Cognitive and psychiatric symptom trajectories 2–3 years after hospital admission for COVID-19: a longitudinal, prospective cohort study in the UK

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Summary

Background COVID-19 is known to be associated with increased risks of cognitive and psychiatric outcomes after the acute phase of disease. We aimed to assess whether these symptoms can emerge or persist more than 1 year after hospitalisation for COVID-19, to identify which early aspects of COVID-19 illness predict longer-term symptoms, and to establish how these symptoms relate to occupational functioning.

Methods The Post-hospitalisation COVID-19 study (PHOSP-COVID) is a prospective, longitudinal cohort study of adults (aged ≥18 years) who were hospitalised with a clinical diagnosis of COVID-19 at participating National Health Service hospitals across the UK. In the C-Fog study, a subset of PHOSP-COVID participants who consented to be recontacted for other research were invited to complete a computerised cognitive assessment and clinical scales between 2 years and 3 years after hospital admission. Participants completed eight cognitive tasks, covering eight cognitive domains, from the Cognitron battery, in addition to the 9-item Patient Health Questionnaire for depression, the Generalised Anxiety Disorder 7-item scale, the Functional Assessment of Chronic Illness Therapy Fatigue Scale, and the 20-item Cognitive Change Index (CCI-20) questionnaire to assess subjective cognitive decline. We evaluated how the absolute risks of symptoms evolved between follow-ups at 6 months, 12 months, and 2–3 years, and whether symptoms at 2–3 years were predicted by earlier aspects of COVID-19 illness. Participants completed an occupation change questionnaire to establish whether their occupation or working status had changed and, if so, why. We assessed which symptoms at 2–3 years were associated with occupation change. People with lived experience were involved in the study.

Findings 2469 PHOSP-COVID participants were invited to participate in the C-Fog study, and 475 participants (191 [40·2%] females and 284 [59·8%] males; mean age 58·26 [SD 11·13] years) who were discharged from one of 83 hospitals provided data at the 2–3-year follow-up. Participants had worse cognitive scores than would be expected on the basis of their sociodemographic characteristics across all cognitive domains tested (average score 0·71 SD below the mean [IQR 0·16–1·04]; p<0·0001). Most participants reported at least mild depression (263 [74·5%] of 353), anxiety (189 [53·5%] of 353), fatigue (220 [62·3%] of 353), or subjective cognitive decline (184 [52·1%] of 353), and more than a fifth reported severe depression (79 [22·4%] of 353), fatigue (87 [24·6%] of 353), or subjective cognitive decline (88 [24·9%] of 353). Depression, anxiety, and fatigue were worse at 2–3 years than at 6 months or 12 months, with evidence of both worsening of existing symptoms and emergence of new symptoms. Symptoms at 2–3 years were not predicted by the severity of acute COVID-19 illness, but were strongly predicted by the degree of recovery at 6 months (explaining 35·0–48·8% of the variance in anxiety, depression, fatigue, and subjective cognitive decline); by a biocognitive profile linking acutely raised D-dimer relative to C-reactive protein with subjective cognitive deficits at 6 months (explaining 7·0–17·2% of the variance in anxiety, depression, fatigue, and subjective cognitive decline); and by anxiety, depression, fatigue, and subjective cognitive deficit at 6 months. Objective cognitive deficits at 2–3 years were not predicted by any of the factors tested, except for cognitive deficits at 6 months, explaining 10·6% of their variance. 95 of 353 participants (26·9% [95% CI 22·6–31·8]) reported occupational change, with poor health being the most common reason for this change. Occupation change was strongly and specifically associated with objective cognitive deficits (odds ratio [OR] 1·51 [95% CI 1·04–2·22] for every SD decrease in overall cognitive score) and subjective cognitive decline (OR 1·54 [1·21–1·98] for every point increase in CCI-20).

Interpretation Psychiatric and cognitive symptoms appear to increase over the first 2–3 years post-hospitalisation due to both worsening of symptoms already present at 6 months and emergence of new symptoms. New symptoms occur mostly in people with other symptoms already present at 6 months. Early identification and management of symptoms might therefore be an effective strategy to prevent later onset of a complex syndrome. Occupation change is common

and associated mainly with objective and subjective cognitive deficits. Interventions to promote cognitive recovery or to prevent cognitive decline are therefore needed to limit the functional and economic impacts of COVID-19.

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Introduction

SARS-CoV-2 infection is associated with increased risks of neuropsychiatric disorders, including depression, anxiety, and cognitive deficits,[1–5] either in isolation or as part of a post-COVID-19 syndrome (also known as long COVID).[6] In studies based on electronic health records, these risks were found to be higher in individuals who were admitted to hospital with COVID-19.[1,3,7] However, the lack of long-term, prospective longitudinal data means that it is unknown whether neuropsychiatric disorders emerge or persist beyond the first year after hospital admission, whether early aspects of COVID-19 illness predict later outcomes, and whether symptoms affect occupational functioning.

Most studies investigating neuropsychiatric outcomes beyond 18 months post-infection have relied on electronic health records.[2,3,7] Such studies cannot distinguish emergent disorders from delayed diagnosis and cannot ascertain the duration and severity of symptoms. Two prospective cohort studies with longer follow-ups investigated mental health outcomes after acute COVID-19,[8,9] including one that reported proportions of persistent symptoms.[9] However, neither study determined the trajectories of emergent and persistent symptoms, nor did they assess cognitive deficits.

In the COVID Fog (C-Fog) study, a Tier 3 study nested within the Post-hospitalisation COVID-19 study (PHOSP-COVID), a subgroup of the PHOSP-COVID cohort[10,11] was prospectively followed for up to 3 years after their hospital admission for COVID-19. We aimed to assess how cognitive, psychiatric, and fatigue symptoms emerge and evolve over time, to identify which early aspects of COVID-19 illness predict these outcomes, and to establish how symptoms correlate

Research in context

Evidence before this study

We searched PubMed for papers published from March 22, 2022 (because we were interested in follow-up of at least 2 years and because a previous review had ended with a search on March 21, 2022, with no article identified that was directly relevant to the current study), until April 25, 2024, with the terms (neuropsychiatr*[Title/Abstract] OR neurologic*[Title/Abstract] OR psychiatric[Title/Abstract] OR depress*[Title/Abstract] OR anxiety*[Title/Abstract] OR cognit*[Title/Abstract] OR brain[Title/Abstract]) AND (evolution[Title/Abstract] OR longitudinal[Title/Abstract] OR trajector*[Title/Abstract]) AND (COVID*[Title] OR SARS*[Title] OR coronavirus[Title]). Only articles published in English or with published English abstracts were considered. We found several studies based on electronic health records data and several studies with follow-ups to 18 months after acute COVID-19. We found one prospective cohort study with follow-up of up to 3 years that did not assess cognition or whether symptoms were emergent or persistent; one study of 51 patients followed up for 2 years but without statistical analyses; and one prospective study investigating which baseline characteristics were associated with psychiatric symptoms at 2 years (but without assessment of cognition). None of the studies with follow-up beyond 18 months investigated occupational impact.

Added value of this study

To our knowledge, this is the first prospective cohort study to assess trajectories of psychiatric and cognitive symptoms over the first 2–3 years after hospitalisation for COVID-19. We found that the burden of symptoms increased compared with 6 months and 12 months post-COVID-19 due to both worsening of existing symptoms and emergence of new ones. We also found that emergence of new symptoms occurred mostly in people with other symptoms present at 6 months and 12 months, rather than in people who were completely well at those earlier timepoints. A significant minority of people changed their occupation at 2–3 years after hospitalisation compared with before they had COVID-19 and were working part time or not working at all, with the most common reason given being poor health. Occupation change was strongly and specifically associated with subjective cognitive decline and objective cognitive deficits, rather than with anxiety, depression, or fatigue.

