQR) number of months since COVID-19 diagnosis at enrollment was 8 (5–12) months. Most participants (67 %) were managed for COVID-19 as outpatients (Table 1).

At baseline (<6 months post-COVID), participants demonstrated mild to moderate cognitive impairment across domains, with mean unadjusted *z*-scores ranging from −0.85 to −0.06 (Table 2). Over the 42-month follow-up period, several cognitive domains showed statistically significant improvement (Table 3, Fig. 1). **Learning and memory** demonstrated the most robust gains. In unadjusted analyses, verbal learning improved from a mean z-score of −0.80 (95 % CI: −0.89 to −0.70) at <6 months to a mean difference (MD) of $z = 0.60$ (95 % CI: 0.42 to 0.79) at 36–42 months. Similarly, memory recall scores improved from $z = -0.86$ (0.05, 95 % CI: −0.96 to −0.75) at <6 months and to $z = 0.54$ (95 % CI: 0.32 to 0.75) at 36–42 months. **Language and initiation/fluency** also demonstrated increasing trajectories. Phonemic fluency scores increased from a baseline of $z = -0.53$ (95 % CI: −0.61 to −0.44) to a MD of $z = 0.39$ (95 % CI: 0.22 to 0.55), while semantic fluency scores improved from $z = -0.65$ (95 % CI: −0.74 to −0.57) to a MD of $z = 0.32$ (95 % CI: 0.16 to 0.49) at 36–42 months. **Processing speed** showed delayed (i.e., after 2 years) but notable gains. Initial scores were $z = -0.75$ (95 % CI: −0.86 to −0.64), with significant improvement beginning after 24 months and reaching $z = -0.51$ (95 % CI: −0.70 to −0.31) at 36–42 months (MD: $z = 0.24$, 95 % CI: 0.03 to 0.46). **Executive functioning** improved modestly, with baseline scores of $z = -0.65$, 95 % CI: −0.76 to −0.55) increasing to $z = -0.40$ (95 % CI: −0.58 to −0.21) at 36–42 months. **Composite cognitive function** scores increased significantly, from a mean of z = −0.56 (95 % CI: −0.61 to −0.50) at baseline to a MD of $z = 0.27$ (95 % CI: 0.18 to 0.37) at 36–42 months. In contrast, **attention**, **working memory**, and **memory retention**, remained relatively stable and did not show statistically significant change over time.

In adjusted analyses (Fig. 2), the overall pattern remained consistent, though baseline impairments appeared more pronounced, ranging from adjusted *z*-scores of −1.78 and −0.46.

Learning, **memory recall**, and **composite cognitive function** scores were initially ≥1 SD below the normative mean, but recovered to within normal limits over time. **Learning** scores improved from $z = -1.26$ (95 % CI: −1.52 to −0.99) to a MD of $z = 0.59$ (95 % CI: 0.41 to 0.78), and **memory recall** improved from $z = -1.51$ (95 % CI: −1.79 to −1.23) to a MD of $z = 0.55$ (95 % CI: 0.35 to 0.76). **Language and initiation/fluency** also showed improvements over time. Phonemic fluency improved from $z = -0.92$ (95 % CI: −1.16 to −0.67) to a MD of $z = 0.38$ (95 % CI: 0.21 to 0.55), and semantic fluency from $z = -0.95$ (95 % CI: −1.18 to −0.71) to a MD of $z = 0.30$ (95 % CI: 0.14 to 0.47). **Composite cognitive function scores** improved from $z = -1.09$ (95 % CI: −1.26 to −0.93) with a corresponding MD of $z = -0.28$ (95 % CI: 0.19 to 0.37). **Processing speed** and **executive function** were initially ≥1.5 SD below the normative mean and, although they improved over time, they remained mildly impaired at 42 months. **Processing speed** improved from $z = -1.78$ (95 % CI: −2.08 to −1.48) to $z = -1.50$ (95 % CI: −1.83 to −1.16) with a MD of $z = 0.29$ (95 % CI: 0.07 to 0.50). **Executive functioning** improved from $z = -1.56$ (95 % CI: −1.86 to −1.26) to $z = -1.28$ (95 % CI: −1.61 to −0.95) with a MD of $z = 0.28$ (95 % CI: 0.08 to 0.48). **Attention** (baseline $z = -0.72$,95 % CI: −0.96 to

Table 1
Baseline characteristics of patients post-coronavirus Disease-19.

Characteristic	N = 1553
Age, years, median (interquartile range)	53 (40–62)
Female, no. (%)	978 (63)
Education, years, no. (%)	
≤12	233 (15)
13-16	310 (20)
>16	1009 (65)
Race/Ethnicity, no. (%)	
Non-Hispanic White	777 (50)
Non-Hispanic Black	267 (17)
Hispanic	331 (21)
Asian/Others	178 (12)
Smoking Status, no. (%)	
Never	962 (67)
Current	49 (3)
Former	430 (30)
Married, no. (%)	638 (41)
Time since Covid-19, months, median (IQR)	8 (5–12)
Income, no. (%)	
<$25,000	357 (23)
$25,000-$60,000	279 (18)
$60,000-$150,000	528 (34)
>$150,000	388 (25)
Comorbidities, no. (%)	
Diabetes	186 (12)
Hypertension	475 (31)
Depression	464 (30)
Anxiety	403 (26)
Fatigue	1248 (86)
Asthma	366 (25)
Chronic obstructive pulmonary disease	63 (4)
Stroke	56 (4)
Coronary artery disease	72 (5)
Congestive heart failure	42 (3)
Covid-19 Vaccinated, no. (%)	679 (44)
Body Mass Index, kg/m^2, median (IQR)	28 (24–32)
Site of Covid-19 care, no. (%)	
Outpatient	1039 (67)
Emergency room	268 (17)
Inpatient	246 (16)

COVID-19: Coronavirus Disease-2019.

