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Individual Participant Data Meta-Analysis (IPDMA) of long-term COVID-19 outcomes in a systematic review-informed, international, multidisciplinary database

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Extended Research Article

Individual Participant Data Meta-Analysis (IPDMA) of long-term COVID-19 outcomes in a systematic review-informed, international, multidisciplinary database

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Abstract

Background: Identifying and addressing long-term health and societal challenges after COVID-19 is a research priority.

Objectives: To create an international, multidisciplinary COVID-19 database, and synthesise long-term outcomes, predictors and costs.

Design: Systematic identification of COVID-19 data sets and meta-analysis of individual participant data on long-term outcomes after COVID-19.

Setting: Contributed data were collected in clinical, community and research settings.

Interventions: Interventions from original studies were included as covariates in models.

Data sources: MEDLINE, Cochrane Central Register of Controlled Trials, EMBASE, Web of Science, PsycInfo® (American Psychological Association, Washington, DC, USA), Cumulative Index to Nursing and Allied Health Literature, World Health Organization Global Index Medicus, Epistemonikos, LitCOVID; World Health Organization International Clinical Trials Registry Platform; ClinicalTrials.gov and supplementary searches for studies (November 2019–November 2021) were searched for studies on > 10 people from cohort, case-control, survey or randomised controlled trial studies, across any setting, describing validated assessment instruments, symptoms, hospitalisation, discharge destination or mortality beyond 28-days after COVID-19 onset. Data were extracted by two independent reviewers.

Methods: Principal investigators contributed fully anonymised individual participant data. Demography, equity and symptoms were described. Assessment instruments were mapped to the International Classification of Functioning, Disability and Health. Factors associated with outcomes at 3–6 months, 9–12 months and beyond 12 months of index infection, for n > 500 individual participant data and > 1 data set were described using ratio of difference, point estimates, odds ratio and 95% confidence interval, as appropriate. The Mixed Methods Appraisal Tool described study quality; models were appraised using a Grading of Recommendations Assessment, Development and Evaluation-informed approach; heterogeneity was described using I^2.

Outcome measures: Included overall perception of health, multidomain cognitive function, anxiety, depression, stress, post-traumatic stress disorder, fatigue, strength, walking ability, mobility, coping with daily life, breathlessness, mortality, later hospitalisation and health-related quality of life.

Results: PRECIOUS collated 116 data sets from 40 countries (individual participant data = 62,849), comprising 20 randomised controlled trials, 13 case-control, 60 cohort 2 longitudinal, 1 survey and 20 other study types. Participants' median age was 58 years interquartile range (45–68); 34,185 (54.4%) were female; 158 unique symptoms and 137 unique assessment instruments were captured, predominantly describing International Classification of Function, Disability and Health-body functions. Women had poorer outcomes across 30/37 models, compared with men. In 15/37 models, pre-existing lung disease and increasing age were associated with poorer outcomes; hospitalisation, diabetes and chronic kidney disease were each associated with poorer outcomes in 8/37 models. Initial hospitalisation resulted in lower health-related quality of life that did not recover for up to 2 years after initial infection. Heterogeneity was low in 34/37 models; 22/37 models were of moderate and 11/37 were of low quality.

Limitations: Use of secondary data limits available covariates, outcomes and time points to those included in primary data sets; evidence was primarily based on high-income countries. There was a lack of data on longer-term healthcare resource use to estimate the costs to the healthcare system.

Conclusions: PRECIOUS contributes to the overall picture of long-term COVID-19 outcomes beyond the long-COVID condition and highlights poorer long-term outcomes in women and people with pre-existing comorbidities.

Future work: Evidence gaps included healthcare resource use, isolation, loneliness, societal participation and return to work outcomes. Data are needed on the role of health inequity on long-term outcomes.

Study registration: This study is registered as PROSPERO (CRD42020224323, IRAS ID: 293578).

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Supplementary material has been provided by the authors to support the article and any files provided at submission will have been seen by peer reviewers, but not extensively reviewed. Any supplementary material provided at a later stage in the process may not have been peer reviewed.

The supplementary materials (which include but are not limited to related publications, patient information leaflets and questionnaires) are provided to support and contextualise the publication. Every effort has been made to obtain the necessary permissions for reproduction, to credit original sources appropriately, and to respect copyright requirements. However, despite our diligence, we acknowledge the possibility of unintentional omissions or errors and we welcome notifications of any concerns regarding copyright or permissions.

Glossary

COVID-19 outcome Describes an impact of COVID-19. In PRECIOUS, this was operationalised, for example using clinical scales (e.g. the Barthel Index) capturing activities of daily living and can include, but is not limited to, end points such as death, hospital discharge, discharge location, return to work and quality of life.

COVID-positive Defined as described in each contributed data set; common definitions were grouped together. Definitions included but were not limited to:

- diagnosis as COVID-positive on a polymerase chain reaction test;
- diagnosis as COVID-positive with a lateral flow test;
- suspected COVID-positive
- multiple methods of diagnosis.

Long-COVID Describes signs and symptoms extending beyond the acute phase of infection [Office for National Statistics. *The Prevalence of Long COVID Symptoms and COVID-19 Complications*. URL: www.ons.gov.uk/news/statementsandletters/theprevalenceoflongcovidsymptomsandcovid19complications (accessed 29 April 2022)] that are not explained by an alternative diagnosis [NICE, SIGN, RCGP. *NICE, SIGN and RCGP Set Out Further Details about the UK Guideline on Management of the Long-Term Effects of COVID-19*. URL: https://www.sign.ac.uk/covid-19-guideline-management-of-the-long-term-effects-of-covid-19/ (accessed 17 June 2026)].

Long-term Defined as a time point ≥ 28 days of initial symptom onset (Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, *et al*. Attributes and predictors of long COVID. *Nat Med* 2021;**27**:626–31) for the purposes of our analyses. Assessment ≥ 28 days was used as it aligns with symptom manifestation and an infectious period of ~2–3 weeks [Maxwell E. *Living with COVID19. A Dynamic Review of the Evidence Around Ongoing COVID19 Symptoms (Often Called Long COVID)*. URL: https://evidence.nihr.ac.uk/wp-content/uploads/2020/10/Living-with-Covid-Themed-Review.pdf (accessed 29 April 2022)], after which, recovery is expected and presence of ongoing problems could be considered 'longer-term'.

List of abbreviations

6-MWT	6-minute walk test
ADL	activities of daily living
AHP	allied health professional
BAI	Beck Anxiety Inventory
BMI	body mass index
CENTRAL	Cochrane Central Register of Controlled Trials
CINAHL	Cumulative Index to Nursing and Allied Health Literature
DASS-21	Depression, Anxiety and Stress Scale-21
DEF	data extraction form
ECMO	extra-corporeal membrane oxygenation
EQ-5D	EuroQol-5 Dimensions
EQ-5D-3L	EuroQol-5 Dimensions, three-level version
EQ-5D-5L	EuroQol-5 Dimensions, five-level version
FAS	Fatigue Assessment Scale
GCU	Glasgow Caledonian University
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HADS-A	Hospital Anxiety and Depression Scale-A
HADS-D	Hospital Anxiety and Depression Scale-D
HRQoL	health-related quality of life
ICD-10	*International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision
ICF	International Classification of Functioning, Disability and Health
ICTRP	International Clinical Trials Registry Platform
ICU	intensive care unit
IESR	Impact of Event Scale – Revised
IMD	Index of Multiple Deprivation
IPD	individual participant data
IPDMA	individual patient data meta-analysis
MMAT	Mixed Methods Appraisal Tool
mMRC	modified Medical Research Council
MoCA	Montreal Cognitive Assessment
NEADL	Nottingham Extended Activities of Daily Living
NICE	National Institute for Health and Care Excellence
NIHR	National Institute of Health
NMAHP	Nursing, Midwifery, and Allied Health Professions
PCCD	Post-COVID cognitive dysfunction
PCR	polymerase chain reaction
PI	principal investigator
PPI	patient and public involvement
PRECIOUS	PREdictors of COVID-19 outcomes
PRESS	Peer Review of Electronic Search Strategies
PROSPERO	International Prospective Register of Systematic Reviews
PSQI	Pittsburg Sleep Quality Index
PTSD	post-traumatic stress disorder
QoL	quality of life
RoB	Cochrane Risk of Bias
SF-36	Rand 36-Item Short Form Health Survey
SPHERE	Somatic and Psychological HEalth REport
VAS	visual analogue scale
WHO	World Health Organization

Plain language summary

As yet, we know little about the long-term effects of COVID-19. With better information, we can provide the right health care and support to the people that need it most.

We aimed to create and analyse a global COVID-19 healthcare database that describes long-term effects of COVID-19.

We searched for studies involving people with COVID-19, including information on their age, health, well-being, work and long-term recovery. We analysed data from this database including on overall perception of health, thinking and memory, anxiety, depression, stress, post-traumatic stress disorder, tiredness, strength, walking ability, mobility, ability to cope with daily life, breathlessness, death, the chances of later hospitalisation and health-related quality of life (a measure of how people viewed their health and quality of life).

Our database included more than 62,000 people from 40 countries. We described 158 unique COVID-19 symptoms and 137 unique measurements of its impacts. Women and vulnerable populations were particularly impacted by COVID-19. In most of our analyses, women had poorer outcomes compared with men. We also saw indications that some outcomes were poorer as a person got older, or if they had existing lung disease, were hospitalised for COVID-19, or had diabetes or chronic kidney problems, when compared to people without these problems. Being hospitalised with COVID-19 resulted in lower health-related quality of life that did not appear to recover for up to 2 years after the initial COVID-19 infection.

Our findings highlighted that women and people with pre-existing health problems were particularly impacted as a consequence of COVID-19 infection compared to men and previously healthy people. We also identified the need for more targeted research on isolation, loneliness and return to work after COVID-19.

Scientific summary

Background

Identifying and addressing the long-term health and societal challenges after COVID-19 is a research priority. Capturing the full range of COVID-19 long-term outcomes is essential to support accurate screening and assessment to establish rehabilitation needs of people facing persistent problems in everyday life, measure change over time, and optimise rehabilitation interventions and service provision.

Objectives

To create an international, multidisciplinary COVID-19 database, and synthesise long-term outcomes, predictors and costs.

Research questions

1. What are the long-term outcomes of people after COVID-19 in relation to the International Classification of Functioning, Disability and Health (ICF) and over time?
2. What are the predictors of long-term COVID-19 outcomes across the ICF?
3. What are the financial costs associated with COVID-19 for individuals, health services and society?

Methods

We conducted systematic identification of COVID-19 data sets and meta-analysis of individual participant data (IPD) on long-term outcomes after COVID-19.

Data sources

We searched MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, Web of Science, PsycInfo® (American Psychological Association, Washington, DC, USA), Cumulative Index to Nursing and Allied Health Literature (CINAHL), World Health Organization (WHO) Global Index Medicus, Epistemonikos, LitCOVID; from November 2019 to November 2021; CENTRAL, MEDLINE, EMBASE, CINAHL, WHO International Clinical Trials Registry Platform; ClinicalTrials.gov and supplementary searches for relevant studies reporting on > 10 people from cohort, case-control, survey or randomised controlled trial (RCT) studies, across any setting, describing validated assessment instruments, symptoms, hospitalisation, discharge destination or mortality beyond 28 days after COVID-19 onset.

Methods

Principal investigators were invited to contribute data. Data were originally collected in clinical, community and research settings in the primary studies. Study descriptors, demography, equity, symptoms and outcomes of interest were extracted by two independent reviewers and cross-checked by data contributors. We described demography, equity, mapped outcome assessment tools to the International Classification of Functioning, Disability and Health (ICF), and described symptom prevalence over time. A one-stage meta-analysis approach described factors associated with available outcomes at 3–6 months, 9–12 months and beyond 12 months, for n > 500 IPD and > 1 data set. Interventions in original studies were included as covariates in long-term outcome models where appropriate. Findings were presented as ratio of difference (RoD), point estimates or odds ratio (OR) and 95% confidence interval (95% CI).

Study quality was described using the Mixed Methods Appraisal Tool; individual models were appraised using a Grading of Recommendations Assessment, Development and Evaluation (GRADE)-informed approach and heterogeneity was described using the I^2 statistic.

Main outcome measures

Outcomes examined included physical functioning and mental health in the context of quality-of-life instruments, overall perception of health, sleep, multidomain cognitive function, anxiety, depression, stress, post-traumatic stress disorder (PTSD), fatigue, strength, walking ability, mobility, coping with daily life, breathlessness, mortality, later hospitalisation and health-related quality of life (HRQoL).

Results

We collated 116 data sets from 40 countries (IPD = 62,849), comprising 20 RCTs, 13 case-control, 60 cohort 2 longitudinal, 1 survey and 20 other study types. Median age of participants was 58 [interquartile range (IQR) (45, 68)], 34,185 (54.4%) were female. We described 158 unique symptoms. Individual studies reported between 1 and 37 symptoms. We categorised 137 unique assessment instruments, predominantly describing ICF-body functions.

After COVID-19 infection: Lower overall perception of health by EuroQoL visual analogue scale (EuroQoL VAS) was associated with increasing age [RoD = 1.006, 95% CI (1.004 to 1.009)], increasing body mass index [BMI, RoD = 0.983, 95% CI (0.978 to 0.988)], female sex [RoD = 1.15, 95% CI (1.07 to 1.24)], initial hospitalisation for COVID-19 [RoD = 0.70, 95% CI (0.60 to 0.82)], presence of existing immunosuppression [RoD = 0.75, 95% CI (0.67, 0.83)], cardiac conditions [RoD = 0.73, 95% CI (0.63 to 0.86)] and lung disease [RoD = 0.89, 95% CI (0.83 to 0.97)] at 3–6 months (*D* = 3, IPD = 1766); initial hospitalisation for COVID-19 [RoD = 0.66, 95% CI (0.58 to 0.75)], female sex [RoD = 1.17, 95% CI (1.10 to 1.25)], unemployment [RoD = 0.78, 95% (0.70 to 0.87)], presence of existing obesity [RoD = 0.79, 95% CI (0.73 to 0.85)], immunosuppression [RoD = 0.74, 95 CI (0.67, 0.83)], diabetes [RoD = 0.79, 95% CI (0.70 to 0.90)], lung disease [RoD = 0.89, 95% CI (0.82 to 0.96)] and chronic kidney disease [RoD = 0.72 (0.57 to 0.90) at 9–12 months (*D* = 4, IPD = 2818); initial hospitalisation for COVID-19 [RoD = 0.61, 95% CI (0.51 to 0.73)], lower education level [RoD = 0.89, 95% CI (0.82 to 0.97)], presence of existing mental/behavioural disorders [RoD = 0.66, 95% CI (0.60 to 0.72)], immunosuppression [RoD = 0.72, 95% CI (0.64 to 0.82)], diabetes [RoD = 0.76, 95% CI (0.68 to 0.86)], lung disease [RoD = 0.88, 95% CI (0.81 to 0.95)] and chronic kidney disease [RoD = 0.75, 95% CI (0.61 to 0.93)], beyond 12 months (*D* = 3, IPD = 1932).

Poorer cognitive function by Montreal Cognitive Assessment was associated with increasing age [RoD = 0.992, 95% CI (0.989 to 0.995)], other ethnicity [RoD = 0.76, 95% CI (0.67 to 0.85)], lower education level (did not complete primary education RoD = 0.54, 95% CI (0.41 to 0.71)] and presence of existing mental/behavioural disorders [RoD = 0.87, 95% CI (0.78 to 0.96)] at 3–6 months (*D* = 2, IPD = 839); and increasing age [RoD = 0.989, 95% CI (0.984 to 0.994)], Black [RoD = 0.53, 95% CI (0.40 to 0.72)], Asian [RoD = 0.80, 95% CI (0.68 to 0.95)] and other ethnicities [RoD = 0.63, 95% CI (0.45 to 0.90)] and lower education level (did not complete primary education RoD = 0.67, 95% CI (0.47 to 0.94)] beyond 12 months (*D* = 2, IPD = 566).

Higher anxiety by Hospital Anxiety and Depression-A scale was associated with female sex [RoD = 0.80, 95% CI (0.74 to 0.87)], younger age [RoD = 0.988, 95% CI (0.985 to 0.991)], presence of existing lung disease [RoD = 1.28, 95% CI (1.17 to 1.40)] and neurological conditions [RoD = 1.32, 95% CI (1.10 to 1.58)] in initially hospitalised populations at 3–6 months (*D* = 5, *N* = 1394); female sex [RoD = 0.78, 95% CI (0.70 to 0.87)] and presence of existing circulatory disorders [RoD = 1.24, 95% CI (1.06 to 1.45)] in initially non-hospitalised populations at 3–6 months (*D* = 2, *N* = 569); initial hospitalisation for COVID-19 [RoD = 1.20, 95% CI (1.08 to 1.33)], female sex [RoD = 0.82, 95% CI (0.78 to 0.87)], presence of existing lung disease [RoD = 1.19, 95% CI (1.07 to 1.33)] and in unemployed smokers [RoD = 1.19, 95% CI (1.04 to 1.36)] at 9–12 months (*D* = 3, IPD = 1679); initial hospitalisation for COVID-19 [RoD = 1.30, 95% CI (1.17 to 1.45)], female sex [RoD = 0.84, 95% CI (0.79 to 0.88)], younger age [RoD = 0.988, 95% CI (0.985 to 0.991)] and those not in employment [RoD = 1.18, 95% CI (1.10 to 1.26)] beyond 12 months (*D* = 4, IPD = 1340).

Higher depression by Hospital Anxiety and Depression-D scale was associated with younger age [RoD = 0.990, 95% CI (0.987 to 0.994)], female sex [RoD = 0.78, 95% CI (0.71 to 0.86)], presence of existing lung disease [RoD = 1.24, 95% CI (1.12 to 1.37)] and mental/behavioural disorders [RoD = 1.61, 95% CI (1.44 to 1.81)] at 3–6 months (*D* = 3, IPD = 1001); younger age [RoD = 0.998, 95% CI (0.996 to 0.999)], female sex [RoD = 0.89, 95% CI (0.86 to 0.93)], people not in employment [RoD = 1.30, 95% CI (1.20 to 1.42)], presence of existing diabetes [RoD = 1.33, 95% CI (1.17 to 1.51)], cancer [RoD = 1.19 [1.07, 1.32)] or smoking [RoD = 1.11, 95% CI (1.06 to 1.18)] at 9–12 months (IPD = 1722, *D* = 4); and initial hospitalisation for COVID-19 [RoD = 1.15, 95% CI (1.06 to 1.24)], female sex [RoD = 0.91, 95% CI (0.88 to 0.95)], obesity [RoD = 1.08, 95% CI (1.02 to 1.13)], smoking [RoD = 1.09, 95% CI (1.02 to 1.17)] and for people not in employment [RoD = 1.07, 95% CI (1.02 to 1.13)], beyond 12 months (*D* = 4, IPD = 1286).

Higher stress by Depression, Anxiety and Stress Scale-21 was associated with smoking [RoD = 1.26, 95% CI (1.12 to 1.42)], presence of diabetes [RoD = 1.42, 95% CI (1.02 to 1.97)], immunosuppression [RoD = 1.55, 95% CI (1.12 to 2.15)] and female sex [RoD = 0.64, 95% CI (0.57 to 0.72)] at 9–12 months (*D* = 2, IPD = 1344); female sex [RoD = 0.66, 95% CI (0.56 to 0.78)], smoking [RoD = 1.34, 95% CI (1.13 to 1.59)] and not being in employment [RoD = 1.50, 95% CI [1.15 to 1.97)] beyond 12 months (*D* = 2, IPD = 698).

Worse PTSD by revised Impact of Event Scale was associated with younger age [RoD = 0.991, 95% CI (0.985 to 0.996)], female sex [RoD = 0.72, 95% CI (0.62 to 0.83)] and presence of existing lung disease [RoD = 1.30, 95% CI (1.10 to 1.53)] at 3–6 months (*D* = 5, IPD = 1036).

Greater fatigue by Fatigue Assessment Scale was associated with younger age [RoD = 0.997, 95% CI (0.995 to 0.998)], female sex [RoD = 0.87, 95% CI (0.83 to 0.90)], presence of existing lung disease [RoD = 1.12, 95% CI (1.08 to 1.17)], neurological conditions [RoD = 1.21, 95% CI (1.10 to 1.33)] and musculoskeletal conditions [RoD = 1.10, 95% CI (1.04 to 1.16)] at 3–6 months (*D*= 3, IPD= 1030); younger age [RoD = 0.998, 95% CI (0.997 to 0.999)], female sex [RoD = 0.90, 95% CI (0.88 to 0.93)], presence of existing immunosuppression [RoD = 1.15, 95% CI (1.06 to 1.24)] and lung disease [RoD = 1.08, 95% CI (1.03 to 1.13)] at 9–12 months (*D* = 5, IPD = 1594); and female sex [RoD = 0.90, 95% CI (0.85 to 0.94)] and presence of existing mental/behavioural disorders [RoD = 1.26, 95% CI (1.18 to 1.34)] beyond 12 months (*D* = 2, IPD = 722).

Poorer ability to cope with daily life by Nottingham Extended Activities of Daily Living Scale was associated with female sex [RoD = 1.30, 95% CI (1.18 to 1.43)], presence of existing lung disease [RoD = 0.72, 95% CI (0.65 to 0.80)], chronic kidney disease [RoD = 0.82, 95% CI (0.67 to 0.995)], increasing age [RoD = 0.995, 95% CI (0.992 to 0.999)] and certain lower education strata (completed high school RoD = 0.82, 95% CI (0.74 to 0.89)] at 3–6 months (*D* = 2, IPD = 1086); and increasing age [RoD = 0.990, 95% CI (0.984 to 0.996)], female sex [RoD = 1.24, 95% CI (1.07 to 1.45)] and certain lower education strata (did not complete primary education RoD = 0.53, 95% CI (0.33 to 0.84)] beyond 12 months (*D* = 2, IPD = 574).

Poorer walking ability by 6-minute walk test was associated with increasing age [estimate of difference = −1.54, 95% CI (−2.18 to −0.91)], female sex [estimate of difference = 46.25, 95% CI (27.80 to 64.71)], increasing BMI [estimate of difference = −4.22, 95% CI (−5.81 to −2.62)], presence of existing cardiac conditions [estimate of difference = −77.46, 95% CI (−113.39 to −41.53)], lung disease [estimate of difference = −31.71, 95% CI (−53.73 to −9.70)] and female sex without cardiac conditions [estimate of difference = 56.73, 95% CI (14.05 to 99.42)] at 3–6 months (*D* = 6, IPD = 567).

Poorer mobility by Short Physical Performance Battery was associated with increasing age [RoD = 0.989, 95% CI (0.986 to 0.992)], female sex [RoD = 1.35, 95% CI (1.25 to 1.47)], presence of existing lung disease [RoD = 0.78, 95% CI (0.72 to 0.85)], chronic kidney disease [RoD = 0.72, 95% CI (0.59 to 0.88)], neurological conditions [RoD = 0.67, 95% CI (0.54 to 0.83)], musculoskeletal conditions [RoD = 0.79, 95% CI (0.71 to 0.89)] and diabetes at 3–6 months (*D* = 2, IPD = 1080).

Worse breathlessness was associated with increasing COVID-19 severity (ventilated population RoD = 1.29, 95% CI (1.08 to 1.54)], presence of existing lung disease [RoD = 1.11, 95% CI (1.02 to 1.20)], immunosuppression [RoD = 1.33, 95% CI (1.15 to 1.54)], obesity [RoD = 1.19, 95% CI (1.10 to 1.29)] and female sex [RoD = 0.91 [0.87, 0.96)] at 3–6

months (*D* = 3, IPD = 744); increasing age [RoD = 1.002, 95% CI (1.001 to 1.003)], increasing age in the presence of existing lung disease [RoD = 1.005, 95% CI (1.002 to 1.008)], presence of obesity [RoD = 1.18, 95% CI (1.12 to 1.25)], existing circulatory disorders [RoD = 1.11, 95% CI (1.06 to 1.16)], immunosuppression [RoD = 1.21, 95% CI (1.11 to 1.32)], female sex [RoD = 0.91, 95% CI (0.88 to 0.94)] and initial hospitalisation for COVID-19 [RoD = 1.18, 95% CI (1.11 to 1.25)] at 9–12 months (*D* = 3, IPD = 1277); increasing age [RoD = 1.003, 95% CI (1.002 to 1.005)], initial hospitalisation for COVID-19 [RoD = 1.24, 95% CI (1.14 to 1.36)], presence of obesity [RoD = 1.21, 95% CI (1.11 to 1.31)] circulatory disorders [RoD = 1.10, 95% CI (1.03 to 1.18)] and female sex [RoD = 0.88, 95% CI (0.84 to 0.92)], beyond 12 months (*D* = 3, IPD = 655).

Mortality was associated with increasing age [RoD = 1.068, 95% CI (1.052 to 1.074)], male sex [RoD = 1.31, 95% CI (1.15 to 1.50)], existing cancer [RoD = 1.23, 95% CI (1.04 to 1.46)], chronic kidney disease [RoD = 1.49, 95% CI (1.19 to 1.72)], dementia/Alzheimer's [RoD = 1.56, 95% CI (1.31 to 1.86)] and lung disease [RoD = 1.25, 95% CI (1.07 to 1.46)] in hospitalised non-ventilated populations (*D* = 5, IPD = 5027); and increasing age [RoD = 1.036, 95% CI (1.028 to 1.044)], male sex [RoD = 1.27, 95% CI (1.05 to 1.54)], existing diabetes [RoD = 1.56, 95% CI (1.30 to 1.87)], chronic kidney disease [RoD = 1.47, 95% CI (1.08 to 2.00)] and liver disease [RoD = 2.10, 95% CI (1.37 to 3.22)] in hospitalised and ventilated populations (*D* = 9, IPD = 969).

Later hospitalisation after infection was associated with increasing age [OR = 1.02, 95% CI (1.01 to 1.02)], existing cerebrovascular disease [OR = 1.68, 95% CI (1.12 to 2.53)], diabetes [OR = 1.56, 95% CI (1.23 to 1.98)], chronic kidney disease [OR = 1.67, 95% CI (1.23 to 2.26)], cancer [OR = 2.64, 95% CI (2.02 to 3.44)] and current smoking status [OR = 0.76, 95% CI (0.61 to 0.94)] (*D* = 2, IPD = 1336). We observed no significant impact of COVID-positivity on later hospitalisation, compared with COVID-negative participants. We were therefore unable to calculate the additional costs of COVID-19 rehospitalisation.

Worse HRQoL by EuroQoL-derived health utilities was associated with exposure to COVID-19 [estimate = −0.03, 95% CI (−0.06 to −0.01)] female sex [estimate = −0.054, 95% CI (−0.07 to −0.04)] initial hospitalisation for COVID-19 [estimate = −0.07, 95%CI [−0.1 to −0.04)], presence of diabetes [estimate = −0.06, 95% CI (−0.09 to −0.04)], obesity [estimate = −0.05, 95% CI (−0.06 to −0.04)], existing lung disease [estimate = −0.05, 95% CI (−0.07 to −0.04)], chronic kidney disease [estimate = −0.05, 95% CI (−0.09 to −0.01)]; better HRQoL was seen in non-smokers [estimate = 0.02, 95% CI (0.01 to 0.04)], people with a higher education status [0.02, 95% CI (0.01 to 0.04)] and those in employment [estimate = 0.04, 95% CI (0.03 to 0.05)]. Initial hospitalisation with COVID-19 consistently resulted in lower HRQoL that did not appear to recover for up to 2 years after the initial COVID-19 infection.

Heterogeneity was low for 34/37 models; using a GRADE-informed assessment of models, 22/37 were of moderate and 11/37 were of low quality.

Limitations

Data were primarily collated from high-income countries; we lacked adequate data on ethnicity and measures of health inequity, which would have enhanced our analyses. No data on healthcare resource use, apart from later hospitalisation, were available; therefore, we were unable to calculate additional costs to the healthcare system for those with COVID-positivity. Use of secondary data for IPD meta-analyses limited available covariates for adjusted analyses to those included in primary data sets. The final models reflected variable significance within the context of data availability and were limited to long-term outcomes of interest to the primary research.

Conclusions

PRECIOUS contribute to the overall picture of long-term COVID-19 outcomes beyond the long-COVID condition and highlights the disproportionate impact of poorer long-term outcomes in female sex, and those with pre-existing comorbidities.

Future work

Gaps in evidence included isolation, loneliness, societal participation and return to work outcomes. Future work should examine the role of health inequity on long-term outcomes.

Study registration

This study is registered as PROSPERO (CRD42020224323, IRAS project ID: 293578).

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Chapter 1 Introduction

The impact of COVID-19

COVID-19 is a multisystem disease caused by the severe acute respiratory syndrome coronavirus 2 virus (SARS-CoV-2). Globally, COVID-19 has now affected more than 779 million people,[1] with more than 6.9 million deaths recorded, costing the global economy more than US$12.5 trillion.[2] As of 9 May 2024, there have been 24.9 million cases in the UK alone and more than 232,000 deaths.[1] Globally, the highest mortality rates have been reported in the USA, Brazil and India.[1]

As a novel virus, initial efforts focused on characterising COVID-19 infection, distinguishing symptoms, methods of transmission, risk of infection and quantifying its impact, for example, on hospitalisation and mortality. The effectiveness of treatments were investigated,[3–7] and vaccinations were developed to mitigate transmission,[8–10] decrease the severity of infection, reduce hospitalisation and death. Within 7 months of the start of the pandemic, the first vaccination was developed and administered, with use outside a clinical trial context commencing in December 2020.[11] Two years after the start of the pandemic, it was estimated that almost 56% of the global population had received at least one dose of a COVID-19 vaccine,[12] and more than 13.59 billion doses have been delivered.[1] Despite heterogeneous access to vaccinations, supply issues, and differing transmission profiles,[11] the administration of COVID-19 vaccinations has decreased mortality,[13] while a reduced rate of transmission (and viral load) was supported by public health initiatives such as mask-wearing and physical distancing.[14] With the immediate priority of reducing transmission and mortality being addressed, research efforts now focus more on the novel impacts of COVID-19 and the interventions required to address them.

Persistent consequences of COVID-19

Several early research studies highlighted the persistence of symptoms following COVID-19.[15–20] Typically, the symptoms of COVID-19 last for a mean of 11 days.[21] Long-COVID, post-COVID condition or post-COVID syndrome refers to symptom persistence after initial infection and virus clearance that remains ongoing, commonly after 12 weeks, which cannot be attributed to alternative diagnoses.[22] The reported length of persistent symptoms frequently differs across studies – from 4 weeks to 3 months – but here we use the term long-COVID in reference to ongoing symptoms beyond the 12-week period. Long-COVID likely affects up to 10% of people with COVID-19,[23] with additional literature suggesting that 31–69% may experience symptoms for varying lengths of time.[24–26] An estimated 2 million people in the UK now live with long-COVID.[27] This multisystem condition is not limited to severe infection,[23] although persistence is associated with severity,[28] female sex, socioeconomic status,[29,30] age < 50 years,[31] higher body mass index (BMI), and history of smoking[32] and substance abuse.[33]

The presentation of long-COVID is heterogeneous, with common symptoms including fatigue, shortness of breath, arthralgia, cough and chest pain.[34] It is also thought to involve elements of post-intensive care syndrome, post-viral fatigue syndrome and permanent organ damage.[35] Reports from Germany indicate that up to 36% of people with COVID-19 may have persistent problems for more than 2 months after onset,[36] while the Office for National Statistics in the UK estimates that 1-in-5 and 1-in-10 will have persistent symptoms for 5 and 12 weeks or longer, respectively.[37] At 4 months post onset, data collected on symptoms reported in the UK included fatigue (98%), muscle aches (88%), breathlessness (87%), headaches (83%), cardiorespiratory (92%) and gastrointestinal (73%) problems; 70% described impairment in one or more organs.[38]

Literature has suggested that around 14% of the COVID-19 population develops new symptoms requiring medical attention: 1.65% higher than other viral conditions affecting the lungs.[15,16] New symptoms are more common in people who are hospitalised with COVID-19 than in community-based cohorts.[15,16,39] A study of non-critical COVID-19 patients also reported symptom persistence in 66% of people at 2 months, with 33% reporting feeling worse than at the onset of COVID-19.[40] Data also suggest that the proportion of people developing long-COVID is smaller in those who have received a vaccination before contracting COVID-19.[32,41] However, existing evidence is mainly from hospitalised populations in single countries[38,42,43] reflecting the most severe COVID-19 cases. Community-based COVID-19

populations or those with milder symptoms are typically under-represented in such data.[44] The persistence of symptoms remains only one facet of the range of COVID-19 impact. A better understanding of the evidence base for long-term impact beyond novel symptoms and symptom profiles needs to be developed to meet the continued diagnostic, intervention, and service challenges posed by the pandemic.

Recurrent waves and continuing impact

COVID-19 overwhelmed health systems worldwide;[45] despite the end of the pandemic being declared in May 2023,[46] significant disruptions to healthcare systems remain. The effects include exacerbation of existing health inequalities, impacts on hospital waiting times, sick leave that reduces healthcare capacity, re-prioritised resources and delays in seeking care, impacts on mental health and employment,[47] health behaviours[48] and disrupted livelihoods and education.[49] Infections are still prevalent, with more than 500,000 cases reported in the first month of 2024.[1] Reinfection with COVID-19 also carries an increased risk of mortality in older people,[50] and hospitalisation in those aged over 60 years.[51] New waves of infection have resulted from mutations of the original Alpha (Wuhan) strain[52] into variants of concern, and these variants have increased the risk of severe infection, ongoing health impacts, and even death compared with non-variants of concern.[53–57] Thus, continued research into the long-term impacts of COVID-19 is still required to address the continuing risks to health and well-being and associated service challenges.

Impact beyond symptoms

As research and understanding of long-COVID have improved, healthcare services continue to face increased burden due to additional morbidity and the emergence of long-term impacts of COVID-19.[58] This potentially includes service reorganisation, with impacts on follow-up, the development of specialist clinics and multidisciplinary rehabilitation teams.[58] Long-term data that extend beyond persistent symptoms are required to describe their impact on everyday life. Identifying and addressing the long-term health and societal challenges and costs of COVID-19 are research priorities.[59,60] These wider, long-term impacts include but extend beyond long-COVID as a condition, affecting domains such as activities of daily living (ADL), participation and return to work. Capturing the full range of COVID-19 long-term outcomes is essential to support accurate screening and assessment to establish the rehabilitation needs of people facing persistent problems in everyday life, measure change over time, and optimise rehabilitation interventions and service provision.

In the initial stages of the COVID-19 pandemic, many research studies used mortality as a primary outcome measure.[61,62] As the focus shifted beyond the emergency COVID-19 public health response, optimising the rehabilitation efforts delivered mainly by the allied health professional (AHP), nursing, primary care and social care services in hospital and community settings became critical. The resulting demand for health and social care services may be long-standing or permanent.[35] Redeployment of existing services and tailored management of the emerging complex, multidomain consequences of COVID-19 are required to avoid or limit significant impact for individuals and society[35] and should be informed by a robust evidence base. However, significant gaps exist in the evidence underpinning long-term COVID-19 rehabilitation efforts, identification of those that have the greatest rehabilitation needs and what those needs are. The volume of people affected by COVID-19 and the prevalence of long-term consequences pose an urgent need for health policy-makers, society and healthcare services to understand and develop interventions that address the needs of this population.[63]

Comprehensive mapping of the full range and longevity of long-term COVID-19 outcomes across the International Classification of Functioning, Disability, and Health (ICF)[64] is urgently needed to describe impact on ADL, participation in society, return to work, quality of life (QoL), overall health and emotional well-being, and relationships. The relevance of demographics (e.g. ethnicity, sex, age, socioeconomic status and comorbidities)[65] and COVID-19 history (e.g. severity, hospitalisation, ventilation) on long-term outcomes remain unclear. It is vital to establish the factors related to poorer long-term outcomes, thereby enabling the rehabilitation response to be tailored, ensuring that services and resources are focused on individuals with the greatest need and experiencing the greatest impacts, and when the greatest gains might be made. The representativeness and generalisability of the COVID-19 populations recruited to current studies need to be established, along with outcomes from typically under-represented populations, such as those who were never hospitalised. The National Institute for Health and Care Excellence (NICE) and the Scottish Intercollegiate Guidelines Network recommend the investigation of the natural history, trajectory and predictors of long-COVID, and

development of personalised rehabilitation and management plans.[66] Examining the full scope of potential rehabilitation needs, establishing the most prevalent needs, evidence gaps, and factors associated with poor long-term outcomes would inform future research priorities and service planning.

The use of data in response to the pandemic

COVID-19 required rapid decision-making at the clinical, health, research and policy levels.[67] However, this was impeded by a lack of available, co-ordinated and relevant data.[67,68] In response, a wealth of data have been collected from electronic health records, registries and research data sets. Clinical data sets have complemented those from clinical trials,[69] providing valuable information from populations that were typically excluded from clinical trials due to multimorbidity, incapacity, or disease severity. Data from every stage of the pandemic are needed to aid in planning and inform future pandemic preparedness.[67] Aggregation across a range of study designs permits the collation of greater data quantity and supports comparisons across international settings, health systems and population groups.[69]

Individual participant data meta-analysis approaches

One approach to harness the potential of existing COVID-19 data is the use of an individual participant data meta-analysis (IPDMA). Examination of IPD within common domains of assessment permits exploration of larger sample sizes, supporting identification of long-term impacts on independence, physical and psychological outcomes and QoL following COVID-19. IPD meta-analysis supports the description of factors related to long-term outcomes, and recovery potentials. An IPD meta-analysis approach offers an important opportunity to address questions relevant to the health and social care of those affected by COVID-19, including evidence gaps relating to COVID-19 associated impairment, activity and participation limitations across the ICF, examination of long-term outcomes and inclusion of data from hospitalised and community cases of COVID-19. Collation and meta-analysis of international IPD permit individual adjustment of covariates, greater statistical power, improved participant representation, examination of patterns of impaired function and participant subgroups, and reduction of ecological bias in a time- and cost-efficient manner.

Research on long-term outcomes

Maxwell *et al.*[70] reported an overview of IPD meta-analyses related to COVID-19. Of the 31 meta-analyses identified, over half (n = 16) focused on interventions for COVID-19. The remaining IPDMA examined windows for detection in one study,[71] three focused on the presentation of COVID-19,[6,72–89] four explored population-specific outcomes,[75–78] long-COVID in one study,[79] multiple outcomes in three studies[80–82] and mortality in one study.[83] Many of these IPDMA are still ongoing. Of the IPD meta-analyses that are reported in Maxwell *et al.*, only PRECIOUS is focused on long-term outcome.

Several individual studies have also examined long-term health outcomes, reporting that symptoms were generally resolved within 1 year of diagnosis,[84] while another study in the long-COVID population reported mild to moderate symptoms at 3 years after hospital discharge, with reinfections contributing to increased symptom prevalence.[85] In a study of 1276 previously hospitalised participants, physical and functional recovery at 1 year was reported in most participants, along with a return to usual work and life activities.[86] Another study reported persistent symptoms, poor QoL, exercise ability, and low return to work rates despite good physical recovery 1 year after discharge.[87] Participants who required mechanical ventilation reported poorer QoL at 3 months after discharge, but improvement by 1 year in one study, and another reported on the factors associated with incomplete recovery, including female sex, obesity and requirement for mechanical ventilation in a hospitalised cohort.[88] Problems with swallowing (dysphagia) and communication have also been reported in previously hospitalised populations between 10 months and 14 months after discharge.[89] The UK Coronavirus Clinical Characterisation Consortium (ISARIC-4C) examined the mechanisms of

COVID-19 spread, diagnosis and screening, immune response, duration of contagiousness, risk of severe illness and pharmacological treatments. Prediction modelling described mortality risk[90] and recovery after critical illness.[91] The ISARIC-4C follow-up study aims to follow up previously hospitalised participants as long as a need exists and resources are available, with scheduled follow-up post-hospital discharge at 1–3 months, > 3–6 months, > 6–9 months and > 9–12 months and beyond, if applicable.[92]

Thus, long-term follow-up data exist but from disparate populations. These data could be combined to permit IPDMA, enabling detailed modelling benefiting from a more diverse, international, participant sample and permitting examination of the wider health, disability and functioning impacts beyond routinely collected health data.

Research priorities for people with COVID-19 and carers

The World Health Organization (WHO) has identified the need for research into the long-term effects of COVID-19, how these problems affect patients, the clinical course and the likelihood of full recovery.[93] Unanswered research questions including the trajectory of people recovering from COVID-19, the proportion of people who will experience problems, the length of time that problems can be expected, and those who will need intensive reconditioning. The predictors of long-term problems were identified based on clinical impressions.[59]

The Cochrane Rehabilitation and WHO Rehabilitation Program published priority research questions for COVID-19 rehabilitation research based on multidisciplinary consensus, highlighting the need to explore impairments, activity limitations and participation restrictions following COVID-19 at the individual, service, and system levels.[60] Specific priority questions include an examination of the natural history of functional limitations and the factors associated with these limitations.[60]

Furthermore, the post-hospital COVID-19 study employed a James Lind Alliance approach to identify research priorities related to long-COVID, highlighting the need for information on the long-term trajectory of the illness and the impact on function, activity and exercise.[94] The lived experience of COVID-19, including input from our own patient and public involvement (PPI) group, highlighted several areas for further investigation, including documenting the varied symptoms; dealing with uncertain prognosis and difficulty identifying, accessing and navigating appropriate services.[44] Long-term outcomes, trajectory and factors related to prognosis have been highlighted as priority areas by people with COVID-19, multidisciplinary researchers and health organisations.

PRECIOUS sought to bring together the wealth of disparate IPD gathered in primary studies and clinical registries to create a clearer picture of the COVID-19 impact, outcomes and costs to inform rehabilitation efforts. PRECIOUS complements existing work by expanding our understanding of long-term COVID-19 outcomes beyond the symptoms and time points at which they occur, by also examining the impact at individual and population levels, through characterisation according to the ICF, and describing societal and personal costs experienced by the COVID-19 population in an international context.

Aim

To create an international, multidisciplinary COVID-19 IPD database, and synthesise long-term outcomes, predictors and costs.

Objectives

- To describe long-term COVID-19 outcomes and factors associated with long-term outcomes (≥ 28 days after index infection), across ICF domains and time.

- To describe the costs of COVID-19.
- To disseminate findings through peer-reviewed papers, a website, conference presentations, social media and project partners.

Research questions

1. What are the long-term outcomes of people after COVID-19 in relation to the ICF and over time?
2. What are the predictors of long-term COVID-19 outcomes across the ICF?
3. What are the financial costs associated with COVID-19 for individuals, health services and society?

Chapter 2 Methods

Overview

This chapter provides an overview of the IPDMA methods used to address the PRECIOUS research questions, including selection and involvement of the PPI group, identification, invitation, and contribution of eligible data sets, data management, data preparation, cleaning and quality checks, data transformation and analyses.

Registrations and approvals

The PRECIOUS IPD protocol was registered with PROSPERO (CRD42020224323). Establishment of the PRECIOUS database was registered with the Integrated Research Application System (IRAS project ID 293578). The Glasgow Caledonian University Ethics Committee granted approval for the PRECIOUS study (HLS/NCH/20/04, October 2021). Inclusion in PRECIOUS required that primary research data sets adhered to the national or regional ethical agreements at the time of data collection.

Design

Systematic identification of COVID-19 data sets and meta-analysis of IPD on long-term outcomes after COVID-19.

Patient and public involvement

Aim of patient and public involvement in PRECIOUS

The aim of PPI in PRECIOUS was to conduct research which is of direct relevance to people with COVID-19 and their carers.

Patient and public involvement methods

Recruitment

Patient and public involvement partners were sought via an advertisement on www.peopleinresearch.org. Parties submitted their interests to the website. PPI for PRECIOUS was led by a co-applicant with lived experience of COVID-19 and caring for a person with COVID-19.

Eligibility

Patient and public involvement partners were asked to confirm eligibility, complete a consent form (see *Report Supplementary Material 1*) and return the form to the PRECIOUS group. Eligible PPI partners included those who had COVID-19 or were closely involved in the care of those with COVID-19 infection, who experienced, or cared for someone who experienced persistent problems due to COVID-19.

Meetings

Five online PPI meetings took place using Zoom (Zoom Video Communications, San Jose, CA, USA; September 2021, June 2022, October 2022, October 2023 and January 2024) to ensure that PPI partners could contribute to each stage of data gathering, analysis and interpretation. Prior to each PPI meeting, PPI partners were sent documents for review and comment and invited to take an active role in disseminating the findings via social media. Partners were remunerated based on guidance from the Department of Health in 2009.

Group composition

The PRECIOUS PPI group included eight partners who met the eligibility criteria.

Patient and public involvement tasks

Our PPI group reviewed the proposed activities and documents and advised on selecting and refining the PRECIOUS research questions. PPI involvement included the following:

- refining data set selection criteria
- refining outcomes for assessment, drawing on their experiences with persistent COVID impacts
- informing content, delivery, and accessibility of project communication and emerging findings on the project website
- identifying the health professions, time points, methods and settings most relevant for effective dissemination
- informing dissemination strategy, messaging and accessibility of all outputs.

Evaluation and reflections

Patient and public involvement partners were sent brief forms adapted from an existing framework to evaluate PPI,[95] evaluate how PPI recommendations were implemented throughout the project, and highlight areas for improvement. This was administered from 11 months into the project to allow course correction, where necessary.

Target population

PRECIOUS sought data from studies that included people with COVID-19 who met the criteria set out in *Table 1*.

Search strategy and information sources

COVID-19 resulted in an unprecedented number of publications. In order to capture the most relevant evidence in a systematic and efficient manner, we conducted our searches using a hierarchical stepped approach.

- Step 1: involved the searches for all relevant systematic reviews and meta-analyses which include studies which met our eligibility criteria. In step 1 we searched nine electronic databases for relevant reviews [MEDLINE, Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, Web of Science, PsycInfo® (American Psychological Association, Washington, DC, USA), Cumulative Index to Nursing and Allied Health Literature (CINAHL), WHO Global Index Medicus, Epistemonikos, LitCOVID; from November 2019 to July 2021; date of last search: 15 July 2021]. We used these high-level studies to rapidly identify any relevant study included within these publications that met the eligibility criteria, so that invitations could be sent to potential collaborators as quickly as possible. Searches for step 1 were run on 15 July 2021.

TABLE 1 Eligibility criteria

Inclusion
• Cohort studies, case-control studies, surveys and randomised controlled trials with more than one time point for assessment
• Any setting
• Minimum IPD of 10 people
• Adults with COVID-19 reflecting a range of severities, symptoms and durations with outcomes assessed at ≥ 28 days post onset
• Outcomes assessments including (but not limited to) presence of:
o A formal tool capturing an ICF domain
o Reporting of presence of a post-COVID complication (e.g. fatigue) ≥ 28 days of initial symptom onset
o Morbidity or continued hospitalisation beyond ≥ 28 days of initial symptom presentation
o Residence in, or discharge to, a long-term care/rehabilitation facility ≥ 28 days of initial symptom presentation, or discharge to another location
Exclusion
• Studies with no available IPD
• Single case studies
• Studies of COVID-19 in children
• Studies focused only on the impact on caregivers
• Healthcare process evaluations
• Qualitative data

- Step 2: involved supplementary and targeted searches conducted between 19 August 2021 and 15 November 2021 for relevant studies that met the eligibility criteria. This included: targeted searches of selected electronic databases (CENTRAL, MEDLINE, EMBASE, and CINAHL); clinical trial registers [WHO International Clinical Trials Registry Platform (ICTRP); ClinicalTrials.gov], backward, and forward citation tracking; preprints on MedRxiv, open data repositories and funding agencies. No language restrictions were applied.

The systematic search was developed by an information specialist (JC) and peer reviewed in accordance with Peer Review of Electronic Search Strategies (PRESS) guidelines.[96] The search was adapted for each of the electronic databases. Further details of the search strategies are available in *Appendix 1*.

Selection process

Records identified were deduplicated in EndNote (Clarivate Analytics (formerly Thomson Reuters), Philadelphia, PA, USA), and imported into Covidence (see *Appendix 1*) and two researchers independently screened record titles and abstracts against the selection criteria (see *Table 1*). Full texts were obtained for all studies that met the inclusion criteria and reviewed independently by two researchers. Where there was a lack of consensus that could not be resolved through discussion, a third researcher (MA) screened the records or the full text and made the final decision.

Studies that were not able to be electronically downloaded, for example, pre-print studies on MedRxiv were screened by one researcher (PC, SR) and the data and weblinks were documented in Microsoft Excel® (Microsoft Corporation, Redmond, WA, USA).

Data collection processes

Individual participant data from primary research studies was sought. Principal investigators (PIs) of eligible studies were sent an invitation e-mail, PRECIOUS study information sheet (see *Report Supplementary Material 2*), were asked to confirm data set eligibility, and invited to contribute anonymised IPD data sets. They were contacted a maximum of three times. Where they expressed an interest, they were asked to confirm ethical approvals to share data, complete a Data Contribution Form, sign a Data-Sharing Agreement, and contribute fully anonymised IPD using a secure file transfer protocol (https://transfer.gla.ac.uk/security). Communication with the primary research data set PIs was managed using an Excel database, in which contacts made, decisions on eligibility, and inclusion, and a file transfer checklist were recorded. Contributing PIs formed the PRECIOUS wider Collaborative Group.

Data items

Data were extracted into a pre-piloted data extraction form (DEF) using all available published and unpublished material and information relating to the research, ascertained through close collaboration with the contributing PIs. This DEF provided an overview of the availability and location of variables relevant to planned analyses.

The following data fields were extracted by one reviewer (PC, SR) and checked by a second reviewer:

- data set demographics: author, year, geographical region, income group
- study aim and design: as reported by authors
- participant demography: medical condition, comorbidities and equity factors
- assessments tools: as reported by authors
- intervention details: profiled using the Template for Intervention Description and Replication checklist and guide (www.equator-network.org/reporting-guidelines/tidier/)
- reported outcomes (as stated by authors)
- health economics data.

Data cleaning

Data cleaning was performed using SAS v9.4 (SAS Institute Inc., Cary, NC, USA), Excel, and SPSS v29 (IBM Corporation, Armonk, NY, USA). Data were formatted to match prespecified variable names and codes. Data cleaning was cross-checked within the project group to discuss, review and harmonise coding decisions. All extracted data were

summarised at the data set level and sent to each contributing PI to cross-check. Data sets from the public domain were cross-checked by a team member who was not involved in cleaning the data set.

Items for extraction

Data were extracted on demography, active interventions administered to treat COVID-19, resource use within hospital [including use of ventilation, length of stay, intensive care unit (ICU) requirement and corresponding length of stay], and out-with hospital (e.g. use of aids or long-term medication use). Data on mortality (time to death) and outcome measurement instruments and outcomes (such as return to work) were extracted at each available follow-up period. We sought data at the IPD level; for data that were only available at summary level, and where this could not be attributed to any specific individuals, variables were marked as 'not reported' at the IPD level.

Standardised conventions for data description

Where possible, we used standard conventions to code the data.

This included:

- Medical history/concomitant conditions: we used the *International Statistical Classification of Diseases and Related Health Problems*, Tenth Revision (ICD-10) to describe (see *Report Supplementary Material 5*) at baseline.
- Health equity data: profiled using PROGnosis RESearch Strategy partnership Plus.[97]
- Study design: categorised according to recommendations from the Cochrane Effective Practice and Organisation of Care group.[98]
- Countries and income categories: described according to the World Bank list of economies (www.isca.org/files/World_Bank_List_of_Economies_(July_2025_-_July_2026).pdf).
- COVID positivity was described as follow:
  - COVID-positive at study inclusion
  - COVID-negative at study inclusion
  - COVID-negative at study inclusion but with documentation of prior COVID.

Where data on BMI were available in continuous form, these were also converted into a categorical format according to the WHO classification.[99]

The time from onset to study inclusion was standardised across studies to reflect the time since COVID-19 onset [defined as positive polymerase chain reaction (PCR) test/symptom onset, where available]. Follow-up times were standardised across data sets relative to COVID-19 onset before the analyses. The intervention data were categorised into common groups (*Box 1*).