Implications of all the available evidence

The neuropsychiatric symptom burden among people who were admitted to hospital with COVID-19 remains 2–3 years after acute disease and appears to have increased compared with the burden 6 months and 12 months after hospital admission. Prompt interventions to treat symptoms present in the months after hospital discharge might prevent the emergence of additional symptoms and the development of a more complex syndrome. Interventions promoting cognitive recovery or preventing cognitive decline might limit the occupational impact of SARS-CoV-2 infections, thereby improving functional and economic outcomes of COVID-19 for the individual and society as a whole.

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See Online for appendix

with occupational change, thereby addressing one of the joint patient and clinician key research questions.[12]

Methods

Study design and participants

For the C-Fog study, we recruited participants from PHOSP-COVID, a large-scale, long-term study of nearly 8000 adults (aged ≥18 years) who were discharged from one of 83 participating UK National Health Service hospitals with a clinical diagnosis of COVID-19 between Feb 1, 2020, and March 31, 2021.[10,11] Participants who consented to be recontacted for other research were invited to complete computerised cognitive tests, clinical scales, and an occupation change questionnaire between Nov 23, 2022, and May 1, 2023, corresponding to a time since hospital admission of 21 to 38 months, which we refer to as a follow-up of 2–3 years. All eligible participants were invited and no predetermined sample size was sought.

Sex at birth was self-reported and the options were female or male. Self-reported ethnicity was recorded with the following options: White (English, Welsh, Scottish, Northern Irish, or British); White Irish; White Gypsy or Irish Traveller; White (any other White background); Mixed or multiple ethnic backgrounds (White and Black Caribbean); Mixed or multiple ethnic backgrounds (White and Black African); Mixed or multiple ethnic backgrounds (White and Asian); Mixed or multiple ethnic backgrounds (any other Mixed or multiple ethnic background); Asian or Asian British Indian; Asian or Asian British Pakistani; Asian or Asian British Bangladeshi; Asian or Asian British Chinese; Asian or Asian British (any other Asian background); Black, African, Caribbean, Black British (African); Black, African, Caribbean, Black British (Caribbean); Black, African, Caribbean, Black British (any other Black African or Caribbean background); other ethnic group (Arab); other ethnic group (any other ethnic group); not known; prefer not to say. These categories were then grouped into Asian, Black, Mixed, White, or other.

Patient and public involvement and engagement have been embedded within the work of PHOSP-COVID throughout the research cycle from research prioritisation and identification of new research topics, through to dissemination. As a PHOSP-COVID Tier 3 sub-study, C-Fog has benefited from this approach such that people with lived experience have contributed to the research question, data interpretation, and writing of this manuscript.

Details of the PHOSP-COVID study, including collection of routine clinical data (Tier 1) and enhanced clinical data collection and research-specific biosampling (Tier 2), have been published previously.[10,11,13] Further details (including a STROBE diagram of the C-Fog study) are provided in the appendix (pp 11–13). Written informed consent was obtained from all PHOSP-COVID study participants and electronic consent was provided for the C-Fog follow-up at 2–3 years. The PHOSP-COVID study (and its Tier 3 substudies) were approved by the Leeds West Research Ethics Committee (20/YH/0225), follows the STROBE reporting guidelines, and is registered on the ISRCTN Registry (ISRCTN10980107).

Procedures

At the remote follow-up at 2–3 years, participants undertook eight computerised tasks from the Cognitron battery (a platform assessing cognition remotely via web browsers);[14] this battery of tests differs from the Montreal Cognitive Assessment (MoCA), a rapid screening instrument for cognitive impairment, which was completed by participants at 6 months and 12 months. Following cognitive testing, participants were invited to complete the following questionnaires online: the 9-item Patient Health Questionnaire (PHQ-9) for depression, the Generalised Anxiety Disorder 7-item scale (GAD-7) for anxiety, an occupation change questionnaire (to establish whether occupation or working status had changed after COVID-19 and, if so, why), the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale for fatigue and its impact on daily activities and function,[15] and the 20-item Cognitive Change Index (CCI-20) questionnaire for subjective cognitive decline (modified to ask about change compared with before COVID-19).[16]

Outcomes

Despite follow-up data being collected after hospital discharge date, from a disease progression perspective, we chose to describe the data in the study in terms of the time after hospital admission to account for differences in health-care systems, hospial capacities, and other factors that might vary on a case-by-case basis. Outcomes at 2–3 years focused on cognitive, psychiatric, and fatigue symptoms, and change in occupation or working status. Eight cognitive domains were assessed with Cognitron, as follows: object memory (immediate), simple reaction speed, two-dimensional mental manipulation, cognitive control, spatial working memory, spatial planning, verbal analogies, and object memory (delayed). Each task resulted in an accuracy-based score. Predefined quality control was applied to the results (appendix p 15). Outcomes on the following clinical scales were recorded: PHQ-9 (total score from 0 to 27, with higher scores indicating more severe depression), GAD-7 (total score from 0 to 21, with higher scores indicating more severe anxiety), FACIT Fatigue Scale (total score from 0 to 52, with lower scores indicating a higher level or higher impact of fatigue), and CCI-20 (total score from 0 to 80, with higher scores indicating perceived cognitive decline). Details of the cognitive tests and clinical scales, including scoring and predefined thresholds to define mild, moderate, and severe symptom burden, are provided in the appendix (pp 13–17). Change in

occupation or working status (after *vs* before COVID-19) was determined on the basis of responses to three questions on the occupation change questionnaire (appendix pp 17–18).

Outcomes at 6 months and 12 months for PHOSP-COVID participants in Tier 2 included scores on PHQ-9, GAD-7, and the FACIT Fatigue Scale. Subjective cognitive deficits were assessed with the cognitive subset of the Patient Symptom Questionnaire (C-PSQ; score from 0 to 7 that indicates subjective cognitive deficits based on self-reported impairment in seven domains) and objective cognitive deficits with MoCA (score from 0 to 30 that assesses different cognitive domains: visuospatial, executive functioning, naming, memory, attention, language, abstraction, delayed recall, and orientation). Further details of assessments at 6 months and 12 months are provided in the appendix (pp 12–13).

Statistical analysis

Baseline characteristics were compared between respondents in C-Fog and all other participants of the PHOSP-COVID study. Characteristics with a standardised mean difference of more than 0·1 were considered to be different between the two groups. Using *t* tests, outcomes at 2–3 years were compared between those who responded only after receiving a reminder and those who responded upon first invitation.

Cognitive scores were transformed to Z scores for each domain based on normative models (learned from the Great British Intelligence study[17]) accounting for age, sex, level of education, ethnicity, and whether English was the participant's first language. Z scores were averaged across cognitive domains to provide an overall cognitive score, indicating the number of standard deviations above or below the expected score for the participant's sociodemographic characteristics.

The evolution of outcomes measured at 6 months, 12 months, and 2–3 years was represented with alluvial diagrams. When the same instrument was used across timepoints, changes in outcomes between 6 months and 2–3 years and between 12 months and 2–3 years were assessed using paired *t* tests. This was repeated among those with at least mild symptoms at both timepoints (to assess for worsening or improvement of existing symptoms) and among those with scores below the threshold of mild burden for at least one timepoint (to assess for emergence or remission of symptoms).