Table 2
Baseline cognitive scores in patients post-coronavirus Disease-19 (COVID-19).

Cognitive Scores	Mean *z*-score (SD)
Number Span Backward	−0.29 (1.05)
Number Span Forward	−0.17 (1.07)
Hopkins Verbal Learning Test- Immediate Recall	−0.70 (1.23)
Hopkins Verbal Learning Test-Delayed Recall	−0.77 (1.32)
Hopkins Verbal Learning Test-Recognition	−0.18 (1.18)
Verbal Phonemic Fluency	−0.44 (1.05)
Verbal Semantic Fluency	−0.60 (1.06)
Trail Making Test-A	−0.76 (1.34)
Trail Making Test-B	−0.61 (1.32)
Cognitive Composite Score	−0.49 (0.75)
Wide Range Achievement Test (WRAT-4) Reading or Word Accentuation Test (WAT-C)	0.58 (1.93)

Table 3
Adjusted trajectory of cognitive functioning over time.

Cognitive Measures	Mean Difference (95 % Confidence Interval) vs. Prior Timepoint						
	6-12 vs. 0-6	12-18 vs 6-12	18-24 vs 12-18	24-30 vs 18-24	30-36 vs 24-30	36-42 vs 30-36	36-42 vs 0-6
Attention (Number Span Backward)	0.13 (0.02–0.24)	−0.08 (−0.19-0.03)	0.05 (−0.08-0.18)	−0.01 (−0.14-0.12)	−0.13 (−0.25-0.00)	0.22 (0.05–0.40)	0.19 (0.02–0.36)
Working Memory (Number Span Forward)	0.06 (−0.04-0.17)	−0.01 (−0.12-0.10)	0.11 (−0.02-0.23)	−0.06 (−0.19-0.06)	0.01 (−0.11-0.14)	0.02 (−0.16-0.19)	0.13 (−0.04-0.30)
Learning (HVLT-R Immediate Recall)	0.16 (0.05–0.28)	−0.02 (−0.14-0.10)	0.23 (0.09–0.37)	0.12 (−0.04-0.27)	0.09 (−0.07-0.24)	0.02 (−0.18-0.22)	0.59 (0.41–0.78)
Memory (HVLT-R Delayed Recall)	0.12 (−0.01-0.25)	0.09 (−0.04-0.23)	0.17 (0.02–0.33)	0.05 (−0.12-0.21)	0.17 (0.01–0.34)	−0.05 (−0.27-0.16)	0.55 (0.35–0.76)
Retention/storage (HVLT-R Recognition)	0.16 (0.03–0.30)	−0.10 (−0.24-0.04)	0.13 (−0.03-0.29)	−0.01 (−0.18-0.16)	−0.01 (−0.17-0.16)	−0.21 (−0.44-0.03)	−0.03 (−0.25-0.20)
Verbal Phonemic Fluency	0.08 (−0.02-0.19)	0.08 (−0.03-0.19)	0.06 (−0.07-0.19)	0.06 (−0.08-0.20)	0.17 (0.03–0.31)	−0.08 (−0.26-0.10)	0.38 (0.21–0.55)
V5rbal Semantic Fluency	0.02 (−0.08-0.13)	0.15 (0.04–0.26)	−0.04 (−0.17-0.09)	0.06 (−0.08-0.19)	0.07 (−0.07-0.20)	0.05 (−0.13-0.22)	0.30 (0.14–0.47)
Processing Sped (Trail Making Test-A)	0.05 (−0.08-0.19)	−0.02 (−0.16-0.12)	0.06 (−0.10-0.21)	0.17 (0.01–0.33)	0.01 (−0.14-0.16)	0.02 (−0.20-0.23)	0.29 (0.07–0.50)
Executive functioning (Trail Making Test-B)	0.10 (−0.03-0.23)	0.02 (−0.11-0.15)	0.11 (−0.04-0.26)	0.06 (−0.10-0.21)	−0.08 (−0.23-0.07)	0.07 (−0.14-0.27)	0.28 (0.08–0.48)
General Cognition (Cognitive Composite)	0.11 (0.04–0.17)	0.00 (−0.06-0.06)	0.10 (0.03–0.17)	0.06 (−0.01-0.12)	0.03 (−0.04-0.09)	0.00 (−0.10-0.09)	0.28 (0.19–0.37)

−0.48) and **working memory** (baseline $z = -0.63$, 95 % CI: −0.87 to −0.40) did not show consistent improvement over time. While small changes were observed (MDs: $z = 0.19$ [95 % CI: 0.02 to 0.36] and $z = 0.13$ [95 % CI: −0.04 to 0.30], respectively), these did not reach clinical significance. **Memory retention** had no significant differences between 6 months and 42 months.

