

COVCOG 3 – Trajectory of Long COVID: Longitudinal Changes in Symptoms and Cognitive Impairment. A Third Publication from the COVID and Cognition Study.

[Author details are provided in the separate title page]

Running Head: COVCOG 3: Cognition in Long COVID

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Abstract

Long COVID has widespread and long-lasting multisystemic impacts on patients' body, cognition and daily functioning, including the ability to work. Longitudinal studies are important in investigating the expected timelines along the course of recovery. This mixed cross-sectional/longitudinal study examines how symptoms (cognitive and non-cognitive) and objective cognitive function evolve in post-COVID-19 patients ($n = 187$) compared to non-infected controls ($n = 207$). Participants completed a questionnaire about their COVID-19 experience and cognitive tasks at baseline and again at 2–3 follow-ups during a 9-month period. While some non-cognitive symptoms improved over time ($d_s = .34-.87$), cognitive symptoms and neurological symptoms, as well as memory function assessed with objective cognitive assessments, remained unimproved (non-significant change over time). Neurological symptoms predicted both cognitive symptoms and cognitive impairment across time. Our finding suggested that people with past COVID-19 infection did not experience improvement in cognitive function over time, at least for the duration of this 9-month longitudinal study.

1. Introduction

Long COVID, or 'Post-COVID-19 syndrome', is recognised as the persistence of COVID-19 symptoms for more than 12 weeks following infection (UK National Institute for Health and Care Excellence [NICE], 2022). It is estimated that nearly 2 million people in the UK (UK Office for National Statistics [ONS], 2023) are now experiencing some version of this condition, in 69% of those at least 1 year, and 41% at least 2 years since infection. Crucially, Long COVID can occur regardless of the severity of initial infection (O'Mahoney et al., 2023): The majority of Long COVID cases are found in non-hospitalised patients having had a mild acute illness (FAIR Health, 2022). Given this alarming prevalence, Long COVID has been referred to as 'the pandemic after the pandemic' (Levine, 2022). At barely 4 years since the emergence of the virus, research on the trajectory in long-term sufferers is vital. This 'COVCOG 3' study applied mixed cross-sectional/longitudinal design to track how physical and cognitive symptoms and objective cognitive function change over time in post-COVID-19 patients, compared to non-infected controls, over a 9-month follow-up period.

Long COVID patients experience symptoms affecting multiple organ systems (Davis et al., 2023; Raveendran et al., 2021). For example, Davis and colleagues (2021) found that systemic symptoms such as fatigue were present in almost all of the 3762 participants surveyed, while 85% also experienced others, such as cardiovascular (e.g. palpitations) and neuropsychiatric symptoms (e.g. cognitive dysfunction, sensorimotor problems, issues with emotion and mood). Systemic and cognitive/neurological symptoms were still present at 7 months following infection. These findings are consistent with our own ('COVCOG 1': Guo et al.,

2022a). Indeed, meta-analysis (Ceban et al., 2022) confirms that fatigue and cognitive symptoms are amongst the most common and debilitating for Long COVID patients.

There is considerable evidence to suggest that post-COVID illness can be long-lasting. For example, 42% of the 33,281 patients studied in Hastie and colleagues' (2022) longitudinal study reported incomplete recovery 6–18 months post infection, with the proportion reporting no recovery reaching 16% in those who had been hospitalised. Similarly, 17% of the 1,106 patients surveyed by Ballouz and colleagues (2023) reported not being recovered at 24 months. Recovery appears to follow different trajectories for different types of symptoms, with symptoms such as sore throat resolving quickly (Huang et al., 2021; Xiong et al., 2021), while fatigue and cognitive dysfunction linger as long as 1–2 years (Dennis et al., 2023; Huang et al., 2022; Petersen et al., 2021). Indeed, recent review papers highlight the persistence of cognitive problems in Long COVID patients – which were less likely to improve if the chronic symptoms lasted more than 12 months – and the frustration these patients experienced. (Ladds et al., 2024; Li et al., 2023). This raises the possibility that COVID-19 infection may increase vulnerability to long-term or permanent cognitive decline, neurodegeneration and dementia (Bougakov et al., 2021; Goldberg et al., 2021; Miners et al., 2020).

Cognitive problems in Long COVID are diverse. In Davis et al. (2021), 85.1% of participants with illness lasting longer than 28 days reported cognitive dysfunction or 'brain fog', 72.8% reported memory impairments, both short- and long-term, and 46.3% had 'tip of the tongue' word-finding difficulties. Among participants at month 7, over half still reported cognitive dysfunction and memory impairments. Consistent with this, the most frequently reported cognitive symptoms in our cohort at baseline assessment ('COVCOG 1') at week 3–31+

included difficulty concentrating (77.8%), brain fog (69%), forgetfulness (67.5%) and tip-of-the-tongue problems (59.5%) (Guo et al., 2022a). Other studies have also shown that these and language and executive function issues are commonly reported in Long COVID (Nalbandian et al., 2021; Ziauddeen et al., 2022).

Studies employing objective screening tools such as the Montreal Cognitive Assessment (MoCA) detected even higher rates of cognitive impairment in Long COVID than subjective reports seemed to imply (Ceban et al., 2022; Davis et al., 2023). Hampshire and colleagues (2021) studied cognitive test performance in 84,285 individuals from the online Great British Intelligence Test. Even those who were considered to have recovered from COVID-19 (no longer reporting respiratory symptoms) showed significant deficits in semantic problem solving, spatial working memory and selective attention tasks compared to uninfected controls. Consistent results were observed in a later study from this research group investigating over 112,000 participants: Those with unresolved persistent symptoms demonstrated large deficits in tasks assessing memory, reasoning and executive function (Hampshire et al., 2024). Similarly, in our COVCOG sample, we found evidence for reduced memory performance, driven by impairment in word recognition memory in those with past COVID-19 infection compared to uninfected individuals ('COVCOG 2': Guo et al., 2022b). Other studies have found a similar pattern of findings, with memory, language, executive function and response speed being particularly affected in post-COVID-19 patients (Becker et al., 2021; Graham et al., 2021; Herrera et al., 2023; Miskowiak et al., 2023; Zhao et al., 2024; see also Crivelli et al., 2022 for a systematic review and meta-analysis).

Cognitive issues are probably underpinned by neurological factors. Neurological symptoms are reported by a large proportion of patients (Mao et al., 2020; Pryce-Roberts et al., 2020; Romero-Sánchez et al., 2020). For example, anosmia is one of the most recognised and widely experienced symptoms of COVID-19 (e.g. Lechien et al., 2020; Mao et al., 2020; Romero-Sánchez et al., 2020). These neurological symptoms can persist months after initial illness (Taruffi et al., 2023). There is mounting evidence that many COVID-19 patients display signs of neurological deficits and abnormal neural activity (Galanopoulou et al., 2020; Helms et al., 2020; Kandemirli et al., 2020). A longitudinal study of pre- and post-infection anatomical magnetic resonance imaging (MRI) brain scans in 394 COVID-19 patients showed abnormalities across multiple regions including the left parahippocampal gyrus, orbitofrontal cortex and cingulate cortex, and right hippocampus (Douaud & colleagues, 2022). These accounts of neurological involvement in COVID-19 also seem to translate into impaired performance on cognitive tests: A PET study of 29 older patients presenting with neurological symptoms found that degree of frontoparietal hypometabolism was associated with lower neuropsychological scores, particularly in tests of verbal memory and executive functions (Hosp et al., 2021).

Various mechanisms have been proposed to explain these COVID-19 induced neurological conditions and cognitive impairments. These primarily involve abnormal inflammation or coagulation (Nalbandian et al., 2021). Long-lasting hypoxia and disruption of the blood-brain barrier through systemic inflammation and cytokine release have been implicated in severe acute COVID-19, which typically leads to neuro-inflammation and long-term cognitive deficits (Baker et al., 2021; Nalbandian et al., 2021). Cognitive impairment could arise from hippocampal and cortical impact associated with neuro-inflammation (Steardo et al., 2020).

Additionally, hypercoagulation in severe COVID-19 is associated with delirium and cognitive deficits (Baker et al., 2021), while microvascular endothelial damage also correlates with haemorrhagic or ischaemic brain lesions in patients with COVID-19 (Østergaard, 2021).

The consequences of chronic Long COVID can be life-altering. The ONS (2023) reports 79% of people with Long COVID experience negative effects on daily activities, which were severe in 20% of cases. Our 'COVCOG 1' study found that 63.9% of participants with ongoing symptoms reported difficulty coping with day-to-day activities, 54.6% had experienced long periods unable to work, and 34.5% had lost their job due to illness. These impacts scaled with symptom severity (Guo et al., 2022a). Specifically, Davis et al. (2021) reported that 86.2% of working respondents felt mildly to severely unable to work specifically because of cognitive dysfunction. In a study with 1,683 individuals following COVID-19 infection, those reporting more daily cognitive symptoms were more likely to experience at least moderate interference with daily functioning and less likely to have full-time employment (Jaywant et al., 2024). As Long COVID becomes a prevalent social problem with far-reaching implications, research is needed to ascertain patterns of development in Long COVID experience over time. Longitudinal studies could provide valuable information of expected timelines along the course of recovery, if any.

There is – to date – little test-based longitudinal research on cognitive function over time in Long COVID. Among these very few studies, Del Brutto et al. (2022) evaluated cognitive function in mild COVID-19 patients before and at 6 and 18 months after infection using the MoCA. Significant decline in MoCA scores was observed at 6 months relative to pre-infection, but these improved again at 18 months, suggesting at least a partial recovery. Similarly, Afzali

et al. (2023) found that across three 45-day intervals, performance on the Paced Auditory Serial Addition Test (PASAT) improved across all patients, but that response speed slowed over time in those who had suffered severe acute illness. This evidence of reduced recovery in those with more severe initial illness is reflected in evidence in hospitalised patients: Using the Cognitive Impairment in Psychiatry (SCIP) assessment, Miskowiak and colleagues (2022) demonstrated that degraded performance on memory and processing speed did not show significant change between 3 months and 1 year post infection.

The two previous papers from COVID and Cognition study (COVCOG) used the baseline data from this mixed cross-sectional/longitudinal study ('COVCOG 1': Guo et al., 2022a; 'COVCOG 2': Guo et al., 2022b). This third longitudinal paper ('COVCOG 3') documents how symptoms (both cognitive and non-cognitive) and objectively measured cognitive function change over time post-COVID. Note that our samples were recruited from the community (such as through social media and word of mouth), with the majority being non-hospitalised patients. Given previous evidence, we form the following hypotheses:

- Hypothesis 1: Changes in COVID-19 symptoms over time. We expect that different symptom areas will follow divergent recovery trajectories, depending on general severity of ongoing illness at baseline. Specifically, we predict that cognitive and neurological symptoms will be persistent, while others may recede more rapidly.
- Hypothesis 2: Changes in cognitive performance over time. We expect the slower recovery in cognitive and neurological symptoms to be reflected in objective cognitive measures of learning and memory, with the deficits in memory evident at baseline (Guo et al., 2022b) reducing but not disappearing during the follow-up period.

- Hypothesis 3: Predictors of cognitive symptoms and cognitive performance. We investigate the relationship between non-cognitive symptoms experienced at different stages of the illness and cognitive symptoms and performance. While we expect to see numerous relationships, we specifically predict that neurological symptoms during the early illness will continue to predict individual differences in cognitive performance across multiple time-points.

2. Method

2.1 Participants

Over the data collection period from October 2020 to July 2022, we recruited 476 adults (321 [67.4%] female) from communities in majority English-speaking countries. The baseline data for 421 participants (181 in the COVID group, 185 in the No-COVID group, 55 with an unknown infection status) and reasons for non-inclusion and detailed recruitment procedure were reported previously (Guo et al., 2022a, 2022b). This paper uses cases with sufficiently complete data on the final baseline dataset from 187 participants in the COVID group and 207 in the No-COVID group.