Five factors were assessed as possible predictors of fatigue, psychiatric, and cognitive outcomes at 2–3 years using linear regressions adjusted for age, sex, and time since hospital admission: (1) markers of acute severity including the WHO Clinical Progression Scale, National Early Warning Scores summarising physical observations, duration of hospital admission, intensive care unit admission, pulmonary embolism, and delirium during admission; (2) history of psychiatric or neurological comorbidity, and of myalgic encephalomyelitis, chronic fatigue syndrome, fibromyalgia, or chronic pain; (3) recovery clusters defined in a previous study to represent the degree of impairment (very severe, moderate to severe, or mild) measured at 6 months post-COVID-19

	C-Fog cohort (n=475)	Others in PHOSP-COVID (n=7460)	SMD
Sociodemographics			
Age, years	58·26 (11·13)	59·32 (13·53)	0·079
Sex			
Female	191 (40·2%)	3015/7451 (40·5%)	0·0052
Male	284 (59·8%)	4436/7451 (59·5%)	0·0052
Ethnicity			
Asian	25 (5·3%)	661/7447 (8·9%)	0·14
Black	12 (2·5%)	363/7447 (4·9%)	0·12
Mixed	<10 (<2·1%)	114/7447 (1·5%)	..
White	417 (87·8%)	5881/7447 (79·0%)	0·24
Other	15 (3·2%)	428/7447 (5·7%)	0·13
Education			
None	<10/449 (<2·2%)	157/6616 (2·4%)	..
Primary school	<10/449 (<2·2%)	168/6616 (2·5%)	..
Secondary school	113/449 (25·2%)	2148/6616 (32·5%)	0·16
Sixth form college	62/449 (13·8%)	816/6616 (12·3%)	0·044
Vocational qualification	66/449 (14·7%)	771/6616 (11·7%)	0·090
Undergraduate university degree	80/449 (17·8%)	916/6616 (13·9%)	0·11
Post-graduate qualification	89/449 (19·8%)	725/6616 (11·0%)	0·25
Prefer not to say	29/449 (6·5%)	915/6616 (13·8%)	0·25
Income per annum			
<£19 000	52/361 (14·4%)	1122/4088 (27·4%)	0·32
£19 001–£26 000	61/361 (16·9%)	696/4088 (17·0%)	0·0034
£26 001–£35 000	46/361 (12·7%)	605/4088 (14·8%)	0·06
£35 001–£48 000	73/361 (20·2%)	580/4088 (14·2%)	0·16
>£48 001	129/361 (35·7%)	1085/4088 (26·5%)	0·20
English as a first language	415/446 (93·0%)	5517/6804 (81·1%)	0·36
Comorbidities			
Cardiovascular condition	213/471 (45·2%)	3667/7429 (49·4%)	0·083
Cerebrovascular accident	<10/472 (<2·1%)	296/7429 (3·9%)	..
Psychiatric or neurological condition	115/470 (24·5%)	1433/7428 (19·3%)	0·13
Myalgic encephalomyelitis, chronic fatigue syndrome, fibromyalgia, or chronic pain	26/471 (5·5%)	314/7435 (4·2%)	0·060
Diabetes	81/474 (17·1%)	1681/7438 (22·6%)	0·14
Respiratory condition	158/474 (33·3%)	2254/7440 (30·3%)	0·065
Rheumatological condition	82/474 (17·3%)	1272/7445 (17·1%)	0·0057
Gastrointestinal condition	104/472 (22·0%)	1472/7428 (19·8%)	0·055
Endocrine condition	41/471 (8·7%)	686/7428 (9·2%)	0·019
Chronic kidney disease	16/474 (3·4%)	416/7447 (5·6%)	0·11
Cancer	29/473 (6·1%)	579/7435 (7·8%)	0·065
Chronic infection	10/474 (2·1%)	185/7398 (2·5%)	0·026
Clinical features at 6 months			
Objective cognitive function (MoCA)	26·89 (2·42)	25·54 (3·60)	0·38
Subjective cognitive function (C-PSQ)	2·53 (2·15)	2·05 (2·05)	0·23
Depression (PHQ-9)	6·99 (6·05)	7·05 (6·60)	0·0084
Anxiety (GAD-7)	4·91 (5·12)	5·38 (5·75)	0·082
Fatigue (52-FACIT)*	17·91 (12·46)	17·88 (13·38)	0·002

(Table 1 continues on next page)

	C-Fog cohort (n=475)	Others in PHOSP-COVID (n=7460)	SMD
(Continued from previous page)			
Clusters of recovery at 6 months			
Mild	57/165 (34·5%)	666/2240 (29·7%)	0·10
Moderate to severe	76/165 (46·1%)	1103/2240 (49·2%)	0·064
Very severe	32/165 (19·4%)	471/2240 (21·0%)	0·041

Data are mean (SD), n (%), or n/N (%). PHOSP-COVID=Post-hospitalisation COVID-19 study. SMD=standardised mean difference. MoCA=Montreal Cognitive Assessment. C-PSQ=cognitive subset of the Patient Symptom Questionnaire. PHQ-9=Patient Health Questionnaire-9. GAD-7=Generalised Anxiety Disorder Questionnaire-7. FACIT=Functional Assessment of Chronic Illness Therapy Fatigue Scale. *For fatigue, the inverted scale is used (reporting 52–FACIT).

Table 1: **Baseline characteristics of participants who reported data at 2–3 years compared with all other participants in the PHOSP-COVID cohort**

across different symptom domains;[10] (4) clinical scales capturing each symptom domain at 6 months (adjusting for the same symptom domain as the outcome); and (5) two biocognitive profiles linking acute blood biomarkers and cognitive outcomes at 6 months.[18] Benjamini–Hochberg correction for multiple testing was applied across outcomes.

We assessed which symptoms at 2–3 years were most associated with occupation change at the same timepoint using univariable logistic regressions and a multivariable logistic Lasso regression (to account for multicollinearity) including all clinical scales, the overall cognitive score, age, sex, and time since hospital admission as independent variables. For each clinical scale found to be associated with occupational change, additional univariable and multivariable logistic Lasso regressions were computed with the items from that scale as independent variables. Adjusted risk ratios (RRs) and 95% CIs were calculated using generalised linear models with binomial outcome and log link functions. Associations with binary outcomes are reported as odds ratios (ORs) and RR with 95% CIs.

Statistical significance was set at two-sided p values of less than 0·05. Further details about the statistical analyses are provided in the appendix (pp 18–19). All analyses were conducted in R version 4.2.0 and used complete data at the 2–3-year follow-up with no imputation (all participants with available data).

Role of the funding source

The funders of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the manuscript.

Results

A total of 2469 participants from the PHOSP-COVID study consented to be recontacted for other research and were invited to participate in C-Fog. A total of 475 participants (19·2% of those invited) provided data at the 2–3-year follow-up (191 [40·2%] females and 284 [59·8%] males; mean age 58·26 [SD 11·13] years; table 1; appendix p 22). Compared with the rest of the PHOSP-COVID cohort, participants followed up at 2–3 years were more likely to be White and native English speakers, have a higher education level and a higher income, and have better objective cognition but worse subjective cognition at 6 months. They were similar in terms of age, sex, pre-COVID-19 comorbidities (except for a lower burden of diabetes and a higher burden of psychiatric or neurological conditions), and in terms of their depression, anxiety, and fatigue measured at 6 months. Compared with those who participated upon first invitation, those who required a reminder had significantly worse objective cognitive deficit at 2–3 years, but similar depression, anxiety, fatigue, and subjective cognitive deficits (appendix p 23).