In exploratory analyses, BMI was the only factor significantly associated with improvement in cognitive function composite scores over time ($p = 0.026$ for interaction). Underweight or normal weight (BMI <25 kg/m^2) was associated with greater improvements in composite scores across all timepoints. No other factors, such as age, sex, COVID-19 severity, COVID vaccination, and comorbidities (i.e., depression, anxiety, diabetes, hypertension, fatigue) were significantly associated with trajectory of general cognition over time ($p > 0.05$ for all interaction terms).

4. Discussion

In this study, we measured cognition post-COVID-19 in a large and diverse cohort of participants over a 42-month period, using validated neuropsychological measures. We found that mild cognitive impairment after COVID-19 was common during the first 18 months after infection, and that gradual improvements in cognitive scores occurred over approximately two years that followed. That is, scores in most domains appeared to improve over time, including learning, memory, processing speed, EF, language, and initiation/fluency, beginning after two years. Measures of basic attention, working memory, and memory retention fluctuated minimally, likely due to relatively intact functioning in these domains. After 32 months, however, scores in most cognitive domains plateaued, potentially indicating a return to baseline levels for some individuals, or a ceiling on cognitive improvement for others. Notably, despite improvements, processing speed and EF remained mildly impaired (i.e., ≥1.5 SD below the normative mean) at 42 months. Additionally, we found that BMI is associated with recovery trajectory, with normal- or low-weight participants showing greater improvement over time. Overall, while our findings are generally reassuring and suggest that on average patients may improve with time, cognitive difficulties in some domains (i.e., processing speed and EF) may persist beyond 3 years. This highlights the importance of monitoring patients post-COVID-19 to ensure appropriate management of cognitive health, including aiding in compensatory strategies or other supports to accelerate recovery.

Other studies have similarly found that cognitive impairment may persist beyond two-years post-infection, although very few have examined cognition beyond the two-year mark (Rass et al., 2022; Frontera et al., 2022; Ferrucci et al., 2022; Liu et al., 2024/07). Furthermore, most studies include cohorts self-reporting LC symptoms, whereas our cohort reflects all participants with confirmed SARS-CoV-2 infection, regardless of whether they reported LC symptoms. Our findings confirm and extend our prior research characterizing cognitive impairment post-COVID-19, in which we found a high frequency of impairment 8 months post-COVID-19,[2] and greater odds of executive dysfunction one-year post-COVID-19 in comparison to non-infected controls (Becker et al., 2023). We further demonstrate that while cognitive improvement did not occur early, there were many domains that improved around two years in most individuals. These findings are consistent with other longitudinal studies of patients with LC (Fernández-de-Las-Peñas et al., 2022; Bowe et al., 2023). For example, in a cohort of 138,818 patients post-COVID-19 and 5,985,227 non-infected controls, one study found that the risk of most (69 %) self-reported LC symptoms, including brain fog, became non-significant at 2 years post-infection in non-hospitalized individuals (Bowe et al., 2023). Another study examined the trajectory of post-COVID symptoms in 1266 previously hospitalized COVID-19 patients using self-report of "brain fog," finding a decreasing trend in its prevalence up to 18 months post-hospital discharge (Fernández-de-Las-Peñas et al., 2023). The finding that lower BMI was associated with greater cognitive improvements is consistent with prior research demonstrating correlations between high BMI and cognitive impairment and decline (Karlsson et al., 2021). High BMI is associated with elevated inflammation, which plays a significant role in LC pathology (Florencio and Fernández-de-Las-Peñas, 2022). It is possible that individuals with lower BMI may have lower baseline inflammation and better vascular health, allowing for better cognitive recovery.

The etiologies of post-COVID cognitive impairment are unknown but have been hypothesized to arise from biological factors related to central nervous system (CNS) damage (e.g., neuroinflammation, cerebrovascular dysfunction, blood-brain barrier perturbations, neural network dysfunction) (Churchill et al., 2023), psychological factors (e.g., depression, anxiety) (Liu et al., 2023), or other factors that are known to impact cognition (e.g., pain, fatigue) (Mueller et al., 2023). While COVID-19 severity may play a role given the increased potential for neurologic insults associated with inpatient care, individuals with mild disease can also develop LC (Panagea et al., 2024). Just as the etiology of deficits is susceptible to individual variability, recovery may also vary depending on each individual's capacity for neuronal regeneration, which can vary based on age, health status, genetic factors, and