The COVID baseline group was further divided into three subgroups according to their severity of ongoing illness experienced up to the time of baseline assessment. At the baseline, participants who had had COVID were asked to describe their experience of the infection after the first 3 weeks of acute illness. Those who reported having been 'never ill' or 'feeling better' were assigned to the 'Recovered' subgroup (R ; $n = 48$). Those who reported having

‘ongoing mild/moderate symptoms’ were assigned to the ‘Ongoing–Mild/Moderate’ subgroup ($C+$; $n = 61$). Those who reported having ‘ongoing severe symptoms’ were placed in the ‘Ongoing–Severe’ subgroup ($C++$; $n = 78$). Figure 1 shows full details of participant grouping (see also Guo et al., 2022a, 2022b and Supplementary Materials for the Supplementary Caption to Figure 1). Attrition statistics are reported with particular analyses in Results. Note that the baseline sample is slightly larger in the current study than in the publications on that data (COVCOG1 and COVCOG2) due to the inclusion of participants who completed the session after publication.

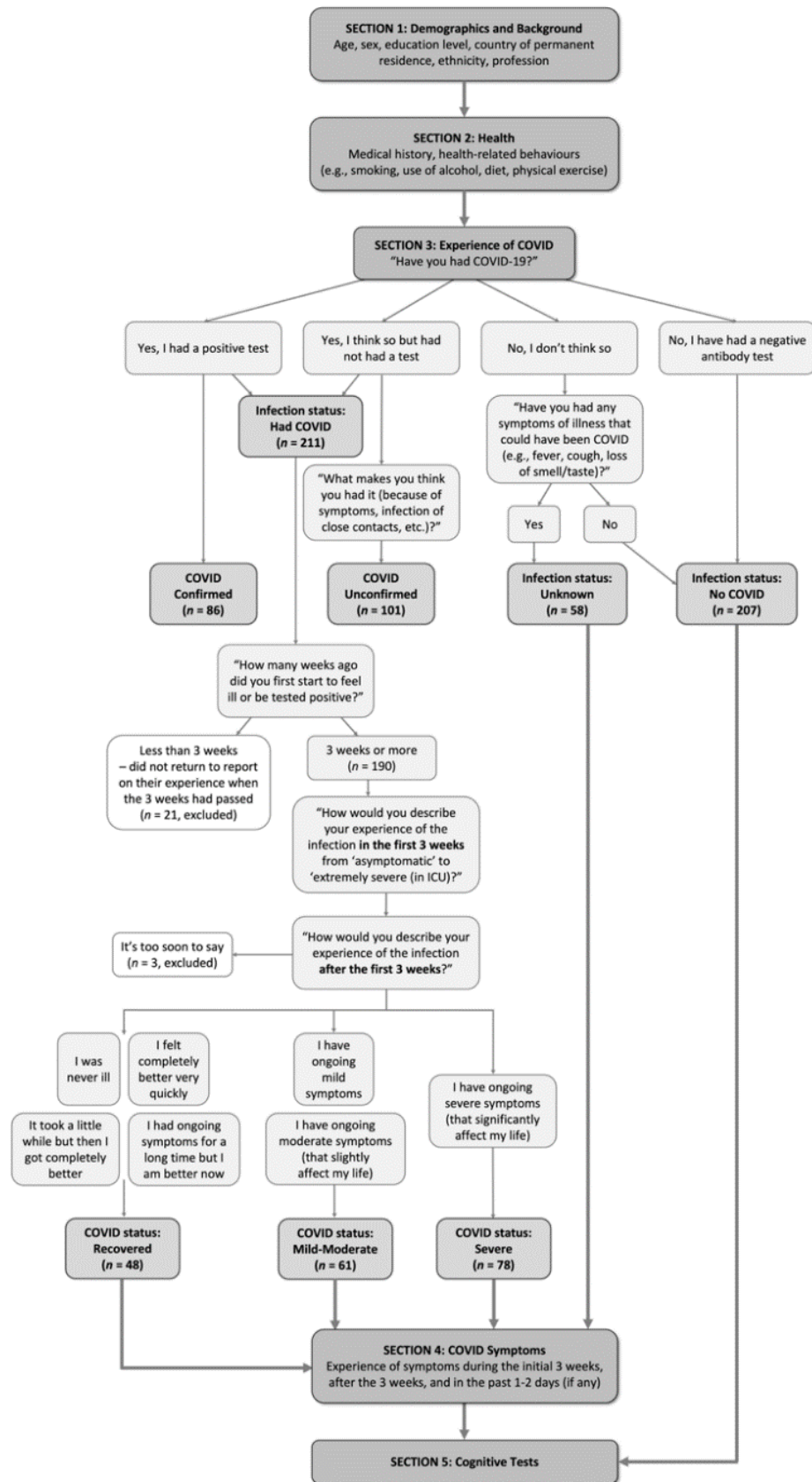


Figure 1. Study procedural flow and participant grouping at baseline.

2.2 Procedures

The COVCOG study was conducted through Gorilla (www.gorilla.sc). Informed consent was obtained from participants prior to testing at each session. The baseline measures included a questionnaire and cognitive tests, which took approximately 1 hour to complete. At the end of the baseline session, participants were asked to indicate whether they were willing to be contacted for a follow-up. Those who fully completed the baseline session (the questionnaire and all cognitive tests) and indicated their wish to continue participation were sent an invitation via email inviting them to complete a follow-up 6 weeks later. Only those within the COVID and No-COVID groups were followed up.

In our original design, the No-COVID group was only asked a short follow-up question ‘have you had COVID yet?’ at each follow-up in order to check whether they developed COVID; if yes, they would join the COVID group for the follow-ups. However, at the time of starting our second follow-up for the COVID group, we changed the recruitment strategy and invited both the COVID and No-COVID groups to complete full follow-up measures. This was due to a change in focus, as understanding of the condition grew between 2020 and 2021, from solely attempting a before-after infection comparison, to longitudinal comparison of performance and experiences between infected and uninfected groups. The No-COVID group thus experienced one fewer follow-up session. At the follow-up, participants completed questionnaire and cognitive tests similar to, but shorter than, those in the baseline session – lasting approximately 35 minutes. At the end of the follow-up session, participants were asked whether they were willing to be contacted again. This process gave 4 sessions for the

COVID group (baseline plus 3 follow-ups) and 3 sessions for the No-COVID group (baseline plus 2 follow-ups) across a 9-month period, with approximate inter-session intervals of 10 to 20 weeks.

2.3 Measures

2.3.1 Questionnaire

At baseline, the questionnaire covered demographics (e.g. sex, age, education level, country of residence, ethnicity, profession and employment status) and health. The health information included height and weight, medical history and health-related behaviours, such as usual diet intake, use of tobacco and alcohol and physical activity level as well as experience of COVID-19. COVID experience was scored as infection status, severity of illness and experience of individual symptoms during the first 3 weeks of infection ('initial illness'; 36 symptoms on a 3-point scale from 1 = 'Not at all' to 3 = 'Very severe'), since the first 3 weeks ('ongoing illness'; 52 symptoms on a 5-point scale from 1 = 'Not at all' to 5 = 'Very severe and often') and in the past 1–2 days ('current symptoms'; 52 symptoms; dichotomously: yes/no). Participants who had not been infected with COVID-19 were not asked about the severity and symptoms of COVID-19, because we were not at first comparing symptom prevalence between the groups. When vaccination became available from December 2020, the questionnaire also asked about vaccination status (including the number of dose(s) received, timing of the most recent dose and the type of vaccine). For full details of the baseline questionnaire, see 'COVCOG 1': Guo et al., 2022a.

The follow-up questionnaires were similar to the baseline questionnaire, but shorter, omitting demographics, medical history and reports of acute-period of COVID-19 symptoms (i.e. ‘initial illness’). At each follow-up, the questionnaire invited participants to provide updates of their vaccination status and any new COVID-19 infections. The COVID group was asked to report on their ongoing (‘since the last session’) and current (‘in the past 1–2 days’) symptoms and illness experience. If a participant in the No-COVID group reported a new infection, they entered the same flow of questions as the COVID group during the baseline. If they remained uninfected, they were also asked to report on their experience of ongoing and current symptoms as the COVID group did at this time – to provide an uninfected control level for each symptom.

2.3.2 Cognitive Tests

After filling the questionnaire, participants completed a set of cognitive tests assessing memory, language and executive function. At baseline, these tests included a Word List Recognition Memory Test (Figure 2a), a Pictorial Associative Memory Test (Figure 2b) to assess memory, a Category Fluency Test (Figure 2c) to assess language ability, the Wisconsin Card Sorting Test (WCST) (Figure 2d) and a 2D Mental Rotation Test to assess executive function. The tasks chosen reflected a combination of well-established tasks that covered memory, language and executive functions, but that were also at that time available on the Gorilla platform. Additionally, a Number Counting Test was included as an attention/‘bot’ check for data quality, whilst a Relational Reasoning Test was given only to the No-COVID group as a means by which to IQ-match control participants for potential pre-post infection longitudinal explorations. Data from these latter two tasks are not within the scope of this

paper. The presentation order of the cognitive tests was counterbalanced for each participant. More detailed descriptions of these tasks were given previously (Guo et al., 2022b). At the first follow-up session, participants had completed these tests again. At subsequent follow-up session(s), to reduce participant burden, the same set of cognitive tests was implemented, but without the 2D Mental Rotation Test (precluding examination of further change in performance on that task). The stimuli and their presentation order in the cognitive tests differed between sessions (see Supplementary Materials for information on cognitive tests at baseline and follow-ups).

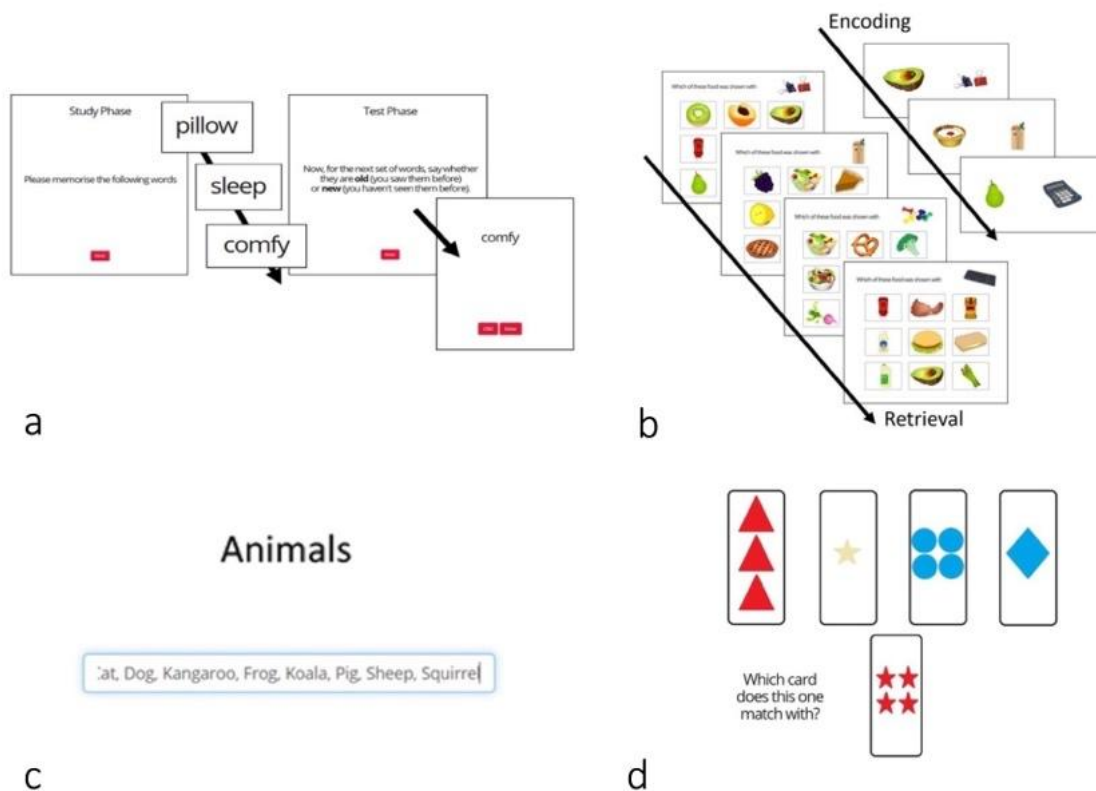


Figure 2. Cognitive tests assessing memory (Word List Recognition Memory Test [a], Pictorial Associative Memory Test [b]), language (Category Fluency Test [c]) and executive function (Wisconsin Card Sorting Test [d]).