BOX 1 Categorisation of interventions

- Corticosteroids group='Combined group of corticosteroids, cortisone, dexamethasone, methyl prednisolone, glucocorticoids, prednisone'
- Anticoagulants group='Combined group of anticoagulants, enoxaparine, heparin, LMWH'
- Renal therapy group='Combined group of dialysis, CVVH, haemodialysis, haemodiafiltration, renal replacement therapy'
- Antibiotics group='Combined group of antibiotics, Azithromycin, Amoxicillin, Ampicillin, Cefoperazone, Cefotaxime, Ceftaroline, Ceftriaxone, Clarithromycin, Doxycycline, Clofazimine, Ivermectin and doxycycline'
- Antiviral group='Combined group of antiviral, combination therapy Favipiravir (10 days) + Hydroxychloroquine (5 days), Favipravir, Tenofovir, Emtricitabine/Tinofovir, Ganciclovir, Lopinavir/Ritonavir, Oseltamivir, Remdesivir, Ribavirin, Umifenavir, Darunavir, Ritonavir, Aciclovir'
- Antiplatelets group='Combined group of antiplatelets, aspirin, clopidogrel, platelet antiaggregant'
- Immunosuppressant group='Combined group of cyclosporine, IL-6 Inhibitors, interferon, immunosuppressants, immunosuppressive therapy, interferons, peginterferon lambda 1a, TNF antagonist therapy, anticytokine therapy, infliximab, tocilizumab'
- Blood products group='Combined group of convalescent plasma, immunoglobulin, PCV transfusion, therapeutic plasma exchange'
- Antihypertensive group='Combined group of antihypertensives, ace inhibitor, alpha blocker, beta blocker, ARB, calcium channel blockers',
- Opioid/benzodiazepine group='Combination of opiates, opioid, opioids and/or benzodiazepines'
- Ivermectin='Ivermectin, including Ivermectin with doxycycline'

Variables with a range

Where age and time since COVID-19 onset were provided as categorical variables that included a range, the mean was taken.

Method of COVID-19 diagnosis

After discussion and consensus, the following COVID-19 diagnosis descriptions were adopted:

- PCR (includes nucleic acid, antigen/lateral flow and swab tests).
- Antibody testing.
- Clinical diagnosis – includes COVID probability/suspected COVID.
- Diagnostic method not reported – includes not reported, other, multiple methods (if indeed the multiple methods of diagnosis are not described).
- PCR or serology reported together.

COVID-19 severity

COVID-19 severity was defined as follows:

- non-hospitalised
- hospitalised
- hospitalised and ventilated.

The hospitalised and ventilated category included patients who received mechanical ventilation, extra-corporeal membrane oxygenation (ECMO), unspecified ventilation, tracheotomy, intubation, or the use of high-flow oxygen devices. Low-flow oxygen or high-flow/non-invasive ventilation were classed as 'hospitalised'.

Outcome selection

The long-term outcomes of interest were prespecified. These included formal, validated assessment instruments, reporting of the presence of a post-COVID symptom, morbidity or continued hospitalisation beyond ≥ 28 days of initial symptom presentation, residence in or discharge to a long-term care/rehabilitation facility, discharge to another location, death and details of resource use. Biomarkers and radiological-related outcomes were excluded.

Mortality data were supplied as status (alive/dead) and/or time to death. As it was not possible to utilise these data in survival analyses, the latest date when data were recorded was considered as the last known time to be alive. When no additional data were available, these partial data were excluded from the analysis of mortality.

Categorisation of outcomes by International Classification of Functioning, Disability and Health domains

We mapped available outcome measurement instruments to the ICF. Mortality, hospitalisation, length of hospital stay and time variables (time to recovery, time in hospital, time to discharge) were not included in the ICF mapping. Single-domain and composite outcome measurement (i.e. those that covered multiple domains of assessment) instruments were identified, symptoms were described verbatim, and outcome measurement instruments were linked to the appropriate ICF domain (https://icd.who.int/dev11/l-icf/en; *Figure 1*).

Three team members (PC, SR, MA) met regularly to reach consensus on mapping the outcome tools to the ICF constructs using the linking rules published in Patel (2022).[100] Where possible, we mapped to level three of the ICF to ensure that sufficient detail was provided.

International Classification of Functioning, Disability and Health domains were:

Body functions: mental functions, sensory functions and pain, voice and speech functions, functions of the cardiovascular, haematological, immunological and respiratory systems, functions of the digestive, metabolic and endocrine systems, genitourinary and reproductive functions, neuromusculoskeletal and movement-related functions, functions of the skin, and related structures.

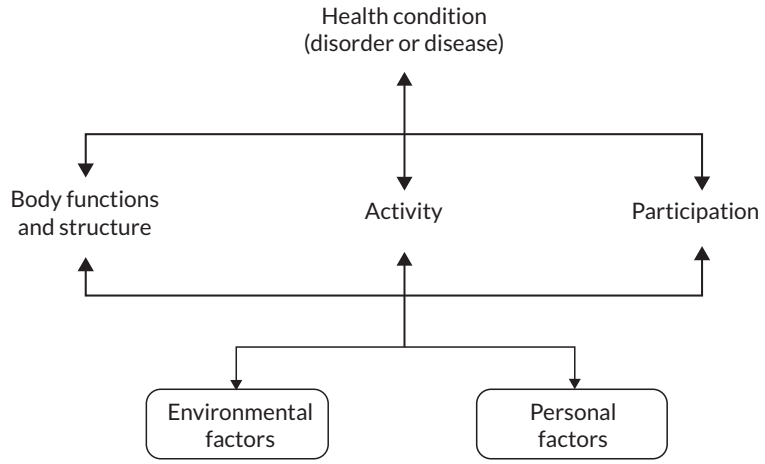

FIGURE 1 International Classification of Functioning, Disability and Health.[101]

Activities and participation: learning and applying knowledge, general tasks and demands, communication, mobility, self-care, domestic life, interpersonal interactions and relationships, major life areas, community, social and civic life.

Environmental factors: products and technology, natural environment, human-made changes to the environment, support and relationships, attitudes, services, systems and policies.

Body structures: structures of the nervous system, eye, ear and related structures, structures involved in voice and speech, structures of the cardiovascular, immunological and respiratory systems, structures related to the digestive, metabolic and endocrine systems, structures related to the genitourinary and reproductive systems, structures related to movement and skin, and related structures.[102]

Data transformation

We used a data transformation algorithm [RELEASE (HS&DR–14 April 2022)[103]], which involved grouping outcome measurement instruments within common categories (e.g. independence, ADL, cognition, psychological outcomes, QoL and cardiorespiratory outcomes). The ICF categories were deemed inappropriate to implement this algorithm, as each assessment instrument could be mapped to multiple levels and domains of the ICF. Therefore, we grouped similar assessment instruments within a common domain.

Consensus

We generated a consensus between the Collaborative and PPI groups on these descriptive outcome domains. We held successive rounds of consensus discussions with our PPI, co-applicant and wider Collaborative Group, as well as a smaller group of experts for specific outcome domains, such as cognition, where data aggregation was particularly complex. Finally, the placement of each outcome measurement instrument under each broad outcome domain was reviewed and approved by the wider PRECIOUS Collaborative Group, comprising more than 116 contributing PIs, and the PPI group. The placement of the outcome measurement instruments within the broad outcome domain is described in *Table 2*.

Each outcome domain was informed by the ICF and refined further to allow for similar outcome measurement instruments to be pooled without compromising the contents of each measurement instrument. For example, pain was commonly measured using a severity scale, or could also include a measure of the impact of pain on everyday life. As the impact of pain on one measure and the severity of pain on another measure constituted two different assessment parameters, the investigative team decided to include 'Pain' as an overarching outcome domain, within which severity and impact could be examined separately. The outcome measurement instruments within each category were then pooled. The most commonly used measurement instrument (by number of data sets) within each outcome category [e.g. the Hospital Anxiety and Depression Scale-A (HADS-A) for Anxiety] served as an 'anchor measure' to which all other measures within the same category [e.g. the Beck Anxiety Inventory (BAI)] were transformed (matching value ranges

TABLE 2 Summary of outcome assessment instrument and available time to follow-up

Broad outcome domain	Subdomain	Subdomain follow-up time [median (IQR)]	Assessment instrument	Number of data sets	IPD (*n*, %)
Anxiety and depression	Anxiety and depression	12 (0–31)	Patient Health Questionnaire-4	1	168 (0.3%)
	Anxiety only	184 (83–278)	Short Form Geriatric Anxiety Index	1	279 (0.4%)
			DASS21	2	1525 (2.4%)
			Beck Anxiety Inventory	1	99 (0.2%)
			HADS-A	9	3058 (4.9%)
			General Anxiety Disorder 7	3	2588 (4.1%)
			Postpartum Anxiety Scale	1	200 (0.3%)
	Depression only	182 (88–278)	DASS21	2	1524 (2.4%)
			Depression in the Medically Ill	1	193 (0.3%)
			HADS-D	9	3069 (4.9%)
			Patient Health Questionnaire-2	1	50 (0.1%)
			Short Form Geriatric Depression Scale	1	279 (0.4%)
			Beck Depression Inventory	3	161 (0.3%)
			Patient Health Questionnaire-9	5	3108 (4.9%)
			Edinburgh Postnatal Depression Scale	1	200 (0.3%)
Breathing	Impact of breathing problems	198 (122–278)	COPD Assessment Test	1	34 (0.1%)
			Leicester Cough Questionnaire	1	378 (0.6%)
			St George Respiratory Questionnaire	2	59 (0.1%)
			Wisconsin Upper Respiratory Symptom Survey	1	30 (0.0%)
	Shortness of breath	180 (76–276)	Dyspnea 12	1	2237 (3.6%)
			Modified Medical Research Council	17	2748 (4.4%)
			MRC	4	1872 (3.0%)
			Nijmegen Score	1	35 (0.1%)
			Self-Evaluation of Breathing Questionnaire	1	208 (0.3%)
	Transfer factor	135 (87–192)	DLCO	6	445 (0.7%)
			DLCOVA	3	304 (0.5%)
			TLCO	1	173 (0.3%)
COVID severity and recovery	COVID severity and recovery	19 (14–25)	7 Point Ordinal Scale	1	258 (0.4%)
			WHO Ordinal Scale for Clinical Improvement Level 5	1	533 (0.8%)
			WHO Clinical Status Scale	1	333 (0.5%)
			WHO-9 COVID Severity Score	2	191 (0.3%)

TABLE 2 Summary of outcome assessment instrument and available time to follow-up (*continued*)

Broad outcome domain	Subdomain	Subdomain follow-up time [median (IQR)]	Assessment instrument	Number of data sets	IPD (*n*, %)
Cognition and thinking	Attention and alertness	204 (124–312)	Test of Attentional Performance	1	41 (0.1%)
			NIH Attention	1	80 (0.1%)
	Multidomain assessment instruments	191 (115–270)	Cogstate Global Deficit Score	1	185 (0.3%)
			Mini Mental State Examination (MMSE)	1	73 (0.1%)
			Montreal Cognitive Assessment (MoCA)	7	3222 (5.1%)
			Short Orientation–Memory–Concentration Test	1	48 (0.1%)
			Short Portable Mental Status Questionnaire (SPMSQ)	1	4 (0.0%)
			Symbol Digits Modality Test	1	25 (0.0%)
	Ease of word production	167.5 (118–211)	PMR Task	1	38 (0.1%)
			CERAD Verbal Fluency	1	15 (0.0%)
	Executive function	203 (124–313)	NIH Toolbox: Executive Function	1	80 (0.1%)
			Trail Making Test B	1	50 (0.1%)
	Figure copy	235 (200–312)	CERAD Figure Copy	1	15 (0.0%)
	Figure recall	234 (200–304)	CERAD Figure Recall	1	14 (0.0%)
	Naming	220 (110–322)	CERAD Boston Naming Test	1	49 (0.1%)
	Orientation	155 (112–201)	Barcelona Test	1	38 (0.1%)
	Processing speed	203 (124–313)	NIH Toolbox: Processing	1	80 (0.1%)
			Trail Making Test A	1	50 (0.1%)
	Verbal learning, memory and recall	112 (102–192)	Rey Auditory Verbal Memory Test	2	102 (0.2%)
			Verbal Learning Memory Test	1	36 (0.1%)
	Working memory	165.5 (110–257)	Digit Span Backwards	3	110 (0.2%)
			Digit Span Forwards	3	110 (0.2%)
			Stroop Test	1	34 (0.1%)
			NIH Toolbox: Working Memory	1	80 (0.1%)
Cognitive failures	Cognitive failures	181 (112–204)	Cognitive Failure Questionnaire	1	458 (0.7%)
Coping with daily living	Coping with daily living	164 (102–217)	Barthel Index	5	1154 (1.8%)
			Functional Independence Measure	1	40 (0.1%)
			Katz Activities of Daily Living	1	279 (0.4%)
			Nottingham Extended Activities of Daily Living Scale	1	2223 (3.5%)
			Post COVID Functional Status Scale (PCFS)	4	894 (1.4%)
			Reintegration with Normal Living Index	1	148 (0.2%)
			WHO Disability Assessment Schedule 2.0	1	12 (0.0%)
Occupational gaps	Occupational gaps	128 (114–162)	Occupational Gaps	1	145 (0.2%)

continued

TABLE 2 Summary of outcome assessment instrument and available time to follow-up (*continued*)

Broad outcome domain	Subdomain	Subdomain follow-up time [median (IQR)]	Assessment instrument	Number of data sets	IPD (*n*, %)
Frailty	Frailty	0 (0–1)	Clinical Frailty Scale	3	928 (1.5%)
			Hospital Frailty Risk Score	1	1700 (2.7%)
Morning and evening Preference	Morning and evening preference	214 (176–383)	Morningness–Eveningness Questionnaire	1	921 (1.5%)
Nutrition	Nutrition	102 (102–192)	SF NMA	1	292 (0.5%)
Overall health status	General health	37.4 (19–54.5)	PROMIS-57	1	33 (0.1%)
			PROMIS-57	1	237 (0.4%)
	Illness perception	360 (360–360)	Illness Perception Questionnaire	1	96 (0.2%)
Pain	Pain severity	193 (147–340.5)	Brief Pain Inventory	1	1926 (3.1%)
			Pain Numeric Rating Scale	1	18 (0.0%)
			Pain Visual Analogue Scale	1	34 (0.1%)
	Pain severity and impact	194 (150–343)	Brief Pain Inventory	1	1926 (3.1%)
Physical activity and performance	Fitness	205 (157–339)	Incremental Shuttle Walk Test (ISWT)	1	1622 (2.6%)
	Exercise tolerance	112 (67.5–196)	30-second chair stand	4	408 (0.6%)
			1-minute sit to stand	1	453 (0.7%)
			2-minute step test	1	25 (0.0%)
	Mobility	193 (138–253)	DeMorton Mobility Index	1	452 (0.7%)
			Functional Ambulation Category	2	425 (0.7%)
			Functional Status Score for the ICU	1	70 (0.1%)
			SARC F	1	2253 (3.6%)
			Short Physical Performance Battery (SPPB)	3	2358 (3.8%)
	Oxygen consumption	119.5 (77–137)	VO_2 peak	2	131 (0.2%)
	Perception of exertion	121.9 (71–185)	Borg 6-minute walk test (0–10)	4	697 (1.1%)
			Borg 6-minute walk test (6–20)	1	26 (0.0%)
			CR10 6-minute walk test	3	236 (0.4%)
	Physical activity	71 (30–134)	Duke Activity Status Index	1	112 (0.2%)
			International Physical Activity Question	1	213 (0.3%)
			Saltin-Grimby Physical Activity Level Scale	1	209 (0.3%)
			Moderate vigorous physical activity per day	1	37 (0.1%)
	Walking ability	136 (102–197)	Walking speed test	1	160 (0.3%)
			6-minute walk test	15	2470 (3.9%)
			10-metre walk test	1	172 (0.3%)

TABLE 2 Summary of outcome assessment instrument and available time to follow-up (*continued*)

Broad outcome domain	Subdomain	Subdomain follow-up time [median (IQR)]	Assessment instrument	Number of data sets	IPD (*n*, %)
Resilience and self-efficacy	Resilience and self-efficacy	360 (360–360)	Brief Resilient Coping Scale	1	100 (0.2%)
			Generalized Self-Efficacy Scale	1	102 (0.2%)
			Short Form Sense of Coherence	1	94 (0.1%)
Sexual function	Sexual function	42 (42–42)	Female Sexual Functioning Index	1	101 (0.2%)
Sleep	Sleep	167 (90–229)	Pittsburgh Sleep Quality Index	6	1266 (2.0%)
			Insomnia Severity Index	2	416 (0.7%)
			Epworth Sleepiness Scale	4	379 (0.6%)
Smell	Smell	146 (105–233)	University of Pennsylvania Smell Identification Test (UPSIT)	1	100 (0.2%)
			Brief Smell Identification Test (BSITC)	1	95 (0.2%)
			Connecticut Chemosensory Clinical Research Center – Olfactory test	1	147 (0.2%)
			16-second Sniffin Stick Test	1	50 (0.1%)
			Total diagnostic interval	2	139 (0.2%)
			Hyposmia Rating Scale	1	82 (0.1%)
Strength	Strength	108 (102–192)	Handgrip strength	7	1346 (2.1%)
			MRC muscle strength	2	496 (0.8%)
			Static Squat Test	1	119 (0.2%)
			Maximum voluntary contraction	1	17 (0.0%)
			Muscle Quality Index	1	34 (0.1%)
General stress	Stress	94 (29–277)	DASS-21 stress	2	1523 (2.4%)
			Perceived Stress Scale 4	1	102 (0.2%)
	PTSD	167 (102–211)	Post-traumatic Stress Disorder Checklist	3	2753 (4.4%)
			Impact of Event Scale – Revised	4	834 (1.3%)
Tiredness and fatigue	Lack of energy	60 (30–270)	DePaul Symptom Questionnaire – Post-Exertional Malaise (DSQ)	1	213 (0.3%)
	Fatigue	182 (42–275)	Functional Assessment of Chronic Illness Therapy (FACIT)	2	2443 (3.9%)
			Brief Fatigue Inventory	1	105 (0.2%)
			Chalder Fatigue Scale	1	342 (0.5%)
			Fatigue Assessment Scale (FAS)	4	2045 (3.3%)
			Fatigue Scale for Motor Cognitive Function	1	41 (0.1%)
			Fatigue Severity Scale (FSS)	4	642 (1.0%)
			Fatigue Visual Analogue Scale	2	190 (0.3%)
			Modified Fatigue Impact Scale	1	39 (0.1%)
			Multidimensional Fatigue Inventory	1	155 (0.2%)
			Daily Fatigue Impact Scale	1	18 (0.0%)

continued

TABLE 2 Summary of outcome assessment instrument and available time to follow-up (*continued*)

Broad outcome domain	Subdomain	Subdomain follow-up time [median (IQR])	Assessment instrument	Number of data sets	IPD (*n*, %)
Well-being and life	Domain-specific QoL	183 (102–287.8)	SF12	2	325 (0.5%)
			SF36	6	1593 (2.5%)
			WHO-QoL	1	39 (0.1%)
	Mental well-being and happiness	227 (94–343)	SPHERE	1	195 (0.3%)
			Warwick and Edinburgh Mental Wellbeing Scores (WEMWBS)	1	111 (0.2%)
	QoL	225 (114–358)	15D	1	205 (0.3%)
			EQ-5D – 3 level	2	18,624 (29.6%)
			EQ-5D – 5 level	12	6415 (10.2%)
			EQ-5D – 5 level index	1	518 (0.8%)
			Recovery After INtensive care (RAIN) questionnaire	1	105 (0.2%)
			Somatic Symptom Disorder Scale	1	101 (0.2%)
			VQ11	1	37 (0.1%)

CERAD, Consortium to Establish a Registry for Alzheimer's Disease; COPD, chronic obstructive pulmonary disease; DASS-21, Depression, Anxiety and Stress Scale-21; DLCO, Diffusing capacity of the Lungs for Carbon monOxide; DLCOVA, Diffusing capacity of the Lungs for Carbon monOxide divided by the Alveolar Volume; EQ-5D, EuroQol-5 Dimensions; HADS-A, Hospital Anxiety and Depression Scale-A; HADS-D, Hospital Anxiety and Depression Scale-D; IQR, interquartile range; MRC, Medical Research Council; NIH, National Institutes of Health; PMR, Spanish Version of the FAS letter fluency task, where participants are requested to orally produce as many words that start with the letters P, M, R as possible within 1 minute; PROMIS-57, Patient Reported Outcomes Measurement Information System-57; PTSD, post-traumatic stress disorder; SARC F, Strength, Assistance with walking, Rising from a chair, Climbing Stairs, and Falls; SF NMA, Short-Form Mini Nutritional Assessment; SF-12, Short Form questionnaire-12 items; SF-36, Short Form questionnaire-36 items; SPHERE, Somatic and Psychological HEalth REport; TLCO, Transfer Factor for Carbon Monoxide.

for the HADS-A but preserving the original BAI distribution). Therefore, all usable data were pooled within the common outcome categories and presented on a clinically relevant assessment scale.

Standardisation checks

Checks were performed on the data, including a review of the measurement instrument values to ensure that they fell within acceptable ranges. We queried instances where the values were entered as zero with contributing PIs to ascertain whether values were truly zero or if they were missing. Where multiple measurement instruments assessing the same outcome domain were captured within the same participants, we investigated the relationships between measurement instruments to ensure that they were behaving in the same manner. As per the established algorithm, we generated thresholds for minimum, quartile 1, median, quartile 3, and maximum for each measurement instrument and examined whether standardisation of other measurement instruments to the anchor measure would be affected by floor and ceiling effects. Where ceiling effects existed, the most commonly used assessment instrument by IPD (rather than by data set) was selected as the anchor measure or the thresholds were adjusted to take into account the heavily skewed distribution. Finally, we checked the distributions of the transformed assessment instruments to the standard anchor measure, to ensure that the values and distributions were consistent with the underlying data.

Finally, assessment that included instruments that did not comprise a sum score/overall score, questionnaires with yes/no answers, or included domains that could not be aggregated with other data and were omitted from further analyses.

All analyses were dependent on the description of the time between COVID-19 onset, study inclusion, and assessment of each outcome domain, as well as the availability of covariates for adjusted analyses.

Study risk-of-bias assessment

Data set quality was initially planned to include the Cochrane Risk of Bias (RoB) tool,[104] the Checklist for Analytical Cross-Sectional Studies,[105] and Critical Approval Skills Programme Risk of Bias checklist for cohort studies.[106] However, appraisal of the included data sets and data types highlighted that the Mixed Methods Appraisal Tool (MMAT)[107,108] would be a more inclusive approach to describe data set-level RoB in a manner that would also permit consideration of RoB across data sets. RoB was performed by two independent reviewers (MA, KV), and the results of the RoB assessment were sent to study authors to provide missing details to ensure that the assessments were as comprehensive as possible.

Assessment of the certainty of the evidence at the level of the model

There is currently no specific guidance for assessing the certainty of evidence for IPDMA, and the impact of pooling data from various study designs is unclear.[109] Following extensive discussion with the PRECIOUS project team, it was decided to assess the certainty of evidence using a modified (informed) Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach at the level of each final model.[110]

We used a GRADE-informed approach, assessing the evidence across four domains:

- Imprecision of results [i.e. width of the generated confidence intervals (CIs), the number of underlying studies contributing to the model and where applicable, the number of events for categorical variables].
- Inconsistency of results (i.e. heterogeneity, assessed using the I^2 statistic).
- Indirectness of evidence (i.e. data from subsets of the COVID-19 population, validity of the assessment instrument to describe the outcome under investigation).
- Publication bias.

We used these assessments to arrive at an overall judgement regarding QoL evidence for each outcome, downgrading the evidence by one level for each criterion. Thus, the confidence in each model was graded as high, moderate, low or very low, depending on the underlying data. We did not include an assessment of RoB in our approach because of a wide range of different study designs.[109] The quality assessment was performed independently by two review authors (MA, KV), with a third reviewer (MB) involved when consensus was required.

Data management

All the identified IPD data sets were collated into a single database. Variables were cleaned and decisions were recorded to ensure consistency across data sets and researchers (e.g. age in years).

A master database was compiled from all contributed data using SAS; common and overlapping variables were standardised. Data samples for each research question were generated based on the availability of the prespecified variables. An analysis data set was created for each research question; each data set included all eligible patients' data, for whom data were available for each of the essential variables.

Data management systems were implemented at the start of the study. The existing infrastructure at Glasgow Caledonian University (GCU) accommodated these data management systems. The Data Management Plan is provided in *Report Supplementary Material 3*.

The data sets provided for the PRECIOUS database were tracked and saved on the GCU server. A working copy of each data set was created and saved using a unique ID along with supporting documents in a unique ID folder accessible to the Project Management Team. In accordance with GCU practice, all files were backed up daily.

Recruitment management

We documented all invitations to participate and the subsequent expressions of interest. Each study was tracked using the author's name and study digital object identifier reference.

Data documentation

Each data set that was contributed electronically was accompanied by an annotated data collection form which detailed each of the variables collected, the time points for collection and the codes used for each of these variables. A full publication was requested along with the data set, where available. These documents were used to clean the data and apply standard data labels to the master data set(s). These documents were also available as data descriptors on a common drive which can be accessed by the analyst/statistician.

Formatting data and data conversions

The data manager and statistician oversaw the conversion of data sets into compatible formats, liaising with contributing PIs to ensure the completeness of contributed data, and to check variable ranges for accuracy. Data were collected in various formats, including SAS, SPSS, Excel and Access. Before commencing the secondary analyses, all data were converted into a uniform format (e.g. SAS). This was determined by the data manager, bearing in mind the future use, long-term storage, and compatibility with other forms of data storage. All contributed data sets were combined into a single master database, merging common variables, such as patient age, sex and medical history variables.

Anonymisation

We requested the contribution of fully anonymised participant data. A unique database-wide identifier was allocated to each participant, comprising their unique study number and study identifier. This ensured that the inclusion of specific participants in subsequent analysis data sets could be traced back to the original trial source for quality assurance and data verification.

Data storage

Data were stored at the Nursing, Midwifery, and Allied Health Professions (NMAHP) Research Unit, GCU, UK, according to the university procedures. All original data sets were stored on a secure, encrypted and hard drive. A single anonymised project master database was generated from the original data sets and stored separately on the designated portion of the NMAHP Research Unit of the university server. Adjustment to this database did not affect the original study data. The analytical data sets were generated using the master data set.

Version control and backups

Version control was used for the analysis of data sets that were stored on a common hard drive. The milestone data sets were identified and updated as necessary (e.g. <Filename version 1.0 date>). The analysis data sets were stored in a folder separate from the master data set. The master data sets were updated only if and when new data were contributed. In this case, the master data set was renamed using a new filename, version number and date. The analyst saved their ongoing work under the new analysis data set file names rather than re-naming existing master data sets.

Encryption

All the university hardware was encrypted. Offsite access to shared folders was only possible through appropriate university IT permissions.

Data retention and disposal

After the completion of the initial PRECIOUS analyses, researchers who had contributed data could choose to lodge their data in a central repository hosted at GCU, UK, for additional data-sharing activities. In this way, data could be reused beyond the scope of the current application and made available to a wider research community for novel exploratory analyses (see *Security and access control*). Anonymised data would be preserved within these databases for at least 15 years for further reuse. These potential secondary analysis activities could include re-use in validation studies, teaching, exploratory analyses and prognostic modelling.

Security and access control

During the project, the data were not accessible to those outside of the project collaboration. Access to data in a legacy database can only occur at the end of the project and will be governed by a PRECIOUS Steering Committee comprising contributing PIs and co-applicants of the current proposal. The PRECIOUS Steering Committee will govern the use of

research data, participate in analyses, and review the manuscripts based on planned analyses. Contributing PIs thereby retain control of the use of their data and will have an opportunity to contribute to planned secondary analyses using this legacy database.

Copyright and intellectual property

Each researcher, funder, or research group is named as a coauthor or acknowledged in subsequent publications from the PRECIOUS study as appropriate, provided that they meet the authorship criteria.

Analyses

Findings are reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) for IPD.

Profiling long-term COVID-19 outcomes

The long-term outcomes after COVID-19 were described in terms of availability of long-term outcome assessments by ICF domain, prevalence of symptoms at different time points and individual outcome domain standardised scores, at different time points. For all outcome domains, descriptive statistics were tabulated, showing proportions for binary and categorical data (e.g. proportions for each level of care) and means and standard deviations (SDs), or medians and interquartile ranges (IQRs) for continuous data as appropriate. Data within each domain were transformed into appropriate standardised measures. As part of the outcome transformation process, we examined the distributions of the assessment instrument values within each overarching domain to establish that they fell within the expected ranges. This allowed us to check that each study scored the assessment instrument in the same way.

Assessment instruments were mapped to the ICF using linking rules[111,112] and presented as an Eppi map to visualise the capture of ICF categories by the assessment instruments in the PRECIOUS database. We identified areas where there was low or no capture of the ICF domain and described these as current gaps in the evidence base for the PRECIOUS database, which could be used to inform future research priorities.

Prevalence of COVID-19 symptoms at different time points

We described the prevalence of COVID-19 symptoms at each time point. Data were extracted verbatim from the original data sets, and where appropriate, variable names were standardised to identify distinct symptoms. For example, wet and dry coughs were presented together, double vision and visual distortion were presented with vision problems; nausea and vomiting were presented together, and joint pain was presented with arthralgia. This was an iterative process that involved the contributing PIs and expert co-applicant group to ensure that the groupings were accurate.

Where possible, we stratified the analyses by COVID-19 positivity at the study baseline. Participants were categorised as being COVID-positive at the study baseline, COVID-negative at the study baseline but with a history of prior COVID (e.g. participation in a follow-up study for people who had previously had COVID), or COVID-negative at study baseline. For the latter group, when examining symptom prevalence data over time, we excluded participants who went on to develop COVID-19 by follow-up assessment time, as symptoms reported at follow-up time points could reflect recent COVID exposure, rather than a negative population.

As this was an IPD meta-analysis, we excluded symptoms that were only reported at baseline in a single data set, and presented data on symptom prevalence where the sample size exceeded 500 participants to provide a more robust estimate of prevalence and prevent confounding due to the small sample size. We described symptom data in terms of prevalence rather than persistence, as it was challenging to ascertain whether the symptom occurrence was due to initial infection, persistence, or newly acquired symptoms. We could not assume that the presence of the same symptom at two time points within the same individual indicated persistence.

Factors associated with poorer long-term outcomes

Report Supplementary Material 68 describes the Logic Models used for analyses. The primary IPD meta-analyses adopted a one-stage method rather than a two-stage meta-analysis approach, as this was more appropriate in the context of small data sets (< 30 participants) or where the outcome is binary or time to event.[113] The one-stage method involved data from all included and relevant data sets combined in a single analysis. Individual data sets and countries were assessed as random effects. Appropriate generalised linear models were used (e.g. analysis of covariance where outcome measures were continuous, and binary logistic regression for dichotomous outcomes).

Owing to the nature of the data, all potentially significant variables at the univariable level may not have been available across all data sets. The first step of each analysis was to explore the variables that were significant at $p < 0.1$. The variables with the strongest signal (e.g. smallest p-value) with the greatest IPD and availability in the greatest number of data sets (D) started the model building. Thereafter, variables were added one at a time, taking into account not only the additional value they offered the model (e.g. those that made the largest significant contribution) but also the available IPD and number of data sets. As each variable was added, the available IPD and number of included data sets (D) decreased. Where IPD ≤ 500 or D < 2, modelling ceased.

Effect sizes [e.g. mean differences, ratio of differences, point estimates or odds ratios (ORs)] were estimated and reported with the corresponding 95% CI. Models were adjusted for baseline demography and intervention variables where possible. We considered performing sensitivity analyses restricted to RCTs if time permitted. The main analyses were complete case analysis, although missing data were addressed in secondary analyses using multiple imputation methods, and missing at-random assumptions were relaxed using sensitivity analyses. We analysed pooled, international, anonymised COVID-19 data sets, including cohort, case-control, RCT, observational studies, and registry data sets. Analyses took the form of meta-analyses of subsets of the pooled available IPD specific to the research question. The proposed analyses were quantitative in nature, employing generalised linear regression models (of the form appropriate to the outcome) and summary statistics of the complete raw data sets.

We explored the effect of baseline variables (age, sex, ethnicity, deprivation, comorbidities, persistent symptoms and type of healthcare system, where available) on the health state ≥ 1 month after COVID-19 onset. In discussion with the clinicians in our investigative group, we prioritised the presentation of outcomes between 3 months and 6 months, 9 months and 12 months, and > 12 months following COVID-19 onset. The first time point was one at which people may be discharged from clinical care or follow-up after treatment for initial COVID-19 infection and sequelae, and the latter 2 time points represented longer-term time points where people may be expected to resume pre-COVID levels of activity. We also considered whether we could develop and validate a prediction algorithm that could provide prognostic information on the outcome trajectory. We also described the data availability for other outcomes that did not meet the threshold for meta-analysis.

Costs of poorer long-term outcomes

Depending on the available IPD, we sought to describe resource use, including length of hospital stay, use of primary and secondary health care, social care services, return to work, and informal care, and describe associated costs using UK sources.[114] Additionally, we examined individual, health service and societal impacts of COVID-19 in terms of later hospitalisation, return to work and impact of health utilities.

Factors associated with later hospitalisation

We mirrored the methodologies employed in the primary IPD meta-analyses described in the previous section. Our focus was on participants who were rehospitalised or later hospitalised, whether due to COVID-related complications or other causes. Summary statistics were used to describe the demographic profile of the participants in accordance with the variables appearing in all included studies.

Following the one-stage meta-analysis model, we integrated data from all relevant studies and treated each study as a random effect in our analysis. This approach allowed us to maintain the integrity of participant clustering within data sets while assessing the impact of baseline characteristics, including demography and initial COVID-19 severity, on factors associated with later hospitalisation. For the statistical examination of later hospitalisation risks, we employed

logistic regression models. These models were preferred given the dichotomous nature of the later hospitalisation outcome (e.g. whether later hospitalisation or rehospitalisation occurred), and allowed us to control for personal characteristics and baseline COVID outcomes.

Factors associated with return to work

We extracted data on return to work/school and the time of return-to-work/school assessment. Where appropriate, we described the availability of return-to-work/school data narratively. We used univariable regression analyses to describe the factors associated with returning to work/school; significant factors at univariable level were retained in the multivariable model, describing OR and 95% CIs.

Examination of health utilities and health-related quality of life

We extracted health state utility data from assessment instruments such as the EuroQol-5 Dimensions (EQ-5D) in both its 3-Level (EQ-5D-3L) and 5-Level (EQ-5D-5L) versions,[115,116] and the Rand 36-item Short Form Survey (SF-36).[117] The EuroQoL EQ-5D, a widely recognised tool for measuring health-related quality of life (HRQoL),[118] comprises a descriptive system and a visual analogue scale (VAS), allowing respondents to rate their overall health. The SF-36 is not preference-based and, as such, could not have been used to calculate utilities without prior conversion to EuroQoL EQ-5D values. Data from these QoL measures were harmonised and categorised by study and time point of assessment. This categorisation allowed the examination of changes in health state utilities over time in an IPD meta-analysis framework.

EuroQoL questionnaire responses were converted into utility values. This was done by following the recommended practice of using country-specific tariffs, where available. In cases where a specific country's tariff was not available, we defaulted using the UK tariff.[116] This decision aligns with common practices in health economics for utility calculations. Moreover, following the guidance of the NICE, we mapped all EQ-5D-5L questionnaire responses into the EQ-5D-3L format, considering factors such age and sex, as recommended by NICE.[119] SF-36 data were converted to EQ-5D using Model EQ (1) from Ara and Brazier.[120] This model was originally designed for mean cohort data, but it was adapted here to predict individual-level data.

To address the known issues around the EQ-5D-3L distribution, we employed an adjusted limited dependent variable mixture model utilising maximum likelihood estimation for the analysis. This model choice, a C-component mixture of densities, was specifically tailored to manage the complexities of EQ-5D-3L data distribution.[121] Throughout our analysis, all models controlled for personal characteristics and were adjusted for clustering within studies, ensuring that our findings were robust and reflective of the studies included in this analysis. Models were run separately for the EQ-5D data, SF-36 data, and a model containing all available data.

This methodology provided us with a comprehensive understanding of utility loss related to poor outcomes in this population. By employing these analytical techniques and using the EQ-5D instruments as primary tools for measuring HRQoL, we were able to quantify the impact of COVID-19 on participants' health states over time. As described earlier, we prioritised the presentation of outcomes between 3 months and 6 months, 9 months and 12 months, and > 12 months following COVID-19 onset.

Heterogeneity

Given the data set diversity, we expected to observe statistical heterogeneity (τ^1) in our proposed analyses. Where statistical heterogeneity was identified, we considered the magnitude of the inconsistencies observed, as significance depended on the number of available studies, and, where appropriate, we adopted the following strategies:

- identified the source of heterogeneity and excluded studies that caused significant heterogeneity in a sensitivity analysis
- considered the clinical importance of identified heterogeneity and whether it was important to the outcome
- considered sensitivity analysis and explored the impact of a fixed-effects model.

The difficulty of not having a set 'treatment' as in traditional meta-analysis meant that I^2 was calculated based on the variable with the largest effect in the final model.

Sample size

Sample size calculations are primarily used in primary research studies and are of lower importance in meta-analyses, where there is less ability to control the number of participants being examined. As our data sets had multiple domains, and levels within multiple predictors, we set a conservative significance level of 1% and a power of 90%. Thus, for each domain, we required 121 participants per level to explore a difference of 0.5 SD, where the SD is the square root of the joint variance within and between studies and the correlation between variables. Thus, we would need 500 IPD per meta-analysis, with approximately equal proportions of IPD per group.

Analyses considered setting; definition of COVID-19 population (positive, negative, or history of prior COVID, documenting method of diagnosis); data set design (RCT, cohort, case-control); time post-symptom onset, follow-up time; healthcare system (e.g. developed and developing countries), and level of evidence (preprint vs. published, if appropriate). The published RCT data on confirmed COVID-19 cases represent the highest level of evidence. Many of these were fixed for all participants within a study, and thus could not be estimated using meta-analysis methods due to lack of within-study comparisons.

Analyses data sets were selected where more than one data set and > 500 IPD contributed to the planned analyses. They were then assessed for collinearity, where there was no crossover between variables and the study. For example, if no study included more than one country, and no country was included in more than one study, then the variable was not included in the analyses.

Chapter 3 The PRECIOUS database: representativeness, data capture, evidence and gaps

Overview

This chapter describes the PRECIOUS database, including the results of the systematic search, the data sets identified from research networks, and a description of the data that were extracted and included in the final analysis data sets.

Systematic identification of data sets

From the hierarchical screening of 10 electronic databases, clinical trial registries, pre-prints, funding agency notifications, communication through personal networks, and the use of forward and backward citations comprising 65,296 records, 1748 data sets were identified as potentially relevant. Further screening to remove duplicate studies and ascertain contact information resulted in invitations being sent to 1682 PIs. Of the responses to these invitations, 340 studies were screened for eligibility and availability of variables of interest. This corresponded to 225,108 IPD. From these studies, 116 were included in PRECIOUS, corresponding to 62,849 IPD (*Figure 2*).

Overview of studies

Of 116 data sets (see *Report Supplementary Material 4*), 20 (IPD = 3140; 5.0%) were from RCTs, 60 (IPD = 49,749; 79.2%) were from cohort studies and 13 (IPD = 6632; 10.6%) were from case-control studies (*Table 3*). The majority of participants were enrolled in the UK (10 studies; IPD = 26,159); however, Italian-based studies contributed the highest number of data sets (*n* = 13). Data within PRECIOUS were predominantly from countries with a 'high' income category according to the World Bank, and almost all studies commenced in 2020 [IPD = 60,936 (97.3%)]. Hospital-based studies were the most common, accounting for 58 data sets (IPD = 22,527), but community-based studies contributed the highest number of IPD (36 data sets, IPD = 31,373) (see *Table 3*).

Overview of participants within PRECIOUS

Participants' median age was 58.0 (IQR 45.0–68.0, from 111 data sets; IPD = 60,743). More participants were female [data sets = 112; IPD = 34,185 (54.4%)] and the median BMI was 26.1 (IQR 23.2–30.0, 52 data sets, IPD = 37,465; *Tables 4* and *5*).

Overview of COVID-19 presentation

The median time since COVID-19 onset was 5 days (IQR 1–30, 108 data sets, IPD = 41,627). At study enrolment, 33,230 (52.9%) participants from 91 data sets were COVID-positive. A further 6128 (9.8%) from 26 studies were COVID-negative but had COVID-19 prior to study enrolment; 28,017 (44.6%) were hospitalised for initial COVID-19 infection. The vast majority of COVID-19 diagnoses were made using PCR/antigen-based methods [45,607 (72.7%), data sets = 99].

The severity of COVID-19 was originally described using a range of different methods including published guidelines,[122] assessment scales, symptoms and clinical presentation,[123] and probability.[124] According to our defined criteria

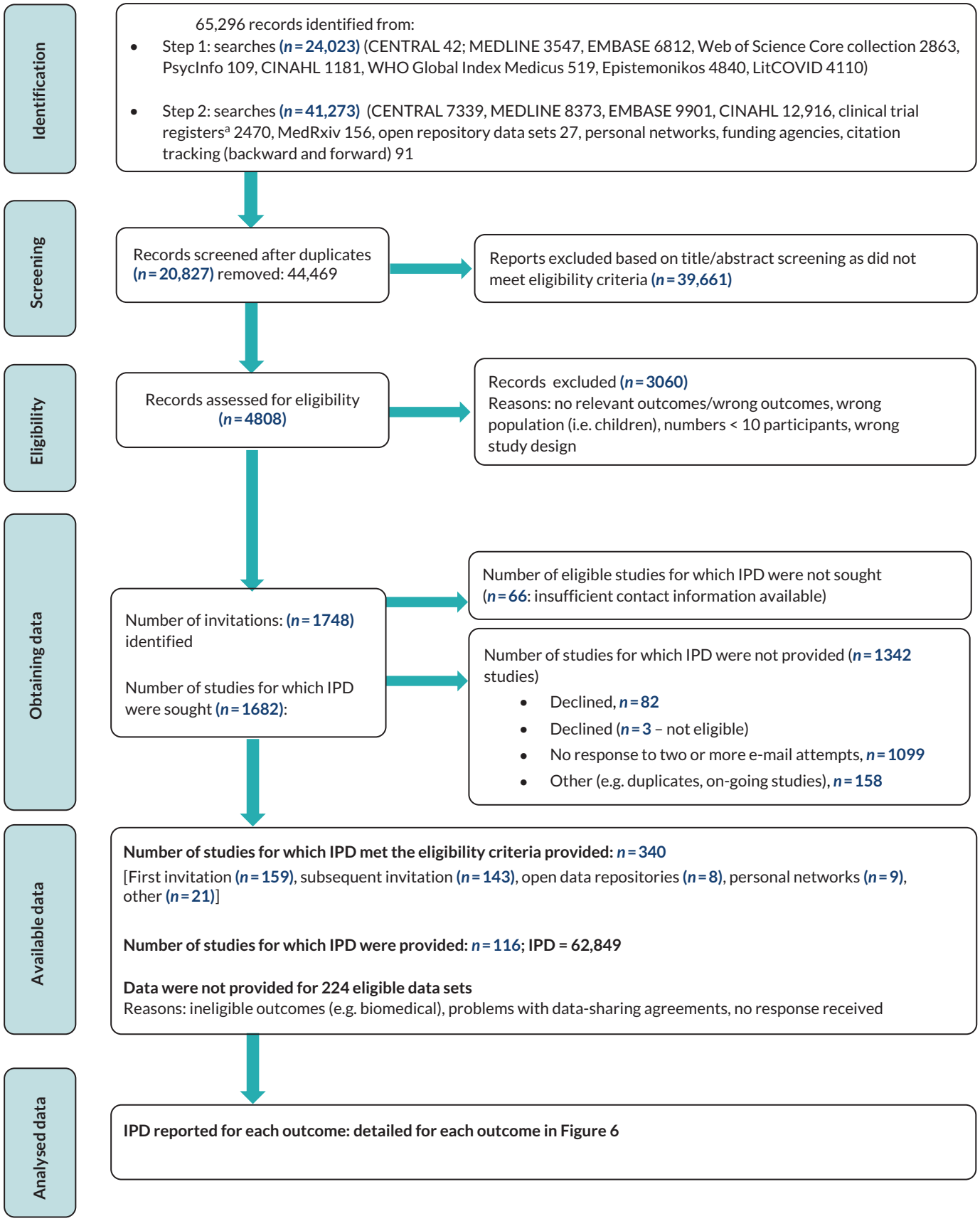

FIGURE 2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses for IPD flow diagram. [a]Clinical trial registers: US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) (*n* = 2470) Simple search function: In condition: Covid19 or long Covid or Covid-19. World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch) search strategy. Multiple attempts to search this database were made between 15 July and 30 August 2021. However, the platform was unstable due to the volume of Covid-19 related studies. We were finally able to download an excel file dated 16 August 2021 which contained the contents of the WHO ICTRP database and searched this file for relevant studies.

TABLE 3 Description of studies included in the PRECIOUS database

IPD = 62,845; *D* = 116	Parameter	Number of data sets	IPD (*n*, %)
Study design	Case-control	13	6632 (10.6%)
	Cohort	60	49,749 (79.2%)
	Longitudinal study	2	716 (1.1%)
	Other	20	2320 (3.7%)
	RCT	20	3140 (5.0%)
	Survey	1	288 (0.5%)
Recruitment country	Argentina	4	1785 (2.8%)
	Australia	2	253 (0.4%)
	Austria	1	145 (0.2%)
	Bangladesh	3	1358 (2.2%)
	Belgium	2	271 (0.4%)
	Brazil	10	872 (1.4%)
	Canada	1	78 (0.1%)
	Chile	1	44 (0.1%)
	China	3	384 (0.6%)
	Colombia	1	17 (0.0%)
	Denmark	3	728 (1.2%)
	Egypt, Arab rep.	3	796 (1.3%)
	Finland	1	2 (0.0%)
	France	5	476 (0.8%)
	Germany	5	814 (1.3%)
	Greece	1	161 (0.3%)
	Hong Kong SAR, China	1	620 (1.0%)
	Iceland	1	1788 (2.9%)
	India	4	546 (0.9%)
	Islamic Republic of Iran	2	195 (0.3%)
	Ireland	1	2 (0.0%)
	Israel	2	922 (1.5%)
	Italy	13	1834 (2.9%)
	Mexico	1	10 (0.0%)
	Moldova	1	45 (0.1%)
	Multiple countries	3	10,069 (16.1%)
	The Netherlands	3	931 (1.5%)
	Nigeria	1	1 (0.0%)
	Norway	2	370 (0.6%)
	Not reported	1	7 (0.0%)

continued

TABLE 3 Description of studies included in the PRECIOUS database (*continued*)

IPD = 62,845; *D* = 116	Parameter	Number of data sets	IPD (*n*, %)
	Poland	6	249 (0.4%)
	Portugal	1	25 (0.0%)
	Qatar	1	1 (0.0%)
	Romania	2	247 (0.4%)
	Russia	4	460 (0.7%)
	Saudi Arabia	1	269 (0.4%)
	Spain	7	2520 (4.0%)
	Sweden	3	731 (1.2%)
	Switzerland	2	1543 (2.5%)
	Turkey	5	571 (0.9%)
	UK	10	26,159 (41.8%)
	USA	12	4338 (6.9%)
Income category	High	77	49,134 (78.2%)
	Lower-middle	12	2746 (4.4%)
	Not reported	2	68 (0.1%)
	Upper-middle	29	4501 (7.2%)
	Upper-middle and lower-middle	1	6396 (10.2%)
Year of recruitment start	2020	101	60,936 (97.3%)
	2021	11	1680 (2.7%)
Recruitment setting	Community	36	31,373 (49.9%)
	Contact tracing	2	1543 (2.5%)
	Hospital	58	22,527 (35.8%)
	Mixed	12	2248 (3.6%)
	Multiple	1	3578 (5.7%)
	Not reported	4	750 (1.2%)
	Outpatient clinic	5	826 (1.3%)

for severity, 3734 (6.3% from 43 data sets) participants identified as having severe COVID-19, as they required hospitalisation and ventilation (see *Table 5*).