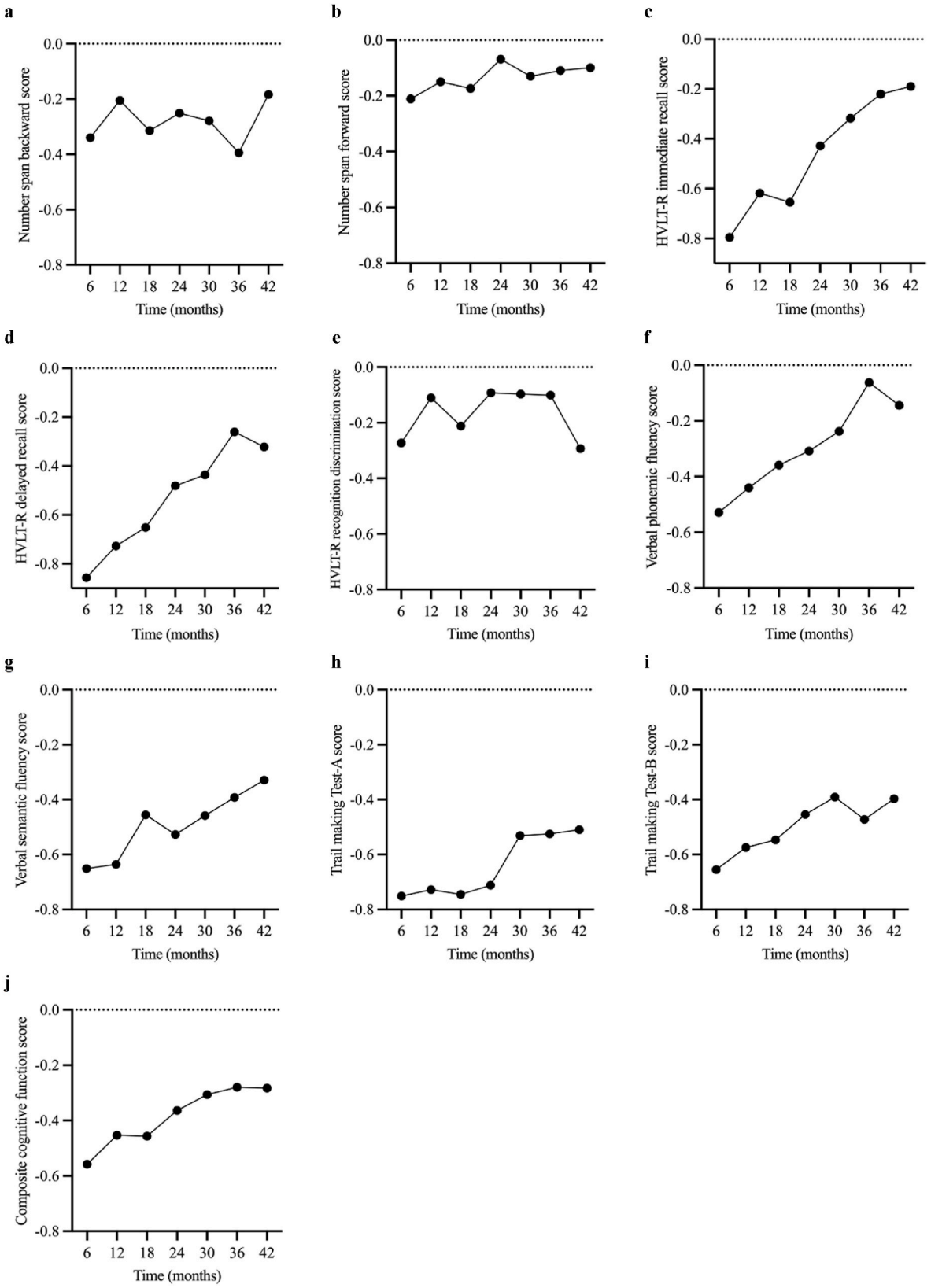

Fig. 1. Unadjusted trajectory of cognitive functioning over time. a); Attention; b) Working memory; c) Verbal learning; d) Memory recall; e) Memory retention; f) Rapid initiation/fluency; g) Language; h) Processing speed; i) Executive functioning. In unadjusted analyses, most cognitive domains showed an increasing trend up to 42 months post-COVID.