2.4 Data Processing and Analysis

Here we present an overview of our analysis plan; full details are documented in the Supplementary Materials. Statistical analyses were conducted using IBM SPSS Statistics. As a preliminary, we performed attrition analysis to understand how attrition could have shaped our samples (sections 3.1.1–3.1.2). Numerous of tests were used to compare sample characteristics, including chi-square tests, Mann-Whitney U tests and ANOVAs.

To examine changes in COVID-19 symptoms (hypothesis 1) and cognitive performance (hypothesis 2) over time, we grouped individual symptom/task variables into factors by exploratory factor analyses (EFA) (see sections 3.2 and 3.3 and Supplementary Tables 10–12 for factor definitions as previously reported). Mixed between-subject (groups) and within-subject (time) ANOVAs controlling for sex, age, education and assessment interval(s) were performed on these factors to compare within-subject changes between groups, i.e. whether and how the COVID and No-COVID groups may differ in symptoms and cognitive performance over time (Time X Group interaction).

Finally, in participants with past COVID 19 infection, we applied multiple linear regressions with forward stepwise variable introduction to explore the relationship between non-cognitive symptoms, cognitive symptoms, and cognitive impairment at various stages of illness. This analysis was conducted both at individual assessment time points and across time (hypothesis 3). Sex, age and education were controlled for in all regression models, thus adjusted R square change (ΔR^2_{adj}) is reported to reflect the additional variance explained by the target predictor(s).

Across all analyses, Sidak correction for multiple comparisons was employed and the Sidak α is quoted where appropriate. Only results surviving correction are reported as significant in the main text. All statistics are recorded in the supplementary material.

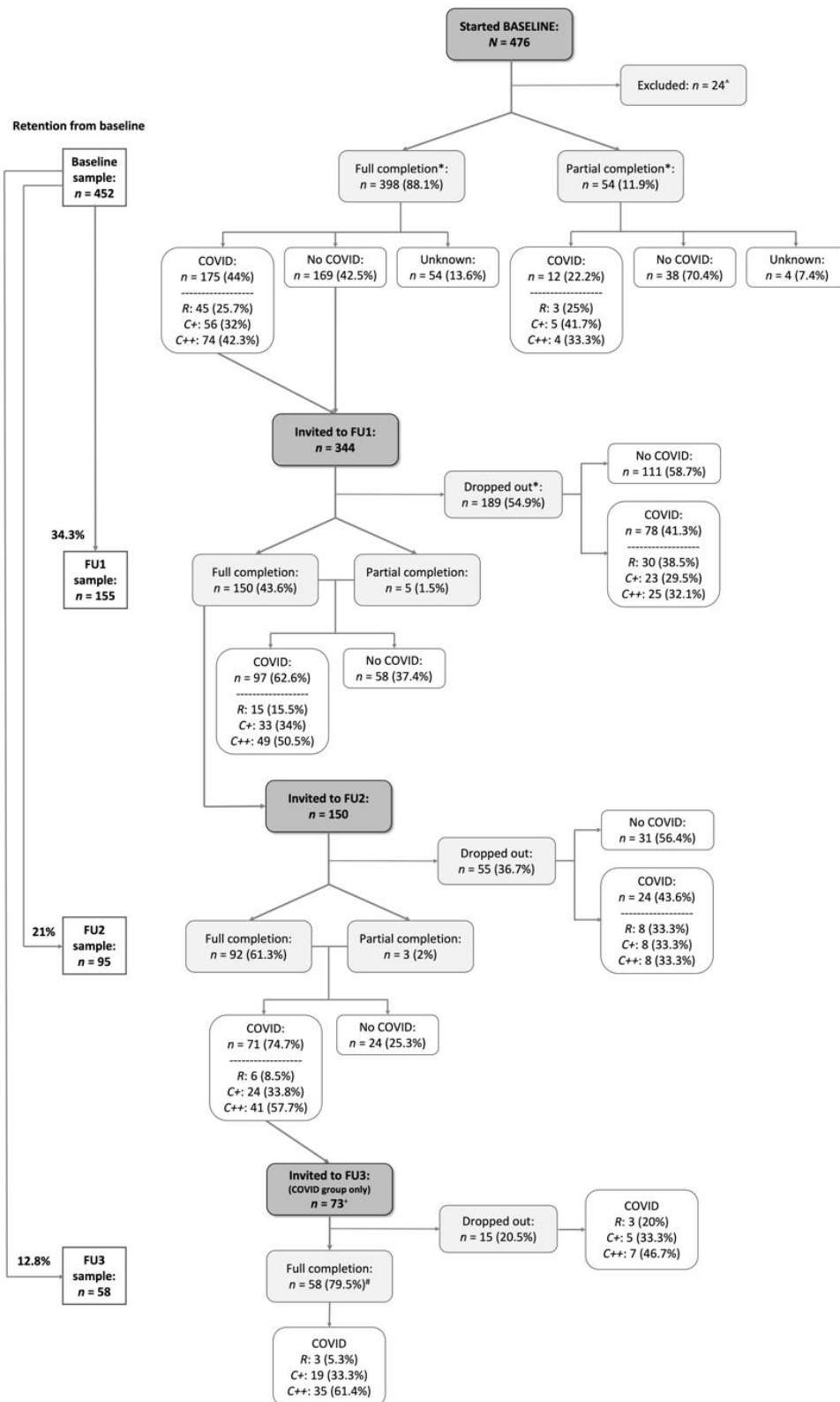
3. Results

3.1 Sample Characteristics at Baseline and Follow-ups

3.1.1 Attrition

Figure 3 shows attrition statistics at the baseline and follow-up sessions (for full details of the characteristics, see Supplementary Tables 1–4). Unsurprisingly, completion of baseline was associated with COVID-19 infection status ($\chi^2[2] = 14.93, p < .001, V = .18$), with the No-COVID group having a higher tendency to drop out before completing the whole baseline session. It was however not associated with any other demographic variable (severity of ongoing illness, sex, age, education level, country of residence or ethnicity). Continued participation into the first follow-up (FU1) was associated with COVID-19 infection status ($\chi^2[1] = 15.48, p < .001, V = .21$), severity of ongoing illness at baseline ($\chi^2[2] = 12.66, p = .002, V = .27$), sex ($\chi^2[2] = 9.36, p = .009, V = .17$), age ($\chi^2[5] = 32.06, p < .001, V = .31$) and education level ($\chi^2[5] = 17.38, p = .004, V = .23$). The No-COVID group and the *R* subgroup were more likely to drop out before FU1. The rate of dropout was also higher in men, those aged 18–30 and those below college-level education. Similarly, participation in the second follow-up (FU2) was associated with COVID-19 infection status ($\chi^2[1] = 14.51, p < .001, V = .31$), ongoing illness severity ($\chi^2[2] =$

9.61, $p = .008$, $V = .32$) and education level ($\chi^2[5] = 25.3$, $p < .001$, $V = .41$), with the No-COVID group, the *R* subgroup and those whose education was below bachelor's degree level showing a higher tendency to drop out between FU1 and FU2. Only the COVID group was invited to the third follow-up (FU3). Completion of FU3 was associated with education level ($\chi^2[5] = 13.35$, $p = .02$, $V = .43$), with more dropouts observed in those at GCSE level or below but also in those with a master's or doctorate degree. Figure 4 shows the characteristics significantly differed between the samples at the baseline and follow-up sessions (see Supplementary Table 5 for full details).



* 'Full completion' means completing the questionnaire and ALL cognitive tests; 'partial completion' means completing the questionnaire but NOT all cognitive tests; 'dropped out' means not starting or completing at the least the questionnaire part.

* 24 participants were excluded from the study: 21 were within their first 3 weeks of infection at the time of testing and asked to report on their experience of symptoms at a later time but did not return to complete the remaining sections. A further 3 participants reported 'it's too soon' to comment on their ongoing symptoms.

* 73 participants were followed up in FU3, with 1 from the No COVID group at baseline developing COVID-19 at the follow-up, and 1 skipping FU2 due to logistic error.

* 1 participant was from the No COVID group at baseline but developed COVID-19 at the follow-up.

Figure 3. Attrition statistics at the baseline and follow-up sessions.

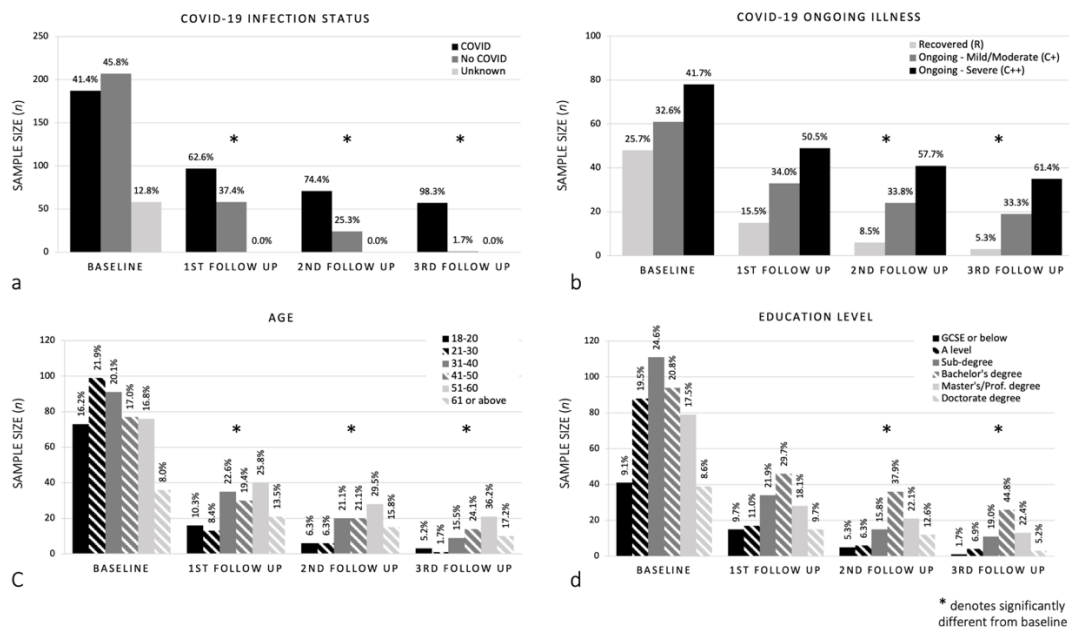


Figure 4. Characteristics significantly differed between the samples at the baseline and follow-up sessions: **COVID-19 infection status** (FU1: $\chi^2(2) = 32.84, p < .001, V = .23$; FU2: $\chi^2(2) = 38.56, p < .001, V = .27$; FU3: $\chi^2(2) = 66.72, p < .001, V = .36$); **ongoing illness severity** (FU2: $\chi^2(2) = 10.18, p = .006, V = .2$; FU3: $\chi^2(2) = 12.37, p = .002, V = .23$); **age** (FU1: $\chi^2(5) = 23.5, p < .001, V = .2$; FU2: $\chi^2(5) = 27.71, p < .001, V = .23$; FU3: $\chi^2(5) = 31.91, p < .001, V = .25$); **education level** (FU2: $\chi^2(5) = 23.8, p < .001, V = .21$; FU3: $\chi^2(5) = 22.6, p < .001, V = .21$).