Overview of equity measures

Residence prior to COVID-19 was not routinely captured; 61,294 (97.6% from 114 data sets) participants' residence were not reported. The participants were most commonly Caucasian/White [24,971 (40.0% from 34 data sets)]. In the data sets where employment status was reported, 22.5% (22 data sets, IPD = 14,110) were employed at the time of COVID-19 onset, 9199 (15 data sets, 14.6%) were retired, and 547 (3 data sets, 0.9%) were unemployed due to health reasons or disability (*Table 6*). Religion was not reported in 62,268 (99.1%) participants. Data on educational level were reported for approximately 44% of the database, and 30.5% (19 data sets, IPD = 19,091) had completed

TABLE 4 Participant characteristics

Variable	Descriptor	Number of data sets	IPD (*n*, %)	Median (IQR)
Age		111	60,743 (96.7%)	58.00 (45.00–68.00)
Sex	Female	112	34,185 (54.4%)	
	Male	110	27,922 (44.4%)	
	Not reported	14	738 (1.2%)	
Ethnicity	Aboriginal/first nations	4	12 (0.0%)	
	Arab	5	301 (0.5%)	
	Asian – not specified	16	755 (1.2%)	
	Black	17	922 (1.5%)	
	East Asian	2	210 (0.3%)	
	Hispanic/Latinx	4	33 (0.1%)	
	Jewish	1	791 (1.3%)	
	Mixed	8	339 (0.5%)	
	Not reported	95	32,670 (52.3%)	
	Not specified	3	87 (0.1%)	
	Other	15	571 (0.9%)	
	Pacific Islander	1	1 (0.0%)	
	South Asian	5	794 (1.3%)	

TABLE 5 Clinical presentation

	Variable	Descriptor	Data sets	IPD (%)	Median (IQR)
Clinical presentation	COVID positivity at baseline	No, with prior COVID	26	6128 (9.8%)	
		No, with unknown prior COVID	15	4577 (7.3%)	
		Not recorded	11	18,910 (30.1%)	
		Yes	91	33,230 (52.9%)	
	Diagnosis method	Antibody test	1	238 (0.4%)	
		Clinical diagnosis	1	5 (0.0%)	
		Method not reported	21	16,814 (26.8%)	
		PCR or serology test	1	88 (0.1%)	
		PCR/antigen-based method	99	45,607 (72.7%)	
	Time since onset in days		108	41,627 (66.2%)	5.00 (1.00–30.00)
	COVID-19 severity reported by study	No	88	31,895 (50.8%)	
		Yes	28	30,950 (49.2%)	

continued

TABLE 5 Clinical presentation (*continued*)

	Variable	Descriptor	Data sets	IPD (%)	Median (IQR)
	Hospitalised with COVID	No	44	31,338 (49.9%)	
		Not reported	24	3490 (5.6%)	
		Yes	98	28,017 (44.6%)	
	COVID-19 severity	Hospitalised	94	24,283 (40.9%)	
		Hospitalised, ventilated	43	3734 (6.3%)	
		Not hospitalised	44	31,338 (52.8%)	
Comorbidities informed by the ICD-10 classification	Other infections	No	4	818 (1.3%)	
		Not reported	114	61,997 (98.7%)	
		Yes	5	30 (0.0%)	
	Cancer	No	59	43,009 (68.4%)	
		Not reported	73	16,476 (26.2%)	
		Yes	54	3360 (5.3%)	
	Diseases of the blood	No	18	26,481 (42.1%)	
		Not reported	102	34,160 (54.4%)	
		Yes	21	2204 (3.5%)	
	Diabetes	No	80	45,574 (72.5%)	
		Not reported	55	9397 (15.0%)	
		Yes	84	7874 (12.5%)	
	Obesity	No	69	32,479 (51.7%)	
		Not reported	76	19,927 (31.7%)	
		Yes	74	10,438 (16.6%)	
	Other endocrine, nutritional and metabolic diseases	No	17	24,559 (39.1%)	
		Not reported	100	37,405 (59.5%)	
		Yes	25	881 (1.4%)	
	BMI		52	37,465 (59.6%)	26.06 (23.18–29.95)
	Mental and behavioural disorders	No	18	21,365 (34.0%)	
		Not reported	99	38,494 (61.3%)	
		Yes	22	2986 (4.8%)	
	Dementia/Alzheimer's disease	No	25	33,214 (52.9%)	
		Not reported	99	29,109 (46.3%)	
		Yes	17	522 (0.8%)	
	Sleep disorders	No	10	1624 (2.6%)	
		Not reported	108	61,035 (97.1%)	
		Yes	12	186 (0.3%)	

TABLE 5 Clinical presentation (*continued*)

Variable	Descriptor	Data sets	IPD (%)	Median (IQR)
Neurological conditions	No	26	25,940 (41.3%)	
	Not reported	94	36,039 (57.3%)	
	Yes	30	866 (1.4%)	
Diseases of the eye and adnexa	No	3	555 (0.9%)	
	Not reported	113	62,278 (99.1%)	
	Yes	5	12 (0.0%)	
Disease of the ear and mastoid process	No	5	693 (1.1%)	
	Not reported	111	62,149 (98.9%)	
	Yes	3	3 (0.0%)	
Cardiac conditions	No	71	41,916 (66.7%)	
	Not reported	59	13,038 (20.7%)	
	Yes	75	7891 (12.6%)	
Cerebrovascular disease	No	38	40,470 (64.4%)	
	Not reported	86	20,816 (33.1%)	
	Yes	34	1559 (2.5%)	
Diseases of the circulatory system	No	59	31,914 (50.8%)	
	Not reported	73	16,994 (27.0%)	
	Yes	67	13,936 (22.2%)	
Lung disease	No	73	42,709 (68.0%)	
	Not reported	60	12,212 (19.4%)	
	Yes	80	7923 (12.6%)	
Liver disease	No	33	12,001 (19.1%)	
	Not reported	92	50,533 (80.4%)	
	Yes	32	311 (0.5%)	
Gastrointestinal conditions	No	13	4817 (7.7%)	
	Not reported	102	57,264 (91.1%)	
	Yes	18	764 (1.2%)	
Chronic kidney disease	No	59	45,471 (72.4%)	
	Not reported	72	14,290 (22.7%)	
	Yes	58	3082 (4.9%)	
Immunosuppressant medication use or condition	No	40	37,398 (59.5%)	
	Not reported	89	23,148 (36.8%)	
	Yes	34	2299 (3.7%)	
Frailty	No	4	219 (0.3%)	
	Not reported	111	60,626 (96.5%)	
	See frailty outcome data set	1	1996 (3.2%)	

continued

TABLE 5 Clinical presentation (*continued*)

Variable	Descriptor	Data sets	IPD (%)	Median (IQR)
Skin conditions	No	5	18,705 (29.8%)	
	Not reported	112	42,686 (67.9%)	
	Yes	6	1454 (2.3%)	
Musculoskeletal conditions	No	16	4570 (7.3%)	
	Not reported	101	57,620 (91.7%)	
	Yes	21	655 (1.0%)	
Other genitourinary conditions	No	4	593 (0.9%)	
	Not reported	112	62,212 (99.0%)	
	Yes	9	40 (0.1%)	
Pregnancy, childbirth and the puerperium	N/A	110	27,922 (44.4%)	
	No	16	17,736 (28.2%)	
	Not reported	102	16,945 (27.0%)	
	Yes	7	242 (0.4%)	
Certain conditions originating in the perinatal period	No	4	689 (1.1%)	
	Not reported	112	62,156 (98.9%)	
Congenital malformations, deformations and chromosomal abnormality	No	4	689 (1.1%)	
	Not reported	112	62,153 (98.9%)	
	Yes	3	3 (0.0%)	
Other conditions	No	16	2699 (4.3%)	
	Not reported	103	59,778 (95.1%)	
	Yes	19	368 (0.6%)	
Injury, poisoning and certain other consequences of external cause	No	6	995 (1.6%)	
	Not reported	110	61,840 (98.4%)	
	Yes	2	10 (0.0%)	
External causes of morbidity and mortality	No	6	20,419 (32.5%)	
	Not reported	112	42,350 (67.4%)	
	Yes	4	76 (0.1%)	
Factors influencing health status and contact with health services	No	7	1207 (1.9%)	
	Not reported	111	61,356 (97.6%)	
	Yes	7	282 (0.4%)	
Codes for special purposes	Not reported	114	62,337 (100%)	

TABLE 6 Sociodemographic characteristics

Variable	Description	Data sets	IPD (%)
Occupation	Benefits	1	21 (0.0%)
	Employed	22	14,110 (22.5%)
	Managing household/caregiving	8	133 (0.2%)
	Never employed	2	25 (0.0%)
	Not reported	108	36,525 (58.2%)
	Other	8	673 (1.1%)
	Retired	15	9199 (14.6%)
	Student	11	633 (1.0%)
	Unemployed	16	772 (1.2%)
	Unemployed due to disability/ill health	3	547 (0.9%)
	Unemployed/retired	1	168 (0.3%)
Religion	Buddhism	1	3 (0.0%)
	Christianity	2	164 (0.3%)
	Hinduism	1	27 (0.0%)
	Islam	2	60 (0.1%)
	Judaism	1	2 (0.0%)
	None	2	283 (0.5%)
	Not reported	116	62,268 (99.1%)
	Other	2	32 (0.1%)
Education level	Completed high school	18	7093 (11.3%)
	Completed higher education/professional training	19	19,091 (30.5%)
	Completed primary school	17	829 (1.3%)
	Did not complete high school	4	397 (0.6%)
	Did not complete higher education	4	56 (0.1%)
	Did not complete primary school	3	74 (0.1%)
	First degree	1	27 (0.0%)
	No formal education	10	128 (0.2%)
	Not reported	109	34,952 (55.8%)
People in household	Multiperson household	15	20,902 (33.3%)
	Not reported	113	36,558 (58.2%)
	Other	7	620 (1.0%)
	Single-person household	14	4765 (7.6%)
Residence	Assisted living	2	3 (0.0%)
	Home	5	1445 (2.3%)
	Hospital	2	31 (0.0%)
	Not reported	114	61,294 (97.6%)
	Other	4	12 (0.0%)

higher education or professional training. Only 9 data sets contained data on socioeconomic status comprising 26,951 IPD and were most commonly captured using the Index of Multiple Deprivation (IMD). Data on socioeconomic status were additionally captured using income (personal and household), minimum wage, presence of sufficient income, and whether the individual was benefiting from welfare support. Where data were reported, most participants lived in a multiperson household (15 data sets, IPD = 20,902; 33.3%).

Pre-existing comorbidities were described according to the ICD-10 classification (see *Report Supplementary Material 5*); 7874 (84 data sets,12.5%) had diabetes, 10,438 (74 data sets, 16.6%) were obese, 7891 from 75 data sets (12.6%) had cardiac conditions, 13,936 from 67 data sets (22.2%) had circulatory disorders, and 7923 from 80 data sets (12.6%) had lung disease (see *Table 5*).

Time to recovery

The time to COVID-19 recovery was reported in two data sets (IPD = 839), with a median time of 12 days (IQR 8–15).

Mortality data

Death was reported in 35 data sets, with a total of 22,956 participants. Data on death took the form of time to death (23 data sets, IPD = 10,576) or survival status at a fixed follow-up time point. Three-month mortality from the study baseline was reported in 24 data sets (IPD = 9304) and 1-year mortality from the study baseline was reported in 21 data sets (IPD = 5515).

Intervention data

The intervention data were available for the selected data sets. The most commonly reported intervention was corticosteroid group medications, which were reported in 35 data sets (IPD = 10,361), followed by antiviral group medications (28 data sets, IPD = 7239; *Table 7*).

Healthcare resource use including later hospitalisation

Data on later hospitalisation after COVID-19 were available in 10 data sets, totalling 4881 IPD. Data were primarily captured in an acute setting, precluding analysis at longer follow-up times. In total, 589/4881 (12.1%) were hospitalised during the course of follow-up; 545/4270 (12.8%) were initially hospitalised with COVID-19 and were rehospitalised, while 44/607 who were not initially hospitalised for COVID-19 infection were later hospitalised during the course of follow-up. Data on other resource use categories including use of primary and secondary health care, social care services or use of informal care were not available. Length of hospital stay was available in 57 data sets (IPD = 12,919) but was related to the acute admission and not to long-term outcomes.

Health utilities

EQ-5D-3L[125] and EQ-5D-5L[126] data were available for 11 data sets (IPD = 7880). A further 6 data sets and 1164 IPD reported on the SF-36.[127]

Impact on work

Data on the impact on working patterns were selectively available, and included return to work, affected ability to work, missed work, burnout, type of work, adjustment to working conditions, employment pre- and post-COVID-19,

TABLE 7 Interventions reported in the PRECIOUS database

Intervention	Number of data sets	IPD
Hydroxychloroquine	21	7602
Antiepileptics	1	533
Catecholamine	1	301
Paracetamol	1	206
Non-steroidal anti-inflammatory drug	1	206
Pembrolizumab	1	620
Statin	4	1329
Thiazolidinedione	1	620
Ivermectin	6	2006
Rehabilitation	7	365
Upamostat	1	61
Inhaler	1	500
Opaganib	1	463
Placebo	1	333
Muscle_relax	1	144
Proning	9	4154
Vasopressors	6	4480
Monoclonal_ab	1	144
_1MNA_supplementation	1	50
Aerobic_exercise	1	30
Anti_fungal_treatment	1	72
Catecolamine	0	0
Cytosorb	1	132
Ecmo	9	4379
Low_dose_pharmacological_venous	0	0
Metamizol__dipirone_	2	208
Multidisciplinary_rehabiltation	0	0
Neuromuscular_blocking_agents	3	608
Olfactory_training	0	0
Oxygen_therapy	20	5818
Physiotherapy	0	0
Pulmonary_rehabilitation	0	0
Rehabilitation_and_treatment	0	0
Respiratory_physiotherapy	0	0
Shenhuang_granule	1	171

continued

TABLE 7 Interventions reported in the PRECIOUS database (*continued*)

Intervention	Number of data sets	IPD
Transcranial_direct_stim	0	0
Nox66	1	45
Corticosteroids_group	35	10,361
Anticoagulants_group	26	10,745
Renal_group	7	6862
Antibiotics_group	27	10,625
Antiviral_group	28	7239
Antiplatelets_group	8	2571
Immunosuppressant_group	22	10,410
Bloodproducts_group	11	2727
Antihypertensive_group	6	2021
Diabetes_group	1	620
AFO_202_BETA_GLUCAN_group	1	24
Opioid_group	2	739
Vitamins_group	3	655

hours worked, and work rhythm (discussed further in *Chapter 12*). Return to work or school was available from two data sets (IPD = 851). Affected ability to work or requirements for adjustments to work were available from four data sets (IPD = 516).

Research question 1: long-term outcomes after COVID-19, by International Classification of Functioning, Disability and Health

Assessment instruments included in PRECIOUS

We conducted an inventory for each of the assessment instruments included in contributed studies. We identified 137 unique assessment instruments; *Table 2* describes available assessment instruments, allocated to an overarching outcome domain. Briefly, outcome assessment data were available across the domains of anxiety and depression, breathing, COVID-19 severity and recovery, cognition and thinking, cognitive failures, coping with daily life, frailty, morning and evening preference, nutrition, occupational gaps, overall health status, pain, physical activity and performance, resilience and self-efficacy, sexual function, sleep, smell, strength, stress, tiredness and fatigue, and well-being and life. Assessment of long-term outcomes varied across studies and domains; anxiety outcomes had a median follow-up time of 184 days (IQR 83–278); breathlessness had a median follow-up time of 180 days (IQR 76–276); cognition multidomain assessment was assessed at a median of 191 days (IQR 115–270); pain severity was assessed at a median of 193 days (IQR 147–340.5); mobility was assessed at a median of 193 days (IQR 138–253); and quality of life was assessed at a median of 225 days (IQR 114–358).

Long-term outcomes, by International Classification of Functioning, Disability and Health domain: evidence availability and gaps

Figure 3 summarises the evidence available by ICF domain. The majority of the outcome data were mapped to the domain of body functions, including measures of anxiety and depression, breathing, cognition and thinking, energy and fatigue. Fewer studies included assessment instruments that mapped to the domain of activity and participation, and evidence gaps were evident for environmental factors and body structure. *Report Supplementary Material 6* describes the full placement of assessment instruments within the ICF framework, grouped by the domain of analysis.

FIGURE 3 Image of the interactive evidence gap map.

Long-term outcomes at different time points

Data on each of the long-term outcomes available for meta-analyses, transformation of assessment instruments into a standardised format and presentation of scores at different time points are presented in *Chapters 4–9*, stratified by domain of assessment, alongside analysis of RQ2 for convenience.

COVID-19 symptom data

The PRECIOUS database collated information on 158 unique COVID-19 symptoms across 71/116 data sets, including 31,210 IPD. A full list of symptom data, sorted by highest prevalence at baseline, is available in *Report Supplementary Material 7*. As this was a meta-analysis, we selected those symptoms that were reported across more than one data set, and where more than 500 participants experienced symptom, to reduce variability due to very small sample sizes. The resultant population described 34 unique symptoms, with the most prevalent at 0–7 days after COVID-19 onset being weakness (IPD = 5397/6553; 82.4%) (*Table 8*). The remaining 5 most common symptoms experienced at 0–7 days of onset were fever (6183/8815; 70.1%), cough (9597/14,650; 65.5%), fatigue (1636/3053; 53.6%) and dyspnoea (6142/12,135; 50.6%). We observed heterogeneity in the reporting of symptom data across different studies; the range of symptoms captured varied between 1 and 37 per data set (*Figure 4*).

Symptom data availability over time

Symptom data were available from 0 day to 7 days post-COVID-19 onset to > 1 year post onset. Overall, 71/116 data sets (IPD = 27,670) reported on participants who were COVID-positive at the time of original study inclusion or who had prior COVID. Among those who were COVID-19 positive at the original study baseline/had prior COVID, symptoms were reported in 44 data sets (IPD = 14,544) between 0 day and 7 days post-COVID-19 onset, 33 data sets (IPD = 6042) at 3 months, 27 data sets (IPD = 5812) at 6 months, and 24 data sets (IPD = 7163) beyond 12 months of COVID-19 onset.

Data from nine studies included participants with a COVID-negative result at the original study's baseline (IPD = 3540). In this population between 0 day and 7 days, IPD was available from 1865 participants in 6 data sets; at 3 months, IPD was available from 2358 participants from 5 data sets; at 6 months IPD was available from 2427 participants from 3 data sets and beyond 12 months, IPD was available from 2539 participants from 2 data sets.

Two data sets reported on the subsequent development of COVID-19 during the follow-up period. Where this was reported, we accounted for COVID-19 development before follow-up assessment by excluding those participants from the prevalence analysis at the corresponding follow-up time points.

Symptom prevalence by COVID-positivity

Symptom prevalence at different time points, stratified by COVID-19 positivity at original study inclusion, is described in *Report Supplementary Material 67*, *Figure S1* for the 34 unique symptoms that were observed in the meta-analysis population (see *Table 8*). Trends in prevalence varied over time; confounding was evident, particularly in the COVID-negative population, due to sparse data or the development of newly acquired COVID-19 during the follow-up period. This meant that symptom prevalence could not be solely attributed to the original infection/negative status but could be due to newly developed or persistent COVID.

Risk of bias

Data on RoB at data set level are described using MMAT, which is available in *Report Supplementary Material 8*; this is categorised by RCTs, non-randomised comparative studies and qualitative descriptive studies (non-comparator studies). Using the MMAT criteria, 20 studies were characterised as RCTs, 43 studies were described as non-randomised comparison studies, and 53 were described as qualitative descriptive studies (including surveys, cross-sectional studies and non-comparison studies).

TABLE 8 Prevalence of unique symptoms in meta-analysis population, where IPD > 500

Unique symptom	Percentage reporting symptoms at 0–7 days post onset	Number reporting symptoms at 0–7 days post onset	Number of usable IPD at 0–7 days post onset
Weakness	82.36	5397	6553
Fever	70.14	6183	8815
Cough	65.51	9597	14,650
Fatigue	53.59	1636	3053
Dyspnoea	50.61	6142	12,135
Headache	48.80	2282	4676
Sleep_problems	38.70	197	509
Chills	36.85	213	578
Nasal_congestion	36.56	242	662
Lethargy	32.28	164	508
Myalgia	30.00	3136	10,452
Anosmia_ageusia	27.50	3907	14,207
Appetite_prob	22.34	162	725
Sore_throat	20.77	2060	9918
Arthralgia	20.12	452	2247
Chest_pain_tight_indrawing	19.47	1923	9876
Nausea_vomit	18.17	637	3506
Pain	17.91	200	1117
Sputum	15.61	1179	7551
Diarrhoea	14.27	1949	13,654
Cognitive_confusion	12.49	222	1777
Abdominal_pain	12.26	239	1950
Asthma_wheezing	10.92	152	1392
Rhinorrhea	10.81	926	8568
Eye_irritation	10.42	69	662
Palpitations	10.36	695	6706
Haemoptysis	4.05	50	1235
Ear_pain	2.11	28	1329
Rash	1.689	23	1361
Bleeding	1.201	17	1407
Seizures	1.049	15	1430
Conjunctivitis	0.77	64	8345
Lymphadenopathy	0.67	9	1344
Skin_ulcer	0.44	6	1366

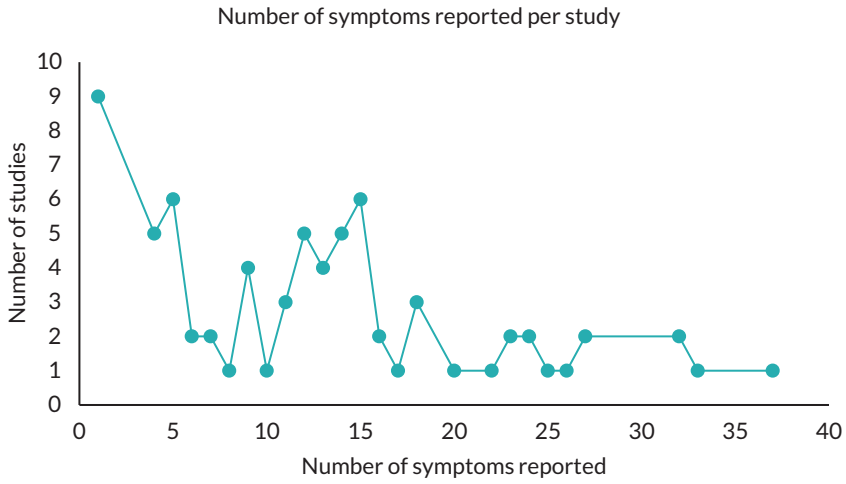

FIGURE 4 Heterogeneity in number of symptoms reported across PRECIOUS studies.

Discussion

Representativeness of participants

The PRECIOUS database synthesised data from 116 COVID-19 studies, including more than 62,000 individuals. We built on prior studies that typically included hospitalised participants[128–130] to include community-based participants representing a range of COVID-19 severities. Additionally, data were collected from 40 countries, including across Europe, South America, North America, East and Southeast Asia, and the Middle East. The data are heavily weighted to high-income countries and Caucasian ethnicity. Given the established disparity in health outcomes across certain ethnicities,[131–133] PRECIOUS would benefit from the increased representation of non-Caucasian ethnicities to enable stronger ethnicity-adjusted analyses.

Comparable with other cohorts,[128] the median age of the PRECIOUS participants was 58 years, which represented an older working-age cohort. PRECIOUS included a higher proportion of women (54.4%) than observed in previous cohorts (36.8–44%),[128,129] but a much lower proportion of very severe cases (6.3% in PRECIOUS vs. 25–30.5% in previous cohorts.[128,129] The majority of participants in PRECIOUS (52.8%) were not hospitalised, which reflected our wide eligibility criteria. Thus, we achieved a good representation of the range of COVID-19 severities. The median BMI in PRECIOUS was 26.1 kg/m^2: indicative of an overweight population.[134] Gao *et al.*[135] reported that an increase in BMI > 23 kg/m^2 was associated with an increased risk of severe COVID-19. Thus, using this metric, the PRECIOUS median BMI could represent a high-risk population.

Socioeconomic status was captured across a range of measures, but was not routinely captured across the majority of data sets. As the literature has established the impact of socioeconomic inequity on risk, severity and COVID-19 outcomes,[136,137] the capture of socioeconomic status in future studies is critical to allow for appropriate adjustment in analyses, particularly in international populations.

We also found heterogeneity in the capture of comorbidities across data sets; while existing core outcome set have focused on recommendations for the collection of COVID-19 outcomes,[138,139] additional work may be needed to refine and recommend standardised collection of data on comorbidities.

Interventions

We searched all available studies up to December 2021 and included 20 RCTs. Available interventions include the use of corticosteroids, anticoagulants, renal therapy, antibiotics, antivirals, antiplatelet agents, immunosuppressants, blood products, antihypertensives, opioids and ivermectin. While many COVID-19 intervention studies were recruited from hospital-based settings, a majority of IPD were from community-based settings and included interventions such as rehabilitation. While the overall aim of PRECIOUS was not to examine the efficacy of COVID-19 interventions, the capture of intervention data permits the inclusion of these data in covariate-adjusted analyses.

Long-term outcomes

As early efforts were focused on stopping COVID-19 infections and developing acute interventions for people with COVID-19, initial studies examined the efficacy of interventions.[3,4,6,7,129,140,141] As such, establishing long-term outcomes was not an immediate priority and the PRECIOUS database may not reflect emerging studies that report on long-term outcomes. Nevertheless, COVID-19 outcomes were captured across 137 different assessment instruments that spanned 21 broad outcome domains within PRECIOUS. Most assessment instruments could be mapped to the ICF domain of body functions. We observed a dearth of evidence on the ICF domains of body structures and environmental factors. Evidence was available on measures of activity limitation and participation but not at the same level as body function. Clusters of evidence availability were found for breathing, physical activity and performance, and well-being and life. Recent literature has highlighted the unequal impacts of COVID-19 that lasted beyond lockdown, including impacts on access to services, systems and policy issues, and social functioning outcomes such as loneliness, isolation, concerns about health, reduction in usual activities and impacts on motivation.[142] This finding is congruent with the observed evidence gaps in the PRECIOUS database. Selected outcomes were available beyond 1 year of index COVID-19 for certain domains; however, more high-quality data are required to fully ascertain the impact of socioeconomic and intervention factors on these outcomes.

Time to recovery and mortality

Data on time to recovery were sparse, only being captured in two data sets (IPD = 839); this could be a reflection of the challenges in defining recovery This variable is of particular importance when capturing data on the long-COVID population.[138] In contrast, mortality has been well documented, reflecting the immediate priority at the start of the pandemic to reduce transmission and death. These outcomes are discussed in more detail in *Chapter 10*.

Later hospitalisation

Data on later hospitalisation were not recorded in most studies with little data on the reasons for re-admission.

Symptoms

The unknown nature of COVID-19 necessitated a broad approach to data collection, including inventorying symptoms as they emerged, assessing persistence, and generating definitions of acute and chronic COVID conditions. Similar to the case of long-term outcomes, many of the initial studies took a long-term perspective on symptom persistence,[142] rather than the long-term effects of COVID-19 symptoms on wider outcomes. Observations from PRECIOUS also highlighted the need to standardise the collection of symptom data items and to apply uniform definitions to different symptoms. Existing data collection reflected the novel pathogen nature of COVID-19; however, planning and use of uniform definitions and data items would facilitate future research and reduce national and international variability in data collection practices.

While previous work has described fatigue,[18] cognitive problems and dyspnoea[19,144] as the most prevalent post-COVID symptoms, we observed weakness as the most common, with fatigue and dyspnoea as fourth and fifth most common, respectively. We aimed to build on previous studies by examining symptom prevalence by COVID positivity, but were unable to accurately account for the subsequent development of COVID-19 in the negative population, nor were we able to account for the number of reinfections. Future data collection should include these variables to permit more accurate and informative analyses.

Similarly, the lack of standardisation in data collection of comorbidities[145] meant that we were unable to accurately assess whether symptoms were attributable to COVID-19 or underlying conditions. Similarly, we were unable to confidently assume that symptom persistence was due to the initial COVID-19 infection, subsequent infection, or an underlying condition. Therefore, we coded symptoms as present or absent at a given time point, without inferring persistence.

PRECIOUS brings together data for more than 62,000 participants, describing 137 unique assessment instruments and 158 unique COVID-19 symptoms. Data reflect the initial focus on the impact of COVID-19 on body functions; few data are available for body structure or environmental factors. We observed heterogeneity in the description of pre-existing comorbidities, definition and standardisation of symptoms. Each of these elements would benefit from standardisation. Nevertheless, PRECIOUS data can be used to examine certain long-term outcomes, inform service provision, and plan for future pandemics.

Summary of key findings

- We build on previous work to describe both hospitalised and community-based populations.
- We require more consistent data collection on ethnicity to enable stronger adjusted analysis.
- The impact of socioeconomic status is known from the literature; this should be collected in a standardised way.
- Collection of comorbidity data should be standardised.
- Time to recovery is important and should be routinely collected, particularly in the context of long-COVID.
- Symptom data collection should be standardised.

Chapter 4 Factors associated with long-term overall health, well-being and life, and sleep after COVID-19

Overview

In this chapter, we present our findings on the factors associated with long-term overall health, well-being and life, and sleep after COVID-19. The analyses used a one-stage IPD meta-analysis approach, including only variables that were significant at univariable level. The absence of a variable in the final model does not necessarily mean that it was not a significant factor; it may also indicate that there were insufficient data to be included in the modelling process.

Overall health data availability

Data on overall health were available for the domains of general health and perception of illness.

Subdomain: general health

Data on general health were captured using the PROMIS-57 and PROMIS-29. Data could not be aggregated into a single sum score across these two outcome measurement instruments; therefore, they were not taken forward for further analysis.

Subdomain: illness perception data availability

The Illness Perception Questionnaire was captured in a single data set. As this did not meet our prespecified criteria for meta-analysis, this outcome was not considered in further analysis.

Subdomain: physical functioning data availability

Data on physical functioning, as captured by QoL assessments, were described across eight data sets (IPD = 1511). Outcomes at 3–6 months were described across eight data sets (IPD = 798), 9–12 months for five data sets (IPD = 404), and beyond 12 months for four data sets (IPD = 309, *Figure 5*). There were insufficient data at 9–12 months and beyond 12 months to permit meta-analyses at these time points.

Data transformation

Table 2 describes the outcome measurement instruments that contributed to QoL physical functioning domain. The anchor measure was the physical functioning domain of the SF-36, and all other measures were converted to fit the range of this score. *Report Supplementary Material 9* describes the scores transformed by study.

Research question 1: long-term outcomes

Exploration of prevalence at different time points

Where assessments were conducted between 3 months and 6 months (eight data sets, IPD = 798), the population's median physical functioning score by SF-36 was 76 (IQR 52–89). For the population where follow-up was conducted between 9 months and 12 months (five data sets, IPD = 404), the median score was 67 (IQR 40–87) and for the population in whom follow-up was conducted beyond 12 months (four data sets, IPD = 309), the median score was 71 (IQR 48–89).

Report Supplementary Material 10 describes the availability of covariates for this domain across each follow-up time point. Country, study design, setting, year of study initiation, and country income were always collinear. For an IPD meta-analysis to be performed, there needed to be comparisons within individual data sets; therefore, factors such as the above were typically fixed by study.

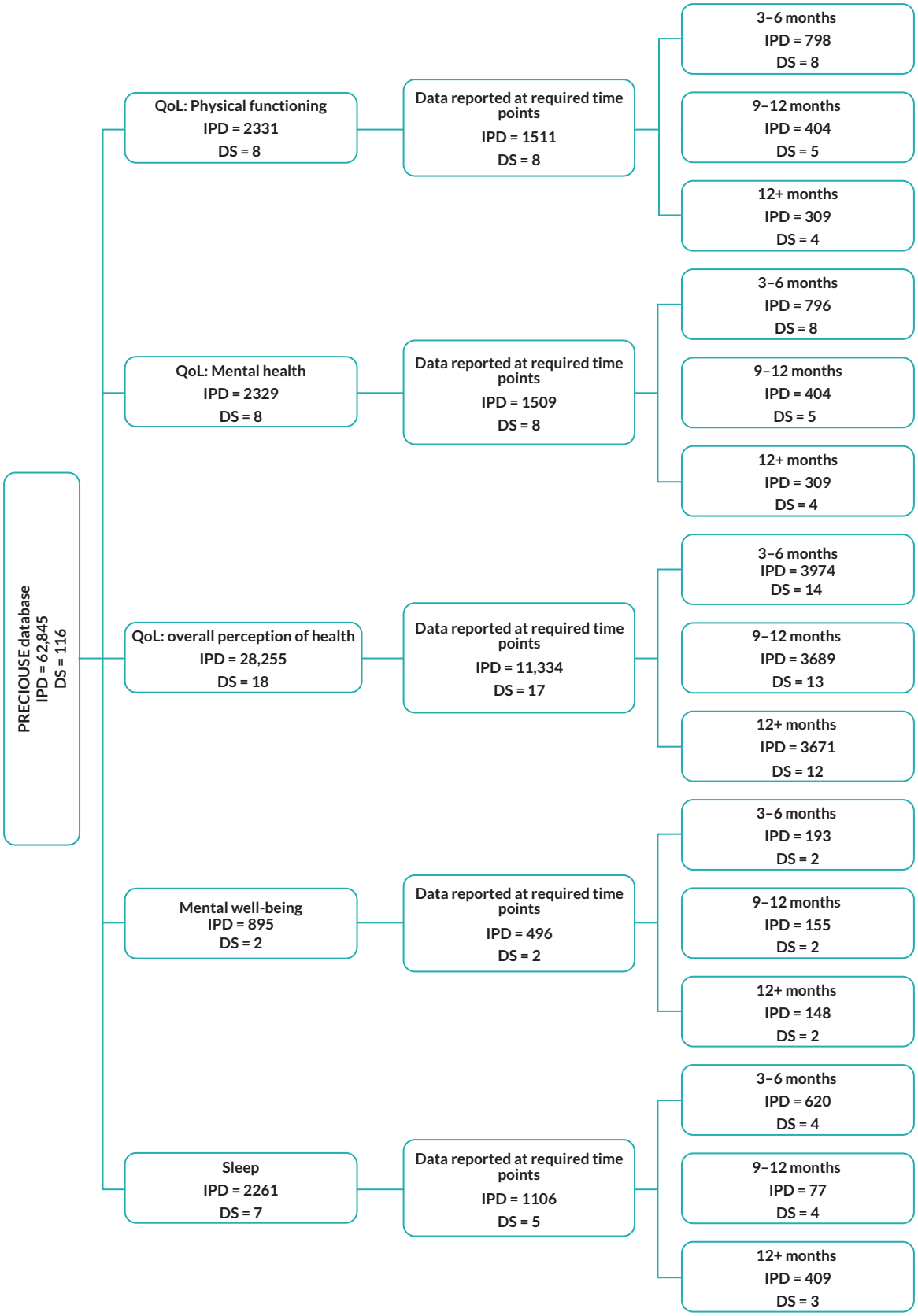

FIGURE 5 Outcome IPD available for analysis, at different long-term time points.

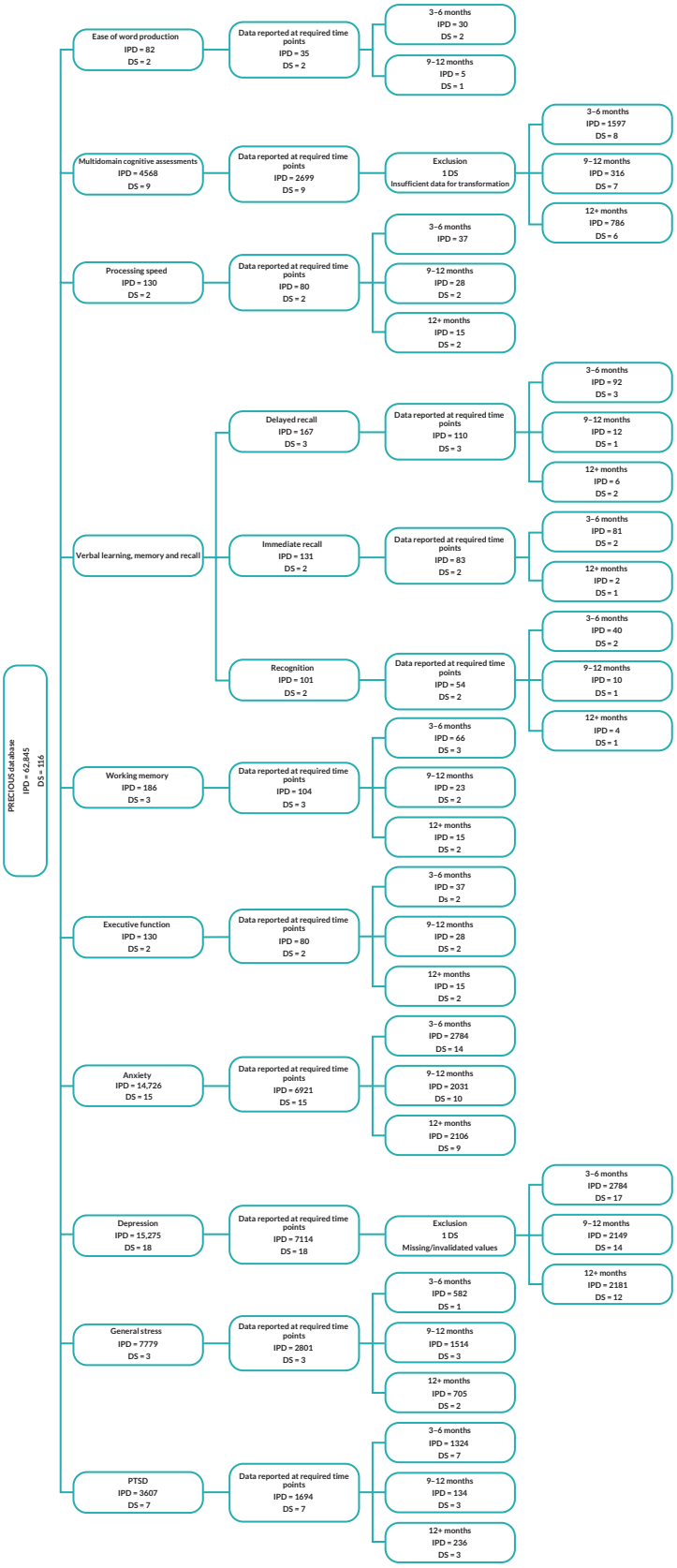

FIGURE 5 Continued

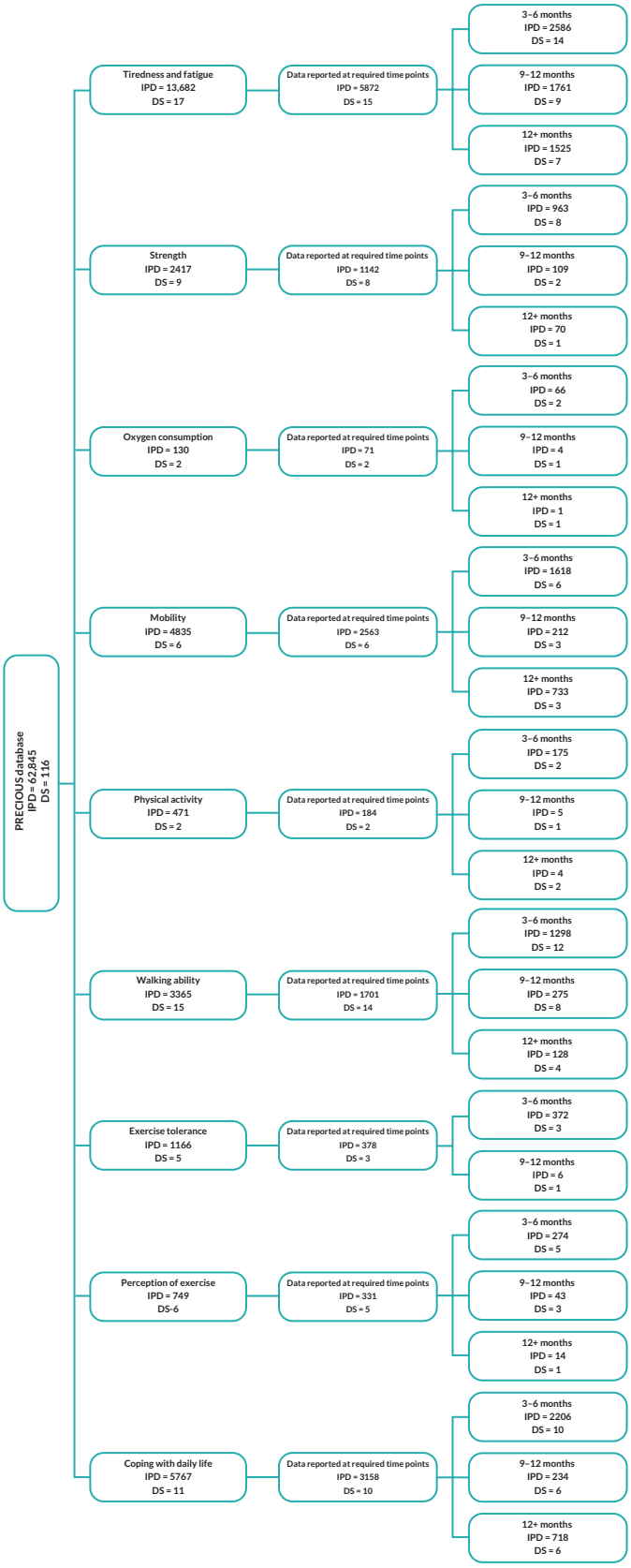

FIGURE 5 Continued

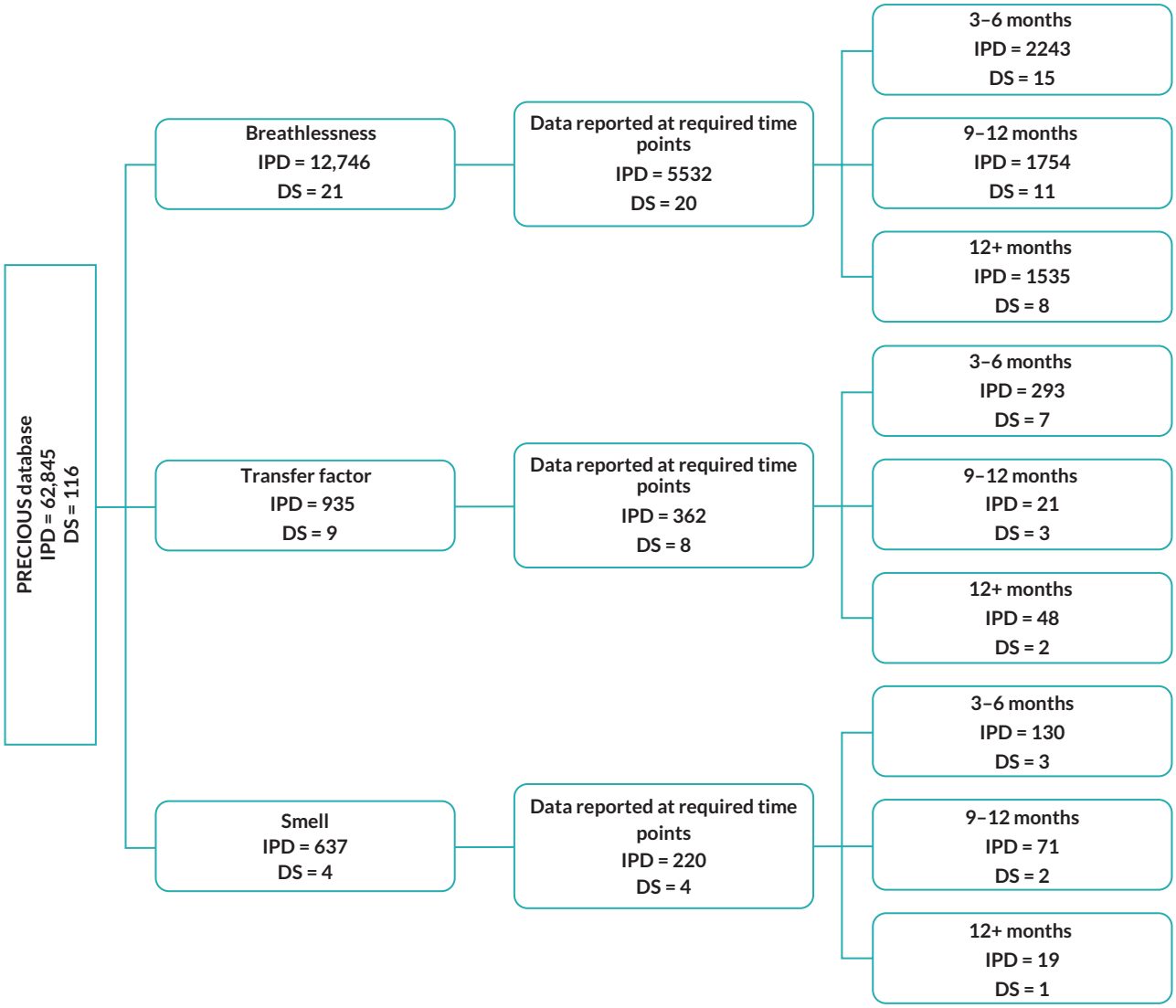

FIGURE 5 Continued

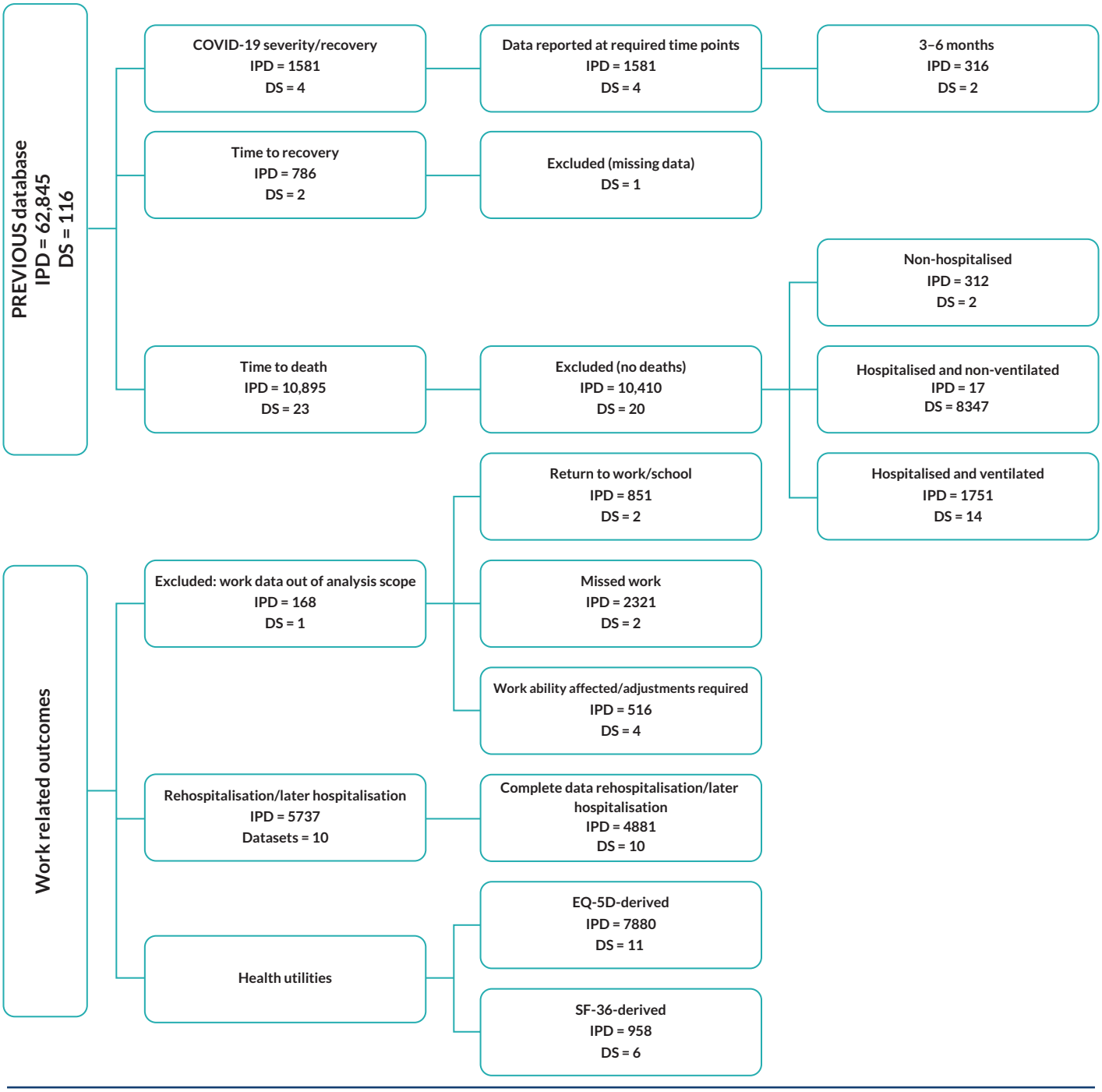

FIGURE 5 Continued

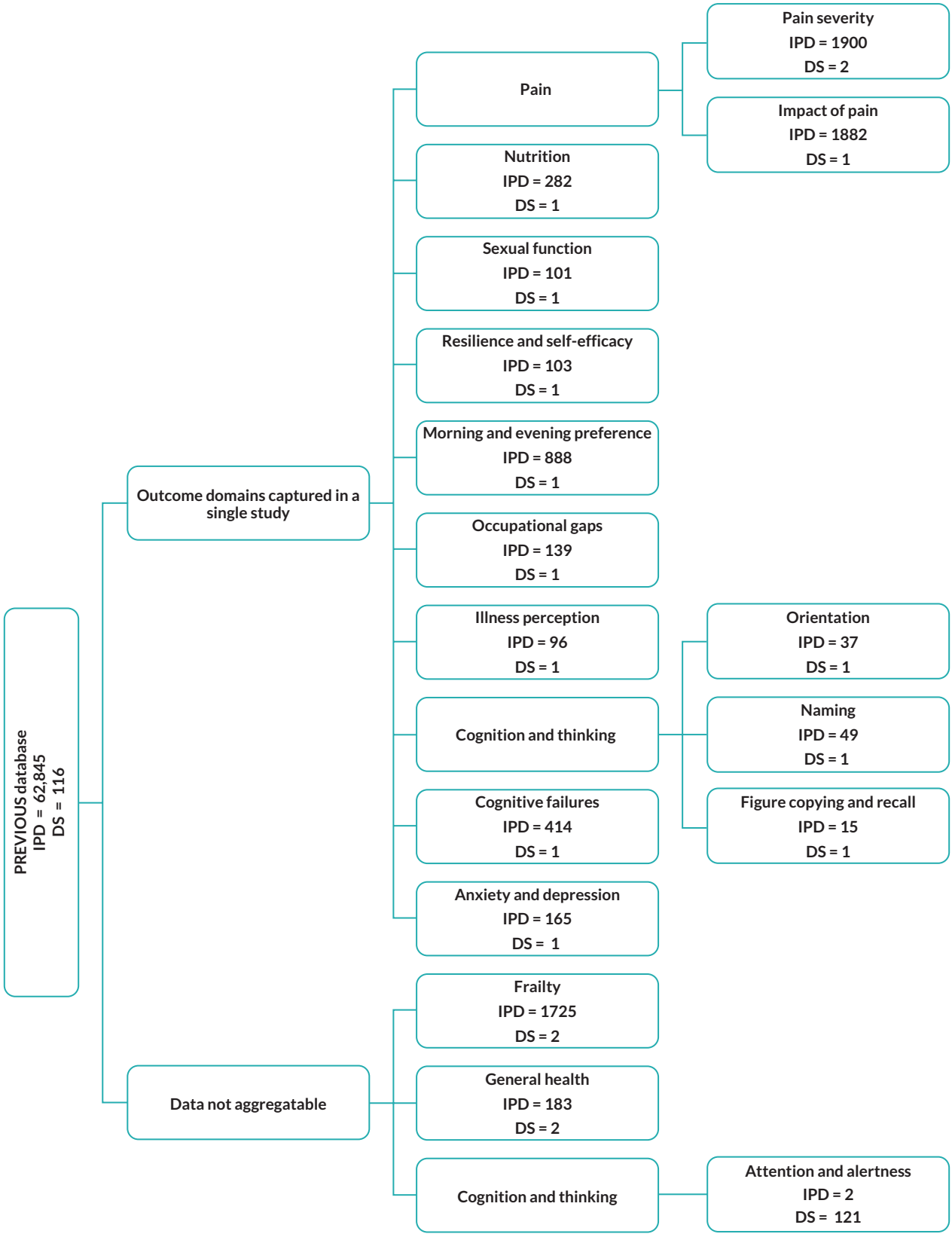

FIGURE 5 Continued

Report Supplementary Material 67, *Figure S2a* describes the physical functioning domain scores at different time points; and *Report Supplementary Material 67*, *Figure S2b-ui* describes scores stratified by demographic and intervention variables. We observed differences in scores over time for sex, BMI category, occupation, year of enrolment, COVID positivity at study baseline, hospitalisation for COVID-19, presence of blood disorders, diabetes, obesity, other endocrine conditions, cardiac conditions, cerebrovascular disease, circulatory disorders, lung disease, chronic kidney disease, factors influencing health status and contact with health services, and use of antivirals. Each of these variables was used in further analyses.

Research question 2: predictors of long-term outcomes

Univariable analysis

For outcomes assessed at 3–6 months, the median age of the population was 56 years, 401 (50.4%) were male, and 328 (42.2%) were community-based participants. At the univariable level, age, sex, COVID-19 positivity at baseline, presence of obesity and lung disease were associated with physical functioning (see *Report Supplementary Material 11*). These were used for multivariable analysis.

Multivariable regression analyses

Where outcomes were available at 3–6 months, in the final multivariable model (six data sets, IPD = 571), physical functioning scores were 0.24 points lower for every year increase in age [p = 0.001, 95% CI (−0.37 to −0.10)]; men had greater physical functioning scores by 6.12 points compared with women [p = 0.001, 95% CI (2.57 to 9.68)], and the presence of obesity was associated with 8.73 lower points scored on the physical functioning scale compared with the absence of obesity [p < 0001, 95% CI (−12.91 to −4.54)] (*Table 9*). The participants who contributed to this final model had a median age of 55 years; 303 (53.1%) were female, and 44 (7.7%) were hospitalised with ventilation.

Assessment of certainty

I^2 based on obesity (as the largest effect size) was 2.55%, indicating a low heterogeneity. GRADE-informed assessment indicated that the quality of the evidence was low certainty downgraded for imprecision and indirectness because of the inclusion of selected populations including hospitalised/critically ill/long-COVID populations; see *Report Supplementary Material 69*, *Table a*).

Subdomain: mental health

Mental health, as reported in QoL assessments, was available for eight data sets (IPD = 1509). Data were available at 3–6 months for eight data sets (IPD = 796), at 9–12 months for five data sets (IPD = 404), and beyond 12 months for four data sets (IPD = 309; see *Figure 5*).

TABLE 9 Final multivariable regression model for factors associated with poorer quality of life physical functioning domain scores

3–6 months ***D* = 6, IPD = 571** **I^2 (obesity) = 2.55%**	**Estimate of difference (95% CI)**	***p*-value**
Age	−0.24 (−0.37 to −0.10)	0.001
Sex (ref = female)	6.12 (2.57 to 9.68)	0.001
Obesity (ref = no)	−8.73 (−12.91 to −4.54)	< 0.001

Note
No evidence of an interaction.