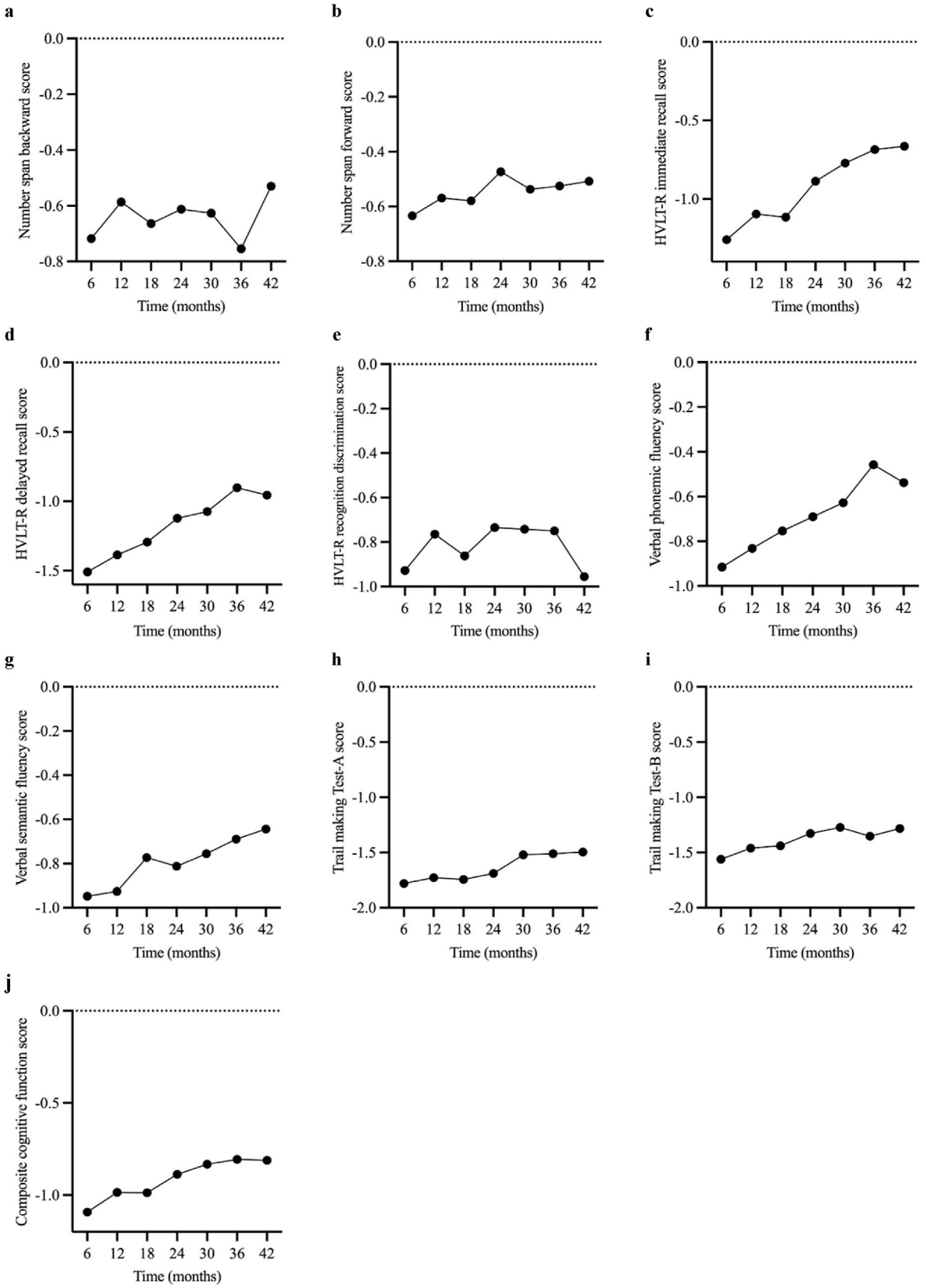

Fig. 2. Adjusted trajectory of cognitive functioning over time. a) Attention; b) Working memory); c) Verbal learning; d) Memory recall; e) Memory retention; f) Rapid initiation/fluency; g) Language; h) Processing speed; i) Executive functioning. All cognitive domains displayed an increasing trend up until 40 months post-COVID after adjusting for race/ethnicity, site of acute care, BMI, comorbidities (i.e., depression, anxiety, hypertension, diabetes, cerebrovascular disease, congestive heart failure, chronic obstructive pulmonary disease, and coronary artery disease), fatigue, COVID-19 vaccination status, and premorbid functioning based on the WRAT-4 test.

pre-existing conditions (Panagea et al., 2024). Cognitive recovery involves a complex and multifaceted process that may be dependent on the specific etiology of deficits. A recent longitudinal study on patients post-COVID-19 noted that normalization of biomarkers of immune dysregulation at 24 months resulted in a parallel reduction in clinical symptoms (Phetsouphanh et al., 2024/04). This suggests that a reduction in inflammation over time may alleviate cognitive symptoms in those with elevated inflammation (Phetsouphanh et al., 2024/04). In other cases of CNS damage, the human brain possesses a capacity for neuroplasticity, which allows it to reorganize itself and repair neural structures over time, a process that can be facilitated by targeted interventions (e.g., cognitive rehabilitation). (Hagen et al., 2022).

Our study has several strengths and limitations. While our cohort consists of a relatively unselected sample, there may be some participation bias where patients who are more impaired, or conversely, those without residual symptoms, may have declined to participate in the registry. Our cohort was relatively young (mean age 53) and well-educated. Thus, results may not generalize to older adults or those with lower levels of educational attainment, as cognitive/neural reserve has been shown to play a significant role in neural recovery (Steward et al., 2018). However, unlike most LC studies, our cohort had robust representation of racially/ethnically diverse individuals, which is a significant strength. Additionally, our cohort was an average of 8.4 months post-COVID-19 to capture post-acute sequelae; however, we acknowledge that variability in time after acute infection could have introduced some selection bias. While there is a small, but inherent possibility of practice effects from serial testing, there was at least a one-year period between assessments, which has been shown to attenuate most practice effects (Bartels et al., 2010). A significant strength is that we were able to obtain validated, in-person cognitive data during a global pandemic. A weakness was that to minimize participant burden, we utilized a brief battery and were unable to measure some cognitive domains in greater depth (e.g., sustained attention, higher-order EFs). We also were unable to utilize stand-alone performance validity measures (Sweet et al., 2021), though we did examine embedded validity indices (e.g., Reliable Digits) and excluded cases with possible suboptimal effort (<2 %) from analyses. Finally, missing data may not have been random, which could potentially bias estimates of the trajectory of cognition over time.