3.1.2 The COVID and the No-COVID Groups

We compared the characteristics of the COVID group and the No-COVID group at the baseline (to confirm findings reported in COVCOG1 in the slightly larger sample) and follow-up sessions. Of the No-COVID group from baseline, 4 participants had developed COVID-19 and 2 reported being unsure of their infection status at the subsequent follow-up. Due to the small number, these participants ($n = 6$) were not included in the analyses of follow-up data.

ANOVAs showed that, as expected due to the design change, the two groups differed in the intervals (in weeks) between the baseline and FU1 (COVID group: $M = 11.72$, $SD = 9.63$; No-COVID group: $M = 20.69$, $SD = 7.2$) ($F[1,147] = 34.73$, $p < .001$, $\eta_p^2 = .19$) but not between FU1 and FU2 (COVID group: $M = 10.88$, $SD = 7.49$; No-COVID group: $M = 13.29$, $SD = 2.74$). (Assessment interval between FU2 and FU3 for the COVID group: $M = 14.56$ weeks, $SD = 5.61$.)

Patterns of differences in demographics between the two groups at baseline were consistent with those previously (Guo et al., 2022a; see Figure 5 and Supplementary Table 6). At FU1, the differences in age, education, profession and employment remained significant; while at FU2, the two groups did not differ in demographics (see Supplementary Tables 7–8). The COVID and the No-COVID groups did not differ in medical history at the baseline or any follow-up session (Sidak $\alpha = .003$). However, ANOVAs showed that, at baseline, the COVID group had higher BMI ($M = 27.08$, $SD = 7.11$) than the No-COVID group ($M = 25.01$, $SD = 5.7$), even when controlling for sex, age and education level ($F[1,385] = 4.07$, $p = .044$, $\eta_p^2 = .01$). Such tendencies persisted at FU1 but were not significant after controlling for demographics. At FU2, there were no differences in BMI between the two groups.

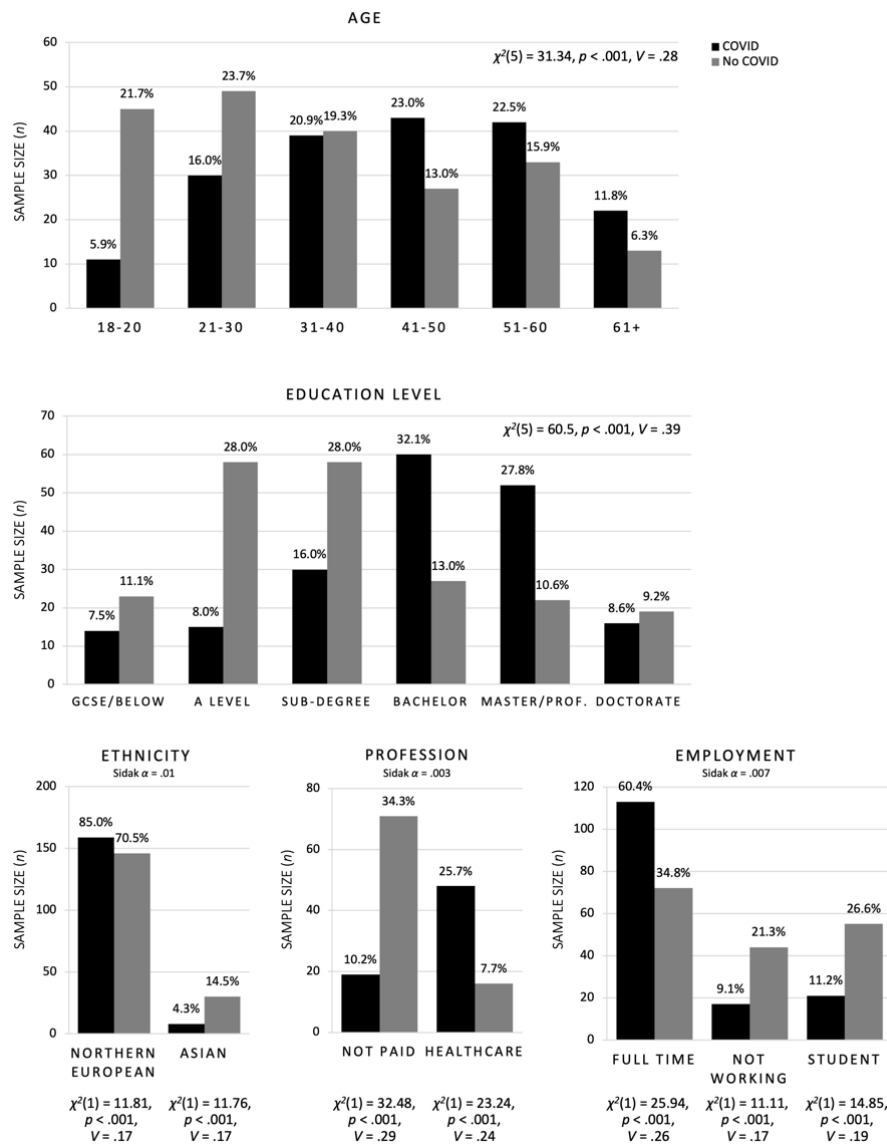


Figure 5. Demographic characteristics significantly differed between the COVID and the No-COVID groups at baseline. Differences were found in age (top panel), education level (middle panel), ethnicity (bottom left), profession (bottom centre) and employment type (bottom right). The COVID group was older, higher educated, more likely to be of Northern European ethnicity (than of Asian descent), and in full-time employment.

Within the COVID group, participants ranged between 3 and 31+ weeks since infection (positive test / symptom onset) at the time of baseline. Based on their report at baseline and the interval between assessments, we calculated weeks since infection at each follow-up

session. At FU1, participants ranged between 10 and 69+ weeks since infection. At FU2, they ranged between 14 and 74+ weeks. At FU3, the range was between 35 and 78+ weeks since infection. 90.9% ($n = 170/187$) of baseline participants had at least one symptom lasting beyond the first 3 weeks of infection. As before (Guo et al., 2022a), these individuals predominantly self-identified as experiencing or having experienced Long COVID at baseline ($n = 125/170$, 73.5%), as well as at FU1 ($n = 74/83$, 89.2%), FU2 ($n = 59/65$, 90.8%) and FU3 ($n = 47/49$, 95.9%).

The impacts of Long COVID on individuals' lives were related to ongoing illness severity. In particular, the majority of those who had ongoing severe illness (the *C++* subgroup) reported inability to work for a long period due to illness ($n = 60/78$, 76.9%) and having difficulty coping with day-to-day activities ($n = 56/78$, 71.8%) at baseline. At all follow-ups, over half of the *C++* subgroup were still unable to work (FU1: $n = 28/49$, 57.1%; FU2: $n = 24/41$, 58.5%; FU3: $n = 17/32$, 53.1%) or cope with daily activities (FU1: $n = 31/49$, 63.3%; FU2: $n = 27/41$, 65.9%; FU3: $n = 21/32$, 65.6%). Other impacts reported by the *C++* subgroup at baseline, which continued over the follow-ups, included having difficulty getting medical professionals to take their symptoms seriously (38.8–56.4%), feelings of having experienced a trauma (43.9–53.1%) and facing financial difficulty as a result of illness (21.9–24.5%). Those who had ongoing mild/moderate illness (the *C+* subgroup) also continued to experience similar difficulties: A material proportion found it hard to cope with day-to-day activities at baseline and across follow-ups (Baseline: $n = 32/61$, 52.5%; FU1: $n = 13/33$, 39.4%; FU2: $n = 10/23$, 43.5%; FU3: $n = 7/17$, 41.2%). Supplementary Table 9 shows full details of the impacts of Long COVID on the subgroups.

3.2 Hypothesis 1: Changes in COVID-19 Symptoms Over Time

Following 'COVCOG 1' (Guo et al., 2022a), we derived symptom factors from individual symptoms using EFA with the updated baseline dataset (see Supplementary Tables 10–12 for full procedure and factor loadings). The 5 initial symptom factors remained 'F1: Neurological/Psychiatric', 'F2: Fatigue/Mixed', 'F3: Gastrointestinal', 'F4: Respiratory/Infectious' and 'F5: Dermatological'. In addition to the 'Cognitive' symptom factor (derived separately from brain fog, forgetfulness, tip-of-the-tongue problems, semantic disfluency and difficulty concentrating), the 6 ongoing/current non-cognitive symptom factors were 'F1: Neurological', 'F2: Gastrointestinal/Autoimmune/Fatigue', 'F3: Cardiopulmonary', 'F4: Dermatological/Fever', 'F5: Mood' and 'F6: Appetite Loss'. Higher scores indicated higher severity in the individual (for ongoing 'since infection/last session' symptoms assessed in ratings) or higher occurrence in the population (for currently-experienced symptoms assessed dichotomously). Results on group differences (COVID vs No-COVID groups; *C++* vs *C+* vs *R* subgroups) in symptoms (factors and individual; cognitive and non-cognitive) are provided for all stages in Supplementary Tables 13–26.

3.2.1 COVID vs No-COVID (FU1–FU2)

Mixed ANOVAs were conducted to examine changes in the ongoing and current Cognitive symptom factor and the 6 non-cognitive symptom factor scores over time across FU1 and FU2 (within-subject) between the COVID and the No-COVID groups (between-subject; ongoing factors from FU1 through FU2: shared $n = 85$; current factors: shared $n = 64$) (Time X Infection interaction). For ongoing symptom factors, there was no main effect of time (across FU1 and

FU2), but main effects of infection group (COVID > No-COVID) in the ongoing Cognitive symptom factor ($F[1,79] = 40.76, p < .001, \eta_p^2 = .34$) and all non-cognitive symptom factors ($ps \leq .001-.005, \eta_p^2 = .09-.45$), except Appetite Loss. Significant Time X Infection interaction effects were found for ongoing Gastrointestinal/Autoimmune/Fatigue ($F[1,79] = 5.45, p = .022, \eta_p^2 = .07$), Cardiopulmonary ($F[1,79] = 6.62, p = .012, \eta_p^2 = .08$) and Mood ($F[1,79] = 7.72, p = .007, \eta_p^2 = .09$) symptom factors, but not the Cognitive symptom factor or Neurological, Dermatological/Fever or Appetite Loss symptom factors (see Figure 6 and Supplementary Table 27). At FU1, the COVID group had higher severity scores on all 3 symptom factors than the No-COVID group ($ps < .001, ds = .95-2.25$). The group differences in the ongoing Gastrointestinal/Autoimmune/Fatigue and Cardiopulmonary ($ps < .001, ds = 1.51-1.69$), but not in Mood, symptom factors persisted at FU2. The COVID group showed improvements in ongoing Gastrointestinal/Autoimmune/Fatigue ($p = .018, d = .22$) and Mood ($p = .013, d = .23$) symptom factors from FU1 to FU2, while no significant changes were found for the No-COVID group. Results of individual symptoms are in Supplementary Table 29.

There was no Time X Infection interaction for any current symptom factor. However, an overall main effect of time was observed for current Gastrointestinal/Autoimmune /Fatigue symptom factor ($F[1,58] = 4.23, p = .044, \eta_p^2 = .07$). Main effects of infection group (COVID > No-COVID) were also found for current Cognitive symptom factor ($F[1,58] = 9.55, p = .003, \eta_p^2 = .14$), and Neurological, Gastrointestinal/Autoimmune/Fatigue and Cardiopulmonary symptom factors ($ps = .001-.027, \eta_p^2 = .08-.16$) (see Supplementary Table 28).