Most participants reported at least mild depression (263 [74·5%] of 353), anxiety (189 [53·5%] of 353), fatigue (220 [62·3%] of 353), and subjective cognitive decline (184 [52·1%] of 353), with a substantial minority experiencing severe depression (79 [22·4%] of 353), severe fatigue (87 [24·6%] of 353), and severe subjective cognitive decline (88 [24·9%] of 353; figure 1). Participants had worse overall cognitive scores than would be expected for people with the same sociodemographic characteristics (but without COVID-19; appendix pp 15–16), by 0·71 SD (IQR 0·16–1·04; p<0·0001). Significant deficits were observed across all cognitive domains, with a median deficit ranging from 0·18 SD for spatial working memory to 1·25 SD for verbal analogies (figure 2).

Evolution of the different scales from 6 months to 2–3 years based on data provided by the same individuals across timepoints is depicted in figure 3 and the appendix (pp 20, 23). Depression increased from 6 months to 2–3 years (mean increase in PHQ-9 score 1·77 [95% CI 0·95–2·59]; p<0.0001). There was evidence of both worsening of persistent depressive symptoms (mean increase in PHQ-9 score from 6 months to 2–3 years 1·74 [95% CI 0·50–2·99]; p=0·0068) and a net emergence of new symptoms among people without symptoms at 6 months (mean increase 1·79 [0·68–2·91]; p=0·0021). Anxiety also increased from 6 months to 2–3 years (mean increase in GAD-7 scores 0.82 [95% CI 0·15–1·48]; p=0·017) and there was evidence of net emergence of symptoms (mean increase 0·82 [0·058–1·58]; p=0·035) while worsening of persistent symptoms was of similar magnitude but not significant. Fatigue first improved from 6 to 12 months, before significantly deteriorating from 12 months to 2–3 years (mean decrease in FACIT 3·90 [95% CI 1·97–5·84]; p=0·0001). Differences in fatigue scores in those with persistent symptoms and those with emerging or remitting symptoms were not significant. Incidences and remission proportions for all outcomes are presented in the appendix (p 24).

Among those with a recorded MoCA within the normal range (>26) at 6 months and 12 months, 11 of 55 (20·0% [95% CI 11·5–32·6]) had an overall cognitive score at 2–3 years at least 1 SD below the score expected for their sociodemographic characteristics. Among

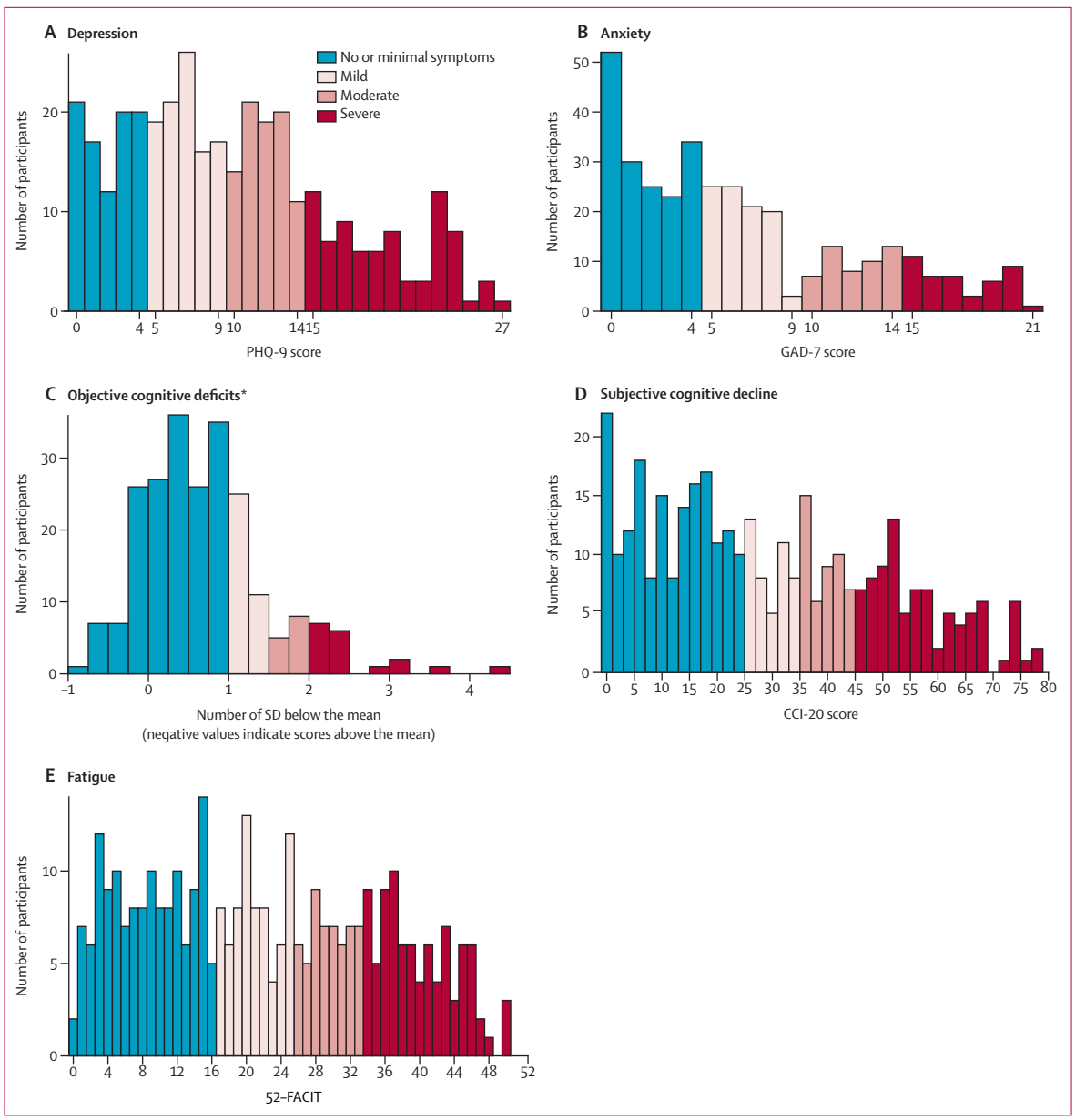

Figure 1: **Distribution of cognitive, psychiatric, and fatigue outcomes at 2–3 years after COVID-19**
Colours encode severity of symptom burden of depression (A), anxiety (B), cognitive outcomes (C and D), and fatigue (E) based on predefined thresholds. For fatigue, the FACIT scale is inverted (reporting 52–FACIT), with worse outcomes appearing on the right. PHQ-9=Patient Health Questionnaire-9. GAD-7=Generalised Anxiety Disorder Questionnaire-7. FACIT=Functional Assessment of Chronic Illness Therapy Fatigue Scale. CCI-20=Cognitive Change Index-20. *Objective cognitive deficits were assessed with eight cognitive tasks from the Cognitron battery.

those who reported no subjective cognitive deficits at 6 months and 12 months post-COVID-19 (as measured by the C-PSQ[18]), four of 52 (7·7% [95% CI 2·6–18·8]) reported at least some subjective cognitive decline at 2–3 years; and among those with subjective cognitive deficits at 6 months and 12 months, 18 of 67 (26·9% [17·7–38·6%]) reported little to no decline at 2–3 years.