In conclusion, we found that post-COVID cognitive impairment appears to improve over time, although some cognitive domains may remain below the normative mean even after 42 months. While the possibility of cognitive improvement demonstrates the brain's remarkable ability to adapt and reorganize itself following neuronal damage, full recovery from LC may be elusive for some. Even mild residual deficits can negatively impact quality of life (Bowe et al., 2023), and thus there is a need to consider the cumulative health burden of LC and its symptoms. Supportive measures such as cognitive rehabilitation, cognitive behavioral therapy, and leading a healthy lifestyle (e.g., given BMI findings) can help promote neuronal regeneration to optimize recovery. Future studies should examine dynamic risk and resilience prediction models to determine factors (e.g., metabolic or immune biomarkers) that may impact cognitive recovery for persons with LC longer term.

CRediT authorship contribution statement

Jacqueline H. Becker: Writing – review & editing, Writing – original draft, Formal analysis, Data curation, Conceptualization. **Jia Li:** Writing – review & editing, Formal analysis. **Jenny J. Lin:** Writing – review & editing, Supervision, Project administration. **Alex Federman:** Writing – review & editing, Supervision, Resources. **Emilia Bagiella:** Supervision, Methodology, Formal analysis, Data curation. **Minal S. Kale:** Supervision. **Daniel Fierer:** Writing – review & editing. **Logan Bartram:** Writing – review & editing. **Juan P. Wisnivesky:** Writing – review & editing, Writing – original draft, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization.

Funding

This work was funded by the Icahn School of Medicine at Mount Sinai.

Declaration of competing interest

JPW has received consulting honorarium from Sanofi, American Medical Association, BionTech, Banook and PPD research grants from Sanofi, Regeneron and Axella. Other authors report no competing interests.

Data availability

Data will be made available on request.

References

Andrade, C. Z Scores, 2021. Standard scores, and composite test scores explained. Indian J. Psychol. Med. 43 (6), 555–557. https://doi.org/10.1177/02537176211046525.
Bailey, K.C., Soble, J.R., Bain, K.M., Fullen, C., 2017. Embedded performance validity tests in the Hopkins verbal learning test—revised and the brief visuospatial memory test—revised: A replication study. Arch. Clin. Neuropsychol. 33 (7), 895–900. https://doi.org/10.1093/arclin/acx111.
Bartels, C., Wegrzyn, M., Wiedl, A., Ackermann, V., Ehrenreich, H., 2010. Practice effects in healthy adults: a longitudinal study on frequent repetitive cognitive testing. BMC Neurosci. 11, 118. https://doi.org/10.1186/1471-2202-11-118.
Becker, J.H., Lin, J.J., Doernberg, M., et al., 2021. Assessment of cognitive function in patients after COVID-19 infection. JAMA Netw. Open 4 (10), e2130645. https://doi.org/10.1001/jamanetworkopen.2021.30645.
Becker, J.H., Vannorsdall, T.D., Weisenbach, S.L., 2023. Evaluation of post–COVID-19 cognitive dysfunction: recommendations for researchers. JAMA Psychiatry 80 (11), 1085–1086. https://doi.org/10.1001/jamapsychiatry.2023.2820.
Becker, J.H., Lin, J.J., Twumasi, A., et al., 2023. Greater executive dysfunction in patients post-COVID-19 compared to those not infected. Brain Behav. Immun. 114, 111–117. https://doi.org/10.1016/j.bbi.2023.08.014.
Benedict, R.H., Schretlen, D., Groninger, L., Brandt, J., 1998. Hopkins verbal learning test–revised: normative data and analysis of inter-form and test-retest reliability. Clin. Neuropsychol. 12 (1), 43–55.
Bowe, B., Xie, Y., Al-Aly, Z., 2023. Postacute sequelae of COVID-19 at 2 years. Nat. Med. 29 (9), 2347–2357. https://doi.org/10.1038/s41591-023-02521-2.
Bowe, B., Xie, Y., Al-Aly, Z., 2023. Postacute sequelae of COVID-19 at 2 years. Nat. Med. 29 (9), 2347–2357. https://doi.org/10.1038/s41591-023-02521-2.
Busse, A., Hensel, A., Gühne, U., Angermeyer, M.C., Riedel-Heller, S.G., 2006. Mild cognitive impairment: long-term course of four clinical subtypes. Neurology 67 (12), 2176–2185. https://doi.org/10.1212/01.wnl.0000249117.23318.e1.
Churchill, N.W., Roudaia, E., Chen, J.J., et al., 2023. Effects of post-acute COVID-19 syndrome on the functional brain networks of non-hospitalized individuals. Front. Neurol. 14, 1136408. https://doi.org/10.3389/fneur.2023.1136408.
Cosentino, S., Manly, J., Mungas, D., 2007. Do reading tests measure the same construct in multiethnic and multilingual older persons? J. Int. Neuropsychol. Soc. 13 (2), 228–236. https://doi.org/10.1017/s1355617707070257.
Díaz-Santos, M., Suárez, P.A., Marquine, M.J., et al., 2021. Updated demographically adjusted norms for the brief visuospatial memory test-revised and Hopkins verbal learning test-revised in Spanish-speakers from the U.S.-Mexico border region: the NP-NUMBRS project. Clin. Neuropsychol. 35 (2), 374–395. https://doi.org/10.1080/13854046.2020.1861329.
Fernández-de-Las-Peñas, C., Martín-Guerrero, J.D., Cancela-Cilleruelo, I., Rodríguez-Jiménez, J., Moro-López-Menchero, P., Pellicer-Valero, O.J., 2022. Exploring trajectory recovery curves of post-COVID cognitive symptoms in previously hospitalized COVID-19 survivors: the LONG-COVID-EXP-CM multicenter study. J. Neurol. 269 (9), 4613–4617. https://doi.org/10.1007/s00415-022-11176-x.
Fernández-de-Las-Peñas, C., Cancela-Cilleruelo, I., Rodríguez-Jiménez, J., et al., 2023. Trajectory of post-COVID brain fog, memory loss, and concentration loss in previously hospitalized COVID-19 survivors: the LONG-COVID-EXP multicenter study. Front. Hum. Neurosci. 17, 1259660. https://doi.org/10.3389/fnhum.2023.1259660.
Ferrucci, R., Dini, M., Rosci, C., et al., 2022. One-year cognitive follow-up of COVID-19 hospitalized patients. Eur. J. Neurol. 29 (7), 2006–2014. https://doi.org/10.1111/ene.15324.
Florencio, L.L., Fernández-de-Las-Peñas, C., 2022. Long COVID: systemic inflammation and obesity as therapeutic targets. Lancet Respir. Med. 10 (8), 726–727. https://doi.org/10.1016/s2213-2600(22)00159-x.
Frontera, J.A., Yang, D., Medicherla, C., et al., 2022. Trajectories of neurologic recovery 12 Months after hospitalization for COVID-19: a prospective longitudinal study. Neurology 99 (1), e33–e45. https://doi.org/10.1212/wnl.0000000000200356.