Data transformation

Table 2 describes the outcome measurement instruments that contributed to this domain. All mental health data were standardised using the SF-36 mental health domain score. *Report Supplementary Material 12* describes the standardised scores by study.

Research question 1: long-term outcomes

Exploration of prevalence at different time points

For the population in whom mental health was assessed between 3 months and 6 months (eight data sets, IPD = 796), the median mental health score by SF-36 was 77 (IQR 58–89). Where mental health was assessed at 9–12 months (five data sets, IPD = 404), the population's median score was 74 (IQR 48–87). Where mental health was assessed beyond 12 months (four data sets, IPD = 309), the population's median score was 76 (IQR 52–89). *Report Supplementary Material 67*, *Figure S3* describes mental health scores at different follow-up time points.

Report Supplementary Material 13 describes covariate availability for this outcome. *Report Supplementary Material 67*, *Figure S3b-si* shows the mental health scores at different follow-up time points, stratified by demographic and intervention groups. We observed differences in scores over time for sex, year of recruitment into the study, presence of blood disorders, circulatory disorders, factors influencing health status and contact with health services, and the use of corticosteroids or antivirals. Each of these variables was used for further analysis.

Research question 2: predictors of long-term outcomes

Univariable analysis

Sufficient data for meta-analyses were only available only for outcomes at 3–6 months. At the univariable level, only sex and obesity were significantly associated with mental health scores (see *Report Supplementary Material 14*).

Multivariable regression analyses

Where outcomes were assessed at 3–6 months, in the final multivariable model (data sets = 8, IPD = 794), men had better mental health scores than women by 6.8 SF-36 domain points [$p < 0.001$, 95% CI (3.67 to 9.87)], and no other variables were significant at the 1% level (*Table 10*). The median age of participants in this final model was 56 years (IQR 46–64), 53 (6.9%) were initially hospitalised, requiring ventilation, and 400 (50.4%) were male.

Assessment of certainty

The I^2 value based on sex was 0.87%, indicating low heterogeneity. GRADE-informed assessment indicated that the quality of evidence was low certainty (downgraded for imprecision and indirectness because of the inclusion of selected populations including hospitalised/critically ill/long-COVID populations; see *Report Supplementary Material 69*, *Table b*).

Subdomain: overall perception of health data availability

Participants' overall perception of health was captured across 17 data sets (IPD = 11,334); data were available at 3–6 months in 14 data sets (IPD = 3974), at 9–12 months in 13 data sets (IPD = 3689), and beyond 12 months in 11 data sets (IPD = 3668; see *Figure 5*).

Data transformation

Table 2 describes the outcome measurement instruments that contributed to this domain. All perception of health data were standardised and presented on the EuroQoL-5L VAS. *Report Supplementary Material 15* describes the transformed measures, by study.

TABLE 10 Final multivariable regression model for factors associated with quality-of-life mental health domain scores

3–6 months ***D* = 8, IPD = 794** **I^2 (sex) = 0.87%**	**Estimate of difference (95% CI)**	***p*-value**
Sex (ref = female)	6.77 (3.67 to 9.87)	< 0.001

Research question 1: long-term outcomes

Exploration of prevalence at different time points

Where assessments were available between 3 months and 6 months (14 data sets, IPD = 3974), the population's median EQ VAS score was 80 (IQR 70–90). Where assessment was available between 9 months and 12 months (13 data sets, IPD = 3689), the median score was 85 (IQR 75–92), and where assessment was conducted beyond 12 months (11 data sets, IPD = 3668), the median score was 84 (IQR 74–90).

Report Supplementary Material 16 describes the covariates available for analysis of this outcome. *Report Supplementary Material 67*, *Figure S4a* shows the EQ-VAS scores at different time points. *Report Supplementary Material 67*, *Figure S4b-eii* describes scores at different time points, stratified by demographic and intervention groups, where available. We observed differences across settings, age groups, sex, ethnicities, education level, BMI categories, smoking status, occupation, number of people in the household, COVID-19 positivity at baseline, hospitalisation with COVID-19, overall COVID severity, COVID-19 vaccination status at baseline, presence of other infections, cancer, diabetes, obesity, other endocrine conditions, mental/behavioural disorders, dementia/Alzheimer's, neurological conditions, cerebrovascular diseases, circulatory disorders, lung disease, chronic kidney disease, immunosuppressant conditions, external causes of morbidity/mortality and use of rehabilitation. Each was taken forward for further analysis.

Research question 2: predictors of long-term outcomes

Population description

Where follow-up was available at 3–6 months (14 data sets, IPD = 3974), the population's median age was 56 years, 1723 (44.1%) were male, and 348 were hospitalised and ventilated (8.8%). Where follow-up was conducted at 9–12 months (13 data sets, IPD = 3689), the median age of the population was 54 years, 1382 (39%) were male and 45 (1.2%) were hospitalised and ventilated. Where follow-up was conducted beyond 12 months (11 data sets, IPD = 3668), the population's median age was 55 years, 1504 (41.3%) were male, and 325 (8.9%) were hospitalised with ventilation requirements.

Univariable analysis

At 3–6 months at the univariable level, age, sex, education level, BMI, smoking status, employment status, number of people in the household, hospitalisation, presence of blood disorders, diabetes, obesity, other endocrine conditions, mental/behavioural disorders, neurological conditions, cardiac conditions, circulatory disorders, lung disease, chronic kidney disease, immunosuppression, musculoskeletal conditions and use of oxygen therapy were each associated with QoL (see *Report Supplementary Material 17*).

At 9–12 months, sex, education, smoking status, employment status, number of people in the household, COVID-19 positivity at baseline, presence of cancer, diabetes, obesity, mental/behavioural disorders, cardiac conditions, circulatory disorders, lung disease, chronic kidney disease and immunosuppression were all associated with QoL (see *Report Supplementary Material 17*).

Beyond 12 months, sex, education, smoking status, occupation, employment status, number of people in the household, COVID-19 positivity at baseline, hospitalisation, vaccination status at baseline, presence of diabetes, obesity, mental/behavioural disorder, neurological conditions, cardiac conditions, circulatory disorders, lung disease, chronic kidney disease, immunosuppression and use of renal therapy were each associated with QoL (see *Report Supplementary Material 17*).

Multivariable regression analyses

Where follow-up was available at 3–6 months, in the final multivariable model (three data sets, IPD = 1766) for every year increase in age, EQ VAS was lower by 0.6%; for every unit increase in BMI, EuroQoL-VAS was lower by 1.7%. Men had a 15% higher EQ VAS score than women; those hospitalised had a 30% lower EuroQoL-VAS than those who were not hospitalised. People with immunosuppression, cardiac conditions and lung disease had lower EuroQoL-VAS scores by 25%, 27% and 11%, respectively (*Table 11*), than those without these conditions. The median age of the population that contributed to this final model was 57 years; 505 (28.6%) were male and 181 (10.3%) were hospitalised and ventilated.

TABLE 11 Final multivariable models for factors associated with poorer overall perception of health scores

	Estimate (95% CI)	Ratio (95% CI)	*p*-value
3–6 months ***D* = 3, IPD = 1766** ***I*²[a]**			
Age	0.006 (0.004 to 0.009)	1.006 (1.004 to 1.009)	< 0.001
Hospitalised (ref = no)	−0.35 (−0.51 to −0.19)	0.70 (0.60 to 0.82)	< 0.001
BMI	−0.017 (−0.022 to −0.012)	0.983 (0.978 to 0.988)	< 0.001
Sex (ref = female)	0.14 (0.06 to 0.21)	1.15 (1.07 to 1.24)	< 0.001
Immunosuppression (ref = no)	−0.30 (−0.40 to −0.19)	0.75 (0.67 to 0.83)	< 0.001
Cardiac conditions	−0.31 (−0.47 to −0.16)	0.73 (0.63 to 0.86)	< 0.001
Lung disease (ref = no)	−0.11 (−0.19 to −0.04)	0.89 (0.83 to 0.97)	0.004
9–12 months ***D* = 4, IPD = 2818** ***I*² (hospitalised) = 0.00%**			
Hospitalised (ref = no)	−0.42 (−0.54 to −0.29)	0.66 (0.58 to 0.75)	< 0.001
Obesity (ref = no)	−0.24 (−0.31 to −0.16)	0.79 (0.73 to 0.85)	< 0.001
Immunosuppression (ref = no)	−0.30 (−0.41 to −0.19)	0.74 (0.67 to 0.83)	< 0.001
Sex (ref = female)	0.16 (0.09 to 0.22)	1.17 (1.10 to 1.25)	< 0.001
Employed (ref = employed/retired/student)	−0.25 (−0.36 to −0.14)	0.78 (0.70 to 0.87)	< 0.001
Diabetes (ref = no)	−0.23 (−0.36 to −0.11)	0.79 (0.70 to 0.90)	< 0.001
Lung disease (ref = no)	−0.12 (−0.20 to −0.04)	0.89 (0.82 to 0.96)	0.003
Chronic kidney disease (ref = no)	−0.33 (−0.56 to −0.10)	0.72 (0.57 to 0.90)	0.004
12 + months ***D* = 4, IPD = 1932** ***I*²[b]**			
Hospitalised (ref = no)	−0.49 (−0.67 to −0.32)	0.61 (0.51 to 0.73)	< 0.001
Mental behavioural disorder (ref = no)	−0.42 (−0.52 to −0.32)	0.66 (0.60 to 0.72)	< 0.001
Immunosuppression (ref = no)	−0.33 (−0.45 to −0.20)	0.72 (0.64 to 0.82)	< 0.001
Diabetes (ref = no)	−0.27 (−0.38 to −0.16)	0.76 (0.68 to 0.86)	< 0.001
Lung disease (ref = no)	−0.13 (−0.21 to −0.05)	0.88 (0.81 to 0.95)	0.002
Education (ref = higher ed)	−0.12 (−0.20 to −0.03)	0.89 (0.82 to 0.97)	0.005
Chronic kidney disease (ref = no)	−0.29 (−0.50 to −0.07)	0.75 (0.61 to 0.93)	0.009

a Unable to calculate I^2 based on hospitalised, as that is a network variable (not all comparisons are available in all studies). As the next largest effect, I^2 will be calculated on cardiac conditions: $I^2 = 0.00\%$.
b Unable to calculate I^2 based on hospitalised, as that is a network variable (not all comparisons are available in all studies). As the next largest effect, I^2 will be calculated on mental behavioural disorder: $I^2 = 0.00\%$.

Where outcomes were assessed at 9–12 months, in the final multivariable model (four data sets, IPD = 2818) patients who were hospitalised for COVID-19 had a 34% lower mean EuroQoL-VAS score than those who were not, men had a 17% higher EuroQoL-VAS score compared to women, and the unemployed had a 22% lower EuroQoL-VAS score compared to the employed, students, or retired people. Those with obesity had a score that was 21% lower than that of the non-obese participants. Participants with immunosuppression, diabetes, lung disease and chronic kidney disease had lower mean EuroQoL-VAS scores (by 26%, 21%, 11% and 28%, respectively) than those without these conditions (see *Table 11*). The median age of the population that contributed to this final model was 54 years; 1004 (35.6%) were male, and one person was hospitalised and ventilated (0.04%).

Where outcomes were available beyond 12 months, in the final multivariable model (three data sets, IPD = 1932) participants who were initially hospitalised had 39% lower mean EQ VAS scores than those who were not, and those who did not attain higher education had 11% lower scores than those who had completed higher education. People with mental/behavioural disorders (34% lower), immunosuppression (28% lower), diabetes (24% lower), lung disease (12% lower) and chronic kidney disease (25% lower) all had lower QoL compared to their non-comorbid counterparts (see *Table 11*). The median age of the population that contributed to the final model was 58.1 years, 663 (34.4%) were male, and 159 (8.2%) were hospitalised and ventilated.

Assessment of certainty

For the final model at 3–6 months, I^2 was calculated based on cardiac conditions (I^2 0.00%), indicating no heterogeneity. GRADE-informed assessment indicated that the quality of evidence was of moderate certainty (downgraded once for indirectness for inclusion of selected populations, see *Report Supplementary Material 69*, *Table c*).

For the model at 9–12 months, I^2 based on hospitalisation was 0.00%, indicating no heterogeneity. GRADE-informed assessment indicated that the quality of evidence was low (downgraded for imprecision and indirectness because of the inclusion of selected populations, see *Report Supplementary Material 69*, *Table c*).

For the model beyond 12 months, we were unable to calculate I^2 based on hospitalised participants as the largest effect size, as this was a network variable. As the next largest effect, I^2 was calculated based on mental/behavioural disorder (I^2 was 0.00%), indicating no heterogeneity. GRADE-informed assessment indicated that the quality of evidence was low certainty (downgraded for imprecision and indirectness because of inclusion of selected populations, see *Report Supplementary Material 69*, *Table c*).

Subdomain: mental well-being and happiness

Two data sets (IPD = 496) captured data on mental well-being. Data were available at 3–6 months from both data sets (IPD = 193), at 9–12 months (IPD = 155) and beyond 12 months (IPD = 148, see *Figure 5*).

Data transformation

Data on mental well-being were standardised to the Somatic and Psychological HEalth REport (SPHERE), with a higher score indicating poorer mental well-being (see *Report Supplementary Material 18*). *Table 2* describes the outcome measurement instruments that contributed to this domain.

Research question 1: long-term outcomes

Exploration of prevalence at different time points

Where follow-up was available between 3 months and 6 months (two data sets, IPD = 193), the population's median SPHERE score was 5 (IQR 1–12). Where follow-up was conducted at 9–12 months (two data sets, IPD = 155), the population's median score was 5 (IQR 1–11). Where follow-up was available beyond 12 months (two data sets, IPD = 148), the population's median score was 6 (IQR 1–11). *Report Supplementary Material 67*, *Figure S5* a shows SPHERE scores at different time points. We observed lower mental well-being scores within the first month of COVID-19 onset, and higher mental well-being scores after 1 month of onset. We also observed lower mental well-being scores around 10 months after onset. *Report Supplementary Material 67*, *Figure S5b-gi* describes SPHERE scores at different time points, stratified by demographic and intervention groups were available. There were insufficient data for inclusion in meta-analysis.

Sleep

Sleep data availability

Data were available on sleep assessments from five data sets (IPD = 1106). Data were available at 3–6 months in four data sets (IPD = 620), between 9 months and 12 months in four data sets (IPD = 77), and beyond 12 months from three data sets (IPD = 409) *Figure 5*. Data were only available in sufficient numbers to permit meta-analysis for 3–6 months' follow-up.

Data transformation

Table 2 describes the outcome measurement instruments that contribute to the sleep outcome domain. All data were standardised the Pittsburgh Sleep Quality Index (PSQI) (see *Report Supplementary Material 19*).

Population description

Where follow-up was conducted at 3–6 months (four data sets, IPD = 620), the median age of the population was 59 years, 369 (64.9%) were male, 30 (4.9%) were initially hospitalised and ventilated. Meta-analyses were not possible for data beyond 9 months.

Research question 1: long-term outcomes

Exploration of prevalence at different time points

Where data were reported between 3 months and 6 months (four data sets, IPD = 620), the population's median PSQI score was 6, (IQR 3–10). Where data were reported between 9 months and 12 months (four data sets, IPD = 77), the population's median PSQI score was 8, (IQR 5–12), and outcomes were reported beyond 12 months (three data sets, IPD = 409), the population's median PSQI score was 7 (IQR 4–10). Applying a cut-off point of ≥ 5 on the PSQI[145,146] to indicate poor sleep, we observed that when assessment was available at 3–6 months, 412 (66.5%) had poor sleep quality; where assessment was available at 9–12 months, 61 (79.2%) had poor sleep quality; and where assessment was available beyond 12 months, 302 (73.8%) had poor sleep quality. *Report Supplementary Material 20* describes the covariates available used for the analyses. *Report Supplementary Material 67*, *Figure S6* shows the PSQI scores at different time points. We observed differences over time in PSQI score across countries, education levels, BMI categories, occupation, number of people in the household, presence of obesity, immunosuppression and use of antihypertensives. Each of these variables was further examined using univariable and multivariable analyses.

Research question 2: predictors of long-term outcomes

Univariable and multivariable analysis

Only sex was significant at the univariable and multivariable levels (see *Report Supplementary Material 21*). A higher score indicates poorer sleep quality. No transformation of the data was performed to normalise the data, so the estimates could be interpreted directly. In the final multivariable model (three data sets, IPD = 569). men had a lower PSQI score, indicative of greater sleep quality compared with women, by 1.27 points on the PSQI scale (*Table 12*). In this final model, 369 were male (64.9%), 29 were hospitalised and ventilated (5.1%) and the median age was 59 (IQR 50–68).

Assessment of certainty

The I^2 based on sex was 0.67%, indicating a low heterogeneity. GRADE-informed assessment indicated that the quality of evidence was low certainty (downgraded for imprecision and indirectness because of the inclusion of selected populations in the final model; see *Report Supplementary Material 69*, *Table d*).

Discussion

Domains of physical functioning and mental health

Physical functioning and mental health domain scores were available from 1511 IPD (eight studies) within PRECIOUS. However, we lacked data on sufficient covariates to allow meaningful analyses. This represents a gap in the evidence available from the PRECIOUS database. We described significantly poorer physical functioning domain scores in women

TABLE 12 Final multivariable regression model for factors associated with sleep

3–6 months ***D* = 3, IPD = 569** **I^2 (sex) = 0.67%**	**Estimate (95% CI)**	***p*-value**
Sex (ref = female)	−1.27 (−2.02 to −0.53)	0.001

at 3–6 months; this is supported by the work of Milesavic *et al.*[148] Our observed lower physical functioning scores in women were comparable to the sex differences seen in non-COVID populations.[149] Our aim was not to limit analyses to the long-COVID population, but to describe long-term outcomes after COVID-19 infection. We were unable to account for the impact of persistent COVID-19 symptoms, as these data could not be reliably ascertained. Nevertheless, we established the association of poorer outcomes in the physical functioning domain with female sex, increasing age and the presence of obesity in the COVID-19 infected population.

Previous work has described deterioration across all domains of the SF-36 at 3 months and 12 months after COVID-19 compared to the general population, with the greatest differences seen in the physical and emotional domains.[150] This is supported by other work,[148] which described substantially lower physical functioning domain scores compared with the general population before and during the pandemic. The importance of these domains of assessment has been highlighted in a recent consensus activity to develop a core outcome set for the post-COVID condition, where the SF-36 was mentioned as a potential instrument that should be considered for further discussion.[138] Further research is needed to ascertain the impact of COVID-19 on the long-term QoL domains of physical functioning and mental health, including adjustment for the presence of long-COVID.

Overall perception of health

Quality of life emerged as a prominent outcome of interest after COVID-19, reflected in the depth of data available for analysis. Initial hospitalisation for COVID-19, the presence of lung disease, and immunosuppression remained significantly associated with poorer perception of health at each long-term follow-up time point. Beyond 9 months, markers of socioeconomic status, such as unemployment and lower education level, were significantly associated with poorer overall perception of health. Socioeconomic status is related to health literacy[151,152] and unhealthy behaviours.[153] Additional work is needed to examine which aspects of overall health are affected across different socioeconomic levels. This will also inform the development of support strategies to improve overall QoL. We observed that female sex was associated with poorer overall perception of health at 3–6 and 9–12 months, but not beyond 12 months of initial infection. Despite the known sex differences in health-related QoL[154] across a range of conditions, further work is needed in the context of COVID-19 to ascertain the factors associated with such sex differences. In particular, living conditions and levels of dependency appear to play a role, with women with children under the age of 14 years and single mothers reporting poorer QoL.[155] While we were able to examine the impact of the number of people in the household on QoL, we did not examine marital status or number of dependents. Previous studies have determined that the presence of a family and partnership is associated with better QoL.[155,156] The adverse impacts of COVID-19 on women have been linked to increased housework and child care owing to the pandemic.[157]

Long-COVID has been identified as a specific target for intervention, with rehabilitation interventions having a positive impact on a range of outcomes, including exercise capacity and QoL.[158] While our analysis did not differentiate between those with and without long-COVID, we highlighted the impact of infection on overall perception of health, as well as the important and changing roles of comorbidities throughout long-term follow-up. We highlight populations who may benefit from extra monitoring such as those with lung disease or those who are immunosuppressed, and the different comorbidity profiles that are significantly associated with poorer outcomes at each time point. We built on previous work to examine an international population using a large sample size and a validated and clinically meaningful assessment instrument.[126]

Mental well-being and happiness

For our purposes, the mental well-being, and happiness domains included the SPHERE, which assesses mental distress and fatigue,[159] and the WEMWBS, which includes affective-emotional, cognitive-evaluative and psychological functioning.[160] Each aspect of mental health requires further investigation in the context of COVID-19.

Sleep

Only four studies included in the PRECIOUS database reported outcomes related to sleep. Thus, sex was available across the three data sets, but we lacked adequate data on covariates for meaningful analyses. Therefore, the impact of COVID-19 on long-term sleep quality remains unclear.

Sleep disturbances are common following any-cause hospital admissions.[161] Pandemic-related lockdown is known to have an impact on sleep disturbances, and links have been established with poorer mental health.[162] In particular,

isolation has been linked to poor sleep quality.[163,164] A previous analysis of 843 participants described ongoing COVID-19 symptoms, mental health issues, sex and rating of general health as being associated with changes in sleep patterns.[162] However, these findings were based on a cross-sectional study. Previous work has also found links between long-COVID and sleep disturbances[165,166] with 41% of people with long-COVID reporting mild-to-moderate sleep issues.[167] Additionally, sleep disturbance has been linked with breathlessness, anxiety and muscle weakness.[168] Future research should include covariate-adjusted analyses to ascertain the relationship between long-term sleep disturbances, long-COVID and mental health in the context of COVID-19.

Summary of key findings

- In the COVID-positive population, we observed that women had poorer QoL-related physical function, mental health and overall perception of health compared with men, across each time point examined.
- Hospitalisation for initial COVID-19 infection was consistently associated with poorer overall perception of health compared with non-hospitalisation.
- We identified several vulnerable populations, including those with immunosuppression and lung disease, who had poorer overall perception of health compared to their unaffected counterparts. These populations may benefit from additional monitoring or support.
- We observed that people with lower levels of education had poorer overall perception of health beyond 12 months of COVID-19 infection, compared to those with higher education levels, potentially indicating a long-term impart of equity and socioeconomic status.

Chapter 5 Factors associated with long-term cognition and thinking after COVID-19

Overview

This chapter describes the factors associated with COVID-19 outcomes in the overarching domain of cognition and thinking. The absence of a variable in the final model does not necessarily mean that it was not a significant factor; it may also indicate that there were insufficient data to be included in the modelling process. For the most part, country, study design, setting, year of study initiation and country income were always collinear. For a meta-analysis to be performed, there needs to be comparisons within studies, so factors such as the above were fixed by study.

Cognition and thinking

Subdomain: attention alertness data availability

Data on attention and alertness was captured using Test of Attentional Performance and the National Institute of Health (NIH) Toolbox: Attention. Attentional Performance data included phasic alertness, intrinsic alertness, reaction times, and errors, while available NIH Toolbox Attention data included a single sum score for the domain. Data from these two assessment instruments could not be aggregated. Thus, the data for each measurement instrument were informed by a single data set that did not meet our minimum sample size; therefore, this outcome was not taken forward for further analysis (see *Figure 5*).

Subdomain: orientation data availability

Orientation was captured using the Barcelona Test in a single data set (IPD = 37) and was therefore not considered for further analysis (see *Figure 5*).

Subdomain: naming data availability

Naming was captured using the Boston Naming Test from the Consortium to Establish a Registry for Alzheimer's Disease – Plus Battery (CERAD) in a single data set (IPD = 49). This outcome was therefore not taken forward in further analysis (see *Figure 5*).

Subdomain: figure copying and recall data availability

The figure copying and recall data were captured in a single data set (IPD = 15) and were therefore omitted from further analyses (see *Figure 5*).

Subdomain: ease of word production data availability

Data were available from 2 data sets on 35 IPD on the ease of word production. Thus, there were insufficient data to perform further analysis (see *Figure 5*).

Subdomain: processing speed data availability

Processing speed was assessed using 2 data sets, including 80 IPD. Two data sets (IPD = 37) captured processing speed at 3–6 months, two data sets captured outcomes at 9–12 months (IPD = 28), and two data sets captured outcomes beyond 12 months (IPD = 15). There were insufficient data to take forward for further analyses (see *Figure 5*).

Subdomain: verbal learning, memory and recall data availability

Data were available on delayed recall for 110 participants from 3 studies, immediate recall for 83 participants from 2 studies, and recognition for 54 participants from 2 studies (see *Figure 5*).

Delayed recall was standardised to the Rey Auditory Verbal Memory (delayed) test, immediate recall was standardised to the Rey Auditory Verbal Memory (immediate) test, and recognition was standardised to the Rey Auditory Verbal

Memory (recognition) test. Examination of data availability across each follow-up time point and the variables available for analysis concluded that there were insufficient IPD to permit further analysis.

Subdomain: cognitive failures data availability

The Cognitive Failures Questionnaire was captured in a single data set and therefore omitted from further analysis (see *Figure 5*).

Subdomain: working memory data availability

Data on working memory were available from three studies (IPD = 104); outcomes were available at 3–6 months from three data sets (IPD = 66); at 9–12 months for two data sets (IPD = 23) and beyond 12 months from two data sets (IPD = 15). There were insufficient data for further analysis (see *Figure 5*).

Subdomain: executive function data availability

Data on executive function were available from two studies (IPD = 80). Outcomes were available at 3–6 months for two studies (IPD = 37); at 9–12 months for two studies (IPD = 28), and beyond 12 months for two studies (IPD = 15). Thus, insufficient data were available for further analyses (see *Figure 5*).

Subdomain: multidomain cognitive assessment data availability

Data were available from 10 studies with a multidomain cognitive assessment. One study that used the Short Portable Mental Status Questionnaire only captured data for four IPD observations, which was insufficient to enter into the transformation algorithm. This study was excluded, leaving nine studies (IPD = 2699) on multidomain cognitive assessment instruments (see *Figure 5*) in the analysis data set.

Data transformation

The anchor measure for multidomain cognitive assessment was the Montreal Cognitive Assessment (MoCA). *Table 2* presents the assessment instruments that have contributed to this domain. All data are presented in terms of the points on the MoCA. *Report Supplementary Material 22* describes the transformed values of the MoCA, by study. A higher MoCA score indicates a better outcome.

Population description

Within the population for whom outcome data were available at 3–6 months (eight studies; IPD = 1597), the median age was 58 years; 987 (64.3%) were male and 170 (10.6%) required hospitalisation with ventilation. There were insufficient data to carry out a meta-analysis of outcomes between 9 months and 12 months (see *Report Supplementary Material 23*). Within the population for whom multidomain cognitive assessment data were available beyond 12 months (six studies; IPD = 786), the median age was 58 years, 488 (64.2%) were male, and 169 (21.5%) required hospitalisation with ventilation.

Research question 1: long-term outcomes

Exploration of prevalence at different time points

Report Supplementary Material 67, *Figure S7a* shows the MoCA scores at different time points. The median MoCA score where the outcome was assessed between 3 months and 6 months was 26 (IQR 24–28), the median MoCA score in the population that was assessed at 9–12 months was 26 (IQR 23–28), and in the population in which assessment was available beyond 12 months, the median MoCA score was 27 (IQR 25–28). Using a cut-off of 26 on the MoCA to indicate mild cognitive impairment,[169] we observed that when outcomes were available between 3 months and 6 months, 647 (40.5%) had MoCA < 26. When outcomes were available between 9 months and 12 months, 141 (44.6%) had MoCA < 26, and when assessments were available beyond 12 months, 254 (32.3%) had MoCA < 26. *Report Supplementary Material 67*, *Figure S7b-eii* shows the MoCA scores at different time points stratified by demographic groups and interventions. Differences in MoCA scores were observed across countries, age groups, ethnicities, education levels, occupations, income categories, presence of diabetes and other endocrine conditions, cardiac conditions, cerebrovascular diseases, circulatory disorders, external causes of morbidity and mortality, and use of antivirals. Each of these steps was considered for further analysis.

Research question 2: predictors of long-term outcomes

Univariable analysis

Report Supplementary Material 23 describes the availability of covariates for the analyses. Country, study design, setting, year of study initiation and country income were always collinear. In order for a meta-analysis to be performed, there needs to be comparisons within studies, so factors such as the above were fixed by study. At the univariable level between 3 months and 6 months post onset, age, ethnicity, education level, number of people in the household, diabetes, mental/behavioural disorders, cardiac conditions, cerebrovascular disease, liver disease, chronic kidney disease and anticoagulant use were each associated with MoCA scores (see *Report Supplementary Material 24*). Beyond 12 months, age, ethnicity, education, presence of diabetes, neurological, cardiac, cerebrovascular conditions and corticosteroid treatment use were each associated with cognitive functioning at the univariable level (see *Report Supplementary Material 24*). These factors were examined using a multivariable analysis.

Multivariable regression analyses

Table 13 presents the results of the final multivariable model. A ratio above one indicates a higher level than the reference level of functioning, and a ratio below one indicates a lower level of functioning compared to the reference level. Where data were available at 3–6 months, in the final model (two data sets, IPD = 839), as age increased, there was a slight but highly significant decline in cognitive levels (of 0.8% per year of increasing age; $p \leq 0.001$, ratio of difference = 0.992, 95% CI (0.989 to 0.995)]. Other ethnicities (Arab, Asian, Hispanic/Latinx and other; $p \leq 0.001$,

TABLE 13 Final multivariable regression model for factors associated with cognitive impairment scores

	Estimate of difference (95% CI)	Ratio of difference (95% CI)	*p*-value
3–6 months ***D* = 2, IPD = 839** **I^2 = 0.00%**			
Age (years)	−0.008 (−0.01 to −0.005)	0.992 (0.989 to 0.995)	< 0.001
Ethnicity (ref = White)			
Black	−0.33 (−0.66 to 0.003)	0.72 (0.52 to 1.00)	0.052
Other	−0.28 (−0.40 to −0.16)	0.76 (0.67 to 0.85)	< 0.001
Education (ref = higher ed)			
Did not complete primary	−0.18 (−0.50 to 0.13)	0.83 (0.61 to 1.14)	0.246
Primary/some high	−0.61 (−0.88 to −0.34)	0.54 (0.41 to 0.71)	< 0.001
High/some higher	−0.11 (−0.20 to −0.03)	0.89 (0.82 to 0.97)	0.009
Mental behavioural disorder (ref = no)	−0.14 (−0.25 to −0.04)	0.87 (0.78 to 0.96)	0.005
12+ months ***D* = 2, IPD = 566** **I^2 = 55.75%**			
Age (years)	−0.011 (−0.015 to −0.006)	0.989 (0.984 to 0.994)	< 0.001
Cardiac conditions (ref = no)	−0.11 (−0.23 to 0.003)	0.89 (0.80 to 1.00)	0.056
Ethnicity (ref = White)			
Black	−0.62 (−0.92 to −0.33)	0.53 (0.40 to 0.72)	< 0.001
Asian	−0.22 (−0.39 to −0.05)	0.80 (0.68 to 0.95)	0.013
Other	−0.46 (−0.81 to −0.10)	0.63 (0.45 to 0.90)	0.012
Education (ref = higher ed)			
Did not complete primary	−0.41 (−0.75 to −0.06)	0.67 (0.47 to 0.94)	0.023
Primary/some high	−0.54 (−0.97 to −0.11)	0.58 (0.38 to 0.90)	0.014
High/some higher	−0.20 (−0.31 to −0.08)	0.82 (0.73 to 0.92)	0.001

ratio of difference = 0.76, 95% CI (0.67 to 0.85)] had significant decreases in cognitive functioning compared to White ethnicity. Those with only a primary education [$p \leq 0.001$, ratio of difference = 0.54, 95% CI (0.41 to 0.71)] scored lower on measures of cognitive functioning than those who completed high school [$p = 0.009$, ratio of difference = 0.89, 95% CI (0.82 to 0.97)], which in turn, was poorer than those who completed higher or professional training. Participants with mental/behavioural disorders also had significantly poorer cognitive functions [$p = 0.005$, ratio of difference = 0.87, 95% CI (0.78 to 0.96)]. The median age of participants in the final model was 57 years (IQR 47–66), 484 (60.4%) were male, and 45 (5.4%) were hospitalised with ventilation.

Where data were available beyond 12 months, in the final model (two data sets, IPD = 566) as age increased, there was a slight but highly significant decline in cognitive levels on this scale (decline of 1.1% per year of increasing age; $p \leq 0.001$, ratio of difference = 0.989; 95% CI (0.984 to 0.994)]. Black, Asian, and Other (Arab, Hispanic/Latinx, other) ethnicities each have significant decreases in cognitive levels compared to White ethnicity. However, the sample sizes were very small in the final data set (IPD = 20, 65, and 13, respectively, compared to 468 White); therefore, the findings should be treated with caution, but noted as marked differences. The median age of the participants who contributed to this model was 59 years; 354 (64.1%) were male and 143 (25.3%) were hospitalised and initially ventilated.

Assessment of certainty

The I^2 based on mental behavioural disorders was 0.00% for follow-up at 3–6 months, indicating no heterogeneity. GRADE-informed assessment indicated that the quality of evidence was low (downgraded for imprecision and inclusion of selected populations). I^2 based on cardiac conditions at follow-up beyond 12 months was 55.75%, indicating moderate heterogeneity.[37] GRADE-informed assessment indicated that the quality of evidence was very low (downgraded for imprecision, inclusion of selected populations and inconsistency, see *Report Supplementary Material 69*, *Table e*).

Discussion

Older age, certain ethnicities and lower levels of education were associated with lower cognitive functioning scores on the MoCA. At 3–6 months, the presence of mental/behavioural disorders was associated with poorer function. Caution is needed when interpreting ethnicity and educational findings, as these were based on small sample sizes. Nevertheless, these findings provide avenues for future research. Data were not widely available on cognitive subdomains of attention and alertness, orientation, naming, figure copying and recall, ease of word production, processing speed, verbal learning, memory and recall, cognitive failures, working memory or executive function; each of these themes also represents areas of further research need.

Post-COVID cognitive dysfunction (PCCD) is a recognised condition arising from an initial infection.[170] Impairments in attention, memory, executive function, processing speed and learning are known complications of COVID-19.[171–174] Each of these subdomains of cognition was represented in the PRECIOUS database, but not in sufficient numbers to allow meta-analysis. A key characteristic of PCCD is its occurrence at least 3 months from the initial onset.[172,173] Additionally, cognitive decline has been linked with severe COVID-19[175] and long-COVID.[176] While COVID-19 severity (non-hospitalised vs. hospitalised participants) was available in our data set and examined for significance as part of univariable analyses, the presence of long-COVID was not examined in the analyses. Future work should include the presence of long-COVID.

Cognitive failure refers to errors during the performance of everyday tasks that ordinarily can be completed successfully.[177,178] Only a single data set in the PRECIOUS database reported cognitive failures, precluding this domain from our meta-analysis. However, this represents an important area for further investigation, as it provides a direct link between cognitive impairment and its impact on everyday life. A recent study demonstrated that people with COVID-19 reported more cognitive failures in the workplace than compared with people who were COVID negative.[174] The median age of participants in the 3–6 months follow-up group was 58 years, with the median ages of participants who contributed to the final model being 57 and 59 years at 3–6 months and beyond 12 months, respectively. This represents a population that will generally remain in the workforce. At 3–6, we observed that, for this population, the median MoCA score was 26, which was the threshold for mild cognitive impairment.[169] In addition, repeated lockdowns

and social isolation have been found to affect cognitive function.[179,180] Further analyses should adjust for loneliness and isolation in the context of post-COVID cognitive functioning.

Analysable data within PRECIOUS were in the form of multidomain cognitive assessments; the data were standardised to the MoCA sum score. The MoCA includes the domains of executive function, naming, memory/recall, attention, language, abstraction and orientation.[169] While subdomain scores are typically scored individually in our sample, only the sum scores were available from the contributed data sets. Therefore, we were unable to synthesise evidence from the individual components of MoCA. Furthermore, we were unable to ascertain which components of the MoCA drive changes in cognitive function.

Studies from early in the pandemic identified changes in brain structure, potentially associated with COVID-19,[181] including effects on the hippocampus and grey matter in people with long-COVID.[182] Further work is needed to examine long-term multidomain cognitive outcomes, supplemented by examination of structural changes in the brain, to provide an evidence base to support rehabilitation.[183]

We observed that for the populations in whom cognitive function was assessed at 3–6 months and 9–12 months respectively, median MoCA was 26, whereas for the population in whom cognitive assessment was conducted beyond 12 months, the median MoCA score was 27. Continued screening of people who have had COVID-19 and have a subclinical score on cognitive functioning may be beneficial.

Summary of key findings

- Future work should include examination of cognitive function in the context of long-COVID.
- We need data on cognitive failures as they provide a link between functioning and impact on everyday life.
- Our models included participants aged 57–59 years, and represented a working age population. Median MoCA where follow-up was conducted at 3–6 months was 26, which is the cut-off for mild cognitive impairment.
- We need additional information on which domains of cognitive function drive changes in cognition.

Chapter 6 Factors associated with long-term anxiety and depression after COVID-19

Overview

This chapter describes the factors associated with long-term outcomes in the overarching domains of anxiety, depression and stress. The latter domain includes assessments of both general stress and post-traumatic stress disorder (PTSD). The absence of a variable in the final model does not necessarily mean that it was not a significant predictor; it may also indicate that there were insufficient data to be included in the modelling process.

Anxiety

Data availability

Data on measures of anxiety alone were available from 15 studies (IPD = 6921). Outcomes at 3–6 months were available for 2784 participants (data sets = 14), at 9–12 months for 2031 participants (10 data sets), and beyond 12 months for 2106 participants (nine data sets; see *Figure 5*).

Population description

Outcomes were assessed between 3 months and 6 months (14 data sets, IPD = 2784), the median age of the population was 60 years, 1654 (60.7%) were male, and 306 (11%) had the highest level of COVID-19 severity and were hospitalised with ventilation. Where outcomes were assessed between 9 months and 12 months (10 data sets, IPD = 2031), the median age of the population was 51 years, 996 (49.7%) were male, and 53 (2.6%) were hospitalised with ventilation. Where outcomes were assessed beyond 12 months (nine data sets, IPD = 2106 participants), the median age of the population was 53.5 years, 1080 (52.1%) were male, and 184 (8.8%) were hospitalised with ventilation.

Data transformation

Data were standardised to the HADS-A. *Table 2* describes the outcome measurement instruments that contributed to this domain. The transformed HADS-A score distributions for each study are described in *Report Supplementary Material 25*. Higher scores on the HADS-A indicate a higher level of anxiety.

Research question 1: long-term outcomes

Exploration of prevalence at different time points

Report Supplementary Material 67, *Figure S8a* shows the prevalence of anxiety scores at different follow-up time points. The median (IQR) anxiety scores for the population in whom anxiety was assessed at 3–6 months was 4 (IQR 1–7); the median score was the same for the populations in whom anxiety was assessed at 9–12 and beyond 12 months. When applying a threshold of HADS-A score > 8 to indicate mild anxiety,[184] 567 (20.8%) in whom follow-up was conducted at 3–6 months had mild anxiety; where follow-up was conducted at 9–12 months, 320 (15.8%) had mild anxiety and where follow-up was conducted beyond 12 months, 363 (17.2%) had mild anxiety. *Report Supplementary Material 67*, *Figure S8b-cii* describes HADS-A scores by demographic groups and intervention category; differences in HADS-A scores were apparent across age categories, sex, religion, BMI categories, smoking status, occupation, number of people in the household, initial hospitalisation for COVID-19, COVID-19 severity, diabetes, obesity, presence of mental/behavioural disorders, dementia/Alzheimer's, neurological conditions, circulatory disorders, lung disease, conditions, chronic kidney disease, immunosuppressant condition and anticoagulant use. Each of these factors was further investigated using univariable and multivariable analyses.

Research question 2: predictors of long-term outcomes

Univariable analysis

Report Supplementary Material 26 describes the variables available for analysis at each time point. Significant univariable associations with anxiety scores at each follow-up time point are described in *Report Supplementary Material 27*. At 3–6 months follow-up, age, sex, smoking status, occupation, number of people in the household, hospitalisation for COVID-19, presence of a mental or behavioural disorder, neurological conditions, circulatory disorder, lung disease, gastrointestinal and musculoskeletal conditions were each significantly associated with greater anxiety at univariable level. At 9–12 months, sex, smoking history, occupation, number of people in the household, hospitalisation, COVID-19 severity at baseline, diabetes, obesity, presence of a circulatory disorder, lung disease and immunosuppression were significantly associated with increased anxiety. Beyond 12 months, age, sex, smoking status, employment status, number of people in the household, initial hospitalisation for COVID-19, COVID-19 severity at baseline, presence of neurological conditions and immunosuppression were each significantly associated with increased anxiety (see *Report Supplementary Material 27*). These variables were taken forward to stepwise multivariable modelling, where $p < 0.1$.

Multivariable regression analyses

The final models for each follow-up period are listed in *Table 14*. A ratio below one indicates that the effective (non-reference) group is lower than the reference group, and a ratio above one indicates that the effective group is greater than the reference group.

For the group in which follow-up was available at 3–6 months, we observed an interaction between hospitalisation and age and therefore performed separate subgroup analyses for initially hospitalised and non-hospitalised participants. In this model (five data sets, IPD = 1394) for the initially hospitalised subgroup, men had lower anxiety scores than women [$p \leq 0.001$; ratio of difference = 0.8, 95% CI (0.74 to 0.87)]; anxiety scores decreased with increasing age [$p < 0.001$, ratio of difference = 0.99, 95% CI (0.985 to 0.991)]; those with lung disease had higher scores (worse anxiety) than those without [$p < 0.001$; ratio of difference = 1.28; 95% CI (1.17 to 1.40)]; and people with neurological conditions had higher anxiety scores than those without [$p = 0.003$; ratio of difference = 1.32; 95% CI (1.10 to 1.58)]. The median age of the population that contributed to this final model was 59 years, and 884 (63.4%) patients were male. For the final model (two data sets, IPD = 569) in the initially non-hospitalised subgroup, men had lower anxiety scores than women ($p \leq 0.001$, ratio of difference = 0.78; 95% CI of the ratio of 0.70 to 0.87), and people with a circulatory disorder had higher anxiety scores than those without ($p = 0.008$, ratio of difference = 1.24, 95% CI 1.06 to 1.44). For the population that contributed to this model, the median age was 47 years and 281 (49.4%) patients were male.

Where data were available between 9 months and 12 months, in this final model (three data sets, IPD = 1679) initially hospitalised participants had higher anxiety scores compared with non-hospitalised participants [$p = 0.001$, ratio of difference = 1.2, 95% CI (1.08 to 1.33)]. Men had lower anxiety scores than women [$p < 0.001$, ratio of difference = 0.82; 95% CI (0.78 to 0.87)]. People with presence of lung disease had higher anxiety scores than those without lung disease [$p = 0.002$, ratio of difference = 1.19; 95% CI (1.07 to 1.33)]. Those not in employment (including retired, students, unemployed, household managers, or not working due to ill health) had higher anxiety scores than those in employment [$p = 0.049$, ratio of difference = 1.08; 95% CI (1.0 to 1.17)]. We also observed an interaction between employment and smoking status such that a person who was unemployed had an 8% higher anxiety score than an employed person. Smokers had a 7% higher anxiety score than non-smokers. However, an unemployed person who smoked had a 38% higher score than employed non-smokers. In the population that contributed to this model, the median age was 49 years, 820 (48.8%) were male, and 135 (8%) were hospitalised.

Beyond 12 months in the final model (four data sets, IPD = 1340), participants who were initially hospitalised had worse anxiety scores compared with non-hospitalised participants [$p < 0.001$, ratio of difference = 1.3, 95% CI (1.17 to 1.45)]. Men had lower anxiety scores compared with women [$p < 0.001$, ratio of difference = 0.84; 95% CI (0.79 to 0.88)]. Anxiety scores decreased with increasing age [$p < 0.001$, ratio of difference = 0.996; 95% CI (0.994 to 0.998)], and non-employed people had higher anxiety scores than those in employment [$p < 0.001$, ratio of difference = 1.18, 95% CI (1.10 to 1.26)]. For the population that contributed to this model, median age was 49 years, 610 (45.5%) were male and 106 (7.9%) were hospitalised.

TABLE 14 Final multivariable regression model for factors associated with anxiety

	Estimate of difference (95% CI)	Ratio of difference (95% CI)	*p*-value
Hospitalised			
3–6 months **D = 5, IPD = 1394** **I^2 (neuro) = 0.00%**			
Sex (ref = female)	−0.22 (−0.30 to −0.14)	0.80 (0.74 to 0.87)	< 0.001
Age (as year increase)	−0.012 (−0.016 to −0.009)	0.988 (0.985 to 0.991)	< 0.001
Lung disease (ref = no)	0.25 (0.16 to 0.34)	1.28 to (1.17 to 1.40)	< 0.001
Neurological conditions (ref = no)	0.28 (0.09 to 0.46)	1.32 (1.10 to 1.58)	0.003
Non-hospitalised			
D = 2, IPD = 569 **I^2 (sex) = 13.29%**			
Sex (ref = female)	−0.25 (−0.36 to −0.14)	0.78 (0.70 to 0.87)	< 0.001
Circulatory disorder (ref = no)	0.21 (0.05 to 0.37)	1.24 (1.06 to 1.45)	0.008
9–12 months **D = 3, IPD = 1679** **I^2 (sex) = 1.35**			
Hospitalised (ref = no)	0.18 (0.07 to 0.29)	1.20 (1.08 to 1.33)	0.001
Sex (ref = female)	−0.20 (−0.25 to −0.14)	0.82 (0.78 to 0.87)	< 0.001
Lung disease (ref = no)	0.18 (0.07 to 0.28)	1.19 (1.07 to 1.33)	0.002
Employed (ref = employed)	0.08 (0.0004 to 0.15)	1.08 (1.00 to 1.17)	0.049
Smoker (ref = non-smoker)	0.07 (−0.005 to 0.15)	1.07 (0.99 to 1.16)	0.067
Employed/smoker interaction (not employed and current/ex smoker)[a]	0.18 (0.04 to 0.31)	1.19 (1.04 to 1.36)	0.01
12+ months **D = 4, IPD = 1340** **I^2 (sex) = 0.00**			
Hospitalised (ref = no)	0.26 (0.16 to 0.37)	1.30 (1.17 to 1.45)	< 0.001
Sex (ref = female)	−0.18 (−0.23 to −0.12)	0.84 (0.79 to 0.88)	< 0.001
Age (years)	−0.004 (−0.006 to −0.002)	0.996 (0.994 to 0.998)	< 0.001
Employed (ref = yes)	0.16 (0.09 to 0.23)	1.18 (1.10 to 1.26)	< 0.001

a A person who is unemployed has an 8% higher score than an employed person. A smoker has an 8% higher score than a non-smoker. However someone unemployed and a smoker has 38% higher score than an employed non-smoker [exp(0.08 + 0.07 + 0.18) or 1.08 × 1.07 × 1.19], rather than just the additive (from the estimates) or multiplicative (ratio) effects of the two factors on their own.

Assessment of certainty

At 3–6 months, I^2 was 0% based on neurological conditions in the hospitalised population and 13.3% based on sex in the non-hospitalised population. At 9–12 months, I^2 based on sex was 1.35%, and beyond 12 months, I^2 based on sex was 0%, indicating low heterogeneity across studies in each model. GRADE-informed assessment indicated that the quality of evidence was low in the hospitalised model at 3–6 months (downgraded for imprecision and indirectness) and high in the non-hospitalised population at 3–6 months (see *Report Supplementary Material 69*, *Table f*). GRADE-informed assessments of the models at 9–12 months and beyond 12 months were of high and low quality, respectively, with the latter model being downgraded for imprecision and indirectness.

Depression

Data availability

Data on measures of depression were available from 18 studies (IPD = 7114). At 3–6 months, 2784 IPD were available from 17 data sets, at 9–12 months, 2149 IPD were available from 14 data sets, and beyond 12 months, 2181 IPD were available from 12 data sets (see *Figure 5*).

Population description

Where outcomes were assessed between 3 months and 6 months (data sets = 17, IPD = 2784), the median age of the population was 57 years, 1620 (59.4%) were male and 306 (11%) were hospitalised with ventilation. For outcomes that were assessed between 9 months and 12 months (14 data sets, IPD = 2149), the median age was 51 years; 1060 (50%) were male and 54 (2.5%) required hospitalisation with ventilation. For outcomes assessed beyond 12 months (12 data sets, IPD = 2181), the median age of the population was 53 years, 1121 (52.2%) were male, and 184 (8.5%) were hospitalised with mechanical ventilation.

Data transformation

Data were standardised to the Hospital Anxiety and Depression Scale-D (HADS-D). *Table 2* shows the outcome measurement instruments that contributed to this domain. The transformed HADS-D score distributions for each study are described in *Report Supplementary Material 28*. A higher HADS-D score indicates worse depression.

Research question 1: long-term outcomes

Exploration of prevalence at different time points

Report Supplementary Material 67, *Figure S9* shows the depression scores at different time points. Where assessments were available at 3–6 months (17 data sets, IPD = 2784), median depression score was 4.33 (IQR 1.5–7), and where depression scores were available at 9–12 months (14 data sets, IPD = 2149 IPD), and beyond 12 months (12 data sets, IPD = 2181), median score was 5 (IQR 1.5–7). Applying a cut-off point of HADS-D > 8 to indicate mild impairment,[184] at 3–6 months 495 (17.8%), at 9–12 months 333 (15.5%), and beyond 12 months, 341 (15.6%) reported mild impairment.

Depression scores differed by country, age group, sex, religion, education level, BMI category, smoking status, occupation, number of people in the household, COVID-19 positivity at study entry, initial hospitalisation for COVID-19, COVID-19 severity, diabetes, obesity, presence of mental/behavioural disorders, neurological conditions, circulatory disorders, lung disease, chronic kidney disease, use of proning and oxygen therapy.

Research question 2: predictors of long-term outcomes

Univariable analysis

Report Supplementary Material 29 describes the covariates available for the analysis at different time points. *Report Supplementary Material 30* describes the significant univariable associations between each variable and depression at follow-up. At 3–6 months age, sex, smoking status, employment, number of people in the household, COVID-19 severity at baseline, presence of other endocrine conditions, mental/behavioural disorders, neurological conditions, lung disease, gastrointestinal conditions, musculoskeletal conditions and antibiotic treatment were each significantly associated with depression. At 9–12 months, age, sex, smoking status, occupation, number of people in the household, initial hospitalisation for COVID-19, presence of cancer, diabetes, obesity, circulatory disorders, lung disease and immunosuppression were each significantly associated with depression. Beyond 12 months, sex, smoking status, employment status, number of people in the household, initial hospitalisation for COVID-19, obesity, mental/behavioural disorders, neurological conditions, lung disease, immunosuppression and musculoskeletal condition were each associated with increased depression.