Severity of the acute illness did not predict outcomes at 2–3 years. By contrast, the predefined clusters of recovery based on symptoms measured at 6 months[10] strongly predicted symptoms, explaining 35–49% of the variance in depression, anxiety, fatigue, and subjective cognitive decline (table 2). Those in the very severe cluster of recovery at 6 months had substantial symptom burden at 2–3 years (figure 4), including 75·0% (18 of 24) experiencing severe depression, 66·7% (16 of 24) with severe subjective cognitive decline, 62·5% (15 of 24) with severe fatigue, 33·3% (eight of 24) with severe anxiety, and 15·0% (three of 20) with an overall cognitive

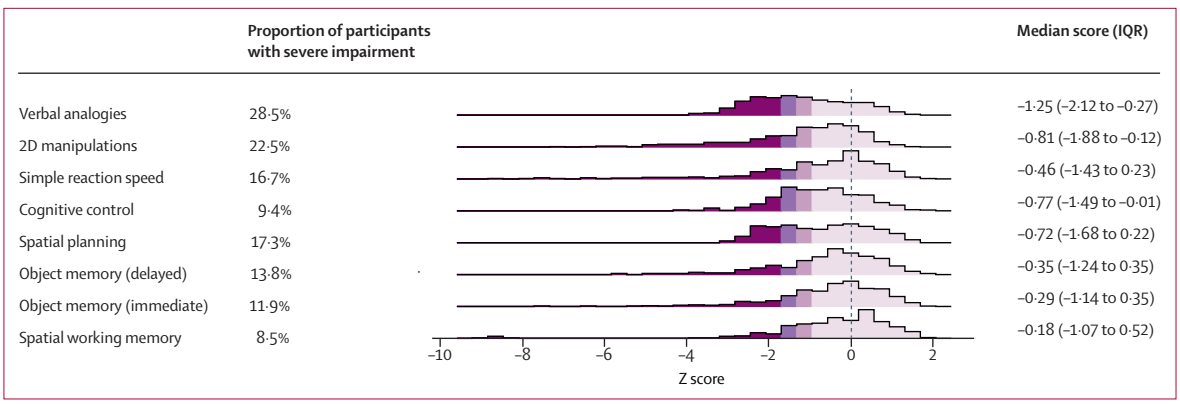

Figure 2: **Distribution of normalised scores for different cognitive domains**
Participants completed eight cognitive tasks from the Cognitron battery, encompassing eight cognitive domains. The units represent the number of standard deviations below (negative) or above (positive) the mean for people with the same sociodemographic characteristics. For each domain, the median Z score and IQR, as well as the proportion of people with severe impairment (ie, Z scores <–2) are provided. All distributions had mean significantly below zero (one-sample Wilcoxon test p<0·0001).

score 2 SD below the score expected for their sociodemographic characteristics. History of a psychiatric or neurological condition increased the prevalence of most outcomes, but history of myalgic encephalomyelitis, chronic fatigue syndrome, fibromyalgia, or chronic pain increased only the prevalence of fatigue and, to a lesser extent, depression. The biocognitive profile linking raised D-dimer relative to C-reactive protein (CRP) during the acute illness with subjective cognitive deficits at 6 months[18] significantly predicted most outcomes at 2–3 years, except for objective cognitive deficits (table 2; appendix p 20). By contrast, the biocognitive profile linking raised fibrinogen relative to CRP with both objective and subjective cognitive deficits at 6 months[18] was not associated with any outcome at 2–3 years.

More than one in four participants (95 of 353 [26·9%; 95% CI 22·6–31·8]) reported having changed their occupation compared with before they had COVID-19, and the main reason given was poor health (appendix p 21). In univariable analyses, change in occupation at 2–3 years was found to be associated with subjective cognitive decline (adjusted OR 1·54 [95% CI 1·21–1·98] and adjusted RR 1·32 [1·14–1·56] for every point increase in CCI-20, p=0·0005), objective cognitive deficit (OR 1·51 [1·04–2·22] and RR 1·34 [1·07–1·63] for every SD decrease in overall cognitive score, p=0·031), and fatigue (OR 1·31 [1·03–1·69] and RR 1·22 [1·02–1·46] for every point decrease in FACIT, p=0·031; appendix p 27). In sparse multivariable modelling, both overall cognitive score (OR 1·13) and subjective cognitive decline (OR 1·35) remained associated with change in occupation. The only two cognitive domains associated with occupation change were simple reaction speed (OR 1·34 [95% CI 1·16–1·55]; p<0·0001 in univariable analysis; OR 1·21 in sparse multivariable modelling) and cognitive control (OR 1·40 [95% CI 1·11–1·77]; p=0·0047 in univariable analysis; OR 1·27 in sparse multivariable modelling). All but one item of the subjective cognitive decline scale were significantly associated with occupation change in univariable analysis (appendix p 28). Notably, in sparse multivariable modelling, the items selected to best correlate with occupation change were a worsening in ability to shift from one activity to the next (item 15; OR 1·13; univariable OR 1·61 [95% CI 1·26–2·05], p=0·00012), and a worsening in the ability to remember what one intended to do (item 8; OR 1·14; univariable OR 1·63 [1·28–2·09], p=0·00010), whereas all other items had OR between 1·0 and 1·05 (appendix p 28).

Discussion

Individuals admitted to hospital with COVID-19 who were included in the C-Fog cohort continued to experience substantial cognitive and psychiatric burden up to 3 years after hospital admission. Almost one in two respondents in this study experienced moderate to severe depression, one in four reported severe cognitive decline, and one in nine had objective signs of severe cognitive deficits (which would equate to a difference of 30 points on a typical IQ scale, in which 1 SD equals 15 points[14]). Fatigue added to this burden. Functional impact of COVID-19 hospitalisation was also evident: more than one in four participants reported a change in their occupation since having COVID-19. Depression, anxiety, and fatigue increased from 6 months to 2–3 years. Symptoms at 2–3 years were best predicted by participants' level of health impairment at 6 months and by a biocognitive profile linking raised D-dimer relative to CRP in the acute illness to 6-month subjective cognitive deficits.

Much of the burden can be attributed to persistence of symptoms already present 6 months and 12 months post-hospitalisation. However, persistence alone cannot explain the significant increase in depression, anxiety, and fatigue scores from 6 months to 2–3 years post-COVID-19. The magnitude of the increase cannot be explained by ageing of the cohort[15,19,20] or by the fact