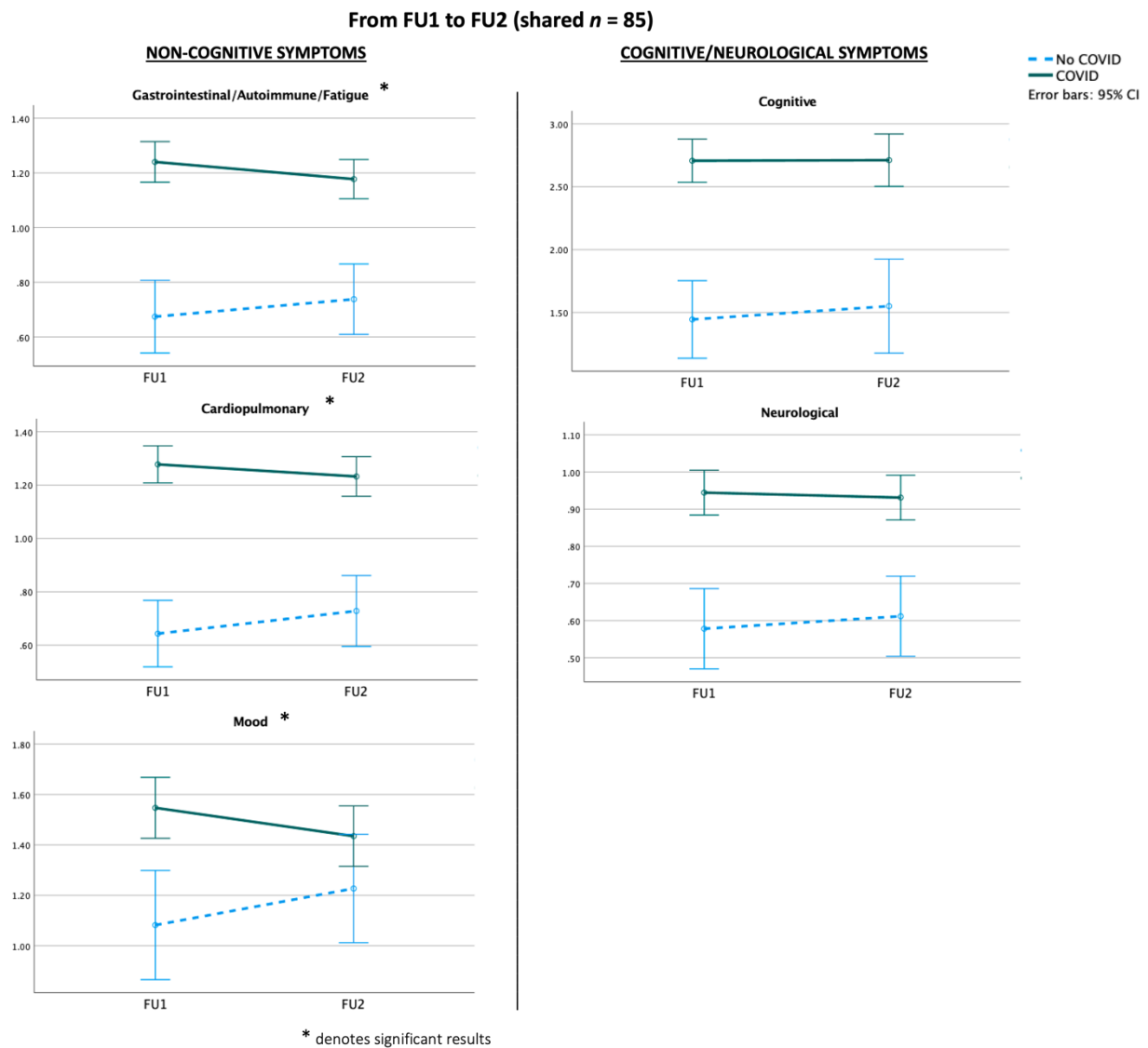


Figure 6. Time X Infection interaction effects in ongoing symptom factors from FU1 to FU2 in the COVID and the No-COVID groups. Significant results were found for Gastrointestinal/Autoimmune/Fatigue, Cardiopulmonary and Mood, but not Cognitive or Neurological symptom factors. The Y-axes show the mean scores.

3.2.2 COVID Ongoing Subgroups (Baseline–FU1–FU2–FU3)

When comparing the $C+$ and the $C++$ subgroups from baseline through FU3 (given a lack of data from the R subgroup at FUs) (see Figure 7 and Supplementary Tables 30–31), mixed

ANOVAs showed that there was no main effect of time across all sessions for ongoing symptom factors. However, from baseline to FU1 (shared $n = 82$), significant Time X Subgroup interactions were found for ongoing Cardiopulmonary ($F[1,76] = 5.95, p = .017, \eta_p^2 = .07$) and Dermatological/Fever ($F[1,76] = 6.33, p = .014, \eta_p^2 = .08$) symptom factors, but not for the Cognitive symptom factor or Neurological, Gastrointestinal/Autoimmune/Fatigue, Mood or Appetite Loss symptom factors. Improvements in the Cardiopulmonary symptom factor were observed in both the $C++$ ($p < .001, d = .82$) and the $C+$ subgroups ($p = .019, d = .34$) from baseline to FU1. The $C++$ subgroup, but not the $C+$ subgroup, also showed improvement in Dermatological/Fever ($p < .001, d = .42$) symptom factor.

From baseline through FU2 (shared $n = 64$), the interaction effects for ongoing Cardiopulmonary ($F[2,114] = 3.53, p = .033, \eta_p^2 = .06$) and Dermatological/Fever ($F[2,114] = 3.79, p = .026, \eta_p^2 = .06$) symptom factors remained significant. The $C++$ subgroup showed improvements in Cardiopulmonary and Dermatological/Fever symptom factors from baseline to FU1 and FU2 ($ps < .001, ds = .77-.8$), while the $C+$ subgroup improved across the time points (from baseline to FU2: $p < .001, d = .7$); from FU1 to FU2: $p = .014, d = .4$) in Cardiopulmonary, but not Dermatological/Fever, symptom factor. From baseline through FU3 (shared $n = 48$), there was a significant interaction for ongoing Cardiopulmonary ($F[3,120] = 2.72, p = .047, \eta_p^2 = .06$) symptom factor only. Improvements were observed in the $C++$ subgroup, but not the $C+$ subgroup, from baseline to FU1, FU2 and FU3 ($ps < .001, ds = .79-.87$). There was no interaction or main effect of time for any *current* symptom factor. Results of individual symptoms are in Supplementary Table 32.

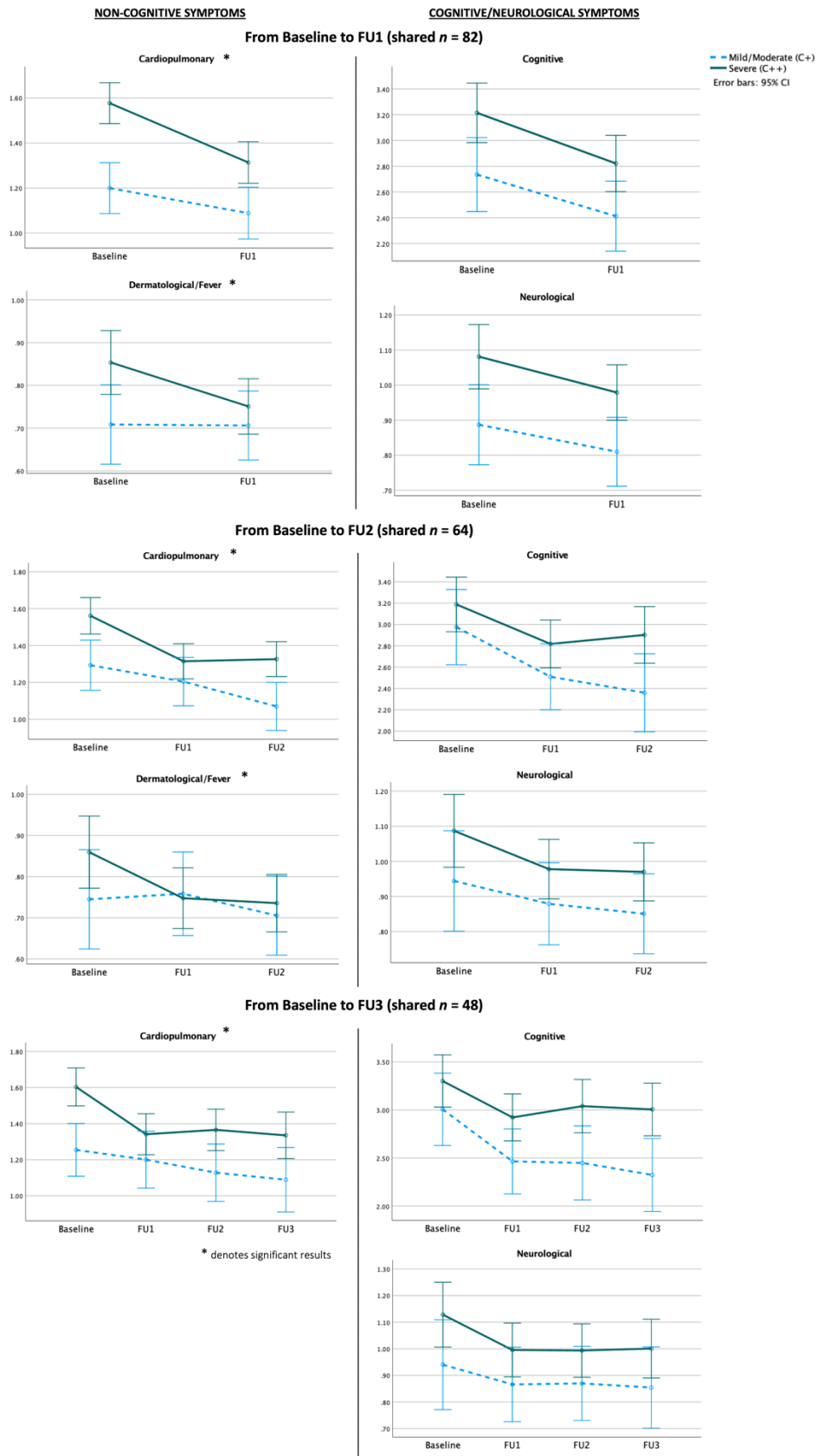


Figure 7. Time X Subgroups interaction effects in ongoing non-cognitive and cognitive symptom factors over time in the C+ and C++ subgroups.

3.3 Hypothesis 2: Changes in Cognitive Performance Over Time

Previously (Guo et al., 2022b), we grouped data of individual cognitive task variables into cognitive task factors, reflecting performance in memory, language and executive function. From the baseline data of this updated dataset, we generated four slightly modified factors. The factor structures of follow-up data followed then that of baseline data. The factors were: 'F1: Memory RT (reaction time)', which included overall RTs, RTs for correct responses and RTs for incorrect responses of the Word List Recognition Memory Test and the Pictorial Associative Memory Test; 'F2: Memory Performance', which included correct percentage and d' of the Word List Recognition Memory Test and correct percentage of the Pictorial Associative Memory Test; 'F3: Category Fluency', which included correct words, related words, incorrect words and correct percentage of the Category Fluency Test; 'F4: Executive Function RT', which included RT for correct responses and for non-perseverative errors of the WCST and 'F5: Executive Function Performance', which included correct responses, number of perseverative and non-perseverative errors of the WCST. Extreme outliers were removed. For full details of factor loadings and procedure, see Supplementary Table 33.

3.3.1 COVID vs No-COVID (Baseline–FU1–FU2)

Cognitive performance was first compared between the COVID group and the No-COVID group with the largest possible sample size (including participants without complete longitudinal data) separately at baseline, FU1 and FU2 using one-way ANOVAs (see Figure 8 and Supplementary Tables 34–35 for detailed results). Then, we performed mixed ANOVAs to

examine within-subject changes in cognitive performance across baseline, FU1 and FU2 between the two groups (Time X Infection interaction). In terms of the 5 cognitive task factors, there was no significant interaction from baseline to FU1 (shared $ns = 145\text{--}147$ depending on the task factor). From baseline through FU2 (shared $ns = 88\text{--}90$), a significant interaction was found for the Memory RT factor ($F[2,166] = 4.43, p = .013, \eta_p^2 = .05$). Pairwise comparisons, although suggesting no difference in RTs between the two groups in this longitudinal sample at any time point, showed that RT of the No-COVID group at FU2 was shorter than their RTs at baseline ($p = .005, d = .81$) and FU1 ($p = .002, d = .77$), while RTs of the COVID group remained unchanged across time (Figure 9; see also Supplementary Tables 36–37 for full details, including the overall main effects of time found for the Executive Function RT and Performance factors, and results of individual variables).