Multivariable regression analyses

The final models for each follow-up time point are listed in *Table 15*. Where outcomes were available at 3–6 months (three data sets, IPD = 1001), depression scores decreased with every year increase in age [$p < 0.001$, ratio of

TABLE 15 Final multivariable regression model for factors associated with depression

	Estimate of difference (95% CI)	Ratio of difference (95% CI)	*p*-value
3–6 months ***D* = 3, IPD = 1001** **I^2 (mental behavioural) 19.12%**			
Age (year increase)	−0.01 (−0.013 to −0.006)	0.990 (0.987 to 0.994)	< 0.001
Sex (ref = female)	−0.24 (−0.34 to 0.15)	0.78 (0.71 to 0.86)	< 0.001
Lung disease (ref = no)	0.22 (0.12 to 0.32)	1.24 (1.12 to 1.37)	< 0.001
Mental behavioural disorder	0.48 (0.37 to 0.59)	1.61 (1.44 to 1.81)	< 0.001
9–12 months ***D* = 4, IPD = 1722** **I^2 (diabetes) = 0%**			
Age (unit change, year)	−0.002 (−0.004 to −0.001)	0.998 (0.996 to 0.999)	0.001
Sex (ref = female)	−0.11 (−0.16 to −0.07)	0.89 (0.86 to 0.93)	< 0.001
Employed status2 (ref = employed, retired, student[a])	0.27 (0.18 to 0.35)	1.30 (1.20 to 1.42)	< 0.001
Diabetes (ref = no)	0.29 (0.16 to 0.42)	1.33 (1.17 to 1.51)	< 0.001
Cancer (ref = no)	0.17 (0.06 to 0.28)	1.19 (1.07 to 1.32)	0.002
Smoker (ref = never)[b]	0.11 (0.05 to 0.17)	1.11 (1.06 to 1.18)	< 0.001
12+ months ***D* = 4, IPD = 1286** **I^2 (hospitalised) = 0%**			
Hospitalised with COVID (ref = no)	0.14 (0.0 to 0.22)	1.15 (1.06 to 1.24)	< 0.001
Sex (ref = female)	−0.09 (−0.13 to −0.05)	0.91 (0.88 to 0.95)	< 0.001
Obesity (ref = no)	0.07 (0.03 to 0.12)	1.08 (1.02 to 1.13)	0.002
Employed (ref = employed)	0.07 (0.02 to 0.12)	1.07 (1.02 to 1.13)	0.006
Smoker (ref = never)[b]	0.09 (0.02 to 0.16)	1.09 (1.02 to 1.17)	0.009

a Grouped employed, retired, and student together, and all the other categories as unemployed.
b Never vs. current and ex combined.

difference = 0.99, 95% CI (0.987 to 0.994)]. Men had lower depression scores than women [$p < 0.001$, ratio of difference = 0.78, 95% CI (0.71 to 0.86)]. People with lung disease [$p < 0.001$, ratio of difference = 1.24, 95% CI (1.12 to 1.37)], and people with a mental/behavioural disorders [$p < 0.001$, ratio of difference = 1.61; 95% CI (1.44 to 1.81)] had higher depression scores than those without lung disease and mental/behavioural disorders, respectively. For the participants who contributed to this model, the median age was 58 years, 609 (60.8%) were male, and 80 (8%) were hospitalised and ventilated.

Where follow-up was available at 9–12 months, in the final model (four data sets, IPD = 1722) as age increased by 1 year, depression scores decreased [$p = 0.001$, ratio of difference = 0.998, 59% CI (0.996 to 0.999)]. Men had lower depression scores than women [$p < 0.001$, ratio of difference = 0.89, 95% CI (0.86 to 0.93)]. Non-employed people had higher depression scores than those employed, retired or a student [$p \leq 0.001$, ratio of difference = 1.30, 95% CI (1.20 to 1.42)]. People with diabetes [$p < 0.001$, ratio of difference = 1.33, 95% CI (1.17 to 1.51)], cancer [$p = 0.002$, ratio of difference = 1.19, 95% CI (1.07 to 1.32)] and people with a history of smoking [$p < 0.001$, ratio of difference = 1.11, 95% CI (1.06 to 1.18)] had higher depression scores than those without these conditions. For the population that contributed to this model, the median age was 49 years, 841 (48.8%) were male, and 1 (0.1%) was hospitalised and ventilated.

Where data were available beyond 12 months, in the final model (four data sets, IPD = 1286) initially hospitalised participants had higher depression scores than those not initially hospitalised [$p < 0.001$, ratio of difference = 1.15, 95% CI (0.85 to 0.94)]. Men had lower depression scores than women [$p < 0.001$, ratio of difference = 0.91, 95% CI (0.88 to 0.95)]. Obese participants had higher scores than non-obese participants [$p = 0.002$, ratio of difference = 1.08, 95% CI (1.02 to 1.13)]. Non-employed participants (including unemployed, those retired, students, or managing households) had higher depression scores than those in employment [$p = 0.006$, ratio of difference = 1.07, 95% CI (1.02 to 1.13)] and people with a history of smoking had higher depression scores than non-smokers [$p = 0.009$, ratio of difference = 1.09, 95% CI (1.02 to 1.17)]. For the participants who contributed to the final model, the median age was 48 years, 600 (46.7%) were male and none were hospitalised with ventilation.

Assessment of certainty

At 3–6 months, I^2 based on mental/behavioural disorder was 19.12%; at 9–12 months, I^2 based on diabetes was 0%, and beyond 12 months, I^2 based on hospitalisation was 0%, indicating low heterogeneity among studies that contributed to each model. GRADE-informed assessment indicated that the certainty of evidence was moderate in each model, with each being downgraded for indirectness (see *Report Supplementary Material 69*, *Table g*).

Subdomain: anxiety and depression data availability

One assessment instrument (Patient Health Questionnaire-4) captured measures of both anxiety and depression in a single data set. As this did not meet our prespecified criteria for meta-analysis, this outcome was not considered in further analysis.

Stress

Subdomain: general stress

Data availability

Data were available from three studies (IPD = 2801) on measures of general stress. Outcomes at 3–6 months were available for 582 participants from one data set, at 9–12 months for 1514 participants from three data sets and at beyond 12 months for 705 participants from two data sets (see *Figure 5*).

Population description

As data on the 3–6 months outcomes were derived from a single study, these data were not analysed further. For outcomes that were assessed between 9 months and 12 months (data sets = 3, IPD = 1514), the median age of the population was 51 years, 700 (49.6%) were male, and IPD = 1317 (87%) were not hospitalised for COVID-19. For outcomes assessed beyond 12 months (two data sets, IPD = 705), the median age of the population was 48 years, 334 (47.4%) were male, and 645 (91.5%) were not hospitalised.

Data transformation

Data were standardised to the Depression, Anxiety and Stress Scale-21 (DASS-21). *Table 2* describes the outcome measurement instruments that contributed to this domain. A higher DASS-21 stress score indicated a higher stress level. The transformed DASS-21 stress scale scores are presented in *Report Supplementary Material 31*.

Research question 1: long-term outcomes

Exploration of prevalence at different time points

Report Supplementary Material 67, *Figure S10a* shows the transformed general stress scores at different time points. Where general stress scores were assessed at 9–12 months (three data sets, IPD = 1514) and beyond 12 months (two data sets, IPD = 705), the median general stress scores for each of these separate populations was 4 (IQR 0–10). Applying a cut-off of DASS-21-stress > 15,[185] for the population assessed at 3–6 months, 53 (9.1%) had mild stress; where participants were assessed at 9–12 months, 153 (10.1%) had mild stress and 76 (10.8%) had mild stress beyond 12 months.

Report Supplementary Material 67, *Figure S10b-ei* describes the general stress scores at different time points stratified by demographic groups. Significant differences in general stress were evident across participants' sex, level of education, occupation, initial hospitalisation due to COVID-19, COVID-19 severity, presence of lung disease, chronic kidney disease and immunosuppression. Each of these factors was further investigated in univariable and multivariable analyses.

Research question 2: predictors of long-term outcomes

Univariable analysis

Report Supplementary Material 32 describes the variables available for analysis at each time point. At the univariable level at 9–12 months, sex, smoking status, employment status, initial hospitalisation, diabetes, presence of a circulatory disorder, lung disease and immunosuppression were associated with stress by DASS-21 (see *Report Supplementary Material 33*). For outcomes beyond 12 months at the univariable level, sex, smoking status, employment status, initial hospitalisation and immunosuppression were each significantly associated with stress. Each of these factors was examined in multivariable regression analyses.

Multivariable regression analyses

At the multivariable level where data were available at 9–12 months, in the final model (two data sets, IPD = 1344) men had lower stress scores than females [$p < 0.001$, ratio of difference = 0.64, 95% CI (0.57 to 0.72)]. Smokers had higher stress scores than non-smokers and ex-smokers [$p < 0.001$, ratio of difference = 1.26, 95% CI (1.12 to 1.42)]. People with diabetes had a higher stress score than those without [$p = 0.037$, ratio of difference = 1.42, 95% CI (1.02 to 1.97)], and those with immunosuppression had higher stress scores than those without [$p = 0.009$, ratio of difference = 1.55, 95% CI (1.12 to 2.15)]. For the population that contributed to this model, the median age was 49 years, 668 (49.7%) were male, and 1 (0.1%) individual was hospitalised and ventilated.

Where data were available beyond 12 months, in the final model (two data sets, IPD = 698) men had lower stress scores than women [$p < 0.001$, ratio of difference = 0.66, 95% CI (0.56 to 0.78)]. Smokers had higher stress scores than non-smokers and ex-smokers [$p = 0.001$, ratio of difference = 1.34, 95% CI (1.13 to 1.59)], and the unemployed had higher stress scores than the employed, retired and students [$p = 0.003$, ratio of difference = 1.50, 95% CI (1.15 to 1.97)], *Table 16*). The median age of the population that contributed to this model was 48 years; 332 (47.6%) were male, and none were hospitalised and ventilated.

Assessment of certainty

At 9–12 months and beyond 12 months, sex contributed the greatest effect size to the model, and I^2 was 0% across both models, indicating low heterogeneity across studies in each model. GRADE-informed assessment indicated that

TABLE 16 Final multivariable regression model for factors associated with general stress

	Estimate of difference (95% CI)	Ratio of difference (95% CI)	*p*-value
9–12 months ***D* = 2, IPD = 1344** **I^2 (sex) = 0.00%**			
Smoker (ref = never)	0.23 (0.12 to 0.35)	1.26 (1.12 to 1.42)	< 0.001
Diabetes (ref = no)	0.35 (0.02 to 0.68)	1.42 (1.02 to 1.97)	0.037
Immunosuppression (ref = no)	0.44 (0.11 to 0.76)	1.55 (1.12 to 2.15)	0.009
Sex (ref = female)	−0.45 (−0.56 to −0.33)	0.64 (0.57 to 0.72)	< 0.001
12+ months ***D* = 2, IPD = 698** **I^2 (sex) = 0.00%**			
Sex (ref = female)	−0.41 (−0.58 to −0.25)	0.66 (0.56 to 0.78)	< 0.001

the certainty of evidence was moderate for each model, and was downgraded for imprecision (see *Report Supplementary Material 69*, *Table h*).

Subdomain: post-traumatic stress disorder data availability

Post-traumatic stress disorder data were available from seven studies (IPD = 1694). Outcomes at 3–6 months were available from seven studies (IPD = 1324); three studies reported on outcomes between 9 months and 12 months (IPD = 134) and three studies (IPD = 236) reported PTSD outcomes beyond 12 months post onset (see *Figure 5*). Only one study included a non-hospitalised population, making it difficult to separate the hospitalisation effect from the study effect. Meta-analysis requires there to be comparisons within studies and for there to be more than one study with populations in each level; there is strong evidence that the hospitalised population is different from the non-hospitalised population. There were insufficient data to be able to statistically test for a difference, so a single data set with a non-hospitalised population was omitted from further analysis.

Population description

Only the 3- to 6-month outcome population had sufficient data to further analyse PTSD scores. The median age in this population (six data sets, IPD = 1302) was 60 years, 853 (66.8%) were male; all participants were hospitalised, with 187 (14.4%) requiring hospitalisation with ventilation.

Data transformation

Table 2 presents the outcome measurement instruments that contribute to the PTSD domain. Data were standardised to the revised Impact of Event Scale (IESR), where a higher score indicates poorer outcome. The transformed IESR scores are presented in *Report Supplementary Material 34*.

Research question 1: long-term outcomes

Exploration of prevalence at different time points

Report Supplementary Material 67, *Figure S11a* shows the PTSD scores at different time points. The median PTSD score for the population in whom assessment was available at 3–6 months (data sets = 7, IPD = 1324) was 9.4, (IQR 4–20.2). Applying a cut-off score of 33 to indicate the presence of PTSD,[186] we observed that for the population that was assessed at 3–6 months (7 data sets, IPD = 1324), 186 (14.1%) had a score indicative of PTSD. For the population at 9–12 months (three data sets, IPD = 134), 20 (14.9%) had a score indicative of PTSD, and in the population assessed beyond 12 months (three data sets, IPD = 236), 30 (12.7%) had a score indicative of PTSD.

Report Supplementary Material 67, *Figure S11b-cii* shows the scores at different time points stratified by demographic groups. We observed differences in the PTSD scores by country, study design, age group, sex, ethnicity, religion, education level, COVID-19 severity, presence of mental/behavioural disorders, neurological condition, cardiac conditions, lung disease and immunosuppression.

Research question 2: predictors of long-term outcomes

Univariable analysis

Report Supplementary Material 35 describes the variables available for analysis at each time point. At the univariable level at 3–6 months post onset, age, sex, number of people in the household, COVID-19 severity at baseline, presence of lung disease, musculoskeletal conditions and renal therapy were each associated with PTSD (see *Report Supplementary Material 36*). Each of these factors was included in multivariable analysis.

Multivariable regression analyses

Table 17 shows the multivariable regression analyses for PTSD at 3–6 months. In the final model (five data sets, IPD = 1036), men had lower PTSD scores than women [$p < 0.001$, ratio of difference = 0.72, 95% CI (0.62 to 0.83)]. PTSD decreased with increasing age [$p = 0.001$, ratio of difference = 0.991, 95% CI (0.985 to 0.996)] and people with lung disease had higher PTSD scores than people without lung disease [$p = 0.002$; ratio of difference = 1.30, 95% CI (1.10 to 1.53)]. In the population that contributed to this model, the median age was 60 years, 678 (65.4%) were male, and 173 (16.7%) were initially hospitalised and ventilated.

TABLE 17 Final multivariable regression model for factors associated with PTSD

3–6 months ***D* = 5, IPD = 1036** **I^2 (sex) = 0.00%**	**Estimate of difference (95% CI)**	**Ratio of difference (95% CI)**	***p*-value**
Age (year increase)	−0.010 (−0.015 to −0.004)	0.991 (0.985 to 0.996)	0.001
Sex (ref = female)	−0.33 (−0.48 to −0.18)	0.72 (0.62 to 0.83)	< 0.001
Lung disease (ref = no)	0.26 (0.10 to 0.43)	1.30 (1.10 to 1.53)	0.002

Assessment of certainty

At 3–6 months, I^2 (sex) was 0.00%, indicating a low level of heterogeneity. GRADE-informed assessment indicated that the certainty of evidence was low (downgraded due to imprecision and inclusion of only previously hospitalised participants, see *Report Supplementary Material 69*, *Table i*).

Discussion

Women reported consistently worse anxiety, depression, stress and PTSD at each time examined time point. We observed that different comorbidities were associated with poor outcomes at each time point. One year after COVID-19 onset, baseline non-employment was significantly associated with poorer performance on measures of anxiety, depression and general stress. Our findings are consistent with previous work that identified vulnerable groups including women, healthcare professionals, older people and people with an existing mental health condition.[187] While some data sets described participants' occupations or specified healthcare workers, specific occupations were not considered in our analyses. Rather, we described employment status, finding associations with later long-term anxiety, depression and stress. Employment status can infer socioeconomic status, which is also associated with COVID-19 incidence.[188] Additionally, employment contributes to security, and economic uncertainty was prevalent during COVID-19.[189] While we were unable to aggregate sufficient data on other markers of socioeconomic status or levels of deprivation, our findings suggest that these factors continue to play a role beyond the initial infection and can adversely affect mental health after COVID-19.

Additionally, we observed that the presence of mental/behavioural disorders was significantly associated with worse depression scores at 3–6 months. This is congruent with existing work that reports the impact of loneliness and isolation on people with existing mental health problems.[190] COVID-19 necessitated lockdowns and enforced social isolation, which had a profound impact even in other populations,[191,192] but especially on those with an existing mental health condition.[193]

Data on anxiety and depression were captured well in the PRECIOUS database, with more than 14,000 IPD available and ~6000–7000 participants' data available at long-term time points. This permitted IPD meta-analyses of more than 1000 participants in each model, spanning early to late long-term follow-up and including both community-based and hospitalised populations. Stress and PTSD were less well captured in the PRECIOUS database. Nevertheless, sufficient data were available to permit analyses beyond 9 months for general stress and between 3 months and 6 months for PTSD.

Anxiety and depression are known consequences of COVID-19, with an estimated global prevalence increasing by 25% since the start of the pandemic.[194] We observed that in those who were assessable at 3–6 months, 9–12 months and beyond 12 months, scores indicating mild anxiety were prevalent in 20.8%, 15.8% and 17.2% of patients, respectively. The pooled prevalence of depression during COVID-19 in community-based samples was estimated to be 25%,[195] and 23.3% in hospitalised populations[196] and is not limited to people with COVID-19 alone, with an impact on family and friends, especially in the context of severe infection.[197] In our sample, we observed that the prevalence of depression in the populations assessable at 3–6 months, 9–12 months and beyond 12 months was 17.8%, 15.5% and 15.6%, respectively.

There is a pressing need to provide services for the increased population of people with mental health conditions due to COVID-19.[198] We identified populations that may benefit from additional screening for anxiety, depression, general stress and PTSD at different time points in the COVID-19 recovery trajectory. Although the majority of participants exhibited subclinical levels of anxiety, depression, general stress and PTSD, support should be offered to ensure that these do not progress to levels of clinical concern. We provide models that extend beyond 1 year of index infection in international populations and highlight the populations of interest for screening and monitoring.

Summary of key findings

- Women reported consistently lower scores on anxiety, depression, stress and PTSD at each time examined time point.
- One year after COVID-19 onset, baseline non-employment was significantly associated with poorer performance on measures of anxiety, depression and general stress.

Chapter 7 Factors associated with long-term energy, fatigue and strength after COVID-19

Overview

Decreased fatigue and strength have been commonly reported as consequences of COVID-19. We examined factors associated with fatigue and strength, for which data were available during long-term follow-ups. The absence of a variable in the final model does not necessarily mean that it was not a significant predictor; it may also indicate that there were insufficient data to be included in the modelling process.

Energy and fatigue

Subdomain: lack of energy data availability

Lack of Energy was captured using the DePaul Symptom Questionnaire in a single data set and was therefore not included in further analysis.

Subdomain: tiredness and fatigue data availability

Data were available from 15 studies (IPD = 5872) on fatigue. Data were available at 3–6 months for 14 data sets (IPD = 2586), at 9–12 months for 9 data sets (IPD = 1761), and beyond 12 months for 7 data sets (IPD = 1525; see *Figure 5*).

Population description

For those in whom follow-up was available at 3–6 months (14 data sets, IPD = 2586), the median age was 57 years, 1033 (40.8%) were female, and 304 (12.1%) were hospitalised and ventilated. Where data were available between 9 months and 12 months (9 data sets, IPD = 1761), the median age was 51 years, 888 (51%) were male and 53 were hospitalised, and ventilated (3.1%). Where follow-up data were available beyond 12 months (seven data sets, IPD = 1525), the median age was 55 years, with 849 (56.5%) being male, and 179 (11.7%) were hospitalised requiring ventilation.

Data transformation

All fatigue data were standardised to the Fatigue Assessment Scale (FAS), with higher scores indicating worse fatigue. *Report Supplementary Material 37* describes the standardised fatigue scores by data set. *Table 2* presents the assessment instruments that contributed to this domain.

Research question 1: long-term outcomes

Exploration of prevalence at different time points

Where data were assessed at 3–6 months, the median fatigue score by FAS was 21 (IQR 18–25); where data were available at 9–12 months, the median score for the population was 21 (IQR 18–24) and where data were available beyond 12 months, the median score for the population was 21 (IQR 18–23). Applying a threshold of ≥ 22 to indicate significant fatigue,[199] we observed that where follow-up was available at 3–6 months, 1124 (43.5%) had significant fatigue; where follow-up was available at 9–12 months, 738 (41.1%) had significant fatigue, and where follow-up was available beyond 12 months, significant fatigue was present in 585 (38.4%) patients.

Report Supplementary Material 67, *Figure S12* shows fatigue scores by FAS at different time points, stratified by demographic and intervention data. We observed differences by setting, age group, sex, religion, BMI category, smoking, occupation, number of people in the household, year of recruitment, hospitalisation with COVID-19, initial

severity, presence of diabetes, obesity, neurological conditions, circulatory disorders, lung disease, gastrointestinal conditions, immunosuppression and use of antibiotics. Each of these variables was used in further analysis.

Research question 2: predictors of long-term outcomes

Univariable analysis

Report Supplementary Material 38 describes the covariates available for analysis of this domain. Where data were available at 3–6 months, age, sex, ethnicity, education, smoking history, employment status, number of people in the household, hospitalisation, presence of a mental/behavioural disorder, neurological conditions, lung disease, immunosuppression, musculoskeletal conditions and use of oxygen therapy were each associated with fatigue at the univariable level (see *Report Supplementary Material 39*).

Where data were available at 9–12 months at the univariable level, age, sex, BMI, employment status, presence of cancer, diabetes, lung disease and immunosuppression were each associated with fatigue (see *Report Supplementary Material 39*).

Where data were available beyond 12 months, age, sex, BMI, smoking history, hospitalisation, COVID-19 severity, presence of diabetes, mental/behavioural disorders, neurological conditions, chronic kidney disease, immunosuppression and use of renal therapy were each significantly associated with fatigue (see *Report Supplementary Material 39*). Each of these variables was used for multivariable analyses.

Multivariable regression analyses

Where data were available at 3–6 months, in the final multivariable model (three data sets, IPD = 1030), as age increased, the FAS score decreased by 0.3% (ratio of difference = 0.997, 95% CI (0.995 to 0.998)], indicating that younger people had greater levels of fatigue. Men reported 13% lower levels of fatigue than women [ratio of difference = 0.87, 95% CI (0.83 to 0.90)], while the presence of lung disease (12% higher score than without lung disease; ratio of difference = 1.12, 95% CI 1.08 to 1.17), neurological conditions (21% higher score than without neurological conditions; ratio of difference = 1.21, 95% CI 1.10 to 1.33) and musculoskeletal conditions (10% higher score than without musculoskeletal conditions; ratio of difference = 1.10; 95% CI 1.04 to 1.16) were each associated with higher levels of fatigue (*Table 18*). In the population that contributed to the final model at 3–6 months, the median age was 59 years, 619 (60.1%) were male, and 90 (8.7%) were hospitalised and ventilated.

Where data were available at 9–12 months, in the final multivariable model (data sets = 5, IPD = 1594) as age increased, the FAS score decreased by 0.2% (ratio of difference = 0.998, 95% CI 0.997 to 0.999), indicating that younger people reported higher levels of fatigue. Men reported 10% lower levels of fatigue than women (ratio of difference = 0.90, 95% CI 0.88 to 0.93), while the presence of immunosuppression (15% higher scores than absence of immunosuppression, ratio of difference = 1.,5; 95% CI 1.06 to 1.24) and lung disease (8% higher scores than absence; ratio of difference = 1.08, 95% CI 1.03 to 1.13) were associated with higher levels of fatigue (see *Table 18*). In this final model, the median age of the population was 52 years; 829 (52.0%) were male and 46 (2.9%) were hospitalised and ventilated.

Where data were available beyond 12 months, in the final model (data sets = 2, IPD = 722), men reported 10% lower levels of fatigue than females (ratio of difference = 0.90; 95% 0.85 to 0.94), while the presence of mental/behavioural disorders was associated with 26% higher levels of fatigue (ratio of difference = 1.26, 95% CI 1.18 to 1.34) than in the absence of mental/behavioural disorders (see *Table 18*). In the population that contributed to the final model beyond 12 months, the median age was 58 years, 453 (62.7%) were male, and 170 (23.6%) were hospitalised and ventilated.

Assessment of certainty

The I^2 for the final model at 3–6 months (neurological conditions) was 8.97%. The I^2 for the model at 9–12 months (immunosuppression) was 0.00%. I^2 for the model beyond 12 months of onset (mental/behavioural disorder) was 7.94%. This indicated low heterogeneity across all models. GRADE-informed assessment indicated that the quality of evidence was moderate for each model, with each downgraded for indirectness (see *Report Supplementary Material 69*, *Table j*).

TABLE 18 Final multivariable regression model for factors associated with fatigue

	Estimate (95% CI)	Ratio (95% CI)	*p*-value
3–6 months ***D* = 3, IPD = 1030** ***I*² (neurological conditions) = 8.97%**			
Age	−0.003 (−0.005 to −0.002)	0.997 (0.995 to 0.998)	< 0.001
Sex (ref = female)	−0.14 (−0.18 to −0.10)	0.87 (0.83 to 0.90)	< 0.001
Lung disease (ref = no)	0.12 (0.07 to 0.16)	1.12 (1.08 to 1.17)	< 0.001
Neurological conditions (ref = no)	0.19 (0.09 to 0.29)	1.21 (1.10 to 1.33)	< 0.001
Musculoskeletal conditions (ref = no)	0.10 (0.04 to 0.15)	1.10 (1.04 to 1.16)	0.001
9–12 months ***D* = 5, IPD = 1594** ***I*² (immunosuppression) = 0.00%**			
Age	−0.0016 (−0.0024 to −0.0008)	0.998 (0.997 to 0.999)	< 0.001
Sex (ref = female)	−0.10 (−0.13 to −0.08)	0.90 (0.88 to 0.93)	< 0.001
Immunosuppression (ref = no)	0.14 (0.06 to 0.21)	1.15 (1.06 to 1.24)	< 0.001
Lung disease (ref = no)	0.08 (0.03 to 0.12)	1.08 (1.03 to 1.13)	0.001
12+ months ***D* = 2, IPD = 722** ***I*² (mental/behavioural disorder) = 7.94%**			
Sex (ref = female)	−0.11 (−0.16 to −0.06)	0.90 (0.85 to 0.94)	< 0.001
Mental behavioural disorder (ref = no)	0.23 (0.17 to 0.30)	1.26 (1.18 to 1.34)	< 0.001

Strength

Strength data availability

Data were available from eight studies (IPD = 1142) on measures of strength; follow-up was reported at 3–6 months in eight data sets (IPD = 963), at 9–12 months in two data sets (IPD = 109), and at 12+ months in one data set (IPD = 70; *Figure 5*). As data availability at 9–12 months and beyond 12 months did not meet the prespecified requirements for meta-analyses, only follow-up at 3–6 months was considered.

Data transformation

The anchor measure for strength was handgrip strength, with higher scores indicating better functioning. *Table 2* describes the assessment instruments that contributed to this domain. Data were standardised and presented as handgrip strength (kg). *Report Supplementary Material 40* presents the value transformed, by study.

Research question 1: long-term outcomes

Exploration of prevalence at different time points

Where assessments took place between 3 months and 6 months, the median handgrip strength was 32 kg (IQR 23–42); where assessments took place at 9–12 months, median score was 39 kg (IQR 27–47), and where assessments were available beyond 12 months, the median score was 35 kg (IQR 28–42).

Handgrip strength was assessed according to age and sex parameters.[200] In the population where assessment was available at 3–6 months, 205 (23.6%) were deemed to have decreased handgrip strength compared with these age- and sex-matched norms;[200] where assessment was available at 9–12 months, 15 (16.9%) had decreased handgrip than age- and sex-matched norms; and beyond 12 months, 11 (17.2%) had decreased handgrip than age- and sex-matched norms.

Report Supplementary Material 67, *Figure S13a* shows the handgrip strength scores over time, and *Report Supplementary Material 67*, *Figure S13b-cii* presents the strength scores stratified by demographic and intervention groups. We observed differences in the scores over time across age groups, sex, religion, occupation, COVID-19 severity, presence of cardiac conditions, lung disease, use of blood products, rehabilitation, proning and neuromuscular blocking agents. These were used for further analysis.

Research question 2: predictors of long-term outcomes

Univariable analysis

Report Supplementary Material 41 describes the covariates available for analyses. Sufficient data were available for analysis of outcomes between 3 months and 6 months; the median age for this population was 59 years, 298 (31.5%) were female, and the population was mainly hospitalised, with only 34 (3.5%) community-based participants. At the univariable level, age, sex, COVID-19 severity at baseline, requirement for ventilation, presence of diabetes, lung disease and use of corticosteroids were each associated with handgrip strength (see *Report Supplementary Material 42*). These were used for multivariable analyses.

Multivariable regression analyses

At the multivariable level at 3–6 months follow-up, in the final model (seven data sets, IPD = 918), only age and sex were significantly associated with outcomes. No other variables met the threshold for statistical significance. Men had a greater handgrip strength than women by 15.48 kg [$p < 0.001$, 95% CI (14.04 to 16.91)], and increasing age was associated with decreased handgrip strength of 0.27 kg per year (*Table 19*). No interactions were observed, indicating that there was no evidence to suggest that there were differences in the behaviours of variables due to sex differences. The median age of the population in this final model was 59 years; 635 (69.2%) were male and 317 (34.5%) were hospitalised and ventilated.

Assessment of certainty

I^2 based on sex was 11.3%, indicating low heterogeneity. GRADE-informed assessment indicated that the quality of evidence was moderate with downgrading for indirectness (see *Report Supplementary Material 69*, *Table k*).

Discussion

Fatigue

Up to 12 months, we observed that reported fatigue decreased with increasing age, women had consistently higher levels of fatigue than men, and people with lung disease had consistently higher fatigue than those without lung disease. The presence of musculoskeletal and neurological conditions, immunosuppression and mental/behavioural disorders contributed to higher levels of fatigue at different time points.

Fatigue is a known consequence of COVID-19, with COVID-positive patients having a 1.68 times higher risk of fatigue than those without COVID-19.[201] Fatigue is a prominent component of long-COVID.[202–204] In our sample, we were unable to adequately describe the presence of long-COVID, as we could not reliably ascertain whether symptom persistence was attributable to the initial infection. Nevertheless, we observed a decreasing prevalence of fatigue in each of the populations examined at each time point (43.5% in the population in which follow-up was available at 3–6 months, and 38.4% in the population where follow-up was available beyond 12 months). Our prevalence was higher than previous estimates of 12.8% at 6 months[205] after COVID-19 infection, and 19% at 9 months after onset,[206]

TABLE 19 Final multivariable regression model for factors associated with strength

3–6 months *D* = 7, IPD = 918	Estimate of difference (95% CI)	*p*-value
Age	−0.27 (−0.33 to −0.21)	< 0.001
Sex (ref = female)	15.48 (14.04 to 16.91)	< 0.001

but lower than estimates generated at 7 months in hospitalised populations.[207] Our estimate of notable fatigue beyond 12 months was congruent with the existing literature, reporting a prevalence of 34% at 12 months.[208]

While previous studies have reported an association between COVID-19 severity and fatigue,[209–212] we observed that COVID-19 severity (by hospitalisation) was not significantly associated with higher levels of reported long-term fatigue in our sample. We were able to establish comorbidity profiles associated with higher levels of long-term fatigue; however, we were unable to examine other psychosocial factors associated with fatigue, such as availability of a partner, resilience, contact with primary care, use of medications and neuroticism, which were examined in other studies.[213] Konig *et al.*[213] established a link between fatigue and low levels of education; while education was available for analysis in our data set, we found that this covariate was not significantly associated with long-term fatigue. Similarly, we did not examine baseline symptom profiles and their relationship with long-term fatigue; the number of acute symptoms has been linked to long-term fatigue.[206] Nevertheless, our observations of worse long-term fatigue in women and younger people are congruent with existing literature.[206]

Notably, at least 38.4% of people assessed beyond 12 months of initial infection had a FAS score ≥ 22, indicating significant fatigue.[199] We observed that fatigue significantly affected younger people, which may also have an impact on functioning, work, ADL[214] and QoL. A recent study by Stapleton *et al.* highlighted the potential benefits of occupational therapy-based approaches for post-COVID fatigue.[215] Exercise-based resistance and endurance training interventions have also been examined in people with long-COVID, decreasing fatigue levels.[216] The implementation of interventions and support is required for this population.

Strength

Where data were available at 3–6 months, our multivariable analysis demonstrated that only age and sex were associated with handgrip strength. There are known sex differences in handgrip strength.[217] We observed no interaction or evidence to suggest that there were sex differences in the behaviours of covariates in our analyses; therefore, we did not investigate strength outcomes stratified by sex. Additionally, there were only 298 women in whom strength was assessed at 3–6 months, which fell below the IPD meta-analysis criteria. We lacked available covariates for a range of comorbidities, and therefore could not include these in our univariable and multivariable analyses. Nevertheless, we were able to investigate the role of education, BMI, initial hospitalisation, presence of diabetes, lung disease, obesity, corticosteroid use and immunosuppressive therapy.

Handgrip strength is lower in people with COVID-19 than in COVID-negative participants.[218] Conditions such as long-COVID are known to affect muscle mass and strength;[219] handgrip strength in people with long-COVID is an indicator of poor functioning.[220] Loss of muscle strength and deconditioning was associated with ICU admission and use of ventilation.[220] Despite the availability of data on hospitalisation and ventilation in our data set, we found this was not significantly associated with strength in our sample. Handgrip strength remains an important outcome measure, particularly in the COVID-19 population, as it is a low-cost measurement tool that is easy to administer across a range of settings and may be considered a proxy for functional ability in people with long-COVID.[220] Further data are needed at longer follow-up times to allow for more in-depth covariate-adjusted analyses.

Summary of key findings

- 38.4% of people who were assessed beyond 12 months of initial infection had a FAS score ≥ 22, indicating significant fatigue.
- Fatigue significantly affected younger people.

Chapter 8 Factors associated with long-term coping with daily life, physical activity and performance outcomes after COVID-19

Overview

We investigated factors associated with the ability to cope with daily life (ADL), physical activity and performance. Data availability was explored in relation to outcome assessment between 3 months and 6 months, 9 months and 12 months, and beyond 12 months of COVID-19 onset. Inclusion in the final multivariable model reflected the available data. The absence of a variable in the final model does not necessarily mean that it was not a significant predictor; it may also indicate that there were insufficient data to be included in the modelling process.

Coping with daily life

Measures of coping with daily life were captured across 10 data sets (IPD = 3158); data were available between 3 months and 6 months for 10 data sets (IPD = 2206), at 9–12 months for six data sets (IPD = 234), and beyond 12 months in six data sets (IPD = 718; see *Figure 5*).

Data transformation

The anchor measure for coping with daily life was the Barthel Index, which was used by the greatest number of data sets. However, the exploration of the transformation algorithm revealed a ceiling effect, with 78% of the scores being at the maximum of 100. This resulted in the algorithm thresholds set at 100 for the 25% quartile, the median, 75% quartile, and maximum. This prevented the meaningful application of the transformation algorithm, as standardisation of other assessment instruments to the Barthel Index would have distorted and misrepresented the original scores. As per the established convention, if the most commonly used assessment instrument by data set could not be used, the most commonly used assessment instrument by the IPD was used. Our anchor measure for coping with daily life was therefore selected as the Nottingham Extended Activities of Daily Living (NEADL) scale, where a higher score indicates better functioning. *Table 2* shows the assessment instruments that contributed to this domain. *Report Supplementary Material 43* describes the standardised scores, by data set.

Research question 1: long-term outcomes

Exploration of prevalence at different time points

Report Supplementary Material 67, *Figure S14a* shows coping with daily life scores at different time points, and *Report Supplementary Material 67*, *Figure S14b-dii* presents scores over time stratified by demographic and intervention groups. The median NEADL score at 3–6 months (10 data sets, IPD = 2206) was 21 (IQR 17–21), 20 (IQR 16–21) at 9–12 months (six data sets, IPD = 234), and 21 (IQR 18–22) beyond 12 months (six data sets, IPD = 718). The coping with daily life scores appeared to vary by setting, age group, sex, education level, occupation, initial hospitalisation, COVID-19 severity, presence of blood conditions, diabetes, mental/behavioural disorders, neurological conditions, cardiac conditions, cerebrovascular disease, lung disease, gastrointestinal conditions, chronic kidney disease, musculoskeletal conditions, use of renal therapy and hydroxychloroquine. All of these variables were included in the meta-analysis.

Research question 2: predictors of long-term outcomes

Univariable analysis

Report Supplementary Material 44 describes the covariates available for the analyses. Where participants were followed up between 3 months and 6 months (10 data sets, IPD = 2206), the median age was 62 years, 1353 (63.2%) were

male, and 1765 (80%) were initially hospitalised. At the univariable level, age, sex, education, the requirement for mechanical ventilation, presence of cardiac conditions, cerebrovascular, lung, or chronic kidney disease, musculoskeletal conditions, and use of anticoagulants or renal therapy were associated with the ability to cope with daily life (see *Report Supplementary Material 45*). There were insufficient data at 9–12 months to take forward to meta-analysis. In the population that was assessed beyond 12 months (6 data sets, IPD = 718), the median age was 59 years, 454 (65.61%) were male, and 526 (73.26%) were initially hospitalised. At univariable level, age, sex and level of education were associated with the ability to cope with daily life (see *Report Supplementary Material 45*).

Multivariable regression analyses

In the final model at 3–6 months (two data sets, IPD = 1086), men [$p < 0.001$, ratio of difference = 1.30, 95% CI (1.18 to 1.43)] reported better ability to cope with daily life than women, and the presence of lung disease [$p < 0.001$, ratio of difference = 0.72, 95% CI (0.65 to 0.80)] or chronic kidney disease [$p = 0.045$, ratio of difference = 0.82, 95% CI (0.67 to 0.995)] were each associated with poorer scores on ability to cope with daily life. As age increased, ability to cope with daily life decreased [$p = 0.024$, ratio of difference = 0.995, 95% CI (0.992 to 0.999)]. The median age of the population that contributed to the final model was 59 years; 699 (64.4%) were male and 144 (13.3%) were initially hospitalised and ventilated.

Beyond 12 months, in the final model (two data sets, IPD = 574) as age increased, ability to cope with daily life decreased [$p = 0.001$, ratio of difference = 0.990, 95% CI (0.984 to 0.996)], men had better scores than women [$p = 0.006$, ratio of difference = 1.24, 95% CI (1.07 to 1.45)], and people who did not complete primary school had poorer scores than those who completed higher education [$p = 0.007$, ratio of difference = 0.53, 95% CI (0.33 to 0.84)], although this needs to be treated with caution due to the very small IPD for those who did not complete primary education (*Table 20*). The median age of the population that contributed to this final model was 59 years; 371 (64.6%) were male and 158 (27.5%) were hospitalised and ventilated.

Assessment of certainty

In the model at 3–6 months, I^2 based on lung disease was 3.46%, indicating low heterogeneity. In the model beyond 12 months, I^2 based on sex was 0.00%, indicating no heterogeneity. GRADE-informed assessment indicated that the quality of evidence was moderate (see *Report Supplementary Material 69*, *Table I*).

Physical activity and performance

Subdomain: fitness availability

Fitness data were captured in a single data set using the Incremental Shuttle Walk Test; as this did not meet the minimum requirement for our IPD meta-analysis, this outcome was not considered for further analysis.

Subdomain: oxygen consumption data availability

Data were available from two data sets, totalling 71 IPD, where oxygen consumption (VO_2 Peak) was recorded. Outcomes were reported at 3–6 months for two data sets (IPD = 66), at 9–12 months in one data set (IPD = 4) and in one data set (IPD = 1) beyond 12 months. As both studies described peak flow using VO_2 Peak, data transformation was not required. The median VO_2 Peak was 28 (IQR 24–35) at 3–6 months and 25 (IQR 21–28) at 9–12 months. There were insufficient data to permit meta-analysis.

Subdomain: walking ability data availability

Data on walking ability were available from 15 data sets; 1 data set captured data out-with the predefined long-term follow-up periods. Data from 14 data sets (IPD = 1701) were used for the analyses. At 3–6 months, data were available from 12 data sets (IPD = 1298), at 9–12 months, data were available from 8 data sets (IPD = 275), and beyond 12 months, data were available from 4 data sets (IPD = 128, see *Figure 5*).

Data transformation

Table 2 presents the assessment instruments that contributed to this domain. The anchor measure for walking ability was the 6-minute walk test (6-MWT). All other measures were standardised to this measure (see *Report Supplementary Material 46*).

TABLE 20 Final multivariable regression model for factors associated with ability to cope with daily life

	Estimate of difference (95% CI)	Ratio of difference (95% CI)	*p*-value
3–6 months ***D*** **= 2, IPD = 1086** ***I*²** **(lung disease) = 3.46%**			
Sex (ref = female)	0.26 (0.17 to 0.36)	1.30 (1.18 to 1.43)	< 0.001
Lung disease (ref = no)	−0.33 (−0.43 to −0.22)	0.72 (0.65 to 0.80)	< 0.001
Age	−0.005 (−0.008 to −0.001)	0.995 (0.992 to 0.999)	0.024
Chronic kidney disease (ref = no)	−0.20 (−0.40 to −0.005)	0.82 (0.67 to 0.995)	0.045
Education simplified (ref = higher ed)			
Did not complete primary	−0.04 (−0.47 to 0.39)	0.96 (0.63 to 1.48)	0.863
Completed primary	−0.14 (−0.36 to 0.08)	0.87 (0.70 to 1.08)	0.205
Completed high	−0.20 (−0.30 to −0.11)	0.82 (0.74 to 0.89)	< 0.001
12+ months ***D*** **= 2, IPD = 574** ***I*²** **(sex) = 0.00%**			
Age	−0.010 (−0.016 to −0.004)	0.990 (0.984 to 0.996)	0.001
Sex (ref = female)	0.22 (0.06 to 0.37)	1.24 (1.07 to 1.45)	0.006
Education (ref = higher ed)			
Did not complete primary	−0.64 (−1.10 to −0.17)	0.53 (0.33 to 0.84)	0.007
Completed primary	0.11 (−0.45 to 0.67)	1.11 (0.64 to 1.96)	0.704
Completed high	−0.11 (−0.27 to 0.04)	0.89 (0.77 to 1.04)	0.143

Population description

Meta-analyses were possible for the 3–6 months post-COVID onset. The median age was 57.4 years, 801 (61.8%) were male, and 335 (26.9%) required hospitalisation with ventilation.

Research question 1: long-term outcomes

Exploration of prevalence at different time points

Where participants were assessed at 3–6 months (12 data sets, IPD = 1298), the median 6-MWT score was 480 m (IQR 390–560 m); where participants were assessed at 9–12 months (eight data sets, IPD = 275), the median score was 542 m (IQR 465–606 m), and where assessment was available beyond 12 months (four data sets, IPD = 128), the median score was 420 m (IQR 330–527 m). *Report Supplementary Material 67*, *Figure S15a-mii* describes the walking ability scores at different time points, stratified by demographic and intervention groups, where available. Recruitment setting, age group, sex, religion, education level, BMI category, occupation, hospitalisation status, COVID-19 severity, presence of diabetes, obesity, neurological conditions, cardiac conditions, lung disease, chronic kidney disease, use of antibiotics and rehabilitation interventions were each associated with walking ability.

Research question 2: predictors of long-term outcomes

Univariable analysis

Report Supplementary Material 47 describes the covariates available for analyses. At univariable level, age, sex, education, BMI, diabetes, obesity, cardiac conditions and lung disease were associated with walking ability at 3–6 months (see *Report Supplementary Material 48*). Each of these variables was taken forward to the multivariable model.

Multivariable regression analyses

A higher score on the 6-MWT score indicated better functioning (greater walking distance). These data did not require transformation to the log scale, and were therefore presented on the original scale. In the final model at 3–6 months (six data sets, IPD = 567), for every increase by 1 year in age, the average distance covered in 6 minutes (the 6-MWT) decreased by 1.54 m [95% CI (−2.18 to −0.91)]. Men walked 46 m further than women [95% CI (27.80 to 64.71)]; for a unit increase in BMI, the distance walked decreased by 4.22 m [95% CI (−5.81 to −2.62)], people with cardiac conditions walked 77.46 m less than those without cardiac conditions [95% CI (−113.39 to −41.53)] and people with lung disease walked 31.71 m less than those without lung disease [95% CI (−53.73 to −9.70)]. There was an interaction between sex and cardiac condition, such that a man with a cardiac condition walked 25.52 m further than a female without a cardiac condition (*Table 21*). Median age of participants in this model was 57, 339 (59.8%) were male and 135 (23.9%) were hospitalised and ventilated.

Assessment of certainty

In the 3–6 months model, I^2 based on cardiac conditions was 0.00%, indicating no heterogeneity. GRADE-informed assessment indicated that the quality of evidence was low (downgraded due to imprecision and inclusion of selected populations, see *Report Supplementary Material 69*, *Table m*).

Subdomain: mobility availability

Data on mobility were available from six data sets (IPD = 2563). Data were available at 3–6 months from six data sets (IPD = 1618), at 9–12 months from three data sets (IPD = 212), and at beyond 12 months from three data sets (IPD = 733, see *Figure 5*). Only data at 3–6 months were included in the meta-analysis; there were insufficient data at 9–12 months and 99.2% of data at beyond 12 months came from a single study.

Population description

At 3–6 months (six data sets, IPD = 1618), the median age was 59 years, 1008 (64.7%) were male, and 232 (14.3%) required hospitalisation with ventilation.

Data transformation

Table 2 describes the outcome measurement instruments that contributed to this domain. Data were standardised to the Short Physical Performance Battery (see *Report Supplementary Material 49*). A higher score indicates better functioning.

Research question 1: long-term outcomes

Exploration of prevalence at different time points

Report Supplementary Material 67, *Figure S16* shows the mobility scores at different time points. The median mobility score for the populations available at each follow-up time point was 11 (9, 12). *Report Supplementary Material 67*, *Figure S16b-aii* describes the scores over time, stratified by the demographic and intervention categories. We observed significant differences in mobility scores for different age groups, sex, ethnicity, education levels, occupations, number

TABLE 21 Final multivariable regression model for factors associated with walking ability

3–6 months ***D* = 6, IPD = 567** **I^2 (cardiac conditions) = 0.00%**	**Estimate of difference (95% CI)**	***p*-value**
Age (unit change, year)	−1.54 (−2.18 to −0.91)	< 0.001
Sex (ref = female)	46.25 (27.80 to 64.71)	< 0.001
BMI (unit increase)	−4.22 (−5.81 to −2.62)	< 0.001
Cardiac conditions (ref = no)	−77.46 (−113.39 to −41.53)	< 0.001
Sex*cardiac (M*yes)	56.73 (14.05 to 99.42)	0.009
Lung disease (ref = no)	−31.71 (−53.73 to −9.70)	0.005

of people in the household, COVID-19 positivity at baseline, presence of other infection, cancer, diabetes, mental/behavioural disorders, dementia/Alzheimer's, neurological or cardiac conditions, cerebrovascular disease, circulatory disorders, lung disease, gastrointestinal conditions, chronic kidney disease, immunosuppression, musculoskeletal conditions, or use of antihypertensive interventions.

Research question 2: predictors of long-term outcomes

Univariable analysis

Report Supplementary Material 50 describes covariates available for the analysis. Univariable analysis (see *Report Supplementary Material 51*) revealed that age, sex, ethnicity, education, number of people in the household, COVID-19 severity, presence of cancer, diabetes, neurological conditions, cardiac conditions, cerebrovascular disease, circulatory disorders, lung disease, chronic kidney disease, musculoskeletal conditions and use of renal therapy were significantly associated with mobility at 3–6 months. These variables were included in the multivariable analysis.

Multivariable regression analyses

Table 22 shows the variables that were significantly associated with mobility at 3–6 months. A higher score is indicative of better functioning. In this final model (two data sets, IPD = 1080), increasing age led to a decrease in functioning [1.1% per year; ratio of difference = 0.989, 95% CI (0.986 to 0.992), $p < 0.001$]. Men had 35% higher mobility than women [ratio of difference = 1.35, 95% CI (1.25 to 1.47)]. The presence of lung disease [ratio of difference = 0.78, 95% CI (0.72 to 0.85)], chronic kidney disease [ratio of difference = 0.72, 95% CI (0.59 to 0.88)], neurological conditions [ratio of difference = 0.67, 95% CI (0.54 to 0.83)], musculoskeletal conditions [ratio of difference = 0.79, 95% CI (0.71 to 0.89)] and diabetes (ratio of difference = 0.82, 95% CI (0.74 to 0.89)] were all associated with decreased mobility.

Assessment of certainty

I^2 at 3–6 months was 0%. GRADE-informed assessment indicated that the certainty of evidence was moderate and was downgraded for indirectness (see *Report Supplementary Material 69*, *Table n*).

Subdomain: physical activity data availability

Two data sets captured information on physical activity (IPD = 184); data were available between 3 months and 6 months in two data sets (IPD = 175), in one data set (IPD = 5) between 9 months and 12 months, and in two data sets (IPD = 4) beyond 12 months of COVID-19 onset. Physical activity scores were transformed to fit the range of the Saltin-Grimby Physical Activity Level Scale. Median physical activity score was 2 (IQR 1–2) where follow-up was conducted between 3 months and 6 months and 9 and 12 months, and 2 (IQR 1–3) beyond 12 months. There were insufficient data available to permit meta-analysis.

TABLE 22 Final multivariable regression model for factors associated with mobility

3–6 months *D* = 2, IPD = 1080 I^2 (neurological conditions) = 0.00	**Estimate of difference (95% CI)**	**Ratio of difference (95% CI)**	***p*-value**
Age (unit change, year)	−0.011 (−0.014 to −0.008)	0.989 (0.986 to 0.992)	< 0.001
Sex (ref = female)	0.30 (0.22 to 0.38)	1.35 (1.25 to 1.47)	< 0.001
Lung disease (ref = no)	−0.25 (−0.33 to −0.16)	0.78 (0.72 to 0.85)	< 0.001
Chronic kidney disease (ref = no)	−0.33 (−0.52 to −0.13)	0.72 (0.59 to 0.88)	0.001
Neurological conditions (ref = no)	−0.41 (−0.62 to −0.19)	0.67 (0.54 to 0.83)	< 0.001
Musculoskeletal conditions (ref = no)	−0.23 (−0.34 to −0.12)	0.79 (0.71 to 0.89)	< 0.001
Diabetes (ref = no)	−0.20 (−0.30 to −0.11)	0.82 (0.74 to 0.89)	< 0.001

Subdomain: exercise tolerance data availability

Data on exercise tolerance were captured across five data sets; two data sets captured data at an early follow-up (< 3 months). Data were available between 3 months and 6 months for three data sets (IPD = 372) and for one data set (IPD = 6) between 9 months and 12 months. Data were standardised to the 30-second sit-to-stand. The median sit-to-stand scores were 12 (IQR 9–14) and 10 (IQR 9–14) at 3–6 months, and 9–12 months, respectively. There were insufficient data to be considered in the meta-analysis.

Subdomain: perception of exertion data availability

Data on the perception of exertion were reported in five data sets (IPD = 331). Data were available between 3 months and 6 months for five data sets (IPD = 274), at 9–12 months in three data sets (IPD = 43), and beyond 12 months for 11 participants in a single data set.

Data transformation

Table 2 describes the assessment instruments that contributed to this domain. The anchor measure for the perception of exercise was the Borg RPE. The median perception of exercise score at 3–6 months was 1 (IQR 0–3); at 9–12 months, the median score was 0 (IQR 0–2) and at beyond 12 months, the median score was 1 (IQR 0–3). There were insufficient data to proceed with the IPD meta-analyses.

Discussion

Coping with daily life

We observed that across both 3–6 and beyond 12 months, men had a better ability to cope with daily life compared to women, and that ADL were poorer as age increased. In the 3–6 months model, the presence of comorbidities (lung or chronic kidney disease) was associated with a poorer ability to cope with daily life, whereas beyond 12 months, a surrogate socioeconomic marker (lower level of education) appeared to be associated with poorer ADLs.