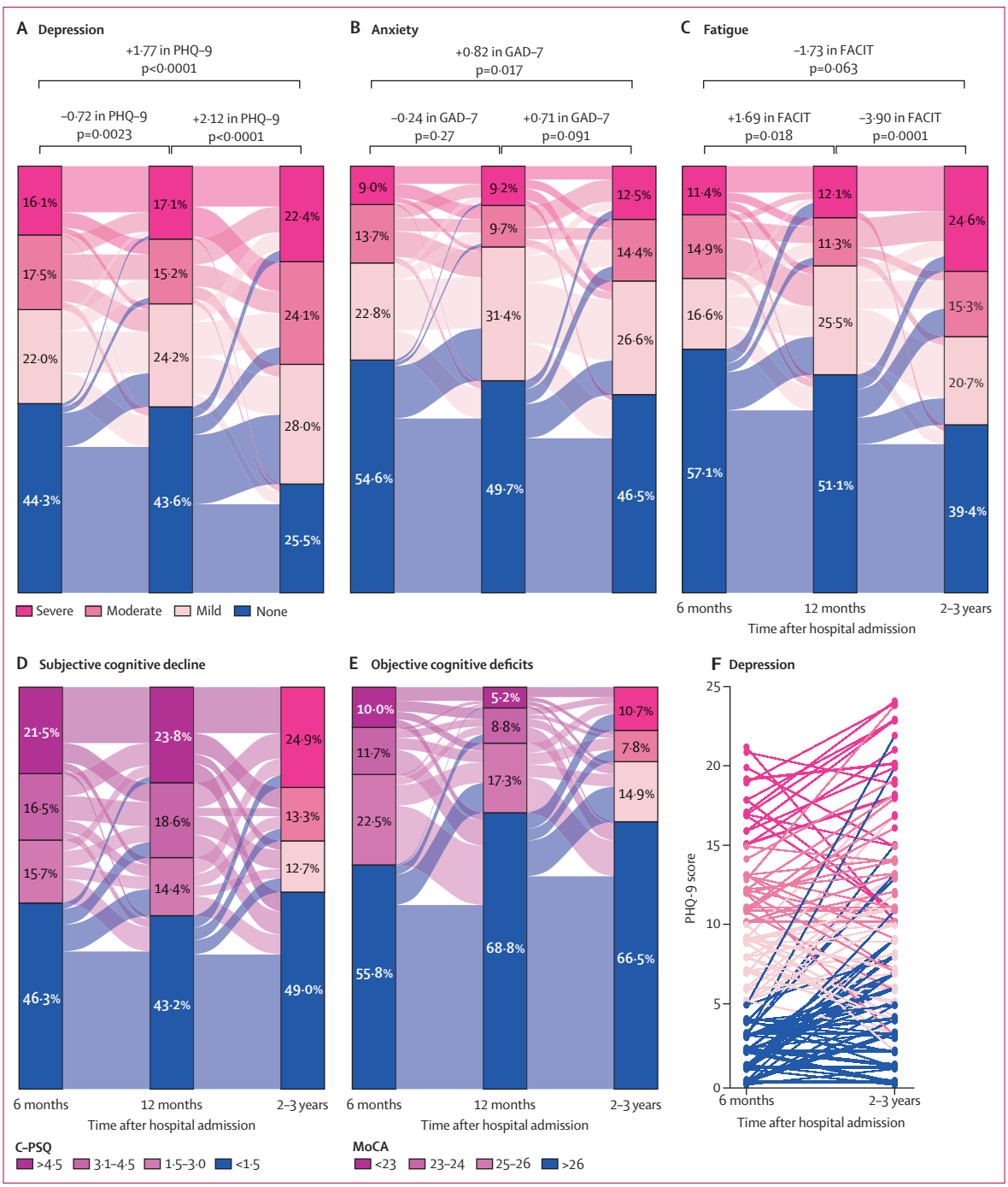

Figure 3: **Change over time in cognitive, psychiatric, and fatigue outcomes after COVID-19**
Evolution of the proportion of participants with no symptoms or mild, moderate, or severe burden of depression (A), anxiety (B), fatigue (C), and cognitive outcomes (D and E). Data are from individuals who provided data at different timepoints. For depression, anxiety, and fatigue, results of the paired *t* tests are displayed in terms of the mean change in score and p values (details, including confidence intervals, can be found in the appendix [p 23]). For fatigue, a negative change in FACIT means a worsening of symptoms, unlike for depression and anxiety. For objective and subjective cognitive outcomes, scales used at 2–3 years after hospital admission (overall cognitive score and CCI-20, respectively) were different from those used at 6 months and 12 months after hospital admission, and are therefore coloured differently. (F) Paired values of PHQ-9 at 6 months and 2–3 years. Graphs of paired values for GAD-7 and FACIT can be found in the appendix (p 20). PHQ-9=Patient Health Questionnaire-9. GAD-7=Generalised Anxiety Disorder-7. FACIT=Functional Assessment of Chronic Illness Therapy Fatigue Scale. C-PSQ=cognitive subset of the Patient Symptom Questionnaire. MoCA=Montreal Cognitive Assessment.

	Depression	Anxiety	Fatigue	Subjective cognitive decline	Objective cognitive deficits
WHO Clinical Progression Scale	0·83 (p=0·66)	2·31 (p=0·24)	0·36 (p=0·75)	1·02 (p=0·66)	0·99 (p=0·66)
National Early Warning Score	0·044 (p=0·94)	0·017 (p=0·94)	0·016 (p=0·94)	0·0019 (p=0·94)	0·20 (p=0·94)
Duration of admission	0·015 (p=0·91)	0·52 (p=0·76)	0·31 (p=0·76)	0·0035 (p=0·91)	0·12 (p=0·91)
Intensive care unit admission	0·41 (p=0·62)	0·95 (p=0·62)	0·36 (p=0·62)	1·49 (p=0·62)	0·14 (p=0·72)
Pulmonary embolism	0·28 (p=0·86)	1·15 (p=0·47)	0·14 (p=0·86)	1·86 (p=0·32)	3·27 (p=0·16)
Delirium	0·29 (p=0·97)	0·52 (p=0·97)	0·00056 (p=0·97)	0·029 (p=0·97)	0·22 (p=0·97)
History of psychiatric or neurological comorbidity	10·87 (p<0·0001)	6·44 (p<0·0001)	8·27 (p<0·0001)	7·19 (p<0·0001)	0·13 (p=0·59)
History of myalgic encephalomyelitis, chronic fatigue syndrome, fibromyalgia, or chronic pain	1·62 (p=0·044)	0·99 (p=0·11)	3·53 (p=0·0022)	0·86 (p=0·11)	0·49 (p=0·29)
Recovery cluster	48·84 (p<0·0001)	39·43 (p<0·0001)	47·46 (p<0·0001)	35·04 (p<0·0001)	2·93 (p=0·12)
Biocognitive profile (D-dimer)	11·04 (p=0·0016)	7·02 (p=0·0089)	17·16 (p<0·0001)	9·75 (p=0·0023)	0·004 (p=0·96)
Biocognitive profile (fibrinogen)	0·46 (p=0·62)	4·87 (p=0·13)	0·82 (p=0·61)	2·53 (p=0·28)	0·21 (p=0·70)

Predictors include aspects of patient history and acute COVID-19 infection measured during the acute infection and aspects of recovery measured 6 months after hospital admission. Each cell in the table contains the proportion of variance (in %) explained by the predictor in a model first adjusted for age, sex, and time since admission to hospital. The p values are Benjamini–Hochberg-corrected for each predictor independently. All coefficients, unadjusted p values, and results of tests for heteroscedasticity can be found in the appendix (pp 25, 29–30). The cutoff value indicating significance for corrected p values is 0·05.