Hagen, B.I., Lerdal, A., Søraas, A., et al., 2022. Cognitive rehabilitation in post-COVID-19 condition: a study protocol for a randomized controlled trial. Contemp. Clin. Trials 122, 106955.

Hampshire, A., Azor, A., Atchison, C., et al., 2024. Cognition and memory after covid-19 in a large community sample. N. Engl. J. Med. 390 (9), 806–818. https://doi.org/10.1056/NEJMoa2311330.

Hays, R.D., Spritzer, K.L., Schalet, B.D., Cella, D., 2018. PROMIS(®)-29 v2.0 profile physical and mental health summary scores. Qual. Life Res. : Int. J. Qual. Life Aspects TAreatment Care Rehabil. 27 (7), 1885–1891. https://doi.org/10.1007/s11136-018-1842-3.

Heaton, R.K., 2004. Revised Comprehensive Norms for an Expanded Halstead-Reitan Battery: Demographically Adjusted Neuropsychological Norms for African American and Caucasian Adults, Professional Manual. Psychological Assessment Resources.

Karlsson, I.K., Gatz, M., Arpawong, T.E., Dahl Aslan, A.K., Reynolds, C.A., 2021. The dynamic association between body mass index and cognition from midlife through late-life, and the effect of sex and genetic influences. Sci. Rep. 11 (1), 7206. https://doi.org/10.1038/s41598-021-86667-4.

Kim, Y., Bae, S., Chang, H.-H., Kim, S.-W., 2023. Long COVID prevalence and impact on quality of life 2 years after acute COVID-19. Sci. Rep. 13 (1), 11207. https://doi.org/10.1038/s41598-023-36995-4.

Kroenke, K., Spitzer, R.L., Williams, J.B., 2001. The PHQ-9: validity of a brief depression severity measure. J. Gen. Intern. Med. 16 (9), 606–613. https://doi.org/10.1046/j.1525-1497.2001.016009606.x.

Krueger, K.R., Lam, C.S., Wilson, R.S., 2006. The word accentuation test - Chicago. J. Clin. Exp. Neuropsychol. 28 (7), 1201–1207. https://doi.org/10.1080/13803390500346603.

Krzyzanowski, M.C., Terry, I., Williams, D., West, P., Gridley, L.N., Hamilton, C.M., 2021. The PhenX toolkit: establishing standard measures for COVID-19 research. Current Protocols 1 (4), e111.

Liu, T.C., Yoo, S.M., Sim, M.S., Motwani, Y., Viswanathan, N., Wenger, N.S., 2023. Perceived cognitive deficits in patients with symptomatic SARS-CoV-2 and their association with post–COVID-19 condition. JAMA Netw. Open 6 (5), e2311974. https://doi.org/10.1001/jamanetworkopen.2023.11974.

Liu, Y.-H., Wu, Q.-X., Wang, Q.-H., et al., 2024. Tracking cognitive trajectories in older survivors of COVID-19 up to 2.5 years post-infection. Nature Aging. https://doi.org/10.1038/s43587-024-00667-3.

Malek-Ahmadi, M., Chen, K., Perez, S.E., He, A., Mufson, E.J., 2018. Cognitive composite score association with Alzheimer's disease plaque and tangle pathology. Alzheimers Res. Ther. 10 (1), 90. https://doi.org/10.1186/s13195-018-0401-z.