Sex differences in activities have been reported in chronic obstructive pulmonary disease populations for items related to home management,[221] and in stroke populations, where women are more dependent than men.[222] Decreases in ADLs are common with ageing populations. However, COVID-19 has accelerated this decline.[223] A previous study identified a reduction in ADLs following COVID-19, with pre-COVID functional status being associated with COVID-19 severity and mortality.[224] We were unable to examine the impact of pre-COVID functional status in our analyses. Nevertheless, our findings of age-related decreases in the ability to cope with daily life were congruent with those of previous work.[29] COVID-19 was found to particularly affect those in care homes; older adults in long-term care had particularly poorer ADLs even if the clinical course of COVID-19 was mild.[225] This population not only experienced disproportionate mortality but also diminished functioning even in mild infections. Maintaining independence in ADLs in this population is an important target for enhancing QoL.[226]

While others have found an association between mechanical ventilation and poorer ADLs,[227] we observed that ventilation was only significant at the univariable level. Our observations may reflect a population that is typically accepted for ventilation, who are typically not frail and have good exercise tolerance. Selected data were available in PRECIOUS on the number of people in participants' households; however, these data were only available for those in whom follow-up was conducted at 3–6 months and was not found to be significant at univariable or multivariable level. Previous work has established that older adults who live alone report difficulties with ADLs.[228] COVID-19-related isolation may have impacted functional activities in older adults;[229] for each additional month spent in physical or social isolation, independence in ADLs decreased.[230] More data are needed to examine the long-term impacts on social functioning, isolation, socioeconomic status and ADLs.

We also observed an association between lower education levels and ADLs beyond 12 months. There is an established link between lower socioeconomic status and disability in older adults.[231] This may also be linked to inequalities in health literacy[151,152] and unhealthy behaviours.[153] Previous work has established that those with poor physical functioning and lower socioeconomic status are less likely to receive support for their ADLs.[232]

Walking ability

We observed that at 3–6 months, walking ability decreased with increasing age and BMI, in women compared with men, and in people with cardiac and lung conditions compared to those without.

Walking ability was measured using the 6-MWT, which is an established measure of exercise capacity in people with lung conditions,[233] and was found to correlate with COVID-19 severity,[233,234] and chronic functional impairment.[233] We investigated the association between COVID-19 severity and walking distance at 3–6 months. While previous work established differences in 6-MWT distances in mild versus moderate/severe COVID-19 at around 2 months follow-up, we observed no significant impact of severity on walking distance. Further work is needed to establish the impact of COVID-19 on the 6-MWT beyond 6 months of index infection, as well as the impact of pre-COVID walking ability on post-COVID outcomes.

We observed no interaction or evidence to suggest that there were differences in the behaviours of variables due to sex differences. Therefore, we decided not to examine walking ability stratified by sex. Additionally, as there were only 495 women in whom walking ability was assessed at 3–6 months, the application of this stratification would have failed to meet our prespecified IPD meta-analysis criteria.

Mobility

We observed that at 3–6 months increasing age by 1 year was associated with decreased mobility; men had better mobility than women, and the presence of lung, chronic kidney, neurological or musculoskeletal conditions, or diabetes were each associated with decreased mobility. Previous data reporting on the first 5 months of the pandemic highlighted a history of falls, unpleasant surrounding neighbourhoods, and the presence of musculoskeletal pain as being associated with mobility.[235] While this study did not specifically include people with COVID-19, similar environmental issues arise in the COVID-affected population; mobility after COVID-19 should be considered in the context of functioning environmental factors and pre-existing conditions.

Evidence gaps

Despite data being recorded on fitness, oxygen consumption (VO_2 Peak), physical activity, exercise tolerance and perception of exertion, data were not present in sufficient numbers to permit meta-analysis. Several studies have found that short-term assessment of physical activity after COVID-19 has been challenging, because of participants' inability to perform common assessment components.[227,236,237]

Summary of key findings

- Men had a better ability to cope with daily life compared to women.
- Further data are needed on exercise tolerance, physical activity and oxygen consumption/peak flow.
- We observed an association between lower education levels and ADLs beyond 12 months.
- Further work is needed to establish the impact of COVID-19 on the 6-MWT beyond 6 months of index infection, as well as the impact of pre-COVID walking ability on post-COVID outcomes.

Chapter 9 Factors associated with long-term breathlessness after COVID-19

Overview

This chapter describes the available outcomes describing breathlessness, impact of breathing problems, and transfer factor within PRECIOUS. The absence of a variable in the final model does not necessarily mean that it was not a significant predictor; it may also indicate that there were insufficient data to be included in the modelling process.

Breathing

Subdomain: breathlessness data availability

Table 2 shows the assessment instruments that were used to capture breathlessness. Data on breathlessness were available for 5532 participants from 20 data sets. Data were available at 3–6 months from 15 data sets (IPD = 2243), at 9–12 months from 11 data sets (IPD = 1754), and beyond 12 months from 8 data sets (IPD = 1535, see *Figure 5*).

Population description

For those in whom outcomes were available at 3–6 months (15 data sets, IPD = 2243), the median age of the population was 56 years, 1126 (55.3%) were male and 623 (28.1%) were not hospitalised for COVID-19. For those in whom outcomes were available at 9–12 months (11 data sets, IPD = 1754), median age was 52 years, 819 (49.9%) were male, and 1270 (74.1%) were not initially hospitalised for COVID-19. Where outcomes were available beyond 12 months (8 data sets, IPD = 1535), the median age of the population was 56 years, 852 (56.4%) were male, and 639 (41.7%) were not initially hospitalised for COVID-19.

Data transformation

All breathlessness data were standardised using the modified Medical Research Council Dyspnoea (mMRC) score. *Table 2* shows the assessment instruments that have contributed to this domain. *Report Supplementary Material 52* describes the transformed mMRC scores, by study. A higher score indicated greater breathlessness.

Research question 1: long-term outcomes

Exploration of prevalence at different time points

Median mMRC scores where assessments took place at 3–6 months, 9–12 months and beyond 12 months was 0 (IQR 0–1). *Report Supplementary Material 67*, *Figure S17* presents the long-term breathlessness scores at different time points. Country of recruitment, age group, sex, BMI category, occupation, number of people in the household, initial hospitalisation with COVID-19, COVID-19 severity, presence of diabetes, obesity, mental/behavioural disorders, neurological conditions, cardiac conditions, cerebrovascular disease, circulatory disorders, lung disease, chronic kidney disease, immunosuppression, musculoskeletal conditions, use of antibiotics, rehabilitation and oxygen therapy were all associated with mMRC scores. These variables were included in the meta-analysis.

Research question 2: predictors of long-term outcomes

Univariable analysis

Report Supplementary Material 53 describes the covariates available for analyses. At 3–6 months at univariable level, age, sex, education level, BMI, occupation, employment status, number of people in the household, hospitalisation, COVID-19 severity at baseline, the presence of diabetes, obesity, other endocrine conditions, mental/behavioural disorders, neurological conditions, lung disease, gastrointestinal conditions, immunosuppression and musculoskeletal conditions

were each associated with worse breathlessness (see *Report Supplementary Material 54*). At 9–12 months, age, sex, BMI, smoking history, occupation, employment, initial hospitalisation, COVID-19 severity at baseline, the presence of cancer, diabetes, obesity, circulatory disorders, lung disease, chronic kidney disease and immunosuppression were all associated with shortness of breath at the univariable level. Beyond 12 months, age, sex, education, BMI, occupation, employment status, hospitalisation, COVID-19 severity at baseline, the presence of cancer, diabetes, obesity, cardiac conditions, circulatory disorders, lung disease, chronic kidney disease, immunosuppression and use of renal therapy were all associated with breathlessness. These were included in multivariable analysis.

Multivariable regression analyses

At 3–6 months (*Table 23*), in the final multivariable model (three data sets, IPD = 744) hospitalised and ventilated participants [$p = 0.006$, ratio of difference = 1.29, 95% CI (1.08 to 1.54)] and hospitalised participants [$p < 0.001$, ratio of difference = 1.27, 95% CI (1.13 to 1.44)] had higher mMRC scores (worse breathlessness) than those who were not hospitalised. Those with lung disease [$p = 0.014$; ratio of difference = 1.11, 95% CI (1.02 to 1.20)] had worse breathlessness than those who did not. Those with immunosuppression [$p < 0.001$, ratio of difference = 1.33,

TABLE 23 Final multivariable regression model for factors associated with breathlessness

	Ratio of difference (95% CI)	*p*-value
3–6 months ***D* = 3, IPD = 744** ***I*² (sex) = 4.59%**		
Severity (ref = not hospitalised) hospitalised	1.27 (1.13 to 1.44)	< 0.001
Hospitalised and ventilated	1.29 (1.08 to 1.54)	0.006
Lung disease (ref = no)	1.11 (1.02 to 1.20)	0.014
Immunosuppression (ref = no)	1.33 (1.15 to 1.54)	< 0.001
Sex (ref = female)	0.91 (0.87 to 0.96)	< 0.001
Obesity (ref = no)	1.19 (1.10 to 1.29)	< 0.001
9–12 months ***D* = 3, IPD = 1277** ***I*² (based on sex) = 0.00% (most other factors are highly unbalanced)**		
Age (years)	1.002 (1.001 to 1.003)	0.001
Obesity (ref = no)	1.18 (1.12 to 1.25)	< 0.001
Lung disease (ref = no)	0.91 (0.77 to 1.07)	0.241
Lung disease*age interaction	1.005 (1.002 to 1.008)	0.002
Sex (ref = female)	0.91 (0.88 to 0.94)	< 0.001
Hospitalised (ref = no)	1.18 (1.11 to 1.25)	< 0.001
Circulatory disorder (ref = no)	1.11 (1.06 to 1.16)	< 0.001
Immunosuppression (ref = no)	1.21 (1.11 to 1.32)	< 0.001
12+ months ***D* = 3, IPD = 655** ***I*² (based on sex) = 0.00% (most other factors are highly unbalanced)**		
Age (years)	1.003 (1.002 to 1.005)	< 0.001
Hospitalised (ref = no)	1.24 (1.14 to 1.36)	< 0.001
Sex (ref = female)	0.88 (0.84 to 0.92)	< 0.001
Obesity (ref = no)	1.21 (1.11 to 1.31)	< 0.001
Circulatory disorder (ref = no)	1.10 (1.03 to 1.18)	0.005

95% CI (1.15 to 1.54)] had worse breathlessness than those without immunosuppression. Men [$p \leq 0.001$, ratio of difference = 0.91, 95% CI (0.87 to 0.96)] had 9% lower mMRC scores (better functioning) than women and people with obesity [$p < 0.001$, ratio of difference = 1.19, 95% CI (1.10 to 1.29)] had worse mMRC scores than those without obesity. In this final model, the median age of the population was 52 years, 393 (52.8%) were male and 86 (11.6%) were hospitalised and ventilated.

In the final model at 9–12 months (three data sets, IPD = 1277), we observed an interaction between age and lung disease such that the average breathlessness score increased by 0.2% per year for those without lung disease and by 0.7% for those with lung disease (exp{0.002 + 0.005} or 1.002 × 1.005, see *Table 23*). The presence of obesity increased the mMRC score by 18% [$p < 0.001$, ratio of difference = 1.18, 95% CI (1.12 to 1.25)]. Men had lower mMRC scores by 9% [$p < 0.001$, ratio of difference = 0.91, 95% CI (0.88 to 0.94)], compared with women, People who were hospitalised had greater breathlessness than those who were not hospitalised [$p < 0.001$, ratio of difference = 1.18, 95% CI (1.11 to 1.25)]. People with a circulatory disorder [$p < 0.001$, ratio of difference = 1.11, 95% CI (1.06 to 1.16)], and those with immunosuppression [$p < 0.001$, ratio of difference = 1.21, 95% CI (1.11 to 1.32)] each had greater breathlessness than those without these conditions. In this final model, participants' median age was 49 years, 625 (48.9%) were male, and only 1 person was hospitalised and ventilated (0.1%).

Beyond 12 months, in the final model (three data set, IPD = 655), as age increased by 1 year, mMRC scores increased by 0.3% [$p < 0.001$, ratio of difference = 1.003, 95% CI (1.002 to 1.005)]. Hospitalisation was associated with an increased breathlessness score by 24% [$p < 0.001$, ratio of difference = 1.24, 95% CI (1.14 to 1.36)]. The presence of obesity was associated with an increased mMRC score by 21% [$p < 0.001$, ratio of difference = 1.21, 95% CI (1.11 to 1.31)]. Presence of circulatory disorders was associated with an increase in mMRC scores by 10% [$p = 0.005$, ratio of difference = 1.10, 95% CI (1.03 to 1.18)]. Male sex was associated with a decreased mMRC score of 12% [$p < 0.001$, ratio of difference = 0.88, 95% CI (0.84 to 0.92)]. In this final model, the median age of the participants was 48 years, 312 (47.6%) were male, and no participant required ventilation.

Assessment of certainty

Where assessment took place at 3–6 months, sex contributed the greatest effect size to the model, and the I^2 based on sex was 4.59%, indicating low heterogeneity. Where assessment took place at 9–12 months, I^2 based on sex was 0.00%. When the assessments took place beyond 12 months, I^2 based on sex was 0.00%. GRADE-informed assessment indicated that the certainty of evidence was moderate for each model and was downgraded for indirectness (see *Report Supplementary Material 69*, *Table o*).

Subdomain: impact of breathing problems data availability

Data on the impact of breathing problems were captured using a range of assessment instruments that could not be standardised. Therefore, these data were not considered in further analysis.

Subdomain: transfer factor data availability

Data were available from eight data sets (IPD = 362). At 3–6 months, data were available from seven data sets (IPD = 293), at 9–12 months from three data sets (IPD = 21) and beyond 12 months from two data sets (IPD = 48). There were insufficient data to perform meta-analyses. Where data were available at 3–6 months, the median transfer factor score was 76 (IQR 61–89), where data were available at 9–12 months, median score was 90 (IQR 84–101), and where data were available beyond 12 months, the median transfer factor was 87 (IQR 80–98).

Discussion

We observed that at each follow-up time point, women, those who were hospitalised, and those with obesity had consistently greater breathlessness scores than men and non-hospitalised and non-obese participants, respectively. Additionally, at 3–6 months and 9–12 months, lung disease and immunosuppression were associated with poorer breathlessness, while at 9–12 and beyond 12 months, circulatory disorders were associated with increased breathlessness. Data were standardised and presented according to the mMRC, which was recommended for collection as part of a core outcome set for people with post-COVID conditions.[138]

Our findings were congruent with previous reports of an increased prevalence of breathlessness in women and those with severe COVID infection.[238] Similarly, previous work has described improved recovery from breathlessness at 1 year in men compared to women, younger people[239] and non-obese participants.[239] Previous studies have reported associations between socioeconomic status, length of hospitalisation and breathlessness.[240] Socioeconomic status was available in our data set through surrogate measures such as the recruiting country's World Bank income category or participants' employment status. Income category was affected by collinearity across our data sets and therefore the analyses could not be used, and we observed that employment status was not significant in any of our final models.

Breathlessness is a continuing issue for many previously hospitalised people with COVID-19, with one in four reporting persistent breathing problems beyond 1 month of initial infection.[238] Potential interventions for early post-COVID breathlessness include sofosbuvir/daclatasvir and hydroxychloroquine[241] and tele-rehabilitation.[242] Tailored information for longer-term breathlessness is needed; existing treatment recommendations in the context of long-COVID include breathing techniques, breathing positions, chest clearance exercises, healthy living and pulmonary rehabilitation.[243]

Summary of key findings

- Women, those who were hospitalised, and those with obesity had consistently worse breathlessness scores.
- At 3–6 months and 9–12 months, lung disease and immunosuppression were associated with poorer breathlessness.
- At 9–12 and beyond 12 months, circulatory disorders were associated with increased breathlessness.

Chapter 10 Long-term outcome domains not taken forward for further analysis

Overview

Data were compiled across a range of broad outcome domains. We prespecified that the meta-analysis would involve more than one data set and include more than 500 IPD. While we described subdomains that did not meet these meta-analysis criteria in the preceding chapters, there were additional domains that did not meet these criteria and therefore could not be analysed; these are detailed below.

Frailty

Data on frailty were reported across three data sets; however, investigation of the distributions of data across two frailty measures captured within the same data set revealed that they appeared to capture two different aspects of frailty. Therefore, it was therefore decided that data across the different frailty assessment instruments could not be confidently aggregated.

Nutrition

As nutrition was captured in a single data set using the Mini Nutritional Assessment Short Form, this outcome was not considered in further analysis.

Sexual function

Sexual function was captured using the Female Sexual Function Index in a single data set, and was therefore not considered in further analysis.

Resilience and self-efficacy

Measures of reliance and self-efficacy were captured using the Brief Resilience Coping Scale, Short Form Sense of Coherence Scale 9, and Generalised Self-Efficacy Scale in a single data set. This outcome did not meet our prespecified criteria for meta-analysis and was therefore not considered in further analysis.

Morning and evening preference

The Morningness–Eveningness Questionnaire was described in one data set and was not considered in further analysis.

Occupational gaps

Data on occupational gaps were captured in a single data set and was therefore not used in further analyses.

Smell

Data on smell were captured across four data sets, totalling 220 IPD. Data were available at 3–6 months for three data sets (IPD = 130), at 9–12 months in two data sets (IPD = 71), and beyond 12 months in one data set (IPD = 19). There were insufficient data to be included in meta-analysis.

Pain

Subdomain: impact of pain data availability

The impact of pain was captured using the Brief Pain Inventory in a single data set and was, therefore, not considered in further meta-analysis.

Subdomain: pain severity data availability

Pain severity, along with the time point for assessment relative to study baseline, was captured in two data sets. Only 18 IPD (< 1%) were available from one data set and was assessed less than 3 months from onset. Thus, analysable data

on pain severity were available only from a single data set at the follow-up time points of interest. As this did not meet our prespecified criteria for meta-analyses, these data were not used in further analyses.

Additional analyses not considered

Prediction algorithms for poor outcomes

Upon reviewing the available data, the generation of prediction algorithms was infeasible for a number of reasons. We observed that each data set captured different variables, leading to a lack of consistency across the data sets and missing or non-aggregatable data. Thus, although we observed significant factors associated with each outcome domain, variables available for one domain may not have been available in others, making the generation of an overall algorithm challenging. Secondly, there was difficulty in defining a 'poor outcome' across each domain; creation of a definition of poor outcome for each assessment instrument was challenging as some assessment instruments did not include threshold values for 'poor health' or had different thresholds for different populations (e.g. MoCA). Finally, considerably more data were collated than expected (more than an eightfold increase in expected data sets), leaving insufficient time to create individual algorithms for each outcome domain.

Costs of resource use

While we had intended to describe the costs associated with poorer long-term outcomes after COVID-19, we were unable to do so due to the lack of data on healthcare resource use beyond the initial COVID-19 episode. We described the individual, health service and societal impact of COVID-19 through later hospitalisation, return to work and impact on health utilities.

Discussion

Frailty is a crucial outcome measure for in ageing populations. It describes vulnerability after a stressor and is associated with age-related decline across a range of physiological systems over time.[244] This decline can erode resilience and reserve such that a smaller stressor can create a disproportionate change in health.[244] Frailty is of particular concern for hospitalised populations, where deconditioning may also play a role in progressing frailty, and critically ill patients share common characteristics with older, frail populations, including changes in mobility, muscle mass, strength, nutrition and endurance.[245] Existing work has described a 12.4% change from 'robust' to 'frail' status at 6 months in older people who were hospitalised for COVID-19, compared with a 4.5% change to 'frail' status at 3.9 years in pre-pandemic conditions.[246,247] Further investigation of long-term post-COVID frailty and its associated impact on health resources are warranted.

Anosmia was identified as a defining characteristic of COVID-19 early in the pandemic,[248,249] with approximately 40% of people with, COVID-19 reporting an impacted taste or smell.[249] Anosmia may persist after acute infection[250] although the underlying mechanisms remain to be elucidated.[251] The impact of anosmia on everyday life, particularly on QoL and nutrition, remains unclear.

COVID-19-related sequelae such as anosmia and ageusia affect appetite and nutritional status, with malnutrition emerging as a common complication of COVID-19 infection.[252] COVID-19 has disproportionately affected older people,[253,254] with worse severity due to existing comorbidities and decreased immune function.[255] Those with the most severe form of infection may require ICU support, which further exacerbates immobilisation and malnutrition.[252] Malnutrition in nursing home residents during the first wave of COVID-19 has increased by approximately 36.8%.[256] Malnutrition is affected by the complex interaction between pre-existing conditions, age-related weight loss, COVID-19 infection and immobilisation due to existing poor functional capacity or ICU stay and remains an important outcome to capture in future studies, particularly as those most profoundly affected by COVID-19 were older adults.

Existing literature describing sexual function after COVID-19 reports on the impact of COVID-19 lockdowns and restrictions on sexual function[257] and a greater impact on women than men.[257] Other studies have reported erectile dysfunction[258,259] after COVID-19 infection with a high prevalence at 3 months after recovery, and associations with

depression during initial infection.[259] Further, sexual dysfunction has been reported in people with long-COVID;[260] however, further work is needed to fully examine the long-term impact of COVID-19 on sexual function in patients with and without long-COVID.

Resilience and self-efficacy are important factors that enable individuals to adapt to challenging circumstances. The COVID-19 pandemic requires resilience on the part of individuals and healthcare systems and is therefore an important outcome measure. Examination of the mechanisms of resilience is critical to permit health systems to adapt to a future pandemic and should be studied further at organisational and personal levels.

Experience from the River Ross virus, *Coxiella burnetti* and Epstein–Barr virus have identified typical responses that include post-viral syndromes of pain.[261] Thus, a range of infections can trigger widespread regional chronic pain.[262] Such pain syndromes are emerging in people with long-COVID[263] and can include chronic pain,[264] testicular pain,[265] headaches[266] and chest pain.[267] Post-COVID pain is expected to increase both in the short and long term.[262] Further work is needed to examine long-term post-COVID pain, particularly considering the complex interactions between infection, biological responses, and psychological and social factors.[268] This includes the consideration of pre-existing conditions, and physical and emotional trauma.[269] Thus, each of these broad outcome domains represents an area in which further research is needed.

Summary of key findings

- Post-COVID frailty, nutrition, sexual function, resilience and self-efficacy, impact on morning and evening routine, occupational gaps, smell and pain each represent areas of research need in IPD meta-analyses.

Chapter 11 Factors associated with COVID-19 severity, recovery and death after COVID-19

Overview

In addition to outcomes that aligned with ICF domains, we examined the impact on measures of clinical severity reduction and mortality, as these measurements were common outcomes in the early stages of COVID-19, when the focus was to reduce mortality and morbidity.

Measures of COVID-19 severity

Data availability

There were 8992 data points where COVID-19 severity was reported as an outcome; data on both time since onset and a formal outcome measurement instrument of severity were available from five studies. Data from one study used the WHO Ordinal Scale for Clinical Improvement level five tool and was excluded, as the data range was outside the published guidelines and clarification could not be sought in time to permit analyses.

As all measures in this domain were categorical, the transformation algorithm used for other domains was not appropriate. Thus, the seven-point ordinal scale and the WHO Clinical Status Scale were mapped to the WHO-9 scale (*Table 24*). *Report Supplementary Material 55* describes the standardised values by study.

Where there were multiple entries within one of the time groups, the average score was kept. Data on long-term outcomes were available at 3–6 months for 316 participants from 2 data sets and did not meet the minimum criteria for the meta-analysis. Therefore, we did not take these data forward for further analysis.

Time to clinical recovery

Data availability

Data on time to recovery were available and usable from only one data set. As this did not meet the meta-analysis criteria, these data were not included in the analysis.

Time to death

Data availability

Data on the time to death were available from 23 studies (IPD = 10,576) (see *Figure 5*). Three data sets did not report any deaths and were therefore excluded. There were insufficient data on those who were not initially hospitalised for the meta-analysis (two data sets, IPD = 312). We also observed an interaction between baseline COVID-19 severity and age. This suggested that a separate analysis of hospitalised participants with and without ventilation was warranted. For participants who were initially hospitalised but not ventilated, data on death were available from 17 data sets (IPD = 8347). For participants who were initially hospitalised and required ventilation, data on death were available (14 data sets, IPD = 1751).

Population description

In the initially hospitalised but not ventilated population (17 data sets, IPD = 8347), the median age was 64 years, and 4870 (58.35%) were male. In the population that required hospitalisation and ventilation (data sets = 14, IPD = 1751), the median age was 63 years, and 1258 (71.8%) were male.

TABLE 24 Transformation of COVID-19 severity data

WHO9 (Anchor)	WHO Clinical Scale	7 point Ordinal Scale
0 = no clinical or virological evidence of infection 1 = ambulatory, no activity limitation	6 = discharged with full return to baseline physical function	1 = not hospitalised with resumption of normal activities
2 = ambulatory, activity limitation	5 = discharged without full return to baseline physical function	2 = not hospitalised but unable to resume normal activities
3 = hospitalised, no oxygen therapy	4 = hospitalised without supplemental oxygen requirement	3 = hospitalisation not requiring supplemental oxygen
4 = hospitalised, oxygen mask or nasal prongs	3 = hospitalised with supplemental oxygen requirement	4 = hospitalisation requiring oxygen
5 = hospitalised, non-invasive mechanical ventilation or high-flow nasal cannula (HFNC)		5 = hospitalisation requiring nasal high-flow oxygen
6 = hospitalised, intubation and invasive mechanical ventilation (IMV)	2 = invasive ventilatory support	
7 = hospitalised, IMV + additional support such as pressors or extra-corporeal membranous oxygenation (ECMO)		6 = hospitalisation requiring ECMO
8 = death	1 = death	7 = death

Research question 2: predictors of long-term outcomes

Survival curves by covariate

Report Supplementary Material 67, *Figure S18* shows survival stratified by available demography, comorbidity and intervention. Each of these factors was considered in univariable and multivariable analyses.

Data availability for regression analyses

Report Supplementary Material 56 describes the covariates available for the analyses. These included age, sex, ethnicity, BMI, smoking status, presence of cancer, diabetes, obesity, other endocrine conditions, mental/behavioural disorders, dementia/Alzheimer's, sleep disorders, neurological conditions, cardiac conditions, cerebrovascular diseases, circulatory disorders, lung disease, liver disease, gastrointestinal conditions, chronic kidney disease, immunosuppression, other conditions, use of corticosteroids, anticoagulants, renal therapy, antibiotics, antivirals, immunosuppressant therapy, hydroxychloroquine and vasopressors. Each was examined in the meta-analysis.

Univariable analyses

For the hospitalised and non-ventilated population, at the univariable level age, sex, ethnicity, smoking status, presence of cancer, diabetes, dementia/Alzheimer's, neurological or cardiac conditions, cerebrovascular disease, circulatory disorders, lung or chronic kidney disease, immunosuppression and use of corticosteroids were each associated with risk of death (see *Report Supplementary Material 57*).

In the hospitalised and ventilated population, age, sex, smoking status, presence of cancer, diabetes, cardiac conditions, cerebrovascular disease, circulatory disorders, lung disease, liver disease, chronic kidney disease, use of renal therapy, antibiotics, immunosuppressants and vasopressors were each associated with the risk of death (see *Report Supplementary Material 57*).

Multivariable regression analyses

In the final model for the hospitalised and non-ventilated population (five data sets, IPD = 5027), as age increased by 1 year, we observed a 6.8% increase in the risk of death. Males had 31% increased risk of death [hazard ratio (HR) 1.31, 95% CI (1.15 to 1.50)], while the presence of cancer, chronic kidney disease, dementia/Alzheimer's and lung disease conferred a 23%, 49%, 56% and 25% increased risk of death, respectively. In this final model, the median age of the population was 64 years and 2898 (57.6%) were male.

In the final model for the hospitalised and ventilated population (data sets = 9, IPD = 969), men had a 27% greater risk of death compared to women [HR = 1.27, 95% CI (1.05 to 1.54)]. The risk of death also increased by 3.6% with each year increase in age [HR = 1.036, 3.6% with each year; 95% CI (1.028 to 1.044)]. The presence of diabetes (56% increased risk), chronic kidney disease (47% increased risk) and liver disease (110% increased risk) were significantly associated with the risk of death (*Table 25*). In this final model, the median age of the included participants was 64 years and 686 (70.8%) were male.

Assessment of certainty

I^2 for the hospitalised and non-ventilated population based on sex was 18.1%, whereas I^2 in the hospitalised population was based on liver disease and was 21.1%. These values were indicative of low heterogeneity. GRADE-informed assessment indicated that the quality of evidence was moderate. Models were developed for hospitalised populations only; therefore, the models were not downgraded based on indirectness (see *Report Supplementary Material 69*, *Table p*).

Discussion

COVID-19 severity reduction

Reduction in COVID-19 severity was an initial target of COVID-19 interventions; vaccination was found to reduce the severity of symptoms in the general population,[270] as well as in people with long-COVID.[271] Selected data were available within PRECIOUS on COVID-19 severity as an outcome. However, these data did not meet the prespecified criteria for meta-analysis. Other studies have reported factors such as age, sex, presence of comorbidities[45,272] and vaccination status as being associated with COVID-19 severity,[272] which remains an area of importance, particularly when examining the efficacy of interventions. Agrawal *et al.* highlighted the need for continued COVID-19 immunisation in people with multimorbidity and comorbidities to decrease the risk of severe COVID-19 infection.[270]

Time to recovery

In general, the estimated time to recovery from COVID-19 is 3 weeks,[273] although for a diagnosis of long-COVID, symptoms should have lasted at least 2 months from the index infection.[274] Consequently, time to recovery is a

TABLE 25 Factors associated with mortality

	Estimate (95% CI)	HR (95% CI)	*p*-value
Hospitalised and non-ventilated ***D* = 5, IPD = 5027** **I^2 (sex) = 18.1%**			
Age	0.065 (0.060 to 0.071)	1.068 (1.052 to 1.074)	< 0.001
Cancer	0.21 (0.04 to 0.38)	1.23 (1.04 to 1.46)	0.015
Chronic kidney disease	0.40 (0.25 to 0.54)	1.49 (1.19 to 1.72)	< 0.001
Dementia/Alzheimer's	0.44 (0.27 to 0.62)	1.56 (1.31 to 1.86)	< 0.001
Sex (ref = female)	0.27 (0.14 to 0.41)	1.31 (1.15 to 1.50)	< 0.001
Lung disease	0.23 (0.07 to 0.38)	1.25 (1.07 to 1.46)	0.004
Hospitalised and ventilated ***D* = 9 IPD = 969** **I^2 (liver disease) = 21.1%**			
Sex (ref = female)	0.24 (0.05 to 0.43)	1.27 (1.05 to 1.54)	0.014
Age	0.035 (0.027 to 0.043)	1.036 (1.028 to 1.044)	< 0.001
Diabetes	0.44 (0.26 to 0.63)	1.56 (1.30 to 1.87)	< 0.001
Chronic kidney disease	0.38 (0.08 to 0.69)	1.47 (1.08 to 2.00)	0.014
Liver disease	0.74 (0.31 to 1.17)	2.10 (1.37 to 3.22)	0.001

recommended parameter for collection as part of a core outcome set in people with long-COVID.[138] Previous studies have ascertained that age, sex, severe COVID-19 and the presence of chronic disease were each associated with time to recovery.[275–278] Within PRECIOUS, data on time to recovery were available from two studies but could not be reliably analysed. Non-resolution of COVID-19 symptoms leads to a diagnosis of long-COVID. Although symptom data at follow-up were available for certain studies, we often could not be certain that symptoms had persisted at later follow-up due to initial COVID-19 infection, a new infection, or presence of a pre-existing condition. Time to long-COVID recovery was therefore not examined in the current analysis, although emerging work suggests that recovery from long-COVID is rare in the first 2 years after infection.[279] Future work should document the development of both long-COVID, the time to recovery from long-COVID and factors associated with long-COVID recovery.

Mortality

We quantified the risk of death in our international population stratified by hospitalisation with or without ventilation. We observed that in both the hospitalised and ventilated, and hospitalised without ventilation populations, increasing age, male sex and presence of chronic kidney disease were consistently associated with increased mortality. The risk of death was also worse in people with cancer, Alzheimer's disease/dementia, and lung disease for those who were hospitalised without a requirement for ventilation compared to people without these comorbidities.

The high mortality rate in hospitalised participants (6.8% per increase in age by 1 year) compared with 3.6% per increase in age by 1 year in hospitalised and ventilated participants may reflect the highly selected group that received ventilation based on the likelihood of survival. It should also be noted that data on the presence of dementia/Alzheimer's were only available for the hospitalised and non-ventilated population, perhaps reflecting the fact that patients with dementia would not have been likely to be accepted for ventilation. In the ventilated population, the presence of diabetes and liver disease conferred a greater risk of death than their absence.

Our observation of higher mortality in men,[280–282] older people and those with chronic kidney disease[282,283] was consistent with the existing literature. Those with existing kidney disease were more likely to be hospitalised with COVID-19,[284] and the mortality rate in those with COVID-19 and kidney disease was estimated to be 20%.[284] Thus, the presence of kidney disease creates a high-risk population and is an important factor associated with mortality in both of the hospitalised (non-ventilated and ventilated) populations.[284]

Diabetes is a known risk factor for COVID-19, and the pandemic has disrupted care for people with diabetes, similar to many other health conditions.[285] Consistent with the existing literature, we observed an increased risk of death in people with diabetes,[285] specifically in the hospitalised and ventilated population. This is consistent with data from smaller studies of 193[286] and 650 patients,[287] that reported an increased need for mechanical ventilation in people with diabetes. Similarly, we observed that liver disease was significantly associated with increased mortality in the hospitalised and ventilated population only, which is consistent with previous literature that describe a significant increase in COVID-19-related mortality in people with alcohol-associated liver disease and non-alcoholic fatty liver disease,[288] with certain ethnicities disproportionately affected.

Other studies have examined the role of deprivation measures, noting worse mortality in areas of greater deprivation[281,289] and disproportionate death in certain ethnicities.[281,289,290] In our sample, ethnicity was only readily available as a covariate in the hospitalised population and was significantly associated with mortality in univariable but not multivariable analyses. Further examination of mortality in an international context, including the impact of socioeconomic status and ethnicity, is warranted.

Mortality was an important outcome of early COVID-19 studies. Nab *et al.* reported that the initial crude COVID-19 mortality rate between March and May 2020 was 4.48/1000 person-years and decreased to 0.67/person-years between June and August 2022.[291] The reduced mortality rate was attributed to the introduction of vaccinations for COVID-19.[291] Within PRECIOUS, we only had sparse data on vaccination status and the number of vaccinations received; there were no corresponding data available on vaccination status and mortality. Thus, we could not fully examine the effect of vaccination on mortality. Future studies should examine the impact of vaccination on the long-term outcomes.

Summary of key findings

- Increasing age, male sex and presence of chronic kidney disease were consistently associated with increased mortality.
- Data are needed on time to recovery, particularly for the long-COVID population.
- We also need data on risk of death in community-based cohorts.

Chapter 12 Individual factors associated with later hospitalisation after COVID-19 infection

Overview

This chapter describes the individual factors associated with later hospitalisation (rehospitalised after initial hospitalisation for COVID-19, or later hospitalisation for those not initially hospitalised) after index COVID-19 infection. Data included in the final model reflects availability of covariates for analyses. The absence of a variable in the final model does not necessarily mean that it was not a significant predictor; it may also indicate that there was insufficient data to include within the modelling process.

Research question 3: individual, health service and societal impact of COVID-19

Later hospitalisation

Data availability

From 10 data sets (IPD = 5737) where later hospitalisation was captured at follow-up, complete data were available for 4881 participants (see *Figure 5*). In total, 589/4881 (12.1%) were hospitalised during the course of follow-up; 545/4270 (12.8%) were initially hospitalised with COVID-19 and were rehospitalised, while 44/607 who were not initially hospitalised for COVID-19 infection were later hospitalised during the course of follow-up.

Two studies captured re-admission as due to COVID-19, six studies described generic hospital re-admission, one study described general re-admission as well as COVID-19-specific re-admission, and one study only described re-admission involving ICU.

Population description

For those in whom data on later hospitalisation was captured, median age was 61 years (IQR 49–72), 2756 (57.1%) were male and 503 (10.3%) were initially hospitalised and required ventilation. *Report Supplementary Material 58* describes covariate availability for the sample in whom data were available for analysis. These were each examined in univariable analyses.

Univariable analyses

At univariable level, age, smoking status, initial hospitalisation, COVID-19 severity, presence of cancer, diabetes, dementia/Alzheimer's disease, cardiac conditions, cerebrovascular, lung or chronic kidney disease, use of renal therapy, hydroxychloroquine or vasopressors were each significantly associated with later hospitalisation at univariable level (see *Report Supplementary Material 59*). These were taken forward to multivariable analysis.

Multivariable analyses

In total, two data sets (IPD = 1336) contributed to the final multivariable model. As age increased by 1 year, the odds of later hospitalisation increased by 2% [$p < 0.0001$, OR = 1.02, 95% CI (1.01 to 1.02)]; presence of pre-existing cerebrovascular disease [$p = 0.01$, OR = 1.68, 95% CI (1.1 to 2.5)], diabetes [$p < 0.0001$, OR = 1.56, 95% CI (1.23 to 1.98)], chronic kidney disease [$p = 0.001$, OR = 1.67, 95% CI (1.23 to 2.26)] and cancer [$p < 0.0001$, OR = 2.64, 95% CI (2.02 to 3.43)] had higher odds of later hospitalisation than absence of these comorbidities, respectively; non-smokers had lower odds of later hospitalisation than current smokers [$p = 0.01$, OR = 0.76, 95% CI (0.61 to 0.94)] (*Table 26*). Median age of participants who contributed to this model was 61 years (IQR 49–73), 1742 (56.6%) were male and 324 (10.5%) were initially hospitalised and ventilated.

TABLE 26 Final multivariable regression model for factors associated with later hospitalisation

D = 2, IPD = 1336 I^2 (age) = 0.00%		*p*-value	OR	95% confidence limits	
Age		< 0.0001	1.017	1.010	1.024
Cerebrovascular disease	Yes vs. no	0.012	1.684	1.119379	2.533186
Diabetes	Yes vs. no	< 0.0001	1.56337	1.23468	1.979558
Chronic kidney disease	Yes vs. no	0.001	1.669278	1.234284	2.257577
Smoker	Current vs. non-smoker	0.012	0.7553611	0.6075233	0.9391745
Cancer	Yes vs. no	< 0.0001	2.635096	2.018694	3.439715

Assessment of certainty

I^2 (age) was 0% in this model, indicating no evidence of statistical heterogeneity. GRADE-informed assessment indicated that the quality of evidence was moderate (downgraded due to imprecision). As all participants in this model were drawn from hospital-based settings and the outcome was later hospitalisation, the inclusion of selected populations (hospitalised) did not contribute to a downgrading (see *Report Supplementary Material 69*, *Table q*).

Discussion

Clinical status at discharge and presence of existing comorbidities helps to inform risk of re-admission.[292] We observed that 12.1% of people initially hospitalised for COVID-19 infection were rehospitalised during follow-up; 7.2% of people not initially hospitalised were later hospitalised. Increasing age and presence of cerebrovascular disease, diabetes, chronic kidney disease, cancer and current smokers were each associated with increased odds of later hospitalisation.

Hospitalisation for initial COVID-19 infection and later rehospitalisation is common.[292] However, COVID positivity was not associated with later hospitalisation outcomes in any of the models presented. COVID-19 severity showed significance at the univariable level, yet this association did not remain significant when age was controlled for, indicating that the initial univariable model may have captured a spurious relationship. Our models suggest that COVID-19 does not have an impact on later hospitalisation which implies a minimal impact on post initial infection resource use. Given this result, we do not present an economic analysis of the impact of COVID-19 on secondary care post the initial COVID-19 episode. These results need to be interpreted with caution due to the small number of studies that included information on later hospitalisation. Studies did not routinely report the reason for later hospitalisation, so this important context was not explored. There was a sizeable imbalance in the data that contained very few individuals who were not COVID-positive at baseline. There may be selection bias in the results if there were unmeasured effects that impacted both the inclusion in the studies and the likelihood of being hospitalised. These models did not take into account risk of death which may have been higher in the COVID-19 group and at the same time affecting later hospitalisation. Our sample included 44 people who were not initially hospitalised due to COVID-19, but were later hospitalised during the course of follow-up. As this was a relatively small sample and meaningful comparisons with those who were initially hospitalised with COVID-19 could not be made, we combined rehospitalisation and later hospitalisation as a single outcome.

The rate of later hospitalisation in our sample was comparable with previous estimates, that ranged between 4.2%[293] and 19.9%.[294] Previous work described an association between presence of cardiovascular conditions, pulmonary disease, and risk or re-admission after COVID infection.[292,295] While data on lung disease were available in our sample, we observed that this was significant at univariable level but not in the final multivariable model.

Our findings are congruent with previous work describing an increased risk in people with end-stage renal disease or diabetes,[296,297] cancer[298,299] and in older people.[300,301] Literature has also suggested additional factors such as cognitive impairment[302] and BMI[301] as factors associated with post-COVID hospital admission. We observed that in our sample,

BMI did not meet the threshold for significance at univariable level. Previous work has also established disproportionate COVID-19 admissions in the immunocompromised population;[303] immunosuppression was captured in the PRECIOUS data set but was not present in significant numbers to permit inclusion in analyses. We observed a significant association between current smokers and later hospitalisation compared to non-smokers. Others have reported a higher proportion of former smokers being initially hospitalised than current or non-smokers,[304] and a link between history of smoking and hospital re-admission.[299] While we did not observe any sex differences in hospital re-admission, others have reported on associations between male sex and rehospitalisation.[299]

Factors that warrant further analysis include markers of socioeconomic status and re-admission; others have suggested links between rehospitalisation and use of government insurance[299] and homelessness.[298] We were unable to examine markers of socioeconomic status on re-admission, as these were not present in sufficient quantity or in formats to support data synthesis.

Summary of key findings

- Our findings highlight a vulnerable population (increasing age, pre-existing cerebrovascular disease, diabetes, chronic kidney disease, cancer, current smoking), with increased odds of later hospitalisation.

Chapter 13 Factors associated with return to work after COVID-19

Overview

This chapter examines the associations between demographic, intervention factors and return to work after COVID-19 infection. Data were captured across a range of variables related to returning to work, including burnout, employment before and after COVID-19, whether an individual was in full-time or part-time employment, receipt of a pension, hours currently worked, number of full-time and part-time hours worked, whether work required sitting, light physical exertion, moderate physical exertion and heavy physical exertion. Where appropriate, these were aggregated into common groups to facilitate analyses.

Research question 3: individual, health service and societal impact of COVID-19

Return to work

Data on repeated measures of return to work or school were available for three data sets. Only one data set included data on work rhythm and was, therefore, not analysed. Two data sets captured return to work or school and work adjustments, respectively, and were therefore not analysed in trajectory analyses, as they did not meet the criteria for meta-analysis (> 2 data sets capturing variable).

Single data sets captured burnout, employment before and after COVID-19, whether an individual was in full-time or part-time employment, receipt of a pension, hours currently worked, number of full-time and part-time hours worked, whether work required sitting, light physical exertion, moderate physical exertion, and heavy physical exertion. These variables did not meet the criteria for meta-analyses and were therefore considered.

Return to work or school was captured in two data sets (IPD = 851), and missed work was captured in two data sets (IPD = 2321 only captured for those who actually missed work and were therefore omitted from analyses), and impacted working ability or requirement for work adjustment was captured in four data sets (IPD = 516, *Figure 5*).

Return to work or school

For those in whom return-to-work/school data were available, all participants (two data sets; IPD = 851) were COVID-19 positive at baseline; the median age was 59 years, 564 (66.4%) were male, and 147 (17.3%) required hospitalisation with mechanical ventilation. (*Report Supplementary Material 60* describes available covariates for analyses.) Return to work/school was treated as a single binary outcome variable, which was independent of the time point for assessment; 490 (57.6%) participants in whom data were captured had returned to work. At the univariable level, age ($p < 0.0001$) and sex ($p = 0.002$) were significantly associated with return to work. In the final model (data sets = 2; IPD = 844), age ($p < 0.0001$) and sex ($p = 0.0038$) were significantly associated with returning to work or school, such that for a 1-year increase in age, the OR for returning to work or school was 0.958 [95% CI (0.947 to 0.969)]; as age increased, the odds of returning to work/school decreased. Women had lower odds of returning to work/school [OR = 0.64, 95% CI (0.47 to 0.86)] compared with men, such that 52.8% of women returned to work/school compared with 63.8% of men (*Table 27*). Median age of participants in this final model was 59 (IQR 51–68) and 559 (66.2%) were male.

Affected ability to work or requirement for adjustments

Report Supplementary Material 61 describes the covariates available for the analyses. Affected ability to work and requirements for adjustments were treated as a single binary outcome variable that was independent of the follow-up time point. From four data sets (IPD = 516), the median age was 53 (IQR 44.5–63), 151 (29.7%) were male, 140 (27.6%) were COVID-positive at the study inclusion, 214 (42.1%) were confirmed as having COVID-19 before study baseline, and 37 (12.3%) required hospitalisation with ventilation. At the univariable and multivariable levels, only age was associated with an affected ability to work or requirement for adjustments ($p = 0.0159$). As age increased, the impacted

TABLE 27 Final multivariable regression model for factors associated with return to work

	Variable I^2 = 44.4%	*p*-value	OR	95% CI		Proportion estimate
Return to work *D* = 2; IPD = 844	**Age**	< 0.0001	0.958	0.947	0.969	0.5279
	Sex (female vs. male)	0.0038	0.636	0.468	0.863	0.6377
	Variable I^2 = 90%	***p*-value**	**OR**	**95% CI**		
Affected work/ adjustments needed *D* = 4; IPD = 513	**Age**	0.0159	0.978	0.960	0.996	–

ability to work or requirement for adjustments decreased [OR = 0.978, 95% CI (0.96 to 0.996); see *Table 27*]. The final model included four data sets (IPD = 513).

Assessment of certainty

The I^2 for the final return-to-work/school model was 44.4%, indicating moderate heterogeneity.[305] The I^2 for the final adjustments to work analysis was 90%, indicating considerable heterogeneity[305] GRADE-informed assessment indicated that the quality of evidence was very low for return to work/school, downgraded for imprecision, inconsistency and indirectness (see *Report Supplementary Material 69*, *Table r*) and low for affected ability to work, downgraded for inconsistency and indirectness (see *Report Supplementary Material 69*, *Table s*).

Discussion

Work has been significantly affected by COVID-19, with some workplaces adapting and implementing flexible working measures, while others became severely impacted.[306] Based on our limited sample, older people and women were less likely to return to work after COVID-19, and we also observed that age contributed to impacted ability to work/ requirement for adjustments, such that older people were less likely to require adjustments or report that their work had been affected, perhaps due to fewer returning to work.

The covariates available for inclusion in the analyses precluded detailed investigation of the personal health factors and impact of interventions on return to work, affected ability to work, or requirement for adjustments to work. We observed that 17.3% of the population included in the return-to-work analysis were hospitalised and mechanically ventilated, with the remaining being hospitalised with no requirement for mechanical ventilation; there were no community-based participants in our return-to-work sample. Literature suggests that return to work is typically low in patients who have required intensive care.[307] We observed that 57.6% of people with COVID-19 in our sample had returned to work, which was comparable with estimates of return to work 1 year after discharge from the ICU.[308] A nationwide registry study on return to work after COVID-19 has highlighted a return to work in 81.9% of participants at 1 month, 98.4% at 6 months,[309] and 5.5% as being absent for longer than 3 months.[306] Later return to work was observed in people with COVID-19 compared to those with flu.[306] Hospitalised patients also had a lower prevalence of returning to work, with 92.6% of hospitalised participants returning to work at 6 months and 36% of the ICU population not returning to work by 6 months.[309] Data were not available during the assessment period for return to work in our sample; however, the inclusion of COVID-19 severity (hospitalised/hospitalised and ventilated) at the univariable level did not yield significant associations with a return to work. Before the pandemic, health-related work absences increased with age, but after COVID-19, this skewed to include younger people.[310] Consistent with our findings, previous studies reported an association between older age and female sex with delayed return to work.[306] Shortness of breath and fatigue have been similarly reported to be associated with a later return to work.[306] Our analyses would have benefitted from the examination of such corresponding symptom profiles and ADLs in relation to returning to work, but this was not possible due to insufficient corresponding data on ADLs.

COVID-19 has had a significant impact not only on individuals, healthcare systems and societies, but also on health insurance systems[311] and employers. It is estimated that the average employment absence due to COVID-19 costs approximately US$9000,[310] with annual lost-labour costs of US$62 billion[310] and QoL losses due to the consequences of COVID-19 totalling US$2.6 trillion.[312] Thus, the full impact, factors associated with, and costs of COVID-19 on work must be further examined.

The impact of socioeconomic status remains to be fully elucidated,[311] along with the role of ethnicity, previous work established that health-related work absences were greater in Asian, Hispanic, and non-Hispanic Black employees than in non-Hispanic White populations.[310] Important aspects such as type of occupation, requirements for moderate physical activity, hours and type of employment, and burnout were captured across single data sets, thereby precluding analysis in PRECIOUS, but representing important aspects of the impact of COVID-19 on work and should be examined further in meta-analyses. Crucially, COVID-19 affected not only working-age people, but also students. We examined return to work or school as this had been jointly categorised in data sets; further work should examine return to work and school separately, as these are often two very different populations with differing demographics and comorbidities. Future work should also examine return to work in the context of symptom profiles, long-COVID, time to return to work, ability to perform ADLs, type of employment, socioeconomic factors, and costs to employers and employees to adequately capture the impact of COVID-19 on work.

Summary of key findings

- Older people and women were less likely to return to work after COVID-19; however, more data are needed to explore this further.
- We also need to establish the link between ADLs, persistent symptoms and return to work.
- We require further information on return to work in community-based participants.
- Data on costs of COVID-19 in relation to return to work require further data.
- Return to school should be examined separately.

Chapter 14 Factors associated with health-related quality of life after COVID-19

Overview

Health-related quality of life or utility describes personal preference assessments of overall health status and can be used to compare participant outcomes across different health conditions.[313] We describe HRQoL in the COVID-19 population and the factors associated with health valuation.

Research question 3: individual, health service and societal impact of COVID-19

Health-related quality of life

Data availability

Health utilities (HRQoL herein) were derived from the EuroQoL EQ-5D and SF-36 separately. From 11 data sets and 8091 IPD where EuroQoL EQ-5D-3L and EuroQoL EQ-5D-5L were reported, data were available for analysis from 11 data sets and 7880 IPD (see *Figure 5*). From 6 data sets and 1164 IPD where SF-36 was reported, data were available for analysis from 5 data sets and 958 IPD. Data were available from COVID-19 onset to 24 months post onset. Data were available from Australia, Germany, Iceland, the Netherlands, Russia, Switzerland, Italy, Canada, USA and UK. Covariates available for analyses are described in *Report Supplementary Materials 62* and *63*.

EuroQol-5 Dimensions-derived health-related quality of life

Population description

The median age of participants in whom data were available on EQ-5D-derived HRQoL was 55 years (IQR 43.4–65), 2836 (36%) were male and 1260 (16%) were initially hospitalised and 205 (2.6%) ventilated. Where HRQoL values were available at 4–6 months, median health valuation was 0.840 (IQR 0.691–0.987); where HRQoL was available at 10–12 months, median value was 0.883 (IQR 0.759–1), and where HRQoL was available at beyond 12 months, median value was 0.860 (IQR 0.725–1).

Report Supplementary Material 64 describes EQ-5D-derived HRQoL values at different time points, stratified by COVID exposure and initial hospitalisation. We observed poorer HRQoL in initially hospitalised participants.

Univariable analyses

Individual factors that were significantly associated with EQ-5D-derived HRQoL are described in *Report Supplementary Material 65*. At univariable level sex, education level, smoking status, employment status, number of people in household, requirement for ventilation, COVID positivity at study inclusion, initial hospitalisation for COVID, vaccination status at baseline, presence of diabetes, obesity, other endocrine conditions, mental/behavioural disorders, neurological conditions, cardiac conditions, cerebrovascular disease, circulatory disorders, lung disease, gastrointestinal conditions, chronic kidney disease, immunosuppression and musculoskeletal conditions were each associated with health valuation.