Table 2: **Prediction of outcomes by factors representing earlier aspects of participants' illness**

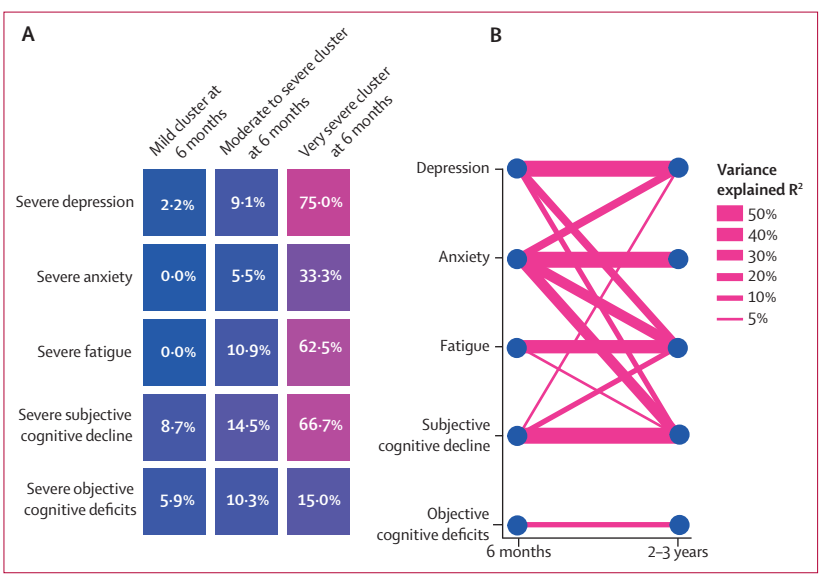

Figure 4: **Prediction of cognitive, psychiatric, and fatigue outcomes at 2–3 years after COVID-19 by symptom burden at 6 months**

(A) Prevalence of severe psychiatric, cognitive, and fatigue outcomes at 2–3 years as a function of recovery at 6 months, based on three predefined clusters of recovery (one per column). (B) Prediction of symptom burden at 2–3 years based on symptoms at 6 months. Each line connecting symptom X at 6 months to symptom Y at 2–3 years represents the proportion of variance in Y at 2–3 years explained by symptom X at 6 months when adjusting for Y at 6 months. Only predictions that were significant at p<0·05 are represented. For subjective cognitive decline and objective cognitive deficits, the instruments used at 6 months and 2–3 years differ, which might have led to a lower proportion of variance explained. All coefficients, p values, and R^2 are provided in the appendix (p 26).

that the follow-up at 2–3 years was performed on a digital device rather than on paper.[21,22] The increase seen might instead be explained by the emergence of new symptoms or worsening of existing symptoms. For depression, there was robust evidence for both. For anxiety and fatigue, subgroup analyses were underpowered to tease apart the effects of worsening and newly emerging symptoms, but there was evidence of emerging anxiety symptoms. Overall, the findings regarding emerging symptoms are consistent with the observed ongoing increased risk of new diagnoses of depression and anxiety beyond 1 year after COVID-19 hospitalisation.[7] They support the hypothesis that this ongoing risk represents, at least in part, newly emergent symptoms and not just delayed diagnosis of persistent symptoms.

Emergence and worsening of cognitive deficits are more difficult to assess because different instruments were used to measure cognition at 6 months and 12 months (MoCA for objective testing and C-PSQ for subjective reporting) and at 2–3 years (Cognitron platform[14] and CCI-20). The proportion of those with a normal MoCA at 6 months and 12 months who had objective cognitive deficits at 2–3 years (20%) is greater than that expected from the correspondence between MoCA and Cognitron scores.[23] However, it might be that some participants with objective cognitive deficits at 6 months or 12 months had a normal MoCA score because the MoCA is not sensitive to cognitive deficits in people with higher baseline cognition. As such, our data at 2–3 years provide a more accurate representation of the subsequent cognitive burden for people admitted to hospital with COVID-19. The ongoing cognitive burden at 2–3 years is compatible with the observation of ongoing increased risk of new diagnoses of cognitive deficits and dementia in those admitted to hospital with COVID-19.[7] All cognitive domains were significantly affected, which mirrors results of a systematic review of smaller studies[24] and a recent large cross-sectional study.[14] Some participants had particularly low scores on specific tasks; these might reflect genuinely poor performance, misunderstanding of the task, or invalid

responses not detected by quality control. The lower participation of people with low MoCA scores at 6 months and the higher participation of those with cognitive deficits only after a reminder suggest that the reported cognitive deficits might underestimate the true burden. However, unmeasured confounding could also bias the estimate in the opposite direction.

Emergence of new symptoms need not be limited to people who were completely well 6 months after COVID-19. People who experienced symptoms in one domain (eg, anxiety) might have started experiencing symptoms in another (eg, depression). This is supported by the strong prediction of many symptom domains at 2–3 years by others at 6 months, even after adjusting for the other domain at 6 months. Moreover, clusters of recovery at 6 months strongly predict all symptoms at 2–3 years. People in the mild recovery cluster (including all those who were completely well at 6 months) experienced almost no severe symptoms at 2–3 years. This contrasts with people in the very severe cluster at 6 months, most of whom experienced severe depression, fatigue, or subjective cognitive decline at 2–3 years. It is therefore possible that from a single or a few symptoms emerges a network of symptoms (or syndrome). Such an emerging network between a range of post-acute features has been observed post-COVID-19 to a greater extent than post-influenza.[6] This network was found to become increasingly connected over time, possibly explaining the initial improvement (from 6 months to 12 months) before a worsening in symptom burden. Whether such a symptom trajectory is specific to COVID-19 or is also observed in other illnesses remains to be determined in controlled studies. If a syndrome indeed emerges from a few core symptoms, then early interventions targeting the core symptoms might be a viable strategy to limit long-term symptom burden. Anxiety at 6 months predicted many symptoms at 2–3 years. Identifying the causes, underlying mechanisms, and development, and managing anxiety early might reduce the symptom burden at 2–3 years. These hypotheses need to be tested in randomised controlled trials since the observational nature of this study makes it prone to unmeasured confounding.

Beyond the symptom burden, assessing the effect of COVID-19 hospitalisation on occupation helps to build understanding of the functional consequences of COVID-19. The robust and specific association between occupation change and cognitive deficits (both objective and subjective) suggests that many people who changed occupation in the months and years after acute COVID-19 did so because they could no longer meet the cognitive demands of their job rather than because they lacked energy, interest, or confidence (which would all be reflected in an association with PHQ-9). Objective deficits in cognitive control, prolonged reaction time, and subjectively reported difficulties with switching activities and remembering what one intended to do were the best predictors of occupation changes. This suggests that people who changed occupation in the wake of COVID-19 have difficulties executing complex tasks with changing demands. Task switching is a particularly demanding cognitive process[25] and important for performance in the workplace.[26] Interventions such as brain training for task switching (provided it is acceptable to the patient and their fatigue level) might help to reduce the effect of long COVID for individuals and the wider economy.[27]

A study of this kind cannot identify the mechanisms underpinning the different symptom trajectories, but it can provide some clues. No association was found between symptom burden and a range of markers of severity of the acute illness, suggesting that the latter cannot explain the psychiatric and cognitive burden (among those whose illness severity had required hospitalisation). In a previous analysis of the PHOSP-COVID study, two biocognitive profiles were found to link acute blood biomarkers with cognitive deficits 6 months and 12 months post-COVID-19.[18] In this study, we found that the profile linking raised D-dimer relative to CRP with subjective cognitive deficits at 6 months explains about 10% or more of the variance in depression, fatigue, and subjective cognitive decline at 2–3 years. This supports the hypothesis that this biocognitive profile captures a biological process with enduring consequences, such as microthrombi in the cerebral vasculature.[18] Conversely, the biocognitive profile linking raised fibrinogen relative to CRP with objective and subjective cognitive deficits was no longer associated with any symptoms at 2–3 years post-COVID, suggesting that it corresponds to a transient biological process such as neuroinflammation.[28] These biological explanations remain hypotheses that need to be tested in mechanistic studies.