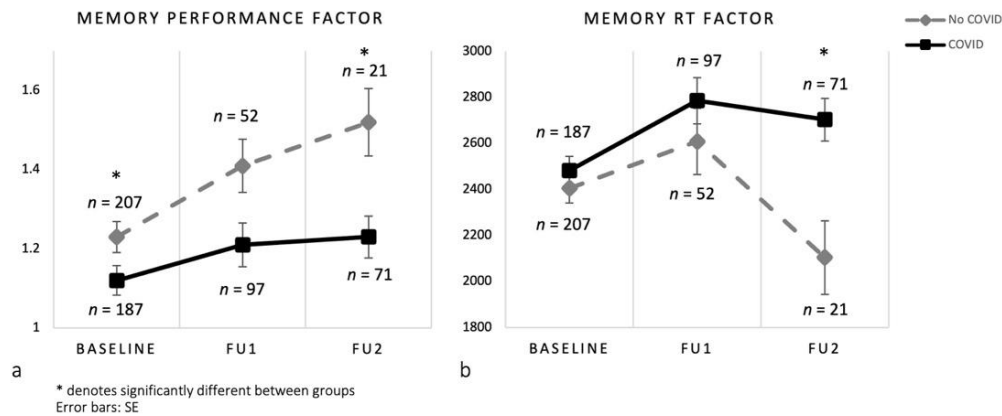


Figure 8. The COVID and the No-COVID groups' scores on the Memory Performance factor and the Memory RT factor. Results on baseline data were largely consistent with 'COVCOG 2' (Guo et al., 2022b). The COVID group had significantly lower scores in the Memory Performance factor than the No-COVID group at baseline ($F[1,347] = 6.01, p = .015, \eta_p^2 = .02$) and at FU2 ($F[1,85] = 5.14, p = .026, \eta_p^2 = .06$). The difference at FU1 did not reach significance (Figure 8a). The COVID group also had longer RTs in the Memory RT factor than the No-COVID

group at FU2 ($F[1,85] = 4.03, p = .048, \eta_p^2 = .05$) (Figure 8b). No significant group differences were found for other factors.

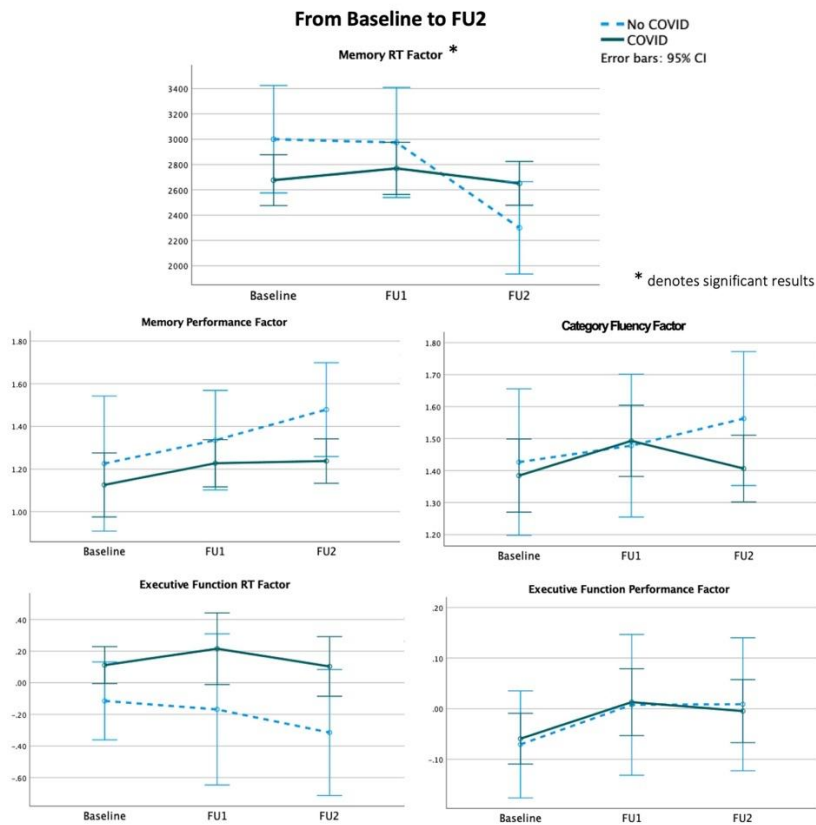


Figure 9. Time X Infection interaction effects in cognitive task factors from baseline to FU2 in the COVID and the No-COVID groups.

3.3.2 Recovered (*R*) vs Mild/Moderate (*C+*) vs Severe (*C++*) vs No-COVID

Figure 10 and Supplementary Tables 38–39 show the one-way ANOVA results of the comparison analyses on the cognitive performance between the No-COVID group and the COVID subgroups (*R*, *C+*, *C++*). Mixed ANOVAs were performed to examine within-subject changes in cognitive performance over time between the four groups (Time X Group interaction). In terms of the 5 cognitive task factors, from baseline to FU1 (shared $ns = 145$ –

147 depending on the task factor), there was a significant interaction for the Executive Function RT factor ($F[3,139] = 3, p = .033, \eta_p^2 = .06$). Pairwise comparisons showed that the RT of the *R* subgroup at FU1 was shorter than at baseline ($p = .024, d = .57$). However there was no main effect of group on RTs at any time point. From baseline through FU2 (shared $ns = 88-90$), there was no significant interaction for any factor. Comparing the COVID subgroups from baseline through FU3 (shared $ns = 54-56$), no significant interaction was observed (see Supplementary Tables 40–41 for full details, including the overall main effects of time found for the Executive Function RT and Performance factors, and results of individual variables).

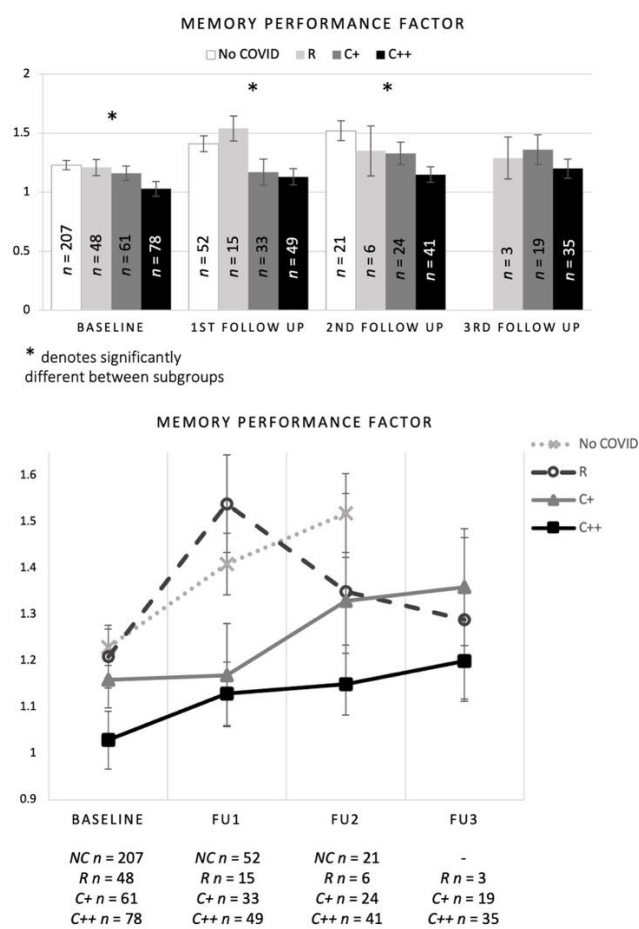


Figure 10. Scores of the Memory Performance factor in the No-COVID group and the *R*, *C+* and *C++* subgroups. One-way ANOVAs suggested results of baseline data are largely consistent

with 'COVCOG 2' as expected (Guo et al., 2022b). Comparison analyses for FU3 were performed only between the COVID subgroups as the No-COVID group did not have data for FU3. Significant group differences were found in the Memory Performance factor at baseline ($F[3,345] = 3.94, p = .009, \eta_p^2 = .03$), FU1 ($F[3,139] = 3.71, p = .013, \eta_p^2 = .07$) and FU2 ($F[3,83] = 3.05, p = .033, \eta_p^2 = .1$). At baseline ($p = .004, d = .49$) and FU2 ($p = .035, d = .8$), the *C++* subgroup had lower scores than the No-COVID group, while at FU1 ($p = .033, d = .87$), the *C++* subgroup also had lower scores than the *R* subgroup. At FU3, there was no significant group difference between the COVID subgroups in any factor (see Figure 10 and Supplementary Table 38).

3.4 Hypothesis 3: Predictors of Cognitive Symptoms and Cognitive Performance

3.4.1 Predicting Cognitive Symptoms from Non-Cognitive Symptoms

3.4.1.1 Within Each Assessment Time Point

Multiple linear regressions were applied to test whether non-cognitive symptom factors would predict the Cognitive symptom factor; this was done at different phases of illness in those infected with COVID-19 (see Supplementary Table 42 for full details). At baseline, Fatigue/Mixed symptoms experienced during the initial illness (the first 3 weeks of infection) ($\beta = .48, p < .001$) predicted Cognitive symptoms experienced since the first 3 weeks ($\Delta R^2_{adj} = .217, F[4,165] = 21.67, p < .001$), while Neurological/Psychiatric symptoms ($\beta = .29, p < .001$) predicted currently experienced Cognitive symptoms ($\Delta R^2_{adj} = .079, F[4,137] = 9.84, p < .001$). Neurological ($\beta = .27, p = .018$), Gastrointestinal/Autoimmune/Fatigue ($\beta = .26, p = .048$) and

Cardiopulmonary ($\beta = .23, p = .018$) symptoms experienced between the 3 weeks and baseline jointly predicted Cognitive symptoms during the same period ($\Delta R^2_{adj} = .44, F[6,163] = 35.6, p < .001$). Neurological symptoms ($\beta = .34, p < .001$) during that period also predicted currently experienced Cognitive symptoms ($\Delta R^2_{adj} = .103, F[4,137] = 11.24, p < .001$). Current Gastrointestinal/Autoimmune/Fatigue symptoms at baseline ($\beta = .43, p < .001$) predicted concurrent Cognitive symptoms ($\Delta R^2_{adj} = .181, F[4,137] = 16.28, p < .001$). Similar patterns were found for the follow-ups (see Supplementary Table 42).

3.4.1.2 Prediction Across Time

Symptoms experienced during the initial 3 weeks of illness (reported at baseline) were able to predict cognitive symptoms across subsequent follow-ups (see full details in Supplementary Table 42). Neurological/Psychiatric symptoms during the initial illness predicted ongoing Cognitive symptoms at FU1 and FU3 ($\beta = .29-.52, ps < .001$), and currently experienced Cognitive symptoms at FU1 and FU2 ($\beta = .32-.4, ps = .003$). Initial Fatigue/Mixed symptoms predicted ongoing Cognitive symptoms at FU2 ($\beta = .52, p < .001$).

Early ongoing symptoms (those experienced between the initial illness and baseline) were also able to predict later cognitive symptoms. Neurological symptoms during this period predicted current Cognitive symptoms at FU1 ($\beta = .3, p = .009$) and ongoing Cognitive symptoms experienced between FU1 and FU2 ($\beta = .28, p = .029$). Baseline ongoing Cardiopulmonary symptoms predicted ongoing Cognitive symptoms across all three follow-ups ($\beta = .39-.72, ps < .001$). Baseline ongoing Mood-related symptoms predicted Cognitive symptoms experienced between baseline and FU1 ($\beta = .22, ps = .024$).