Multivariable analysis

We examined data in two models; model 1 focused on the impact of COVID positivity and infection severity on HRQoL. A second model investigated how the results change in the presence of comorbidities, socioeconomic and other characteristics such as diabetes, lung disease, education level, employment and smoking status. The second model excludes the most serious cases of COVID for whom we did not have information on these characteristics, so the results may not be directly comparable between models. In model 1 (11 data sets and 7880 IPD), women had a HRQoL value of 0.06 points lower than men [$p < 0.001$, 95% CI (−0.07 to −0.05)], COVID positivity was significantly

associated with poorer HRQoL [p = 0.031, point estimate = −0.028, 95% CI (−0.05 to −0.003)]. Hospitalisation with COVID accounted for a reduction in health valuation of 0.08 points [p < 0.0001, 95% CI (−0.11 to −0.06)]. We would typically expect a recovery over time for many health conditions; however, we did not observe a statistically significant interaction between hospitalisation with COVID and time, indicating that people initially hospitalised for COVID may experience a moderate recovery in HRQoL, but did not experience significant recovery to their original health valuations in the 2-year period we examined. We also observed a general improvement, irrespective of COVID-19 positivity, in HRQoL over time, but these increments were small (*Table 28*). Median age of the participants who contributed to this model was 55 (IQR 43–65), 36% were male and 15.3% were initially hospitalised.

Our second model included comorbidities (data sets = 6; IPD = 4642). Women experienced a 0.05-point decrease in HRQoL when compared with men [p < 0.0001, 95% CI (−0.06 to −0.04)], COVID positivity accounted for a decrease in 0.03 points [p = 0.006, 95% CI (−0.06 to −0.01)] which did not change over time. In addition to the effect of hospitalisation on poorer HRQoL, presence of diabetes [p < 0.0001, point estimate = −0.06, 95% CI (−0.09 to −0.04)], obesity [p < 0.0001, point estimate = −0.05, 95% CI (−0.06 to −0.04)], lung disease [p < 0.0001, point estimate = −0.05, 95% CI (−0.07 to −0.04)] and chronic kidney disease [p = 0.010, point estimate = −0.05, 95% CI (−0.09 to −0.01)] were each associated with worse HRQoL. Higher education status, employment and non-smoking status were each associated with better HRQoL. We observed small but significant improvements in HRQoL over time beyond 7 months (see *Table 28*). Median age of the participants who contributed to this model was 54 (IQR 42–64), 31% were male and 4% were initially hospitalised.

Rand 36-Item Short Form Health Survey-derived health-related quality of life

Population description

Where HRQoL was derived from the SF-36, median age of the population was 58 (IQR 48–65), 517 (54%) were male and 498 (52%) were initially hospitalised with COVID-19. Where HRQoL values were available at 4–6 months, median health valuation was 0.883 (IQR 0.722–0.972); where HRQoL was available at 10–12 months, median value was 0.789 (IQR 0.636–0.916), and where HRQoL was available at beyond 12 months, median value was 0.825 (IQR 0.634–0.956).

Report Supplementary Material 64 describes HRQoL values at different time points, stratified by initial hospitalisation. We observed poorer HRQoL in initially hospitalised participants.

Univariable analyses

Individual factors that were significantly associated with SF-36-derived HRQoL are described in *Report Supplementary Material 66*. At univariable level sex, age, education status, smoking status, BMI, employment status, ventilation, initial hospitalisation with COVID-19, diabetes, obesity, presence of cardiac conditions, circulatory disorders, lung, or chronic kidney disease, immunosuppression, blood disorders and cerebrovascular disease were each associated with health valuation.

Multivariable analyses

The final model included 5 data sets and 958 IPD (see *Table 28*). Increasing age [p < 0.0001, point estimate = 0.002, 95% CI (−0.003 to −0.001)] and female sex [p < 0.0001, point estimate = −0.06, 95% CI (−0.08 to −0.04)] were each associated with poorer HRQoL. Initial hospitalisation [p = 0.003, point estimate = −0.11, 95% CI (−0.18 to −0.04)] and need for ventilation [p = 0.001, point estimate = −0.09, 95% CI (−0.14 to −0.04)] were each associated with poorer HRQoL (see *Table 28*). Participants that contributed to this final model had a median age of 58 (IQR 48–65), 54% were male and 52% were initially hospitalised with COVID-19.

Assessment of certainty

I^2 for EQ-5D-derived HRQoL in model 1 was 29.99% and for model 2 was 26.44%. For the SF36-derived HRQoL, I^2 was 18.57%, indicating low heterogeneity between studies throughout. GRADE-informed assessment of models indicated moderate quality for each model, with downgrading for indirectness (see *Report Supplementary Material 69*, *Table t*).

TABLE 28 Final multivariable regression model for factors associated with lower health utilities

	EuroQoL EQ-5D-derived utility D = 11 IPD = 7880	*p* > |z|	Point estimate	(95% CI)	
Model 1	Female	< 0.0001	−0.0623762	−0.0717476	−0.0530049
	COVID positivity*	0.031	−0.0280673	−0.0535431	−0.0025914
	COVID positivity*period				
	1*4–6 months	0.650	0.002712	−0.0090102	0.0144343
	1*7–9 months	0.687	−0.0021749	−0.0127452	0.0083955
	1*10–12 months	0.323	−0.0055596	−0.0165884	0.0054691
	1*13–15 months	0.124	−0.009469	−0.0215358	0.0025978
	1*16–18 months	0.532	−0.0061413	−0.0254111	0.0131284
	1*19–24 months	0.064	−0.0287439	−0.0592059	0.0017182
	Hospitalisation	< 0.0001	−0.0849237	−0.1113849	−0.0584626
	Hospitalisation*period				
	1*4–6 months	0.070	−0.0200569	−0.0417422	0.0016283
	1*7–9 months	0.649	−0.004783	−0.025395	0.015829
	1*10–12 months	0.196	−0.0153452	−0.0385949	0.0079044
	1*13–15 months	0.679	−0.0047339	−0.0271293	0.0176614
	1*16–18 months	0.908	−0.0019217	−0.0343631	0.0305197
	1*19–24 months	0.615	−0.0120591	−0.059077	0.0349588
	Ventilated	< 0.0001	−0.0623407	−0.0827187	−0.0419627
	Period				
	4–6 months	0.572	0.0021828	−0.0053805	0.0097462
	7–9 months	0.009	0.0102469	0.0025151	0.0179788
	10–12 months	< 0.0001	0.0159572	0.0078536	0.0240608
	13–15 months	< 0.0001	0.0187187	0.0098114	0.0276261
	16–18 months	< 0.0001	0.0191501	0.0085473	0.0297529
	19–24 months	0.013	0.0282609	0.005875	0.0506469
	_cons	0.000	0.8903863	0.8410821	0.9396905
	Reference category for time interactions and period is utility at 0–3 months COVID positivity refers to COVID exposure at baseline				
	EuroQoL-derived utility ***D* = 6** **IPD = 4642**	***p* > |z|**	**Point estimate**	**(95% CI)**	
Model 2	Female	< 0.0001	−0.0538096	−0.0647699	−0.0428493
	COVID positivity*	0.006	−0.0328078	−0.0560787	−0.0095369
	COVID positivity *period				
	1*4–6 months	0.865	0.0010523	−0.0111144	0.013219
	1*7–9 months	0.829	−0.0011774	−0.0118926	0.0095378

continued

TABLE 28 Final multivariable regression model for factors associated with lower health utilities (*continued*)

	EuroQoL-derived utility *D* = 6 IPD = 4642	*p* > |z|	Point estimate	(95% CI)	
	1*10–12 months	0.434	−0.0044512	−0.0156053	0.0067028
	1*13–15 months	0.175	−0.0084162	−0.0205852	0.0037528
	1*16–18 months	0.338	−0.0095438	−0.0290812	0.0099936
	1*19–24 months	0.077	−0.0289994	−0.0611929	0.0031942
	Hospitalised	< 0.0001	−0.0694563	−0.0995272	−0.0393853
	Hospitalised*period				
	1*4–6 months	0.206	−0.0211628	−0.0539421	0.0116165
	1*7–9 months	0.086	−0.0262585	−0.0562459	0.0037289
	1*10–12 months	0.417	−0.0123056	−0.0420456	0.0174345
	1*13–15 months	0.344	0.0152362	−0.0162951	0.0467676
	1*16–18 months	0.664	0.0096739	−0.033953	0.0533009
	1*19–24 months	0.808	−0.0069487	−0.0628469	0.0489495
	higher_education	0.002	0.0214614	0.0079026	0.0350202
	non_smoker	< 0.0001	0.024398	0.0131546	0.0356415
	employed	< 0.0001	0.0437317	0.0325173	0.0549461
	diabetic	< 0.0001	−0.0646733	−0.0877324	−0.0416141
	obese	< 0.0001	−0.0488602	−0.0618952	−0.0358252
	lung_dis	< 0.0001	−0.0501326	−0.0651853	−0.0350799
	kidney_dis	0.010	−0.0495184	−0.0871346	−0.0119021
	Period				
	4–6 months	0.528	0.0024184	−0.0050851	0.0099219
	7–9 months	0.009	0.010271	0.0026114	0.0179305
	10–12 months	< 0.0001	0.0157425	0.0077208	0.0237642
	13–15 months	< 0.0001	0.0186451	0.0098357	0.0274545
	16–18 months	< 0.0001	0.0189157	0.0084292	0.0294023
	19–24 months	0.013	0.0280928	0.0058998	0.0502859
	_cons	0.000	0.8446646	0.7862023	0.903127
	Reference category for time interactions and period is utility at 0–3 months COVID positivity refers to COVID exposure at baseline				
	SF-36-derived utilities *D* = 5 IPD = 958	***p* > |z|**	**Point estimate**	**(95% CI)**	
Model 1	Age	0.000	−0.0019573	−0.0027641	−0.0011505
	Female	0.000	−0.0594639	−0.0822067	−0.0367212
	COVID positivity	0.171	0.0329537	−0.0142344	0.0801417
	COVID positivity*period				
	1*7–9 months	0.931	0.0048797	−0.1053417	0.1151011

TABLE 28 Final multivariable regression model for factors associated with lower health utilities (*continued*)

SF-36-derived utilities *D* = 5 IPD = 958	*p* > |z|	Point estimate	(95% CI)	
1*10–12 months	0.106	−0.0317411	−0.0702765	0.0067943
1*12 + months	0.829	0.0044154	−0.0356162	0.0444469
Hospitalised	0.003	−0.1099873	−0.1825349	−0.0374397
Hospitalised *period				
1*0–3 months	0.305	0.1752366	−0.1598555	0.5103287
1*7–9 months	0.486	0.0165219	−0.0300044	0.0630481
1*10–12 months	0.000	0.0764645	0.0343158	0.1186131
1*12 + months	0.003	0.0611429	0.0207999	0.1014859
Ventilated	0.001	−0.089158	−0.1402573	−0.0380586
Ventilated *period				
1*0–3 months	0.034	−0.0822087	−0.1580586	−0.0063588
1*7–9 months	0.045	0.0528147	0.0011966	0.1044327
1*10–12 months	0.971	002513	−0.1323518	0.1373777
1*12 + months	0.503	0.0513938	−0.0989448	0.2017324
Period				
0–3 months	0.297	−0.177446	−0.5106075	0.1557155
7–9 months	0.601	−0.0272155	−0.1292021	0.0747712
10–12 months	0.000	−0.060211	−0.0862363	−0.0341858
12 + months	0.000	−0.0750937	−0.1016678	−0.0485196
_cons	0.000	0.9778638	0.8985667	1.057161

Discussion

Across both derivation methods and all three models, hospitalisation with COVID-19, during the initial episode consistently resulted in lower HRQoL that did not appear to recover for up to 2 years after the initial COVID-19 infection. COVID positivity was associated with poorer HRQoL in the EQ-5D-derived models. Irrespective of the method of HRQoL derivation (EQ-5D or SF-36), women had worse HRQoL when compared with men. Additional populations reporting health utility loss included people with diabetes, obesity, lung or chronic kidney disease. Employment, higher levels of education and non-smoking status were associated with better HRQoL when compared with lower education, non-employment or a smoking history, respectively.

COVID-19 is unlikely to be completely eradicated, so the long-term impact and costs of COVID-19 will continue to be necessary to inform resource allocation and planning.[314] The overall burden of COVID-19 would be underestimated if solely based on mortality.[315] Decision-making requires consideration of QoL, morbidity and mortality.[316] HRQoL forms an important aspect of quantifying the impact of COVID-19, and includes the effects of the pandemic, environment and the impact of infection.

Previous work has estimated health utilities of 0.78 in non-hospitalised, 0.82 in hospitalised and 0.71 in ICU populations.[317] Beyond the direct impact of COVID-19 infection, the impact of light pandemic restrictions was estimated to be associated with a utility of 0.71, while severe restrictions were associated with a utility of 0.65.[316]

Consistent with other health conditions,[318] we observed sex differences in health utilities. We built on existing work by examining health utilities at different post-COVID time points, up to 2 years post-COVID-19 infection and the specific impact of pre-existing comorbidities. Our findings are strengthened by our use of country-specific value sets, where these were available.[317] Data were available from an international data set, mainly reflecting high-income countries. Additional work is needed to profile health utilities from lower- and lower-middle-income countries.

Summary of key findings

- Hospitalisation with COVID-19 consistently resulted in lower HRQoL that did not appear to recover for up to 2 years after the initial COVID-19 infection.
- Women had worse HRQoL when compared with men.
- Utility loss was seen in people with diabetes, obesity, lung or chronic kidney disease.
- Employment, higher levels of education and non-smoking status were associated with better HRQoL.

Chapter 15 Confidence in cumulative evidence

Overview

In this chapter, we discuss the methodological quality of the PRECIOUS study, considering our meta-synthesis methodological approach, RoB and the confidence in the evidence generated from our analyses. RoB for the underlying data sets that contributed to our secondary meta-analyses are described in each chapter (4–14) using a GRADE-informed method (see *Report Supplementary Material 69*, *Tables a–t*). Here, we discuss our overall methodological and model quality.

Methodological duality of data sets contributing to PRECIOUS

All data were derived from recent data sets, reflecting the novel pathogen nature of COVID-19. Relevant research data sets on COVID-19 included a range of designs to facilitate rapid generation of knowledge and thus included RCTs and non-randomised cohort studies. With the lack of widespread testing available early in the pandemic and few data sets including data on previously negative participants who subsequently tested positive for COVID-19, evidence was mainly available from observational/cohort study designs. Thus, while we had originally aimed to base our meta-analyses on data from published RCTs (as the highest level of evidence), only 20/116 of eligible contributed data sets were RCTs. Where data were available on RCTs, we assessed the quality of these data sets using the MMAT tool (see *Report Supplementary Material 8*).

Ten of 20 RCTs used blinded assessment of outcomes, 11/20 RCTs described concealment of group allocation, and 17/20 studies described adherence to the assigned intervention. From 43 non-randomised comparator studies, 32 studies reported that interventions were administered as intended. For qualitative descriptive studies, 44/53 studies reported on use of validated outcome assessment instruments/outcomes. Only 3/53 studies reported on piloting the use of questionnaires prior to commencing the studies.

Methodological quality of model assessment

The quality of each model was assessed using a GRADE-informed approach, describing imprecision (width of the generated CIs, the number of underlying studies contributing to the model and where applicable, the number of events for categorical variables), inconsistency (heterogeneity, assessed using the I^2 statistic), indirectness (inclusion of data on subsets of the COVID-19 population, validity of the assessment instrument to describe the outcome under investigation) and publication bias. Thus, the confidence in each model was graded as high, moderate, low or very low, depending on the underlying data. Additionally, for each model we provided information on the underlying population, to facilitate the application of findings to an appropriate population. These are detailed in our summary of findings (*Table 29*).

Meta-synthesis and risk of bias

Selection bias

PRECIOUS employed broad eligibility criteria to maximise representativeness of the COVID-19 population. Long-term outcomes included validated assessment instruments, symptom data, morbidity, mortality, hospitalisation, or discharge destination/residence reported beyond 28 days of index COVID-19 infection.

Our systematic review-based identification of data sets yielded 65,296 records, which were screened for eligibility by two independent reviewers. Our use of systematic data set identification using a priori eligibility criteria supported the identification of data sets that would otherwise may have been difficult to identify; this was supported through

TABLE 29 Summary of findings

Evidence gaps	• Impact of socioeconomic status on outcomes • Impact of ethnicity on long-term outcomes • Outcomes in low-middle-income countries • Impact on specific outcomes: frailty, nutrition, sexual function, resilience and self-efficacy, morning/evening preference, occupational gaps, smell, pain severity and impact of pain, general health, illness perception, attention and alertness, orientation, naming, figure copying and recall, ease of word production, processing speed, verbal learning, memory and recall, cognitive failures, working memory, executive function, combined anxiety and depression, lack of energy, fitness, oxygen consumption, physical activity, exercise tolerance, perception of exercise, impact of breathing problems and examination of transfer factor • Impact of interventions on long-term outcomes • Impact on activities and participation outcomes • Impact on social functioning, isolation, social networks and resilience • Impact on healthcare resource use and costs to the healthcare system		
Recommendations	• A need to define and capture an exposed vs. non-exposed population for future pandemic preparedness • A need for methodologies to facilitate rapid development of a core data set for future pandemics that reflects both acute and long-term perspectives • Long-term, consistent outcome monitoring for COVID-19 populations and for future pandemics • Standardisation of comorbidity description • Standardisation of symptom definitions • Standardisation of symptom data collection		
Outcome domain	**Who does worse?**		
QoL domain: physical functioning	**3–6 months** ***D* = 6, IPD = 571** **I^2 (obesity) = 2.55%** **GRADE = low** **Population** Median age = 55 years Male = 46.9% Hospitalised and ventilated = 7.7% Increasing age Women Obesity		
QoL domain: mental health	**3–6 months** ***D* = 8, IPD = 794** **I^2 (sex) = 0.87%** **GRADE = low** **Population** Median age = 56 years Male = 50.4% Hospitalised and ventilated = 6.9% Women		
Overall perception of health	**3–6 months** ***D* = 3, IPD = 1766** **I^2 (cardiac conditions) = 0.00%** **GRADE = moderate** **Population** Median age = 57 years Male = 28.6% Hospitalised and ventilated = 10.3% Increasing age Increasing BMI Women Hospitalisation Immunosuppression Cardiac conditions Lung disease	**9–12 months** ***D* = 4, IPD = 2818** **I^2 (hospitalised) = 0.00%** **GRADE = low** **Population** Median age = 54 years Male = 35.6% Hospitalised and ventilated = 0.004% Hospitalisation Women Unemployment Obesity Immunosuppression Diabetes Lung disease Chronic kidney disease	**12± months** ***D* = 3, IPD = 1932** **I^2 (mental/behavioural disorder) = 0.00%** **GRADE = low** **Population** Median age = 58.1 years Male = 34.4% Hospitalised and ventilated = 8.2% Hospitalisation Lower education levels Mental/behavioural disorders Immunosuppression Diabetes Lung disease Chronic kidney disease

TABLE 29 Summary of findings (*continued*)

Sleep	**3–6 months** ***D* = 3, IPD = 569** **I^2 (sex) = 0.67%** **GRADE = low** **Population:** Median age = 59 Male = 64.9% Hospitalised and ventilated = 5.1% Women		
Multidomain cognitive functioning	**3–6 months** ***D* = 2, IPD = 839** **I^2 (mental/behavioural disorders) = 0.00%** **GRADE = low** **Population** Median age = 49 years Male = 60.4% Hospitalised and ventilated = 5.4% Increasing age Other ethnicity Lower education Mental/behavioural disorders		**12+ months** ***D* = 2, IPD = 566** **I^2 (cardiac conditions) = 55.75%** **GRADE = very low** **Population** Median age = 59 years Male = 64.1% Hospitalised and ventilated = 25.3% Increasing age Black, Asian and other ethnicity Lower education
Anxiety	**3–6 months (hospitalised)** ***D* = 5, IPD = 1394** **I^2 (neurological conditions) = 0.00%** **GRADE = low** **3–6 months (non-hospitalised)** ***D* = 2, *N* = 569** **I^2 (sex) = 13.29%** **GRADE = high** **Population (hospitalised)** Median age = 59 years Male = 63.4% **Population (non-hospitalised)** Median age = 47 years Male = 49.4% **Hospitalised:** Women Younger age Lung disease Neurological conditions **Non-hospitalised:** Women Circulatory disorders	**9–12 months** ***D* = 3, IPD = 1679** **I^2 (sex) = 1.35%** **GRADE = high** **Population** Median age = 49 Male = 48.8% Hospitalised and ventilated = 0.1% Hospitalised Women Lung disease Unemployed and a smoker	**12+ months** ***D* = 4, IPD = 1340** **I^2 (sex) = 0.00%** **GRADE = low** **Population** Median age = 49 years Male = 45.5% Hospitalised and ventilated = 0% Hospitalised Women Younger age Non-employment
Depression	**3–6 months** ***D* = 3, IPD = 1001** **I^2 (mental behavioural) 19.12%** **GRADE = moderate** **Population** Median age = 58 years Male = 60.8% Hospitalised and ventilated = 8% Younger age Women Lung disease Mental/behavioural disorders	**9–12 months** **IPD = 1722, *D* = 4** **I^2 (diabetes) = 0%** **GRADE = moderate** **Population** Median age = 49 years Male = 48.8% Hospitalised and ventilated = 0.1% Younger age Women Non-employment Diabetes Cancer Smoker	**12+ months** **IPD = 1286, *D* = 4** **I^2 (hospitalised) = 0%** **GRADE = moderate** **Population** Median age = 48 years Male = 46.7% Hospitalised and ventilated = 0% Hospitalised Women Obesity Non-employment Smoker

continued

TABLE 29 Summary of findings (*continued*)

Stress		**9–12 months** ***D* = 2, IPD = 1344** **I^2 (sex) = 0.00%** **GRADE = moderate** **Population** Median age = 49 years Male = 49.7% Hospitalised and ventilated = 0.1% Smoker Diabetes Immunosuppression Women	**12+ months** ***D* = 2, IPD = 698** **I^2 (sex) = 0.00%** **GRADE = moderate** **Population** Median age = 48 years Male = 47.6% Hospitalised and ventilated = 0% Women Smoker Non-employment
PTSD	**3–6 months** ***D* = 5, IPD = 1036** **I^2 (sex) = 0.00%** **GRADE = low** **Population** Median age = 60 years Male= 65.4% Hospitalised and ventilated = 16.7% Younger age Women Lung disease		
Fatigue	**3–6 months** ***D* = 3, IPD = 1030** **I^2 (neurological conditions) = 8.97%.** **GRADE = moderate** **Population** Median age = 59 years Male = 60.1% Hospitalised and ventilated = 8.7% Younger people Women Lung disease Neurological conditions Musculoskeletal conditions	**9–12 months** ***D* = 5, IPD = 1594** **I^2 (immunosuppression) = 0.00%.** **GRADE = moderate** **Population** Median age = 59 years Male = 52% Hospitalised and ventilated = 2.9% Younger people Women Immunosuppression Lung disease	**12+ months** ***D* = 2, IPD = 722** **I^2 (mental/behavioural disorder) = 7.94%** **GRADE = moderate** **Population** Median age = 58 years Male = 62.7% Hospitalised and ventilated = 23.6% Women Mental/behavioural disorders
Strength	**3–6 months** ***D* = 7, IPD = 918** **I^2 (sex) = 11.34%** **GRADE = moderate** **Population** Median age = 59 years Male = 69.2% Hospitalised and ventilated = 34.5% Increasing age Women		
Coping with daily life	**3–6 months** ***D* = 2, IPD = 1086** **I^2 (lung disease) = 3.46%** **GRADE = moderate** **Population** Median age = 59 years Male = 64.4% Hospitalised and ventilated = 13.3% Women Lung disease Increasing age Chronic kidney disease Certain lower education strata		**12+ months** ***D* = 2, IPD = 574** **I^2 (sex) = 0.00%** **GRADE = moderate** **Population** Median age = 59 years Male = 64.6% Hospitalised and ventilated = 27.5% Increasing age Women Certain lower education strata

TABLE 29 Summary of findings (*continued*)

Walking ability	**3–6 months** ***D* = 6, IPD = 567** ***I*² (cardiac conditions) = 0.00%** **GRADE = low** **Population** Median age = 57 years Male = 59.8% Hospitalised and ventilated = 23.9% Increasing age Women Increasing BMI Cardiac conditions Lung disease Women without cardiac conditions		
Mobility	**3–6 months** ***D* = 2, IPD = 1080** ***I*² (neurological conditions) = 0.00%** **GRADE = moderate** **Population** Median age = 59 years Male = 61.3% Hospitalised and ventilated = 8.9% Increasing age Women Lung disease Chronic kidney disease Neurological conditions Musculoskeletal conditions Diabetes		
Breathlessness	**3–6 months** ***D* = 3, IPD = 744** ***I*² (sex) = 4.59%** **GRADE = moderate** **Population** Median age = 52 years Male = 52.8% Hospitalised and ventilated = 11.6% Increasing COVID-19 severity Lung disease Immunosuppression Women Obesity	**9–12 months** ***D* = 3, IPD = 1277** ***I*² (sex) = 0.00%** **GRADE = moderate** **Population** Median age = 49 years Male = 48.9% Hospitalised and ventilated = 0.1% Increasing age Increasing age + lung disease Obesity Women Hospitalisation Circulatory disorders Immunosuppression	**12+ months** ***D* = 3, IPD = 655** ***I*² (based on sex) = 0.00%** **GRADE = moderate** **Population** Median age = 48 years Male = 47.6% Hospitalised and ventilated = 0% Increasing age Hospitalisation Obesity Circulatory disorder Women
Mortality	**Hospitalised non-ventilated** ***D* = 5, IPD = 5027** ***I*² (sex) = 18.1%** **GRADE = moderate** **Population (hospitalised non-ventilated)** Median age = 64 Male = 57.6% Increasing age Men Cancer Chronic kidney disease Dementia/Alzheimer's Lung disease	**Hospitalised and ventilated** **D = 9 IPD = 969** ***I*² (liver disease) = 21.1%** **GRADE = moderate** **Population (hospitalised and ventilated)** Median age = 64 Male = 70.8% Increasing age Men Diabetes Chronic kidney disease Liver disease	

continued

TABLE 29 Summary of findings (*continued*)

Later hospitalisation	***D* = 2, IPD = 1336** **I^2 = 0%** **GRADE = moderate** **Population** Median age = 61 years Male = 56.9% Hospitalised and ventilated = 11.8% Increasing age Cerebrovascular disease Diabetes Chronic kidney disease Cancer Current smokers		
Return to work/school	***D* = 2, IPD = 844** **I^2 = 44.4%** **GRADE = very low** **Population** Median age = 59 Male = 66.4% Hospitalised and ventilated = 17.3% Increasing age Women		
Affected ability to work/adjustments required	***D* = 4, IPD = 513** **I^2 = 90%** **GRADE = low** **Population** Median age = 53 years Male = 29.7% Hospitalised and ventilated = 12.3% Younger age		
HRQoL	**EuroQoL-derived model 1** ***D* = 11, IPD = 7880** **I^2 = 29.99%** **GRADE = moderate** **Population** Median age = 55 years Male = 36% Hospitalised and ventilated = 15.3% Women COVID exposure Hospitalisation Ventilation Up to 7 months after infection	**EuroQoL-derived model 2** ***D* = 6, IPD = 4642** **I^2 = 26.44%** **GRADE = moderate** **Population** Median age = 54 years Male = 31% Hospitalised and ventilated = 4% Women COVID-19 exposure Hospitalisation Diabetes Obesity Lung disease Chronic kidney disease Lower education status Non-employment Smoking history Up to 7 months after infection	**SF-36-derived model** ***D* = 5, IPD = 958** **I^2 = 18.6%** **GRADE = moderate** **Population** Median age = 58 years Male = 54% Hospitalised = 52% Women Increasing age Hospitalisation Ventilation

investigation of grey literature and inclusion of data sets available in the public domain. This reduced the risk of selection bias.

Study PIs identified in our systematic searching were invited to contribute data sets. Being a novel pathogen, we did not have an established COVID-19 research network to facilitate communication; only two data contributors had prior collaborations with the PRECIOUS PI.

Our use of a priori eligibility criteria (see *Table 1*) was reflective of our research questions, available data sets and methods of data collection. Early in the pandemic, COVID-19 testing was not routinely available. We therefore accepted data sets that used symptom-based diagnosis of COVID-19. Exclusions were data that were qualitative, healthcare processes, insufficient IPD and paediatric populations. No language, country, recruitment date, or setting exclusions were applied.

Data set identification and selection; availability bias

We aimed to identify all potentially available data sets for inclusion in PRECIOUS. This was reflected in our inclusive search strategy (see *Appendix 1*) which included public domain data sets and grey literature. Of 1682 data sets where IPD were sought, 340 met the eligibility criteria, 224 did not provide eligible data; 1354 data sets could not be included in the database due to no response (n = 1099), declined participation (n = 82), ineligibility (n = 3) or other reasons (n = 158). Inclusion of these data sets would have strengthened our analyses, potentially permitting examination of outcome domains where we lacked data, examination of participant subgroups or time points. Nevertheless, the data sets and IPD that were collated to support the analyses conducted in PRECIOUS permitted us to examine each of our proposed research questions and highlighted important factors associated with long-term outcomes.

We noted that contributed data were derived predominantly from high-income countries (77 data sets, IPD = 49,134) with well-developed healthcare systems; further data are needed on low- and lower-middle-income countries (lower-middle-income countries included in 12 data sets, IPD = 2746).

Availability bias

Data were contributed from 6.9% of invited studies. This was reflective of the vast scope and volume of COVID-19 research to date, the initial priority to reduce mortality and transmission, and within the context of an ongoing pandemic, where many researchers were often active healthcare professionals. As our study was focused on long-term outcomes, it is possible that many studies that were reporting on long-term outcomes were unavailable at the time of our systematic search. Nevertheless, we were able to analyse data from more than 62,000 IPD, in 37 different multivariable models and describing outcomes across a range of domains.

Detection bias

Detection bias refers to potential bias arising from differences in the methods, rigour or criteria by which outcomes are determined across the data sets.[319] In PRECIOUS, COVID-positivity was described using antibody tests, clinical diagnosis, PCR or serology tests (combined category), or PCR/antigen-based methods (combined category). As widespread testing was not available at the start of the pandemic, we accepted clinical/symptom-based diagnosis of COVID-19. Clinicians and researchers in our investigative and wider collaborative groups discussed the various testing and diagnosis methods and agreed on the above categorisation. Additional communication with contributing PIs reassured the investigative team of the COVID-positive diagnoses within each data set.

Additionally, outcomes of interest were described using a range of methods. Data were excluded from analyses where assessments included a non-validated questionnaire, or categorical data that could not be aggregated with other similar measurement instruments using our algorithm. Thus, only data from validated assessment instruments were standardised and included in analyses. While we had specified in our protocol that we would consider examination of detection bias, in practice, this would only have been possible where COVID-19 interventions had been present in sufficient numbers and remained significantly associated with outcomes at multivariable level. As this was not the case in our analyses, we did not examine detection bias as it was not applicable to our analyses.

Performance bias

Similarly, performance bias refers to systematic differences in the care/interventions provided between groups.[320] As the impact of interventions could not be fully examined in our study, we did not assess performance bias.

Attrition bias

Across PRECIOUS, data were derived from COVID-19 studies with different aims, across a range of settings and including different conditions. Many studies within PRECIOUS reported on a single follow-up outcome data point per participant. Therefore, reporting the attrition data with respect to a data set or specific outcomes was not possible. Limited availability of repeated-measures data contributed to our decision to examine outcomes at static follow-up time points, rather than analysing longitudinal outcomes, which would have been more informative. Some studies were observed to have potential follow-up bias with follow-up focused on selected populations, for example, those in whom symptoms persisted, or in whom particular symptoms warranted specialist investigation. Nevertheless, for RCTs, follow-up ranged between 54.1% and 100% of participants, with 11/20 RCTs reporting on 100% of participants at follow-up. Median follow-up times for each outcome domain of are described in *Table 2*. For non-randomised studies, follow-up ranged between 43.2% and 100% of participants, with 20/43 non-RCTs reporting on 100% of participants at follow-up. For qualitative descriptive studies, 24/53 were described as having low risk of non-response bias. For the purposes of RoB analyses, we applied the recommended 30% allowance for dropout in long-term outcome studies;[321] thus, studies that completed long-term follow-up in at least 70% of participants were awarded the highest level of judgement.

Data extraction

We employed double data extraction, with checking of data set summaries, outputs and RoB by each contributing PI. The PPI, co-applicant and wider collaborative groups informed development and categorisation of each assessment instrument under a broad outcome domain, strengthening the robustness of our analyses.

Analysis and model quality

Individual/primary study quality was apprised using MMAT (see *Report Supplementary Material 8*) and model quality was informed by GRADE (see *Report Supplementary Material 69*, *Tables a-t*). RoB and appraisal of models were completed by two independent investigators and cross-checked by each contributing PI. All generated models were generally of moderate (22/37 models) or low (11/37 models) quality with ratings most commonly downgraded due to wide confidence limits (imprecision) and inclusion of selected participant groups (indirectness).

Synthesis and examination of results

The PRECIOUS study commenced in the context of the rapid and parallel implementation of several initiatives to collect data on the COVID-19 population. There was a high risk of uncoordinated data collection, lack of overlap in common data elements[322] and use of diverse definitions of COVID-positive participants. Such issues are common across health and social care research, and limit the ability to compare research findings across different studies and meta-analyses to inform evidence-based decision-making.[139] We mitigated some of these issues through use of existing frameworks to classify outcomes (e.g. ICF[111,112]), categorisation of comorbidities according to the ICD-10,[323] and using an existing core outcome set to inform reporting of outcomes.[138,139]

Data synthesis

Data contributed to PRECIOUS were representative of the wider COVID-19 population and included hospitalised participants, those requiring ventilation, and those who were not hospitalised. Settings included hospitals, outpatient clinics, community and mixed settings across 40 countries, representing a range of personal socioeconomic status, employment status and incomes. For each analysis, we used a one-stage meta-analysis approach, on data that met our prespecified eligibility criteria of at least 2 data sets and > 500 IPD. Models reflected appropriate subgroups, where analyses indicated an interaction between certain variables.

Heterogeneity

Heterogeneity between studies included in each model was assessed using the I^2 statistic and for 34/37 models were deemed to be low.[305] Where heterogeneity was moderate or high, we identified these as research areas in need of

further evidence. Data sets were most commonly hospital- (58 data sets, IPD = 22,527) or community-based (36 data sets, IPD = 31,373). While 33,230 (52.9%) were COVID-positive at primary study enrolment, 6128 (9.8%) had COVID-19 prior to primary study enrolment. Thus, we included a mix of mild and moderate–severe COVID-19 infection, including both acute and chronic populations.

Missing data

Where possible, we liaised with contributing trialists to ascertain missing data items. Where appropriate, these were imputed into analyses data sets and reviewed by contributing PIs. Analyses were based on complete cases.

Publication and other bias

We included published and unpublished data sets; use of funnel plots was inappropriate for our purposes. Seventeen of 20 RCTs were published and 1 was available as a pre-print; 35/43 non-randomised comparison studies and 50/53 qualitative descriptive studies were published.

Modelling

The model was checked with respect to the addition and removal of variables by comparing the size and CIs of the variables that were already in the model with those in the next step, to ensure that they remained independent of the new variable, and were not affected by the loss of data sets.

Summary

Models generated in the PRECIOUS outcomes analyses were of moderate or low quality based on GRADE-informed assessment (see *Report Supplementary Material 69*, *Tables a–t*). We mitigated common issues with selection, availability, data collection, study quality assessment and data synthesis bias. We observed low statistical heterogeneity in all but 3 models.

Chapter 16 Discussion

Summary of findings

A summary of research findings related to long-term COVID-19 outcomes is described in *Table 29*. Below we discuss our key findings and recommendations.

Representation in the PRECIOUS database

Following a systematic identification of data sets, we amassed data from 116 studies, totalling more than 62,000 IPD. Data were derived from both hospital-based and community settings from across 40 countries, reflecting a range of COVID-19 severities. Data were heavily weighted towards cohort study design, with only 20 RCTs included in the database. In intervention trials, investigative agents were primarily pharmacological in nature with only selected studies describing rehabilitation approaches. As a result, there were insufficient data to fully examine the impact of specific interventions on long-term COVID-19 outcomes. We documented 137 different outcome measurement instruments and 158 unique symptoms related to COVID-19.

Evidence gaps in outcome assessment

Available outcomes were weighted heavily to the body function domain of the ICF. Data captured in a single data set, where follow-up was conducted before 3 months, where the format of the data prevented aggregation and analyses, or in insufficient numbers to permit covariate-adjusted meta-analyses are detailed in *Table 29*. Thus, while our inventory indicated that relevant data were present, these data did not meet the threshold for meta-analysis and represent an evidence gap in PRECIOUS.

Beyond the outcome measurement instruments described and meta-analysed in PRECIOUS, we lacked data on social functioning, isolation, social networks and resilience. Societal participation is associated with enhanced sense of identity, improved sense of value, belonging, and a sense of belonging within a community.[324] As such, the improvement of societal participation has been highlighted as an important target for healthcare professionals.[325] The impact of enforced restrictions on individuals' movements and the need for social distancing on psychosocial health is yet to be fully elucidated.[326] The negative effects of home confinement on societal participation were previously found to be associated with lower satisfaction with life.[326] While data on overall perception of health were widely available within PRECIOUS, we were unable to investigate corresponding links with measures of societal participation.

In particular, the impact of COVID-19 on societal participation in the elderly should be examined further, as this population may be especially vulnerable as they are less likely to be in regular contact with others through activities such as employment.[327] Furthermore, home confinement has been found to impact on physical activity levels,[328] sleep,[329] diet[328] and emotional disorders. While data were available in PRECIOUS on physical activity, this was in insufficient quantity to permit meta-analysis. Similarly, data on nutrition (captured using the Mini Nutritional Assessment Short Form) were only available in a single included data set and, therefore, could not be analysed further. These represent further evidence gaps that should be examined in future research.

Across each of the domains examined, we described factors associated with poorer outcomes in the COVID-19 population. Where data permitted, we included COVID-19 positivity at study inclusion as a covariate in adjusted analyses; however, in most cases, analyses were based on only those with COVID-19. Long-term comparison studies are required to fully elucidate differences in outcomes between COVID-positive and -negative populations.

Data on healthcare resource use beyond the initial COVID-19 episode were restricted to data on later hospitalisations. The lack of data precluded the calculation of costs associated with the longer-term outcomes of COVID-19 for healthcare systems.

Impact of COVID-19 on outcomes

Across many domains of assessment, we observed similar vulnerable populations that had consistently poorer long-term outcomes after COVID-19 infection; those hospitalised, those with diabetes, lung disease, chronic kidney disease, immunosuppression and obesity. Such populations with pre-existing and ongoing health conditions are often subjected to disrupted routine care, overburdened health systems[330] and the impact of lockdowns, which may delay detection of, and exacerbate potential complications.[331,332] Vulnerable populations[333] have been found to experience significant impacts on long-term QoL, anxiety, depression, stress, PTSD, fatigue, ability to cope with daily life, mobility, breathlessness, mortality, rehospitalisation and overall health valuation. Many such vulnerable populations in our analysis were later hospitalised (e.g. those with a history of smoking, presence of cerebrovascular disease, diabetes, chronic kidney disease, increasing age and cancer). With notable increases in the cost of COVID inpatient care (from US$10,394 in March 2020 to US$13,072 in March 2022),[334] and significant burden on health systems worldwide, preventative measures and improved routine care are needed. Our findings support the need to increase resource for the long-term physical and mental impacts of COVID-19.[330]

We also observed a disproportionate impact on poorer long-term outcomes in women when compared with men. We noted an increased mortality risk in men when compared to women. This may indicate that, as with many other health conditions,[335] men may be more likely to die, while the burden of long-term impairments impacts women, as more women survive. Despite this, we observed that when adjusting for sex and other demographic factors, women had poorer overall perception of health (3–6 months and 9–12 months), worse anxiety, depression, stress, PTSD (3–6 months), fatigue, ability of cope with daily life (3–6 months, 12+ months), breathlessness and lower HRQoL compared with men.

Existing work has highlighted a disproportionate impact of COVID-19 on women including on carers, single mothers, those with chronic health conditions, income and employment and those from ethnic minority backgrounds.[336] Postulated mechanisms of impact include family and relationship dynamics, working conditions, loss of income and unemployment, or changes to employment status.[336]

Furthermore, existing literature has highlighted that COVID-19 has exacerbated existing inequalities.[157,289,337] Good population health and financial security that is equitably distributed across all members of society[330] is critical to successful navigation of the next pandemic. The British Medical Association recommends that pandemic recovery efforts should take into account groups who were disproportionately affected by reduced access to care.[330] We identified such populations and our analyses included measures of socioeconomic status such as employment and education level and their impacts on long-term outcomes where these were available. Socioeconomic status has a direct impact on health outcomes, health literacy,[152] resilience[338] and everyday life. It is therefore an important measure that should be captured in health research. However, measurement of socioeconomic status is complex, with a range of different markers such as race,[339] the IMD, income amount and neighbourhood disadvantage[339] being indicative of poorer outcomes. A uniform method to characterise socioeconomic status would be beneficial for use in future studies.

COVID-19 disrupted routine care and overburdened health systems; delivery of non-COVID care became challenging, resulting in unmet needs.[339] Lockdowns and social restrictions affected mental health. Based on our analyses, we set out further recommendations for research.

Strengths

Our study has several strengths. We employed a systematic search to identify potential data sets with COVID-19 long-term outcomes. We did not restrict our search to any particular outcome assessment, but included use of any validated assessment instrument that could be linked to the ICF, presence of post-COVID complications, rehospitalisation, resource use, discharge destinations or mortality. Thus, we were able to combine and categorise a breadth of outcomes across a range of different domains. Our use of systematically sourced IPD increased sample sizes, reduced research waste and reduced the risk of ecological bias (with no additional burden on COVID-19 survivors). We built a

collaboration of more than 100 COVID-19 researchers across acute respiratory care, infectious diseases, neurology, rehabilitation and internal medicine. Analysis of IPD facilitated the identification of clinically relevant interactions and specific clinical populations than could be found with aggregated data alone, which in turn can inform the development, and implementation of timely rehabilitation and social care approaches.

Data represented 40 countries, including a range of incomes, socioeconomic status, and demography and healthcare resources and contexts. Analyses included complete cases, adjusting for confounding variables such as comorbidities, and included more than 1 data set and > 500 IPD for each model, lending strength to the findings. Data items that were selected for inclusion in the analysis data set were informed by the core outcome sets developed by Munblit *et al.*[139] These consensus efforts concluded that further work was needed to establish which assessment instruments were most appropriate to measure the core outcomes. PRECIOUS offers data presented according to the most commonly used assessment instruments within each overarching outcome domain and could inform decisions on the appropriate assessment instruments that should be used to measure the core outcomes.

Limitations

Our study had several limitations. Data were primarily from high-income countries; further data are needed that reflect lower-middle and lower-income countries. Literature has established the impact of COVID-19 on different ethnicities.[130–132] While we endeavoured to include ethnicity in adjusted analyses, often sample sizes for different ethnic groups were insufficient to permit reliable interpretation of results. Use of existing data sets limits analyses to those variables that were already included in the primary studies.

The unprecedented volume of published COVID-19 literature, the unstable clinical trials platforms coupled with the lack of reported time frames for outcome measures in many of the papers mean that it is likely that we will have missed some potentially relevant studies. Additionally, the shift from immediate COVID-19 priorities of reducing transmission and mortality to examination of the long-term impact of COVID-19 meant that some studies with longer-term follow-up may not have been published at the time of our systematic search. These newer studies may contain additional data of relevance to PRECIOUS. A majority of data sets within PRECIOUS recruited participants in 2020, where widespread testing was not commonplace. Nevertheless, we were able to confirm COVID positivity using confirmed PCR tests or through symptom onset data. Data were also not readily available on whether participants who initially tested negative for COVID-19 then developed COVID-19 test positivity during the course of follow-up. Further data are needed on a confirmed COVID-negative population.

Additionally, while we systematically searched for potentially eligible data sets, we were only able to secure the contribution of 6.9% of available data sets. This forms a small proportion of potentially available data sets. We acknowledge the challenges involved with systematic identification of data sets, particularly due to the volume of COVID-19 studies that were being published, as well as the limited indexing systems through which to identify potential data sets. Nevertheless, we amassed data on more than 62,000 participants from 116 studies, thereby greatly contributing to the available body of evidence.

We were unable to examine long-term costs associated with COVID-19 as data on resource use were primarily collected in an acute setting. Potential cost data could have been inferred from sources such as rehospitalisation or later hospitalisation, data on loss of income or later use of primary care and support services; however, these data were either not available or could not be aggregated. For example, occupational data were present, but not in sufficient quantity or detail to permit calculations of loss of income. This lack of long-term data represents a key research need.

Statistical considerations

Unfortunately, the data we received from our collaborators had very few patients with no exposure to COVID. Of the 62,845 patients, from 116 studies, 33,230 (53%) were confirmed positive at baseline; 6128 (10%) were negative, but had had prior COVID; 4577 (7%) were negative with unknown prior COVID and 18,810 (30%) had unknown COVID status. Much of our data came from the early days of the pandemic, when the aim was to treat, rather than explore

the natural history of the disease. Attempts to compare groups under the assumption that 'unknown' was 'not COVID' would have resulted in too many caveats to permit informative analyses.

Potential analysis methods could have included calculation of relative risk or hazard ratio. However, the majority of outcomes for the measurement types were continuous variables, a majority of which did not have validated thresholds by which we could easily compare proportions by group/exposure. Thus, relative risk was not a useable option. In those few cases where data could be summarised as a proportion, ORs were used, as relative risk with covariates is computationally complex, particularly for meta-analysis. The continuous data were often right or left skewed, and in order to get a reasonably symmetric distribution, the natural log of the score was applied (either positively or negatively, depending on the direction of the tail). Thus, when the data were meta-analysed, the ratio of difference was presented. Those rare outcomes that did not require transformation to then are reported as actual differences. Similarly, time-to-event data were not available, as the event (COVID) had already happened, and the majority of outcome measures were continuous and could not be considered as events. Time itself was also difficult, with some very short-term studies and some long-term studies; many studies reported follow-up time periods, rather than actual time since start of study. For example, several studies reported the follow-up time point as '1 month', but actually meant 1 month ±1 week, so we had no precise data for a many of participants.

Ratio of difference was used when the continuous data were not symmetric. Actual differences were reported in the cases that had non-skew data, but these were rare. Very few metrics of QoL were binary within our study, and those that were could not be used as they could not be fit to the transformation anchor measure.

Data were often sparse, with studies usually having baseline (i.e. first visit within the trial, rather than baseline as in the patient's normal status) and one follow-up time point. Occasionally, only baseline data were available, and were not necessarily taken at study entry. Therefore, we decided against any form of repeated-measures analysis, as the covariance matrix would be sparse and likely struggle to converge. In order to explore early, medium and late effects, the data were split by time and analysed separately. The rare patients who had more than one data point within a time period had the average taken.

A one-stage versus two-stage modelling approach was considered, whereby the potential impact of combining our IPD results with reported results of identified studies that address the research question but did not provide IPD could be examined. However, resources did not permit additional analyses beyond the vast number of models already completed. The data are available for future research, and this could be examined separately.

Patient and public involvement

Involvement of PPI in PRECIOUS, including aims, recruitment, group composition, tasks and reflections, is described in *Chapter 2*. *Chapters 3–14* reflect PPI-informed decisions. Five PPI meetings were held during the research period. All were online meetings with the first meeting serving as an introduction to the project. PPI group members were instrumental in contributing to decisions on which ICF categories COVID-19-related outcomes related to and provided meaningful suggestions on the language used for outcomes. They read and provided comments on the papers produced, and suggested formatting, outcome summaries and posters to make the information more accessible and meaningful to the lay audience. Their input was essential in ensuring that the output of the research was valuable to them in relation to their lived experience of COVID-19.

Reflections/critical perspective

We started with eight PPI group members, and this had reduced to five by the end of a 2-year period. There was no further contact with those who left before the end of the project, despite attempts to make contact with them. From the evaluation, time was built in for PPI members to get to know each other and share their experience of COVID-19. An evaluation of PPI group member experience of the first two meetings indicated that the PPI members felt comfortable sharing their thoughts and that they felt listened to. There was uncertainty on whether their contributions affected change to the project.

From the first meeting, expectations of the PPI members were clarified as the IPD meta-analysis methodology had already been established. All had been involved in previous research and possibly had input into the design. There was also new learning through the need to become familiar with the ICF framework and how it related to COVID-19 outcomes. Early contributions included comments on papers and providing opinion on outcome classifications, but by the fifth meeting, this had developed into drafting summary and poster formats and providing comment on the impact that some outcomes may have on sections of the audience, for example the outcome that women experienced greater anxiety than men and emphasising the need for some meaning to be behind some of these outcomes. Our project was conducted during the pandemic, where meeting face-to-face was prohibitive. We endeavoured to include a wide range of people in our PPI group; however, this was inevitably restricted to those versed in PPI participation and who had access to the technology to enable them to participate in virtual meetings. This is a limitation to our PPI.

Equality, diversity and inclusion

Language and terminology used in PRECIOUS were reviewed and refined by our PPI group to ensure that concepts and reporting were understandable and informative. We also sought IPD from a wide range of studies, employing no language restrictions in our systematic search. We included data from 40 countries, from community, hospital-based and mixed settings, as well as those that were focused on specific subpopulations of people with COVID-19, thereby increasing representation. We extracted data on settings and populations and presented assessments of evidence quality for each model. We additionally provided information on the number of data sets, IPD, median age, proportion of men and women, and proportion who were initially hospitalised, thereby providing an indication of the population on whom evidence is based, to inform appropriate application of our findings. We inventoried all available outcome assessments and the time points at which data were available. We identified gaps in available evidence and highlighted areas were more data were needed.

Our research team also reflected EDI, including people with lived experience of COVID-19, experienced, mid-career and early-career researchers; development opportunities were identified and supported through mentorship.

Implications

The UK House of Commons Health and Social Care Committee reported on lessons learnt from the COVID-19 pandemic, highlighting the narrow focus of the UK's pandemic planning that did not take into account lessons from severe acute respiratory syndrome, Ebola and Middle Eastern Respiratory Syndrome. Additionally, the lack of data gathered and shared in the UK was highlighted as a major issue limiting adequate planning.[340] The PRECIOUS database is a resource with which to inform future pandemic planning.

Decision-makers may be interested in our finding of consistently poorer long-term outcomes in women, compared with men, and in those with existing comorbidities, compared to those without certain comorbidities. We also observed signals of the impact of socioeconomic status such as employment and education level on certain outcomes. Thus, vulnerable populations and those with poorer health outcomes due to inequity may benefit from additional support.

Research recommendations

Recommendations emerging from PRECIOUS include:

- A need to define and capture an exposed versus non-exposed population for future pandemic preparedness.
- A need for methodologies to facilitate rapid development of a core data set for future pandemics that reflects both acute and long-term perspectives.
- Long-term, consistent outcome monitoring for COVID-19 populations and for future pandemics.

- Inclusion of ethnicity and socioeconomic status variables in a core data set and inclusion in future analysis.
- Description of existing comorbidities should be collected using a standard language, for example by ICD-10[323] and included in a core data set.
- Further data that represent low-middle income countries as well as a wider range of ethnicities to enable examination of ethnicity differences in long-term outcomes.
- Standardisation of symptom data with respect to specific items to include in data collection, and standard definitions that can be applied internationally.
- Aspects of long-term mental health including mental distress, affective-emotional aspects, cognitive-evaluative dimensions and psychological functioning, and sleep disturbances require further investigation in the context of COVID-19.
- Further analyses of specific domains of cognitive functioning are warranted, including on executive function, naming, memory/recall, attention, language, abstraction and orientation.
- Continued screening of people who have had COVID-19, and who have a subclinical score on cognitive functioning may be beneficial.
- Further characterisation of the apparent associations between socioeconomic status, anxiety, depression, stress and PTSD in the context of COVID-19 may further highlight populations requiring support.
- The greater impact of fatigue on younger people may warrant further support in this population as it may have implications for overall functioning, work and QoL.
- Additional strength data at longer-term follow-up time points are needed, along with in-depth availability of covariates to fully examine post-COVID strength outcomes.
- The role of socioeconomic status on ability to cope with daily life warrants further investigation.
- Targeted examination of the impact of poor ability to complete ADLs, exercise tolerance, perception of exercise, peak performance and fitness, as clinical measures in isolation on functioning and impact on daily life.
- Time to recovery should be captured not just for the COVID-19 clinical population but also for the long-COVID population.
- It is known that vaccinations reduced mortality.[291] Further research is needed to examine the impact of vaccination on long-term outcomes.
- Description of length of recovery from index COVID-19, development of long-COVID and time to recovery from long-COVID as per Gorst *et al.*,[138] should be routinely collected.
- Further research is needed on the impact of interventions on long-term outcomes.
- Data are needed on the cost of not returning to work; this requires pre- and post-COVID employment status and occupation data to be collected.
- Additional areas of future work that have been identified include the long-term consequences by variant, and lessons for management of long-COVID from other viral diseases (e.g. Epstein-Barr virus).