Objective cognitive deficits stood out as an outcome: they were not predicted by any of the other symptoms (not even subjective cognitive deficits) and they did not predict other symptoms, and unlike other symptoms, they were not predicted by biocognitive profiles, history of neurological or psychiatric comorbidity, or clusters of recovery. This suggests that objective cognitive deficits might have their own separate neurobiology, whereas mechanisms underpinning subjective cognitive decline might, in part, be shared with fatigue, depression, and anxiety.

The C-Fog study has several strengths, including a longitudinal follow-up for up to 3 years, detailed phenotyping of cognitive and psychiatric symptoms using validated instruments, and assessment of both clinical and occupational effects. However, the study also has limitations. First, data are limited to patients admitted to hospital with COVID-19 and might not generalise to patients who were not admitted to hospital. In addition, the low response rate (19·2% of those invited) means that there is a risk of selection bias. Comparison at baseline

and at 6-month follow-up showed that respondents and non-respondents were similar in many baseline characteristics and 6-month outcomes but differed in other respects (eg, more likely to have a higher education level and a higher cognitive score at 6 months). Differences between those who required a reminder to participate and those who did not provide additional clues about differences between respondents and non-respondents (assuming that the non-respondents are more like those who required a reminder). The fact that these two groups differed only in objective cognitive deficits provides evidence against large discrepancies between respondents and non-respondents. However, there might also be unmeasured differences between respondents and non-respondents that affect outcomes at 2–3 years post-COVID-19. Results (especially absolute risks) should therefore be interpreted cautiously. Second, because of the focus on a long follow-up, participants were all diagnosed early in the pandemic (before emergence of the delta variant) and results might not apply to people infected with other variants and people who were vaccinated before being infected. Although variants have changed the risks of cognitive and psychiatric outcomes,[2] previous vaccination is not associated with a lower risk of psychiatric outcomes.[5,29,30] Third, we do not know which participants have been reinfected or their vaccination status after they had COVID-19. Although reinfection[8] and subsequent vaccination[31] might affect absolute risks of cognitive, psychiatric, and fatigue outcomes, they are likely to affect the cohort as a whole so that contrasts between subgroups remain similar. Fourth, the absence of a control group of individuals who never had COVID-19 means that it is unclear whether psychiatric and cognitive outcomes would have been observed during the study period in this population in the absence of COVID-19. However, the increased risk of cognitive and psychiatric diagnoses within 2 years after COVID-19 hospitalisation compared with hospitalisation for other causes[7] or the general population[3,4] is well established, and this study focused on identifying symptom trajectories and their predictors.

In summary, psychiatric and cognitive symptoms continue to be present up to 3 years after hospital admission in a significant proportion of people who were admitted to hospital for COVID-19, and fatigue adds to this burden. The burden increased from 6 months to 2–3 years, probably due to both worsening of existing symptoms and onset of new symptoms. Newly arising symptoms affect mostly people with symptoms in other domains at 6 months, which might reflect the emergence of a syndrome stemming from an individual symptom. As such, early treatment of the initial symptom domain might be an effective way to prevent later onset of a complex syndrome. Adults with severe ongoing health impairments at 6 months are at particularly high risk of severe symptoms at 2–3 years. Medical attention and follow-up are warranted for this group. Occupation change is a common outcome in people who were admitted to hospital with COVID-19, especially those with objective and subjective cognitive deficits. Interventions to promote cognitive recovery or to prevent cognitive decline are therefore needed to limit the functional and economic effects of COVID-19.

Contributors

The manuscript was initially drafted by MT and further developed by PJHa, JDC, L-PH, AHa, AHo, MM, KP, BR, OCL, MR, OE, HJCM, ASh, ASi, MS, RMS, VCH, NR, LH-W, NJG, PM, EMH, ABD, NIL, JQ, PJHe, JRG, CEB, LVW, and RAE. MT, JRG, and PJHa made substantial contributions to the conception and design of the work. CEB, LVW, RAE, and MT made substantial contributions to the acquisition of data. MT, ZS, TDD, and WRT made contributions to the analysis of data. MT and PJHa contributed to interpretation of data. MT, ZS, TDD, WRT, AHa, CEB, LVW, and RAE accessed and verified the underlying data. All authors contributed to critical review and revision of the manuscript. All authors had access to the data in the study and accept responsibility for the decision to submit for publication.

Declaration of interests

AHa is co-director and owner of H2CD, and owner and director of Future Cognition, which support online studies and develop custom cognitive assessment software, respectively. PJHe is director and CEO of H2CD. JDC declares grants from AstraZeneca, Boehringer Ingelheim, Insmed, Novartis, Gilead Sciences, and Genentech; and consulting fees from AstraZeneca, Boehringer Ingelheim, Insmed, Novartis, Gilead Sciences, Chiesi, Zambon, and Genentech. L-PH declares grants to their institution from UK Research and Innovation (UKRI), Regenerative Medicine Platform, Celgene, British Lung Foundation, and Oxford Boehringer Ingleheim; the author is on the advisory board for the CATALYST trial and acts as chair of the Respiratory Translational Research Collaboration. AHo declares a grant to their institution from UKRI and the UK National Institute for Health Research (NIHR) to complete this work, funding from NIHR Manchester Clinical Research Facility to support study delivery, and personal funding from NIHR Manchester Biomedical Research Centre (BRC). AHo declares institutional payments to support grant-funded research from NIHR, UK Medical Research Council (MRC), Cystic Fibrosis Trust, Cystic Fibrosis Foundation, North West Lung Centre Charity, and Moulton Trust; consulting fees from Mylan Pharmaceuticals for advisory board participation; and payment from Vertex Pharmaceuticals for educational presentation, participation on a clinical trials advisory board, and writing of a review article. AHo's non-paid roles include chair of the Cystic Fibrosis Clinical Trials Accelerator Program, deputy chair of the NIHR Respiratory Translational Research Collaboration, and director of a university spin-out company (Mi-trial). BR declares payments from the British Heart Foundation Oxford Centre of Research Excellence, NIHR Oxford BRC, and UKRI for grants and contracts; and consulting fees from Axcella Therapeutics. ASh, ASi, and MM declare a grant to their institution from UKRI and NIHR to complete this work. ASh declares unremunerated participation on the AstraZeneca Thrombotic Thrombocytopenic Taskforce and Scottish and UK Governments COVID-19 advisory groups. LH-W declares a grant from NIHR unrelated to the submitted work; acting as independent chair of the NIHR Health Technology Assessment Committee for Colour COPD trial; and membership of the American Thoracic Society Pulmonary Rehabilitation Assembly Web and Planning Committees. NIL declares acting as director of research at the Intensive Care Society UK. CEB declares a grant to their institution from UKRI and NIHR to complete this work; the author reports grants from GSK, AstraZeneca, Sanofi, Boehringer Ingelheim, Chiesi, Novartis, Roche, Genentech, Mologic, and 4DPharma; and consultancy fees paid to their institution from GSK, AstraZeneca, Sanofi, Boehringer Ingelheim, Chiesi, Novartis, Roche, Genentech, Mologic, 4DPharma, and Teva. LVW declares research funding unrelated to the submitted work from GSK and Orion; consulting fees unrelated to the submitted work from Galapagos; a Wellcome Conference speaker honorarium; travel support from Genentech;

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Data sharing

The PHOSP-COVID protocol, consent form, definition and derivation of clinical characteristics and outcomes, training materials, regulatory documents, requests for data access, and other relevant study materials are available via the PHOSP-COVID website.

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For the **PHOSP-COVID website** go to https://www.phosp.org

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