Finally, symptoms experienced at the time of the baseline (baseline current symptoms) also predicted later cognitive symptoms. Current neurological symptoms experienced at baseline predicted currently experienced Cognitive symptoms at FU1 and ongoing Cognitive symptoms between FU1 and FU2 ($\beta = .38-.44$, $ps \leq .001-.004$). Baseline current Gastrointestinal/Autoimmune/Fatigue symptoms negatively predicted current Cognitive symptoms at FU1 ($\beta = -.36$, $p = .036$). Baseline current Cardiopulmonary symptoms predicted ongoing Cognitive symptoms at all three follow-ups and currently experienced Cognitive symptoms at FU1 and FU3 ($\beta = .24-.54$, $ps \leq .001-.047$).

3.4.2 Predicting Cognitive Performance from Non-Cognitive and Cognitive Symptoms

3.4.2.1 Non-cognitive Symptoms as Predictors of Cognitive Performance

We tested the effects of non-cognitive symptoms on concurrent cognitive performance (5 task factors: Memory RT, Memory Performance, Category Fluency, Executive Function RT, Executive Function Performance) at different phases of illness (see Figure 11 and Supplementary Table 43 for full details). Because the natural scale directions of ‘better’ symptoms and performance are inverse, all correlations and regression coefficients are expected to be negative and were so found. As reported previously (Guo et al., 2022b), baseline Fatigue/Mixed symptoms experienced during the initial illness ($\beta = -.26$, $p = .001$) predicted the baseline Memory Performance factor ($\Delta R^2_{adj} = .054$, $F[4,170] = 3.69$, $p = .007$). Additionally, ongoing Neurological symptoms between FU2 and FU3 ($\beta = -.45$, $p = .001$) predicted the FU3 Memory Performance factor ($\Delta R^2_{adj} = .187$, $F[4,44] = 4.37$, $p = .005$). Across

time, early ongoing Neurological symptoms experienced between the initial illness and baseline ($\beta = -.38, p = .005$) predicted the Memory Performance factor at FU3 ($\Delta R^2_{adj} = .116, F[4,51] = 4.45, p = .004$). No significant association between non-cognitive symptoms and other cognitive task factors was found.

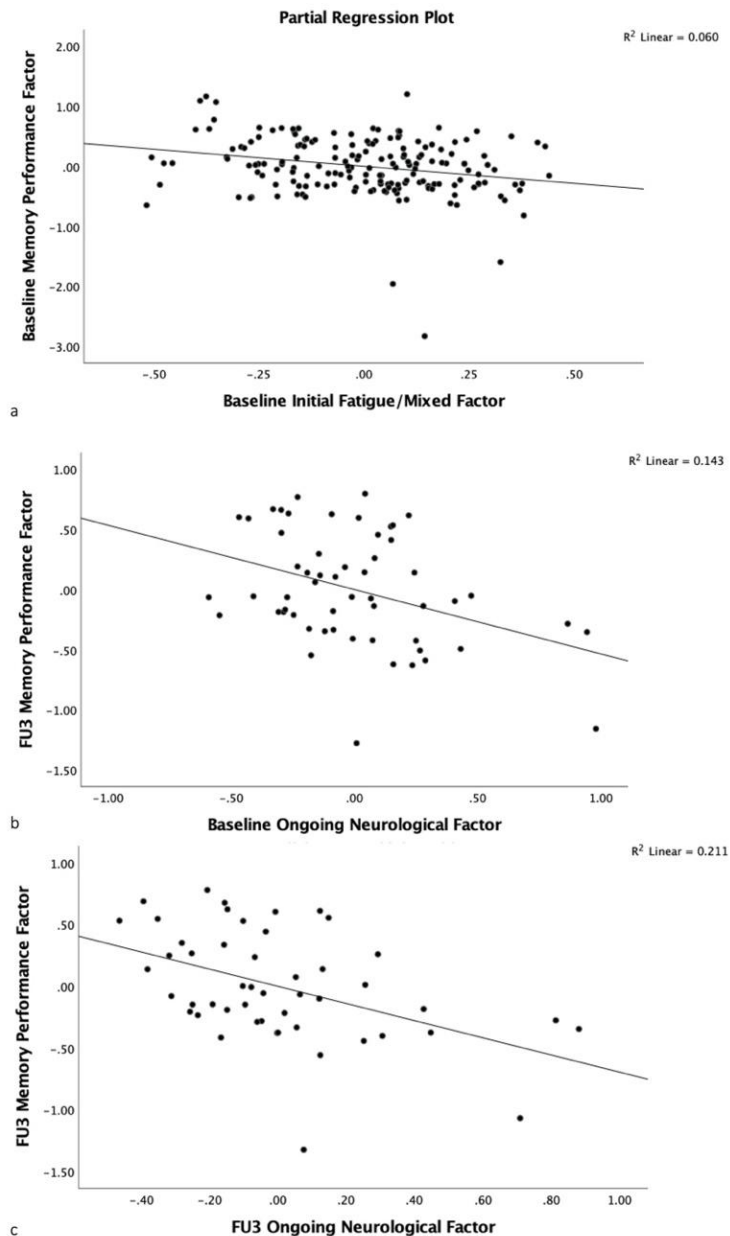


Figure 11. Plot of significant linear regressions with forward stepwise method controlling for demographics predicting cognitive performance factors from non-cognitive symptom factors.

Further analyses were carried out on the individual task variables of the Memory Performance factor, which included correct percentage and d' from the Word List Recognition Memory Test and correct percentage from the Pictorial Associative Memory Test (Sidak $\alpha = .017$) (see full details in Supplementary Table 44). Consistent with our previous results (Guo et al., 2022b), at baseline, Fatigue/Mixed symptoms experienced during the initial illness ($\beta = -.26$ to $-.27$, $ps < .001$) predicted percentage of items correct and d' of the Word List Recognition Memory Test. At FU1 and FU2, current Cardiopulmonary symptoms ($\beta = -.27$ to $-.32$, $ps = .01-.017$) predicted the correct percentage of the Pictorial Associative Memory Test at each time point. At FU3, ongoing Neurological symptoms between FU2 and FU3 ($\beta = -.45$, $p = .001$) predicted d' of the Word List Recognition Memory Test. Across time, Neurological symptoms at baseline were a significant predictor of performance on the Word List Recognition Memory Test at FU3. The initial, ongoing and current Neurological factors at baseline ($\beta = -.35$ to $-.37$, $ps = .007-.009$) all predicted the correct percentage of the Word List Test at FU3. The ongoing and current Neurological factors at baseline ($\beta = -.33$ to $-.39$, $ps = .004-.013$) also predicted d' of the Word List Test at FU3.

3.4.2.2 Cognitive Symptoms as Predictors of Cognitive Performance

Finally, we tested the effects of cognitive symptoms on cognitive performance. There was no significant association between the ongoing/current Cognitive symptom factors and the cognitive task factors at any time point (see Supplementary Table 45). Given that some specific cognitive symptoms may be related more directly to specific areas of cognitive performance, for exploratory purposes, we further examined the role of 5 individual ongoing/current cognitive symptoms (i.e. brain fog, forgetfulness, tip-of-the-tongue

problems, semantic disfluency and difficulty concentrating) as predictors (see full details in Supplementary Table 46). In line with our previous results (Guo et al., 2022b), at baseline, current difficulty concentrating ($\beta = -.24, p = .005$) predicted the Category Fluency factor ($\Delta R^2_{adj} = .093, F[4,129] = 4.41, p = .002$). At FU1, ongoing semantic disfluency ($\beta = -.32, p = .003$) predicted the Category Fluency factor ($\Delta R^2_{adj} = .299, F[4,78] = 9.73, p < .001$). At FU2, ongoing tip-of-the-tongue problems ($\beta = -.6, p = .001$) and semantic disfluency ($\beta = .63, p = .002$), together with difficulty concentrating (although this did not individually survive Sidak correction ($\beta = -.31, p = .04$)), predicted the Category Fluency factor, although in different directions ($\Delta R^2_{adj} = .264, F[6,58] = 4.82, p < .001$). At FU3, current brain fog ($\beta = -.47, p < .001$) predicted the Memory Performance factor ($\Delta R^2_{adj} = .24, F[4,43] = 4.72, p = .003$). Across time, there was no significant association between individual ongoing/current cognitive symptoms at baseline and any of the cognitive task factors at the follow-ups.

We conducted further analyses on the individual task variables of the Category Fluency factor (including the repeated words variable that did not load into the factor; Sidak $\alpha = .01$) and the Memory Performance factor (Sidak $\alpha = .017$). Results from the baseline were largely consistent with our COVCOG 2 report (Guo et al., 2022b). In terms of the Category Fluency test variables (see Supplementary Table 47), at baseline, ongoing tip-of-the-tongue problems ($\beta = -.47, p < .001$), together with semantic disfluency which did not survive Sidak correction ($\beta = .31, p = .024$), predicted the number of correct words ($\Delta R^2_{adj} = .058, F[5,152] = 5.19, p < .001$). Current difficulty concentrating ($\beta = -.24, p = .005$) also predicted the number of correct words ($\Delta R^2_{adj} = .049, F[4,130] = 5.09, p < .001$). At FU1, ongoing semantic disfluency ($\beta = -.33, p = .002$) predicted the number of correct words ($\Delta R^2_{adj} = .081, F[4,78] = 10.15, p < .001$). At FU2, the pattern was similar at baseline, with ongoing tip-of-the-tongue problems ($\beta = -.52, p$

= .004), together with semantic disfluency (although this did not survive Sidak correction ($\beta = .37, p = .038$)), predicted the number of correct words ($\Delta R^2_{adj} = .08, F[5,59] = 6.94, p < .001$). There were no significant associations at FU3. Across time, ongoing tip-of-the-tongue problems at baseline ($\beta = -.41, p = .004$) predicted the number of correct words at FU3 ($\Delta R^2_{adj} = .133, F[4,51] = 3.69, p = .01$). Ongoing difficulty concentrating at baseline ($\beta = -.78, p < .001$), together with brain fog (which did not survive Sidak correction ($\beta = .53, p = .014$)), predicted the number of related words at FU3 ($\Delta R^2_{adj} = .175, F[5,50] = 4.68, p = .001$).

In terms of variables of the Memory Performance factor (see Supplementary Table 48), at baseline, ongoing tip-of-the-tongue problems ($\beta = -.3, p < .001; \Delta R^2_{adj} = .071, F[4,156] = 4.56, p = .002$) and current forgetfulness ($\beta = -.21, p = .014; \Delta R^2_{adj} = .035, F[4,133] = 3.99, p = .004$) predicted the correct percentage of the Word List Recognition Memory Test. At FU2, current brain fog ($\beta = -.32, p = .011$) predicted the correct percentage of the Pictorial Associative Memory Test ($\Delta R^2_{adj} = .089, F[4,52] = 4.81, p = .002$). At FU3, current brain fog ($\beta = -.47, p < .001$) predicted d' of the Word List Test ($\Delta R^2_{adj} = .205, F[4,43] = 4.65, p = .003$). Across time, the extent of ongoing tip-of-the-tongue problems at baseline ($\beta = -.28, p = .017$) predicted the correct percentage of the Word List Test at FU1 ($\Delta R^2_{adj} = .053, F[4,82] = 3.48, p = .011$). Ongoing forgetfulness at baseline ($\beta = -.35, p = .016$) predicted d' of the Word List Test at FU3 ($\Delta R^2_{adj} = .084, F[4,51] = 3.66, p = .011$).

4. Discussion

The present 'COVCOG 3' paper aimed at understanding the trajectory of cognition in post-acute COVID-19 (Long COVID). (Long COVID). A longitudinal analysis examined how

symptoms (both cognitive and non-cognitive) and objective cognitive function changed over time in people with past COVID-19 infection and varying levels of Long COVID severity (the COVID group and subgroups), compared to uninfected controls (the No-COVID group). We also investigated how diverse symptom patterns may predict cognitive problems. Results were largely consistent with our expectations given previous evidence.