Marquine, M.J., Parks, A., Perales-Puchalt, J., et al., 2023. Demographically-adjusted normative data among latinos for the version 3 of the alzheimer's disease centers' neuropsychological test battery in the uniform data set. Alzheimer's Dement. 19 (9), 4174–4186.

Matias-Guiu, J.A., Herrera, E., González-Nosti, M., et al., 2023. Development of criteria for cognitive dysfunction in post-COVID syndrome: the IC-CoDi-COVID approach. Psychiatry Res. 319, 115006. https://doi.org/10.1016/j.psychres.2022.115006.

Mueller, M.R., Ganesh, R., Hurt, R.T., Beckman, T.J., 2023. Post-COVID Conditions. Elsevier, pp. 1071–1078.

National Academies of Sciences E, and Medicine, 2024. A Long COVID Definition: A Chronic, Systemic Disease State with Profound Consequences.

National Center of Health Statistics. National health Interview survey. https://www.cdc.gov/nchs/nhis/index.htm. (Accessed 3 February 2021).

Panagea, E., Messinis, L., Petri, M.C., et al., 2024. Neurocognitive impairment in long COVID: a systematic review. Arch. Clin. Neuropsychol. https://doi.org/10.1093/arclin/acae042.

Phetsouphanh, C., Jacka, B., Ballouz, S., et al., 2024. Improvement of immune dysregulation in individuals with long COVID at 24-months following SARS-CoV-2 infection. Nat. Commun. 15 (1), 3315. https://doi.org/10.1038/s41467-024-47720-8.

Rass, V., Beer, R., Schiefecker, A.J., et al., 2022. Neurological outcomes 1 year after COVID-19 diagnosis: a prospective longitudinal cohort study. Eur. J. Neurol. 29 (6), 1685–1696. https://doi.org/10.1111/ene.15307.

Rickards, T.A., Cranston, C.C., Touradji, P., Bechtold, K.T., 2018. Embedded performance validity testing in neuropsychological assessment: potential clinical tools. Appl Neuropsychol Adult 25 (3), 219–230. https://doi.org/10.1080/23279095.2017.1278602.

Sachs, B.C., Steenland, K., Zhao, L., et al., 2020. Expanded demographic norms for version 3 of the Alzheimer disease centers' neuropsychological test battery in the uniform data set. Alzheimer Dis. Assoc. Disord. 34 (3), 191–197.

Sáez-Atxukarro, O., Del Pino, R., Peña, J., Schretlen, D.J., Ibarretxe-Bilbao, N., Ojeda, N., 2021. [Hopkins verbal learning test-revised: normalization and standardization for Spanish population]. Rev. Neurol. 72 (2), 35–42. https://doi.org/10.33588/rn.7202.2020412. Test de aprendizaje verbal de Hopkins revisado: normalización y estandarización de la prueba en población española.

Sawyer, Ii RJ., Testa, S.M., Dux, M., 2017. Embedded performance validity tests within the Hopkins verbal learning test – revised and the brief visuospatial memory test – revised. Clin. Neuropsychol. 31 (1), 207–218. https://doi.org/10.1080/13854046.2016.1245787, 2017/01/02.

Spitzer, R.L., Kroenke, K., Williams, J.B., Löwe, B., 2006. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch. Intern. Med. 166 (10), 1092–1097. https://doi.org/10.1001/archinte.166.10.1092.

Steward, K.A., Kennedy, R., Novack, T.A., Crowe, M., Marson, D.C., Triebel, K.L., 2018. The role of cognitive reserve in recovery from traumatic brain injury. J. Head Trauma Rehabil. 33 (1), E18–e27. https://doi.org/10.1097/htr.0000000000000325.

Sweet, J.J., Heilbronner, R.L., Morgan, J.E., et al., 2021. American Academy of Clinical Neuropsychology (AACN) 2021 consensus statement on validity assessment: update of the 2009 AACN consensus conference statement on neuropsychological assessment of effort, response bias, and malingering. Clin. Neuropsychol. 35 (6), 1053–1106. https://doi.org/10.1080/13854046.2021.1896036.

Tombaugh, T.N., 2004. Trail Making Test A and B: normative data stratified by age and education. Arch. Clin. Neuropsychol. 19 (2), 203–214. https://doi.org/10.1016/S0887-6177(03)00039-8.

Weintraub, S., Besser, L., Dodge, H.H., et al., 2018. Version 3 of the Alzheimer disease centers' neuropsychological test battery in the Uniform Data Set (UDS). Alzheimer Dis. Assoc. Disord. 32 (1), 10–17. https://doi.org/10.1097/WAD.0000000000000223.

Wilkinson, G.S., Robertson, G.J., 2006. Wide Range Achievement Test (WRAT4). Lutz, FL. Psychological Assessment Resources.

Wisnivesky, J.P., Stone, K., Bagiella, E., et al., 2021. Long-term persistence of neutralizing antibodies to SARS-CoV-2 following infection. J. Gen. Intern. Med. 36 (10), 3289–3291. https://doi.org/10.1007/s11606-021-07057-0.

Wisnivesky, J.P., Govindarajulu, U., Bagiella, E., et al., 2022. Association of vaccination with the persistence of post-COVID symptoms. J. Gen. Intern. Med. 37 (7), 1748–1753. https://doi.org/10.1007/s11606-022-07465-w.