4.1 Symptoms

With regard to changes in Long COVID symptoms, we found varying profiles for some symptoms, but cognitive and neurological symptoms proved persistent over time. Some non-cognitive symptoms improved in the COVID group relative to the No-COVID group (i.e. ongoing gastrointestinal/autoimmune/fatigue and mood symptoms appeared to reduce), but cardiopulmonary symptoms were persistently higher in the COVID group across time. The lack of improvement in cognitive and neurological symptoms was particularly notable in those who had reported moderate to severe ongoing Long COVID at baseline (*C++* and/or *C+* subgroups). This finding is in line with other studies showing that cognitive/neurological symptoms could persist for long periods after COVID-19 infection (e.g. Ceban et al., 2022; Davis et al., 2021; Dennis et al., 2023), potentially due to neurological damage and abnormal neural activity in areas of the brain pivotal to cognitive functioning such as the hippocampus and frontal lobes (Douaud et al., 2022; Hosp et al., 2021).

4.2 Cognitive Performance

With regard to objective cognitive function, consistent with ‘COVCOG 2’ (Guo et al., 2022b), memory function – both response accuracy and speed – is particularly impacted in the COVID group (most noticeably in the *C++* subgroup). Most of the group differences found at baseline remained at subsequent follow-ups. Analysis of change in performance over time showed that while the No-COVID group demonstrated practice-related improvement (shorter RTs and some improvement in performance), such progress was not seen in the COVID group.

Our findings suggest that people with past COVID-19 infection overall, particularly those who suffered mild to severe ongoing illness, did not experience improvement in cognitive function over time – or at least not over the 10–15 months post infection covered by this study.

Previous studies showed differing patterns of change in cognitive function in people with varying initial illness severity (Afzali et al, 2023; Del Brutto et al., 2021; Miskowiak et al., 2022). However, given that almost all our participants showed a relatively mild initial illness (non-hospitalised), our study suggests that lack of cognitive improvement may be associated with the presence of *ongoing* illness. Those who had experienced infection but considered themselves recovered (the *R* subgroup) showed a trajectory roughly similar to those without infection history; however, those who reported some symptoms of Long COVID at 1–6 months post infection, regardless of severity, (i.e. the *C+* and *C++* subgroups) tended to still be experiencing some level of cognitive impairment as long as 9 months post infection.

4.3 Predictors of Cognitive Problems

As expected, neurological symptoms consistently predicted both cognitive symptoms and cognitive performance at/across different phases of illness following COVID-19 infection.

Neurological/psychiatric symptoms during the initial 3 weeks of illness predicted both concurrent memory performance and performance at the final follow up, #9 months later. Indeed, neurological symptoms across the entire follow-up period predicted ongoing/concurrent cognitive symptoms and performance (particularly of the Word List Test) at the final follow-up. Additionally, cardiopulmonary symptoms experienced since the initial illness consistently predicted concurrent cognitive symptoms, with currently experienced cardiopulmonary symptoms at FU1 and FU2 also predicting lower accuracy in the Pictorial Associative Memory Test during the same sessions. Fatigue/mixed symptoms during the initial illness predicted baseline and follow-up ongoing cognitive symptoms and baseline memory performance (specifically Word List Test), but gastrointestinal/autoimmune/fatigue symptoms experienced since the initial illness predicted ongoing/concurrent cognitive symptoms at baseline and follow-ups. There were also some associations between mood-related symptoms and follow-up cognitive symptoms. Overall, more severe neurological, cardiopulmonary and fatigue-related symptoms were associated with more severe cognitive symptoms and worse memory; neurological symptoms were mostly predictive of future cognition, while cardiopulmonary symptoms were more predictive of concurrent cognition. These support other findings for example that headache during acute COVID predicts cognitive symptoms one year later in older adults (Cavaco et al., 2023).

In the absence of neurophysiological data, these results cannot speak directly to mechanism. However, they do suggest that cognitive problems may be driven both by neurological events during the acute and post-acute period, and ongoing effects from cardiovascular and breathing pathology. This may suggest that acute neurological events during the initial illness may lead to long term issues, particularly with memory. Were such events to result in

structural damage such as ischemic lesions, it might be predicted both that these would be associated with long term cognitive change, and that this change might be relatively non-specific in nature (as the location of the lesion would not be prescribed). On the other hand, ongoing cardiopulmonary issues may result in reduced oxygen supply to the brain (either via respiratory issues or through inefficient oxygen transfer) which would be expected to lead to concurrent cognitive issues. Notably, it is predominantly ongoing cardiopulmonary, rather than systemic inflammation-related (e.g. autoimmune/fatigue/fever) symptoms that appear to best predict variance in cognitive symptoms and performance. However, given that inflammation can be a risk factor for cardiovascular problems, particularly abnormal clotting (e.g. Levi, 2017; Obeagu et al., 2024), this does not rule out inflammation as a mechanistic factor. Indeed, previous work has demonstrated suggestive evidence for multiple mechanistic pathways, often citing systemic- and neuro-inflammation as underlying causal factors (e.g. Adingupu et al., 2023; Quan et al., 2023; Sarkar et al., 2023).

Subjective cognitive symptoms were also predictive of objective cognitive function, particularly in the memory and language areas. Higher levels of ongoing tip-of-the-tongue problems, ongoing/current forgetfulness and current brain fog since the initial illness predicted lower accuracy in the verbal (Word List) memory test at baseline and/or subsequent follow-ups. Currently experienced brain fog at the final two follow-ups also predicted lower accuracy in the nonverbal (Pictorial) memory test and overall memory performance during the same period, respectively. Moreover, ongoing tip-of-the tongue problems, ongoing semantic disfluency and current difficulty concentrating since the initial illness predicted fewer correct responses in the language (Category Fluency) test at baseline and/or follow-ups. Some previous studies found week associations between subjective

reports and objective measures of cognition in COVID-19 patients (Godoy-Gonzalez et al., 2023; Pihlaja et al., 2023). These studies suggested pandemic-related psychological factors, such as post-traumatic stress disorder or depression, as underlying causes of cognitive impairments, but neglected a potential issue of low statistical power. However our results from the community sample suggest that self-reported cognitive symptoms are broadly consistent with objective cognitive performance in this population.

4.4 Impacts associated with ‘Long COVID’

The majority of our participants (over 70% at baseline and rising through follow-ups) self-identified as experiencing ‘Long COVID’, and many reported severe and persistent impact on quality of life. In particular, those with severe ongoing illness at baseline continued to report being unable to work or cope with daily activities, and suffering resultant financial distress through to the final follow-ups, i.e. approximately 10–15 months from infection. A further persistent challenge was difficulty in getting medical professionals to take their symptoms seriously, and many continued to feel that they had experienced a trauma. These findings align with the UK national report (ONS, 2023) and other previous studies on Long COVID (Davis et al., 2021; Ziauddeen et al., 2022). Notably, over 80% of participants in the Davis et al. (2021) study who reported reduced ability to work attributed this to cognitive dysfunction. These long-lasting impacts are striking, particularly the combination of degree and severity of impact with the dismissal by medical professionals (Guo et al., 2022a; ONS, 2023). Cognitive sequelae of COVID-19 thus have the potential for long-term consequences not just for individuals but also—given the prevalence of Long COVID—for the economy and wider

society, e.g. workforce morbidity (e.g. Alexandri et al., 2024). It is of great importance to prevent, predict, identify and treat issues associated with Long COVID (Guo et al., 2022a).

Long COVID might lead into long-term or even permanent cognitive decline, with increased vulnerability to neurodegeneration and dementia (Bougakov et al., 2021; Goldberg et al., 2021; Miners et al., 2020). Such effects have been suggested in some older adults (e.g. Liu et al., 2022; Taquet et al., 2022) but a definite answer for younger sufferers is not yet available. Severe and long-lasting cognitive deficits have been reported in participants who experienced very severe COVID (i.e. including ICU care and mechanical ventilation; e.g. Hampshire et al., 2022). This and the evidence of some long-lasting cognitive deficits in the relatively young, and in those who suffered mild initial illness must leave continuing concerns. Further longitudinal research is needed to monitor COVID-related cognitive dysfunction and its impacts over the longer term.

4.5 Limitations and Future Research

Limitations of the baseline study design were discussed in our previous reports (Guo et al., 2022a, 2022b). There are also limitations specific to the longitudinal follow-ups. The first major issue arises from the change in the follow-up procedure for the No-COVID group. Originally, we regularly asked the No-COVID group to indicate whether they had been infected with COVID-19; they would join the COVID group for the follow-ups only if they answered 'Yes', and otherwise did not complete any measures. However, we changed our design to also invite the No-COVID group to complete the same follow-up measures for between-group comparisons. This change resulted from both the changing narrative and

knowledge about Long COVID (including widespread denial that the condition existed (e.g. Yong, 2023)), and from fewer than expected individuals developing new COVID infections after baseline (indeed only 6 did so across the entire length of the study). By the time that the COVID group was at their final, third follow-up, the No-COVID group was at their second follow-up, after which the study ended. Because of this design change, there was no data from the No-COVID group to compare with the COVID group at FU3. The two groups also differed in the intervals (in weeks) between the baseline and the first follow-up, with the No-COVID group falling approximately 9 weeks apart. To offset a possible ambiguity of interpretation, the assessment intervals were precisely controlled for in analyses examining changes over time. A related issue (see also Guo et al., 2022a) is that due to the original design, symptom information was not collected for the No-COVID group at baseline, or (in terms of ongoing/current symptoms) from those who had had COVID but reported never having felt ill or having recovered (the *R* subgroup). This has limited our ability to compare changes in COVID-19 symptoms across the full time course of the study in all groups. In the current study, we were only able to look at group differences in symptom data between the COVID and the No-COVID group at FU1 and FU2 (but not the baseline or the final, third follow-up), and between the *C++* and *C+* subgroups (rather than the *R* subgroup) from baseline through the final follow-up.

The third issue concerns the composition of the samples; our participants with past COVID-19 infection tended to be older and more educated than the uninfected controls. Such demographic differences were present at baseline and remained at the first follow-up. Attrition across time was higher in men, younger participants and those with lower education level. Thus, the proportions of the older age groups and more educated participants were

even higher in the follow-ups than the baseline. Where possible, we controlled for sex, age and education in our analyses to mitigate some of these biases. Importantly, the No-COVID group and the *R* subgroup were more likely to drop out from follow-ups than participants who had ongoing Long COVID symptoms. This may be because people who had not been infected with COVID-19 or who had recovered from it perceived less relevance in the study and were thus less motivated to continue participation. This common form of bias in longitudinal research may have biased our results towards the more severe end of the post-COVID spectrum, and this may limit generalisability.

Finally, the specific cognitive tasks chosen for the baseline assessment were done so within the limitations of which well-established tasks were available and ready in the limited time scale during which the baseline study was arranged. Due to the urgent nature of capturing data from early in the pandemic, there was insufficient time to create and curate an ideal battery of tasks. As such, the use of tasks such as the Wisconsin card sorting task, which has recently attracted criticism as to its informational value (e.g. Nyhus et al., 2009), may limit the ability of the study to detect individual differences in executive function. Similarly, while both verbal and nonverbal item and associative memory tasks were employed, memory- and stimulus- type were confounded across these, raising the question of whether differential deficits may be the result of the type of recall required or the stimulus type. As a longitudinal follow-up, the current study inherits the shortcomings of the original study in this respect. Future research should address these shortcomings by more carefully selecting cognitive assessments.

Summary and Conclusion

Notwithstanding some limitations in this study, the findings are consistent in message and notable in implications. Cognitive dysfunction, both self-reported and objectively measured, appears to be a persistent feature of Long COVID even many months post infection. The performance element was particularly notable in memory, which was the most impaired at baseline and throughout follow-ups. The failure to observe notable long-term improvement in these conditions – highlighted as particularly relevant to quality of life – is highly concerning and warrants continued monitoring and evaluation. In particular, neurological symptoms experienced early in the illness continued to be predictive of cognitive issues many months later, while cardiopulmonary symptoms were more likely to track concurrent deficits. These findings offer the possibility to develop triage tools for follow-up, as well as to test rehabilitative and therapeutic regimens.

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