Impact and learning

Lay summaries and posters of our main findings have been generated by our PPI group, and will be available on the PRECIOUS website (www.preciouscovidoutcomes.org). PPI-informed accessible findings will be shared with clinical and AHP leads at health board level, research advisory groups, COVID-19 Mutual Aid & PPI groups, COVID-19 Twitter (e.g. @COVIDSolidarity, @COVID-Rehab #LongCovid; #COVIDPersistente), Royal Colleges of Nursing, Physicians, Surgeons, Speech and Language Therapists, Ophthalmology, Occupational Therapists, Chartered Society of Physiotherapists, British Psychological Society, Rehabilitation Workers' Professional Network and Health and Social Care Alliance. Our dissemination strategy also includes publication of our findings across at least five papers in peer-reviewed journals.

Areas of learning have been highlighted in the recommendations above; these form the basis of future plans to examine the impact on societal participation, isolation and mental health outcomes and issues surrounding return to work in a further IPD meta-analysis. We will seek to expand on the existing PRECIOUS database to address these research areas. Further, data from the PRECIOUS database will be made available upon application, for novel exploratory analyses and future pandemic planning.

Conclusions

Effective rehabilitation after COVID-19 requires a whole-person approach, considering impacts on a range of outcomes. We provide data on a clinically relevant population, including hospitalised and community-based participants. We comprehensively mapped available outcomes using the ICF framework, and generated evidence to inform rehabilitation needs. We identified particularly vulnerable populations who may benefit from support or early intervention.

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Data-sharing statement

PRECIOUS collated fully anonymised data from individual studies including people with COVID-19. Appropriate data from PRECIOUS will be made available upon submission of a project proposal to precious@gcu.ac.uk. Project proposals will be reviewed and approved by the contributing PIs of original studies.

Ethics statement

Establishment of the PRECIOUS database was registered with the Integrated Research Application System (IRAS project ID 293578). The Glasgow Caledonian University Ethics Committee granted approval for the PRECIOUS study (HLS/NCH/20/04, Oct 2021).

Information governance statement

Glasgow Caledonian University is committed to handling all personal data in line with the Data Protection Act (2018) and the UK General Data Protection Regulation (UK GDPR). Under Data Protection legislation, Glasgow Caledonian University is the Data Controller, and you can find out more about how we handle personal data, including how to exercise your individual rights and the contact details for our Data Protection Officer at: dataprotection@gcu.ac.uk. PRECIOUS included fully anonymised data from contributed studies. Anonymised data will be held for 15 years on Glasgow Caledonian Corporate Systems. Information held will only be used for the purpose of the PRECIOUS project and legacy dataset and the University will not use this information for any other purpose. The PRECIOUS database contains no identifiers that can be used to link to individual participants.

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References

1. The World Health Organization. *WHO Coronavirus (COVID-19) Dashboard*. URL: https://covid19.who.int/ (accessed 12 July 2023).
2. Shalal A. IMF sees cost of COVID pandemic rising beyond $12.5 trillion estimate. *Reuters*, 2022.
3. Reis G, Silva EASM, Silva DCM, Thabane L, Milagres AC, Ferreira TS, *et al.*; TOGETHER Investigators. Effect of early treatment with ivermectin among patients with Covid-19. *N Engl J Med* 2022;**386**:1721–31.
4. Naggie S, Boulware DR, Lindsell CJ, Stewart TG, Slandzicki AJ, Lim SC, *et al.*; Accelerating Covid-19 Therapeutic Interventions and Vaccines (ACTIV)-6 Study Group and Investigators. Effect of higher-dose ivermectin for 6 days vs placebo on time to sustained recovery in outpatients with COVID-19. *JAMA* 2023;**329**:888–97.
5. The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med* 2021;**384**:693–704.
6. Troxel AB, Petkova E, Goldfeld K, Liu M, Tarpey T, Wu Y, *et al*. Association of convalescent plasma treatment with clinical status in patients hospitalized with COVID-19. *JAMA Netw Open* 2022;**5**:e2147331.
7. Goldfeld KS, Wu D, Tarpey T, Liu M, Wu Y, Troxel AB, Petkova E. Prospective individual patient data meta-analysis: evaluating convalescent plasma for COVID-19. *Stat Med* 2021;**40**:5131–51.
8. Voysey M, Clemens SAC, Madhi SA, Weckx LY, Folegatti PM, Aley PK, *et al.*; Oxford COVID Vaccine Trial Group. Safety and efficacy of the ChAdOx1 nCoV-19 vaccine (AZD1222) against SARS-CoV-2: an interim analysis of four randomised controlled trials in Brazil, South Africa, and the UK. *Lancet (London, England)* 2021;**397**:99–111.
9. Polack FP, Thomas SJ, Kitchin N, Absalon J, Gurtman A, Lockhart S, *et al.*; C4591001 Clinical Trial Group. Safety and efficacy of the BNT162b2 mRNA Covid-19 Vaccine. *N Engl J Med* 2020;**383**:2603–15.
10. Baden LR, El Sahly HM, Essink B, Kotloff K, Frey S, Novak R, *et al.*; COVE Study Group. Efficacy and safety of the mRNA-1273 SARS-CoV-2 Vaccine. *N Engl J Med* 2021;**384**:403–16.
11. Watson OJ, Barnsley G, Toor J, Hogan AB, Winskill P, Ghani AC. Global impact of the first year of COVID-19 vaccination: a mathematical modelling study. *Lancet Infect Dis* 2022;**22**:1293–302.
12. Mathieu E, Ritchie H, Rodés-Guirao L, Appel C, Gavrilov D, Giattino C, *et al*. *Coronavirus Pandemic (COVID-19)*. 2020. URL: https://ourworldindata.org/coronavirus (accessed 20 May 2025).
13. Harris RJ, Hall JA, Zaidi A, Andrews NJ, Dunbar JK, Dabrera G. Effect of vaccination on household transmission of SARS-CoV-2 in England. *N Engl J Med* 2021;**385**:759–60.
14. Talic S, Shah S, Wild H, Gasevic D, Maharaj A, Ademi Z, *et al*. Effectiveness of public health measures in reducing the incidence of covid-19, SARS-CoV-2 transmission, and covid-19 mortality: systematic review and meta-analysis. *BMJ* 2021;**375**:e068302.
15. Daugherty SE, Guo Y, Heath K, Dasmariñas MC, Jubilo KG, Samranvedhya J, *et al*. Risk of clinical sequelae after the acute phase of SARS-CoV-2 infection: retrospective cohort study. *BMJ* 2021;**373**:n1098. https://doi.org/10.1136/bmj.n1098
16. Office for Naitonal Statistics. *Prevalence of Ongoing Symptoms Following Coronavirus (COVID-19) Infection in the UK: 2021*. 2021 URL: www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/1april2021#:~:text=COVID%2D19%20syndrome.-,Prevalence%20of%20self%2Dreported%20long%20COVID,Northern%20Ireland%20(Table%201) (accessed 20 May 2025).
17. Morin L, Savale L, Pham T, Colle R, Figueiredo S, Harrois A, *et al.*; Writing Committee for the COMEBAC Study Group. Four-month clinical status of a cohort of patients after hospitalization for COVID-19. *JAMA* 2021;**325**:1525–34.

18. Mahmud R, Rahman MM, Rassel MA, Monayem FB, Sayeed SKJB, Islam MS, Islam MM. Post-COVID-19 syndrome among symptomatic COVID-19 patients: a prospective cohort study in a tertiary care center of Bangladesh. *PLOS ONE* 2021;**16**:e0249644.
19. del Rio C, Collins LF, Malani P. Long-term health consequences of COVID-19. *JAMA* 2020;**324**:1723–4.
20. Maxwell E. Unpacking post-covid symptoms. *BMJ* 2021;**373**:n1173.
21. Lechien JR, Chiesa-Estomba CM, Place S, Van Laethem Y, Cabaraux P, Mat Q, *et al*.; COVID-19 Task Force of YO-IFOS. Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. *J Intern Med* 2020;**288**:335–44.
22. NHS England. *Post-COVID Syndrome (Long COVID)*. 2024. URL: www.england.nhs.uk/coronavirus/post-covid-syndrome-long-covid/ (accessed 13 February 2024).
23. Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute covid-19 in primary care. *BMJ* 2020;**370**:m3026.
24. Tenforde MW, Kim SS, Lindsell CJ, Billig Rose E, Shapiro NI, Files DC, *et al*.; IVY Network Investigators. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network — United States, March–June 2020. *MMWR Morb Mortal Wkly Rep* 2020;**69**:993–8.
25. Su Y, Yuan D, Chen DG, Ng RH, Wang K, Choi J, *et al*.; ISB-Swedish COVID-19 Biobanking Unit. Multiple early factors anticipate post-acute COVID-19 sequelae. *Cell* 2022;**185**:881–95.e20.
26. Koc HC, Xiao J, Liu W, Li Y, Chen G. Long COVID and its management. *Int J Biol Sci* 2022;**18**:4768–80.
27. Office for National Statistics. *Prevalence of Ongoing Symptoms Following Coronavirus (COVID-19) Infection in the UK*. 2023. URL: www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/30march2023 (accessed 4 January 2024).
28. Hirschtick JL, Titus AR, Slocum E, Power LE, Hirschtick RE, Elliott MR, *et al*. Population-based estimates of post-acute sequelae of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (PASC) prevalence and characteristics. *Clin Infect Dis* 2021;**73**:2055–64.
29. Halpin SJ, McIvor C, Whyatt G, Adams A, Harvey O, McLean L, *et al*. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: a cross-sectional evaluation. *J Med Virol* 2021;**93**:1013–22.
30. Arnold DT, Hamilton FW, Milne A, Morley AJ, Viner J, Attwood M, *et al*. Patient outcomes after hospitalisation with COVID-19 and implications for follow-up: results from a prospective UK cohort. *Thorax* 2021;**76**:399–401.
31. Sigfrid L, Drake TM, Pauley E, Jesudason EC, Olliaro P, Lim WS, *et al*.; ISARIC4C Investigators. Long Covid in adults discharged from UK hospitals after Covid-19: a prospective, multicentre cohort study using the ISARIC WHO clinical characterisation protocol. *Lancet Reg Health Eur* 2021;**8**:100186.
32. Tsampasian V, Elghazaly H, Chattopadhyay R, Debski M, Naing TKP, Garg P, *et al*. Risk factors associated with post–COVID-19 condition. *JAMA Intern Med* 2023;**183**:566–80.
33. Catalan A, Aymerich C, Bilbao A, Pedruzo B, Pérez JL, Aranguren N, *et al*. Psychosis and substance abuse increase the COVID-19 mortality risk. *Psychol Med* 2023;**53**:4236–44.
34. CDC. *Long-Term Effects of COVID-19*. URL: https://www.cdc.gov/long-covid/about/index.html (accessed 12 May 2026).
35. Maxwell E. *Living with COVID19. A Dynamic Review of the Evidence Around Ongoing COVID19 Symptoms (Often Called Long COVID)*. 2020. URL: https://evidence.nihr.ac.uk/wp-content/uploads/2020/10/Living-with-Covid-Themed-Review-October-2020.pdf (accessed 12 May 2026).

36. Puntmann VO, Carerj ML, Wieters I, Fahim M, Arendt C, Hoffmann J, *et al*. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol* 2020;**5**:1265–73.
37. Office for National Statistics. *The Prevalence of Long COVID Symptoms and COVID-19 Complications*. 2020. URL: www.ons.gov.uk/news/statementsandletters/theprevalenceoflongcovidsymptomsandcovid19complications (accessed 29 April 2022).
38. Dennis A, Wamil M, Alberts J, Oben J, Cuthbertson DJ, *et al*. Multiorgan impairment in low-risk individuals with post-COVID-19 syndrome: a prospective, community-based study. *BMJ Open* 2021;**11**:e048391. https://doi.org/10.1136/bmjopen-2020-048391
39. Al-Aly Z, Xie Y, Bowe B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature* 2021;**594**:259–64.
40. Carvalho-Schneider C, Laurent E, Lemaignen A, Beaufils E, Bourbao-Tournois C, Laribi S, *et al*. Follow-up of adults with noncritical COVID-19 two months after symptom onset. *Clin Microbiol Infect* 2021;**27**:258–63.
41. Antonelli M, Penfold RS, Merino J, Sudre CH, Molteni E, Berry S, *et al*. Risk factors and disease profile of post-vaccination SARS-CoV-2 infection in UK users of the COVID Symptom Study app: a prospective, community-based, nested, case-control study. *Lancet Infect Dis* 2022;**22**:43–55.
42. Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, *et al*. Attributes and predictors of long COVID. *Nat Med* 2021;**27**:626–31.
43. Docherty AB, Harrison EM, Green CA, Hardwick HE, Pius R, Norman L, *et al*.; ISARIC4C Investigators. Features of 20 133 UK patients in hospital with COVID-19 using the ISARIC WHO clinical characterisation protocol: prospective observational cohort study. *BMJ* 2020;**369**:m1985.
44. Ladds E, Rushforth A, Wieringa S, Taylor S, Rayner C, Husain L, Greenhalgh T. Persistent symptoms after COVID-19: qualitative study of 114 'long Covid' patients and draft quality principles for services. *BMC Health Serv Res* 2020;**20**:1144.
45. Meister T, Pisarev H, Kolde R, Kalda R, Suija K, Milani L, *et al*. Clinical characteristics and risk factors for COVID-19 infection and disease severity: a nationwide observational study in Estonia. *PLOS ONE* 2022;**17**:e0270192.
46. Rigby J, Satija B. *WHO Declares End to COVID Global Health Emergency*. 2023. URL: www.reuters.com/business/healthcare-pharmaceuticals/covid-is-no-longer-global-health-emergency-who-2023-05-05/ (accessed 10 August 2023).
47. The British Academy. *The COVID Decade: Understanding the Long-Term Societal Impacts of COVID-19*. 2021. URL: www.thebritishacademy.ac.uk/documents/3238/COVID-decade-understanding-long-term-societal-impacts-COVID-19.pdf (accessed 20 May 2025).
48. Chaves E, Reddy SD, Cadieux A, Tomasula J, Reynolds K. The continued impact of the COVID-19 pandemic on pediatric obesity: a commentary on the return to a healthy new 'normal'. *Int J Environ Res Public Health* 2022;**19**:5597.
49. The World Health Organization. *Current Context: The COVID-19 Pandemic and Continuing Challenges to Global Health*. 2022. URL: www.who.int/about/funding/invest-in-who/investment-case-2.0/challenges (accessed 17 June 2026).
50. Armstrong JN, Campbell L, Rabatsky-her T, Leung V, Parikh S. Repeat positive SARS-CoV-2 RNA testing in nursing home residents during the initial 9 months of the COVID-19 pandemic: an observational retrospective analysis. *Lancet Reg Health Am* 2021;**3**:100054.
51. Bowe B, Xie Y, Al-Aly Z. Acute and postacute sequelae associated with SARS-CoV-2 reinfection. *Nat Med* 2022;**28**:2398–405.
52. Centres for Disease Control and Prevention. *SARS-CoV-2 Variant Classifications and Definitions*. URL: www.cdc.gov/locs/2021/09-22-2021-lab-advisory-cdc-updates-sars-cov-2-variant-classifications_1.html (accessed 12 May 2026).

53. Twohig KA, Nyberg T, Zaidi A, Thelwall S, Sinnathamby MA, Aliabadi S, *et al*.; COVID-19 Genomics UK (COG-UK) Consortium. Hospital admission and emergency care attendance risk for SARS-CoV-2 delta (B.1.617.2) compared with alpha (B.1.1.7) variants of concern: a cohort study. *Lancet Infect Dis* 2022;**22**:35–42.

54. Augusto G, Mohsen MO, Zinkhan S, Liu X, Vogel M, Bachmann MF. In vitro data suggest that Indian delta variant B.1.617 of SARS-CoV-2 escapes neutralization by both receptor affinity and immune evasion. *Allergy* 2022;**77**:111–7.

55. Liu Y, Rocklöv J. The reproductive number of the Delta variant of SARS-CoV-2 is far higher compared to the ancestral SARS-CoV-2 virus. *J Travel Med* 2021;**28**:taab124. https://doi.org/10.1093/jtm/taab124

56. Lin L, Liu Y, Tang X, He D. The disease severity and clinical outcomes of the SARS-CoV-2 variants of concern. *Front Public Health* 2021;**9**:775224. https://doi.org/10.3389/fpubh.2021.775224

57. Patone M, Thomas K, Hatch R, Tan PS, Coupland C, Liao W, *et al*. Mortality and critical care unit admission associated with the SARS-CoV-2 lineage B.1.1.7 in England: an observational cohort study. *Lancet Infect Dis* 2021;**21**:1518–28.

58. Sivan M, Rayner C, Delaney B. Fresh evidence of the scale and scope of long covid. *BMJ* 2021;**373**:n853.

59. Yelin D, Wirtheim E, Vetter P, Kalil AC, Bruchfeld J, Runold M, *et al*. Long-term consequences of COVID-19: research needs. *Lancet Infect Dis* 2020;**20**:1115–7.

60. WHO Rehabilitation Programme and Cochrane Rehabilitation REH-COVER (Rehabilitation – COVID-19 Evidence-Based Response) International Multiprofessional Steering Committee. *Priorities for Research Defined in Collaboration with WHO Rehabilitation Programme*. 2020. URL: www.cochrane.org/about-us/news/cochrane-rehabilitation-reh-cover-rehabilitation-covid-19-evidence-based-response-action (accessed 24 June 2026).

61. Verity R, Okell LC, Dorigatti I, Winskill P, Whittaker C, Imai N, *et al*. Estimates of the severity of coronavirus disease 2019: a model-based analysis. *Lancet Infect Dis* 2020;**20**:669–77.

62. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, *et al*. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;**395**:1054–62.

63. Latronico N, Peli E, Rodella F, Novelli MP, Rasulo FA, Piva S. Three-month outcome in survivors of COVID-19 associated acute respiratory distress syndrome. *SSRN Electronic J* 2020. https://doi.org/10.2139/ssrn.3749226

64. The World Health Organization. *International Classification of Functioning, Disability and Health (ICF)*. URL: www.who.int/classifications/icf/en/ (accessed 20 May 2025).

65. McGrath J, Saha S, Welham J, El Saadi O, MacCauley C, Chant D. A systematic review of the incidence of schizophrenia: the distribution of rates and the influence of sex, urbanicity, migrant status and methodology. *BMC Med* 2004;**2**:13.

66. The National Institute for Health and Care Excellence. *COVID-19 Rapid Guideline: Managing the Long-Term Effects of COVID-19* URL: www.nice.org.uk/guidance/ng188/resources/covid19-rapid-guideline-managing-the-longterm-effects-of-covid19-pdf-66142028400325 (accessed 29 April 2022).

67. Dhami S, Thompson D, El Akoum M, Bates DW, Bertollini R, Sheikh A. Data-enabled responses to pandemics: policy lessons from COVID-19. *Nat Med* 2022;**28**:2243–6.

68. The World Health Organization. *Pandemic Influenza Preparedness and Response*. 2009. URL: www.ncbi.nlm.nih.gov/books/NBK143061/ (accessed 20 February 2024).

69. Peñalvo JL, Mertens E, Ademović E, Akgun S, Baltazar AL, Buonfrate D, *et al*.; unCoVer network. Unravelling data for rapid evidence-based response to COVID-19: a summary of the unCoVer protocol. *BMJ Open* 2021;**11**:e055630.

70. Maxwell L, Shreedhar P, Levis B, Chavan SA, Akter S, Carabali M. Overlapping research efforts in a global pandemic: a rapid systematic review of COVID-19-related individual participant data meta-analyses. *BMC Health Serv Res* 2023;**23**:735.

71. Mallett S, Allen AJ, Graziadio S, Taylor SA, Sakai NS, Green K, *et al*. At what times during infection is SARS-CoV-2 detectable and no longer detectable using RT-PCR-based tests? A systematic review of individual participant data. *BMC Med* 2020;**18**:346.

72. Christophers B, Gallo Marin B, Oliva R, Powell WT, Savage TJ, Michelow IC. Trends in clinical presentation of children with COVID-19: a systematic review of individual participant data. *Pediatr Res* 2022;**91**:494–501.

73. van Werkhoven C, Schure J, Bonten MJM, *et al*. *Anytime Live and Leading Interim* Meta-Analysis of the Impact of Bacillus Calmette-Guérin Vaccination in Health Care Workers and Elderly During the SARS-CoV-2 Pandemic (ALL-IN-META-BCG-CORONA)*. PROSPERO; 2021 URL: www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021213069 (accessed 20 May 2025).

74. Victory J, Freilich D, Hanley D, *et al*. *ACEi/ARB Medications for Hospitalised Patients with COVID-19: An Individual Patient Data (IPD)-Based Pooled Analysis*. PROSPERO; 2022. URL: www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021267770 (accessed 20 May 2025).

75. Beyrouti R, Best JG, Chandratheva A, Perry RJ, Werring DJ. Characteristics of intracerebral haemorrhage associated with COVID-19: a systematic review and pooled analysis of individual patient and aggregate data. *J Neurol* 2021;**268**:3105–15.

76. Tan BKJ, Han R, Zhao JJ, Tan NKW, Quah ESH, Tan CJW, *et al*. *Prognosis & Persistence of Smell & Taste Dysfunction in COVID-19: A Meta-Analysis with Parametric Cure Modelling of Recovery Curves. PROSPERO*. 2021. URL: www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42021283922 (accessed 20 May 2025).

77. Lee DS, Mirmirani P, McCleskey PE, Mehrpouya M, Gorouhi F. Cutaneous manifestations of COVID-19: a systematic review and analysis of individual patient-level data. *Dermatol Online J* 2020;**26**:13030/qt7s34p8rw.

78. Lant S, Cividini S, Singh B, *et al*. *Neurological Associations of COVID-19 (COVID-Neuro): A Protocol for a Systematic Review and Meta-Analysis of Individual Patient Data. PROSPERO 2020 CRD42020196542*. 2020. URL: www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020196542 (accessed 20 May 2025).

79. Harwood R, Yan H, Talawila Da Camara N, Smith C, Ward J, Tudur-Smith C, *et al*. Which children and young people are at higher risk of severe disease and death after hospitalisation with SARS-CoV-2 infection in children and young people: a systematic review and individual patient meta-analysis. *EClinicalMedicine* 2022;**44**:101287.

80. Hasan I, Saif-Ur-Rahman K, Hayat S, Papri N, Jahan I, Azam R, *et al*. Guillain-Barré syndrome associated with SARS-CoV-2 infection: a systematic review and individual participant data meta-analysis. *J Peripher Nerv Syst* 2020;**25**:335–43.

81. Smith E. *Protocol for a Sequential, Prospective Meta-Analyses (PMA) to Rapidly Addressing Priority Perinatal COVID-19 Questions. PROSPERO 2020 CRD42020188955*. 2020 URL: www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020188955 (accessed 20 May 2025).

82. Subramaniam A, Anstey C, Curtis JR, Ashwin S, Ponnapa Reddy M, Aliberti MJR, *et al*. Characteristics and outcomes of patients with frailty admitted to ICU with coronavirus disease 2019: an individual patient data meta-analysis. *Crit Care Explor* 2022;**4**:e0616.

83. de Jong VMT, Debray TPA. *Clinical Prediction Models for Mortality in COVID-19 Patients: An External Validation and Individual Participant Data Meta-Analysis (COVID-PRECISE)*. OSF; 2021. URL: https://osf.io/96wgn/ (accessed 20 May 2025).

84. Mizrahi B, Sudry T, Flaks-Manov N, Yehezkelli Y, Kalkstein N, Akiva P, *et al*. Long covid outcomes at one year after mild SARS-CoV-2 infection: nationwide cohort study. *BMJ* 2023;**380**:e072529.

85. Zhang H, Huang C, Gu X, Wang Y, Li X, Liu M, *et al*. 3-year outcomes of discharged survivors of COVID-19 following the SARS-CoV-2 omicron (B.1.1.529) wave in 2022 in China: a longitudinal cohort study. *Lancet Respir Med* 2024;**12**:55–66.

86. Huang L, Yao Q, Gu X, Wang Q, Ren L, Wang Y, *et al*. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. *Lancet* 2021;**398**:747–58.

87. Bels JLM, van Gassel RJJ, Timmerman L, Hemmen B, van de Poll MCG, Peters NHGM, *et al*. One-year outcomes of mechanically ventilated COVID-19 ICU survivors: a prospective cohort study. *Am J Respir Crit Care Med* 2022;**206**:777–80.

88. PHOSP-COVID Collaborative Group. Clinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following hospitalisation in the UK: a prospective observational study. *Lancet Respir Med* 2022;**10**:761–75.

89. Dawson C, Clunie G, Evison F, Duncan S, Whitney J, Houchen-Wolloff L, *et al*.; PHOSP-COVID Collaborative Group. Prevalence of swallow, communication, voice and cognitive compromise following hospitalisation for COVID-19: the PHOSP-COVID analysis. *BMJ Open Respir Res* 2023;**10**:e001647.

90. Knight SR, Ho A, Pius R, Buchan I, Carson G, Drake TM, *et al*.; ISARIC4C Investigators. Risk stratification of patients admitted to hospital with covid-19 using the ISARIC WHO clinical characterisation protocol: development and validation of the 4C Mortality Score. *BMJ* 2020;**370**:m3339.

91. Pauley E, Drake TM, Griffith DM, Sigfrid L, Lone NI, Harrison EM, *et al*.; ISARIC4C and RECOVER Investigators. Recovery from Covid-19 critical illness: a secondary analysis of the ISARIC4C CCP-UK cohort study and the RECOVER trial. *J Intensive Care Soc* 2023;**24**:162–9.

92. Sigfrid L, Drake T, Munblit D, Holter JC, Kildal AB, Jesudason E, *et al*. *What Is the Recovery Rate and Risk of Long-Term Consequences Following A Diagnosis of COVID19? – A Harmonised, Global Longitudinal Observational Study Protocol*. 2020. URL: https://isaric.org/wp-content/uploads/2020/11/ISARIC-Covid-19-follow-up-protocol.pdf (accessed 8 March 2024).

93. The World Health Organization. *What We Know About Long-Term Effects of COVID-19. The Latest Information on the COVID-19 Global Situation & Long-Term Sequelae*. 2025. URL: https://www.who.int/news-room/fact-sheets/detail/post-covid-19-condition-(long-covid) (accessed 24 June 2026).

94. Houchen-Wolloff L, Poinasamy K, Holmes K, Tarpey M, Hastie C, Raihani K, *et al*. Joint patient and clinician priority setting to identify 10 key research questions regarding the long-term sequelae of COVID-19. *Thorax* 2022;**77**:717–20.

95. NIHR Oxford Health Biomedical Research Centre. *Evaluating Patient and Public Involvement*. URL: https://oxfordhealthbrc.nihr.ac.uk/patient-and-public-involvement/ppi-strategy/evaluating-patient-and-public-involvement/ (accessed 20 May 2025).

96. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. *J Clin Epidemiol* 2016;**75**:40–6.

97. Cochrane Methods Equity. *PROGRESS-Plus*. URL: https://methods.cochrane.org/equity/projects/evidence-equity/progress-plus (accessed 23 April 2024).

98. Cochrane WG. *What Study Designs Should Be Included in an EPOC Review and What Should They Be Called?* URL: https://epoc.cochrane.org/sites/epoc.cochrane.org/files/public/uploads/EPOC%20Study%20Designs%20About.pdf (accessed 29 April 2022).

99. The World Health Organization. *A Healthy Lifestyle – WHO Recommendations*. 2025. URL: www.who.int/europe/news-room/fact-sheets/item/a-healthy-lifestyle---who-recommendations (accessed 24 June 2026).

100. Patel K, Straudi S, Yee Sien N, Fayed N, Melvin JL, Sivan M. Applying the WHO ICF framework to the outcome measures used in the evaluation of long-term clinical outcomes in coronavirus outbreaks. *Int J Environ Res Public Health* 2020;**17**:6476.

101. World Health Organization. *How to Use the ICF. A Practical Manual for Using the International Classification of Functioning, Disability and Health (ICF).* 2013. p. 7. URL: https://icfeducation.org/wpcontent/uploads/2023/09/ICFFramework.png (accessed 31 May 2024).

102. World Health Organization. *International Classification of Functioning, Disability and Health (ICF) Geneva*. 2026. URL: www.who.int/standards/classifications/international-classification-of-functioning-disability-and-health (accessed 24 June 2026).

103. The RELEASE Collaborators. *RELEASE: An Individual Participant Data Meta-analysis, Incorporating Systematic Review and Network Meta-analysis, of Complex Speech-language Therapy Interventions for Stroke-related Aphasia*. Southampton (UK): National Institute for Health and Care Research; 2022.

104. Cochrane. *Cochrane. RoB 2 Tool. A Revised Cochrane Risk of Bias Tool for Randomized Trials* URL: https://sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool?authuser=02021 (accessed 20 May 2025).

105. The Joanna Briggs Institute. *The Joanna Briggs Institute Critical Appraisal Tools for Use in JBI Systematic Reviews. Checklist for Analytical Cross Sectional Studies*. 2017. URL: https://jbi.global/sites/default/files/2019-05/JBI_Critical_Appraisal-Checklist_for_Analytical_Cross_Sectional_Studies2017_0.pdf (accessed 29 April 2022).

106. Critical Appraisal Skills Programme. *Critical Appraisal Skills Programme Checklist for Cohort Studies*. 2026. URL: https://casp-uk.net/casp-tools-checklists/cohort-study-checklist/ (accessed 12 May 2026).

107. Hong QN, Fàbregues S, Bartlett G, Boardman F, Cargo M, Dagenais P, *et al*. The mixed methods appraisal tool (MMAT) version 2018 for information professionals and researchers. *Educ Inf* 2018;**34**:285–91.

108. Hong Q, Pluye P, Fabregues S, Bartlett G, Boardman F, Cargo M, *et al*. *Mixed Methods Appraisal Tool (MMAT), Version 2018. User Guide*. 2018. URL: http://mixedmethodsappraisaltoolpublic.pbworks.com/w/file/fetch/127916259/MMAT_2018_criteria-manual_2018-08-01_ENG.pdf (accessed 20 September 2023).

109. Schwingshackl L, Nagavci B, Stadelmaier J, Werner SS, Cuello Garcia CA, Schünemann HJ, Meerpohl JJ. Pooling of cohort studies and RCTs affects GRADE certainty of evidence in nutrition research. *J Clin Epidemiol* 2022;**147**:151–9.

110. Brozek JL, Canelo-Aybar C, Akl EA, Bowen JM, Bucher J, Chiu WA, *et al*.; GRADE Working Group. GRADE guidelines 30: the GRADE approach to assessing the certainty of modeled evidence – an overview in the context of health decision-making. *J Clin Epidemiol* 2021;**129**:138–50.

111. Cieza A, Fayed N, Bickenbach J, Prodinger B. Refinements of the ICF Linking Rules to strengthen their potential for establishing comparability of health information. *Disabil Rehabil* 2019;**41**:574–83.

112. Cieza A, Brockow T, Ewert T, Amman E, Kollerits B, Chatterji S, *et al*. Linking health-status measurements to the International Classification of Functioning, Disability and Health. *J Rehabil Med* 2002;**34**:205–10.

113. Burke DL, Ensor J, Riley RD. Meta-analysis using individual participant data: one-stage and two-stage approaches, and why they may differ. *Stat Med* 2017;**36**:855–75.

114. NHS England. *National Cost Collection for the NHS*. URL: www.england.nhs.uk/national-cost-collection/#ncc1819 (accessed 29 April 2022).

115. Devlin NJ, Brooks R. EQ-5D and the EuroQol Group: past, present and future. *Appl Health Econ Health Policy* 2017;**15**:127–37.

116. Dolan P. Modeling valuations for EuroQol health states. *Med Care* 1997;**35**:1095–108.

117. Ware JE, Kosinski M, Keller SD. *SF-36 Physical and Mental Health Summary Scales: A User's Manual*. Boston, MA: Health Assessment Lab; 1994.

118. Karimi M, Brazier J. Health, health-related quality of life, and quality of life: what is the difference? *PharmacoEconomics* 2016;**34**:645–9.

119. Hernández Alava M, Wailoo A, Pudney S, Gray L, Manca A. Mapping clinical outcomes to generic preference-based outcome measures: development and comparison of methods. *Health Technol Assess* 2020;**24**:1–68.

120. Ara R, Brazier J. Deriving an algorithm to convert the eight mean SF-36 dimension scores into a mean EQ-5D preference-based score from published studies (where patient level data are not available). *Value Health* 2008;**11**:1131–43.

121. Hernández-Alava M, Wailoo A. Fitting adjusted limited dependent variable mixture models to EQ-5D. *STATA Journal* 2015;**15**:737–50.

122. National Health Commission. *Chinese Clinical Guidance for COVID-19 Pneumonia Diagnosis and Treatment*. 2020. URL: http://kjfy.meetingchina.org/msite/news/show/cn/3337.html (accessed 31 May 2024).

123. Gandhi RT, Lynch JB, del Rio C. Mild or moderate Covid-19. *N Engl J Med* 2020;**383**:1757–66.

124. Menni C, Valdes AM, Freidin MB, Sudre CH, Nguyen LH, Drew DA, *et al*. Real-time tracking of self-reported symptoms to predict potential COVID-19. *Nat Med* 2020;**26**:1037–40.

125. EuroQol Research Foundation. *EQ-5D-3L User Guide. Basic Information on How to Use the EQ-5D-3L Instrument*. URL: https://euroqol.org/publications/user-guides (accessed 22 April 2024).

126. EuroQoL. *EQ-5D-5L*. 2026. URL: https://euroqol.org/information-and-support/euroqol-instruments/eq-5d-5l/ (accessed 31 January 2024).

127. Ware JE Jr, Sherbourne CD. The MOS 36-item short form health survey (SF-36): conceptual framework and items selection. *Med Care* 1992;**30**:473–83.

128. Amstutz A, Speich B, Mentré F, Rueegg CS, Belhadi D, Assoumou L, *et al*. Effects of remdesivir in patients hospitalised with COVID-19: a systematic review and individual patient data meta-analysis of randomised controlled trials. *Lancet Respir Med* 2023;**11**:453–64.

129. Di Stefano L, Ogburn EL, Ram M, Scharfstein DO, Li T, Khanal P, *et al*.; Pandemic Response COVID-19 Research Collaboration Platform for HCQ/CQ Pooled Analyses. Hydroxychloroquine/chloroquine for the treatment of hospitalized patients with COVID-19: an individual participant data meta-analysis. *PLOS ONE* 2022;**17**:e0273526.

130. Singh B, Lant S, Cividini S, Cattrall JWS, Goodwin L, Benjamin L, *et al*. Prognostic indicators and outcomes of hospitalised COVID-19 patients with neurological disease: an individual patient data meta-analysis. *PLOS ONE* 2022;**17**:e0263595. https://doi.org/10.1371/journal.pone.0263595

131. Zaccardi F, Tan PS, Shah BR, Everett K, Clift AK, Patone M, *et al*. Ethnic disparities in COVID-19 outcomes: a multinational cohort study of 20 million individuals from England and Canada. *BMC Public Health* 2023;**23**:399.

132. Irizar P, Pan D, Kapadia D, Bécares L, Sze S, Taylor H, *et al*. Ethnic inequalities in COVID-19 infection, hospitalisation, intensive care admission, and death: a global systematic review and meta-analysis of over 200 million study participants. *EClinicalMedicine* 2023;**57**:101877.

133. Wan YI, Apea VJ, Dhairyawan R, Puthucheary ZA, Pearse RM, Orkin CM, Prowle JR. Ethnic disparities in hospitalisation and hospital-outcomes during the second wave of COVID-19 infection in east London. *Sci Rep* 2022;**12**:3721.

134. World Health Organization. *Obesity*. 2026. URL: www.who.int/westernpacific/health-topics/obesity#tab=tab_1 (accessed 13 July 2023).

135. Gao M, Piernas C, Astbury NM, Hippisley-Cox J, O'Rahilly S, Aveyard P, Jebb SA. Associations between body-mass index and COVID-19 severity in 6·9 million people in England: a prospective, community-based, cohort study. *Lancet Diabetes Endocrinol* 2021;**9**:350–9.

136. Magesh S, John D, Li WT, Li Y, Mattingly-App A, Jain S, *et al*. Disparities in COVID-19 outcomes by race, ethnicity, and socioeconomic status. *JAMA Netw Open* 2021;**4**:e2134147.

137. Khanijahani A, Iezadi S, Gholipour K, Azami-Aghdash S, Naghibi D. A systematic review of racial/ethnic and socioeconomic disparities in COVID-19. *Int J Equity Health* 2021;**20**:248.

138. Gorst SL, Seylanova N, Dodd SR, Harman NL, O'Hara M, Terwee CB, *et al*.; PC-COS Study Group. Core outcome measurement instruments for use in clinical and research settings for adults with post-COVID-19 condition: an international Delphi consensus study. *Lancet Respir Med* 2023;**11**:1101–14.

139. Munblit D, Nicholson T, Akrami A, Apfelbacher C, Chen J, De Groote W, *et al*.; PC-COS Project Steering Committee. A core outcome set for post-COVID-19 condition in adults for use in clinical practice and research: an international Delphi consensus study. *Lancet Respir Med* 2022;**10**:715–24.

140. Singh B, Ryan H, Kredo T, Chaplin M, Fletcher T. Chloroquine or hydroxychloroquine for prevention and treatment of COVID-19. *Cochrane Database Sys Rev* 2021;**2**:CD013587. https://doi.org/10.1002/14651858.CD013587.pub2

141. Juul S, Nielsen EE, Feinberg J, Siddiqui F, Jørgensen CK, Barot E, *et al*. Interventions for treatment of COVID-19: a living systematic review with meta-analyses and trial sequential analyses (The LIVING Project). *PLOS Med* 2020;**17**:e1003293.

142. Patulny R, Bower M. Beware the 'loneliness gap?' Examining emerging inequalities and long-term risks of loneliness and isolation emerging from COVID-19. *Australian J Soc Issues* 2022;**57**:562–83.

143. Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, Villapol S. More than 50 long-term effects of COVID-19: a systematic review and meta-analysis. *Sci Rep* 2021;**11**:16144.

144. Soriano JB, Murthy S, Marshall JC, Relan P, Diaz JV; WHO Clinical Case Definition Working Group on Post-COVID-19 Condition. A clinical case definition of post-COVID-19 condition by a Delphi consensus. *Lancet Infect Dis* 2022;**22**:e102–7.

145. Brightling C, Evans R. Long COVID: which symptoms can be attributed to SARS-CoV-2 infection? *Lancet* 2022;**400**:412–3.

146. Shahid A, Wilkinson K, Marcu S, Shapiro CM. Pittsburgh Sleep Quality Index (PSQI). In Shahid A, Wilkinson K, Marcu S, Shapiro C,. editors. *STOP, THAT and One Hundred Other Sleep Scales*. New York, NY: Springer New York; 2011, pp. 279–283.

147. Buysse DJ, Reynolds CF, Monk TH, Berman SR, Kupfer DJ. The pittsburgh sleep quality index: a new instrument for psychiatric practice and research. *Psychiatry Res* 1989;**28**:193–213.

148. Malesevic S, Sievi NA, Baumgartner P, Roser K, Sommer G, Schmidt D, *et al*. Impaired health-related quality of life in long-COVID syndrome after mild to moderate COVID-19. *Sci Rep* 2023;**13**:7717.

149. Sialino LD, Picavet HSJ, Wijnhoven HAH, Loyen A, Verschuren WMM, Visser M, *et al*. Exploring the difference between men and women in physical functioning: how do sociodemographic, lifestyle- and health-related determinants contribute? *BMC Geriatr* 2022;**22**:610.

150. Rodríguez-Galán I, Albaladejo-Blázquez N, Ruiz-Robledillo N, Pascual-Lledó JF, Ferrer-Cascales R, Gil-Carbonell J. Impact of COVID-19 on health-related quality of life: a longitudinal study in a Spanish clinical sample. *Int J Environ Res Public Health* 2022;**19**:10421.

151. Alberti TL, Morris NJ. Health literacy in the urgent care setting. *J Am Assoc Nurse Pract* 2017;**29**:242–7.

152. van der Heide I, Wang J, Droomers M, Spreeuwenberg P, Rademakers J, Uiters E. The relationship between health, education, and health literacy: results from the dutch adult literacy and life skills survey. *J Health Commun* 2013;**18**:172–84.

153. Ma T, Meng H, Ye Z, Jia C, Sun M, Liu D. Health literacy mediates the association between socioeconomic status and productive aging among elderly Chinese adults in a newly urbanized community. *Front Public Health* 2021;**9**:647230. https://doi.org/10.3389/fpubh.2021.647230

154. Cherepanov D, Palta M, Fryback DG, Robert SA. Gender differences in health-related quality-of-life are partly explained by sociodemographic and socioeconomic variation between adult men and women in the US: evidence from four US nationally representative data sets. *Quality Life Res* 2010;**19**:1115–24.

155. Hettich-Damm N, Petersen J, Zahn D, Baumkoetter R, Wild PS, Muenzel T, *et al*. Gender differences and the impact of partnership and children on quality of life during the COVID-19 pandemic. *Int J Public Health* 2023;**68**:1605826. https://doi.org/10.3389/ijph.2023.1605826

156. Ferreira LN, Pereira LN, da Fé Brás M, Ilchuk K. Quality of life under the COVID-19 quarantine. *Quality Life Res* 2021;**30**:1389–405.

157. Borrescio-Higa F, Valenzuela P. Gender inequality and mental health during the COVID-19 pandemic. *Int J Public Health* 2021;**66**:1604220. https://doi.org/10.3389/ijph.2021.1604220

158. Pouliopoulou DV, Macdermid JC, Saunders E, Peters S, Brunton L, Miller E, *et al*. Rehabilitation interventions for physical capacity and quality of life in adults with post–COVID-19 condition. *JAMA Netw Open* 2023;**6**:e2333838.

159. Couvy-Duchesne B, Davenport TA, Martin NG, Wright MJ, Hickie IB. Validation and psychometric properties of the Somatic and Psychological HEalth REport (SPHERE) in a young Australian-based population sample using non-parametric item response theory. *BMC Psychiatry* 2017;**17**:279.

160. Tennant R, Hiller L, Fishwick R, Platt S, Joseph S, Weich S, *et al*. The Warwick-Edinburgh Mental Well-being Scale (WEMWBS): development and UK validation. *Health Qual Life Outcomes* 2007;**5**:63.

161. Altman MT, Knauert MP, Pisani MA. Sleep disturbance after hospitalization and critical illness: a systematic review. *Ann Am Thorac Soc* 2017;**14**:1457–68.

162. Pérez-Carbonell L, Meurling IJ, Wassermann D, Gnoni V, Leschziner G, Weighall A, *et al*. Impact of the novel coronavirus (COVID-19) pandemic on sleep. *J Thorac Dis* 2020;**12**:S163–75.

163. Zhou J, Liu L, Xue P, Yang X, Tang X. Mental health response to the COVID-19 outbreak in China. *Am J Psychiatry* 2020;**177**:574–5.

164. Li Y, Qin Q, Sun Q, Sanford LD, Vgontzas AN, Tang X. Insomnia and psychological reactions during the COVID-19 outbreak in China. *J Clin Sleep Med* 2020;**16**:1417–8.

165. Moura AEF, Oliveira DN, Torres DM, Tavares-Júnior JWL, Nóbrega PR, Braga-Neto P, Sobreira-Neto MA. Central hypersomnia and chronic insomnia: expanding the spectrum of sleep disorders in long COVID syndrome: a prospective cohort study. *BMC Neurol* 2022;**22**:417.

166. Tedjasukmana R, Budikayanti A, Islamiyah WR, Witjaksono AMAL, Hakim M. Sleep disturbance in post COVID-19 conditions: prevalence and quality of life. *Front Neurol* 2023;**13**:1095606. https://doi.org/10.3389/fneur.2022.1095606

167. Cleveland Clinic. *Cleveland Clinic Researchers Find Sleep Disturbances Prevalent in Long COVID*. 2023. URL: https://newsroom.clevelandclinic.org/2023/04/05/cleveland-clinic-researchers-find-sleep-disturbances-prevalent-in-long-covid/ (accessed 20 May 2025).

168. Jackson C, Stewart ID, Plekhanova T, Cunningham PS, Hazel AL, Al-Sheklly B, *et al*.; PHOSP-COVID Study Collaborative Group. Effects of sleep disturbance on dyspnoea and impaired lung function following hospital admission due to COVID-19 in the UK: a prospective multicentre cohort study. *Lancet Respir Med* 2023;**11**:673–84.

169. Nasreddine ZS, Phillips NA, Bédirian V, Charbonneau S, Whitehead V, Collin I, *et al*. The montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. *J Am Geriatr Soc* 2005;**53**:695–9.

170. Quan M, Wang X, Gong M, Wang Q, Li Y, Jia J. Post-COVID cognitive dysfunction: current status and research recommendations for high risk population. *Lancet Reg Health West Pac* 2023;**38**:100836.

171. Helms J, Kremer S, Merdji H, Clere-Jehl R, Schenck M, Kummerlen C, *et al*. Neurologic features in severe SARS-CoV-2 infection. *N Engl J Med* 2020;**382**:2268–70.

172. Ceban F, Ling S, Lui LMW, Lee Y, Gill H, Teopiz KM, *et al*. Fatigue and cognitive impairment in post-COVID-19 syndrome: a systematic review and meta-analysis. *Brain Behav Immun* 2022;**101**:93–135.

173. Matias-Guiu JA, Herrera E, González-Nosti M, Krishnan K, Delgado-Alonso C, Díez-Cirarda M, *et al*. Development of criteria for cognitive dysfunction in post-COVID syndrome: the IC-CoDi-COVID approach. *Psychiatry Res* 2023;**319**:115006.

174. Beck JW, Flow A. The effects of contracting Covid-19 on cognitive failures at work: implications for task performance and turnover intentions. *Sci Rep* 2022;**12**:8826.

175. Liu YH, Chen Y, Wang QH, Wang LR, Jiang Li, Yang Y, *et al*. One-year trajectory of cognitive changes in older survivors of COVID-19 in Wuhan, China. *JAMA Neurol* 2022;**79**:509–17.

176. Zhao S, Martin EM, Reuken PA, Scholcz A, Ganse-Dumrath A, Srowig A, *et al*. Long COVID is associated with severe cognitive slowing: a multicentre cross-sectional study. *EClinicalMedicine* 2024;**68**:102434.

177. Broadbent DE, Cooper PF, FitzGerald P, Parkes KR. The cognitive failures questionnaire (CFQ) and its correlates. *Br J Clin Psychol* 1982;**21**:1–16.

178. Elfferich MD, Nelemans PJ, Ponds RW, De Vries J, Wijnen PA, Drent M. Everyday cognitive failure in sarcoidosis: the prevalence and the effect of Anti-TNF-α treatment. *Respiration* 2010;**80**:212–9.

179. Ingram J, Hand CJ, Maciejewski G. Social isolation during COVID-19 lockdown impairs cognitive function. *Appl Cogn Psychol* 2021;**35**:935–47.

180. Prommas P, Lwin KS, Chen YC, Hyakutake M, Ghaznavi C, Sakamoto H, *et al*. The impact of social isolation from COVID-19-related public health measures on cognitive function and mental health among older adults: a systematic review and meta-analysis. *Ageing Res Rev* 2023;**85**:101839.

181. Lu Y, Li X, Geng D, Mei N, Wu PY, Huang CC, *et al*. Cerebral micro-structural changes in COVID-19 patients: an MRI-based 3-month follow-up study. *EClinicalMedicine* 2020;**25**:100484.

182. Rothstein TL. Cortical Grey matter volume depletion links to neurological sequelae in post COVID-19 'long haulers'. *BMC Neurol* 2023;**23**:22.

183. Li Z, Zhang Z, Zhang Z, Wang Z, Li H. Cognitive impairment after long COVID-19: current evidence and perspectives. *Front Neurol* 2023;**14**:1239182. https://doi.org/10.3389/fneur.2023.1239182

184. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand* 1983;**67**:361–70.

185. Lovibond SH, Lovibond PF. *Manual for the Depression Anxiety & Stress Scales*. 2nd edn. Sydney: Psychology Foundation; 1995.

186. Impact of Events Scale: Revised (IES-R). URL: https://movingahead.psy.unsw.edu.au/documents/research/outcome%20measures/adult/Psychological%20Status/Website%20Impact%20of%20Events%20Scale.pdf (accessed 7 February 2024).

187. García-Fernández L, Romero-Ferreiro V, Rodríguez V, Alvarez-Mon MA, Lahera G, Rodriguez-Jimenez R. What about mental health after one year of COVID-19 pandemic? A comparison with the initial peak. *J Psychiatr Res* 2022;**153**:104–8.

188. Fernández-Martínez NF, Ruiz-Montero R, Gómez-Barroso D, Rodríguez-Torronteras A, Lorusso N, Salcedo-Leal I, Sordo L. Socioeconomic differences in COVID-19 infection, hospitalisation and mortality in urban areas in a region in the South of Europe. *BMC Public Health* 2022;**22**:2316.

189. Hu Y, Ye B, Tan J. Stress of COVID-19, anxiety, economic insecurity, and mental health literacy: a structural equation modeling approach. *Front Psychol* 2021;**12**:707079. https://doi.org/10.3389/fpsyg.2021.707079

190. Qiu J, Shen B, Zhao M, Wang Z, Xie B, Xu Y. A nationwide survey of psychological distress among Chinese people in the COVID-19 epidemic: implications and policy recommendations. *Gen Psychiatr* 2020;**33**:e100213.

191. Catling JC, Bayley A, Begum Z, Wardzinski C, Wood A. Effects of the COVID-19 lockdown on mental health in a UK student sample. *BMC Psychol* 2022;**10**:118.

192. Singh S, Roy D, Sinha K, Parveen S, Sharma G, Joshi G. Impact of COVID-19 and lockdown on mental health of children and adolescents: a narrative review with recommendations. *Psychiatry Res* 2020;**293**:113429.

193. Lewis KJS, Lewis C, Roberts A, Richards NA, Evison C, Pearce HA, *et al*. The effect of the COVID-19 pandemic on mental health in individuals with pre-existing mental illness. *BJPsych Open* 2022;**8**:e59.

194. The World Health Organization. *COVID-19 Pandemic Triggers 25% Increase in Prevalence of Anxiety and Depression Worldwide*. 2022. URL: www.who.int/news/item/02-03-2022-covid-19-pandemic-triggers-25-increase-in-prevalence-of-anxiety-and-depression-worldwide (accessed 17 October 2023).

195. Bueno-Notivol J, Gracia-García P, Olaya B, Lasheras I, López-Antón R, Santabárbara J. Prevalence of depression during the COVID-19 outbreak: a meta-analysis of community-based studies. *Int J Clin Health Psychology* 2021;**21**:100196.

196. Saidi I, Koumeka PP, Ait Batahar S, Amro L. Factors associated with anxiety and depression among patients with Covid-19. *Respir Med* 2021;**186**:106512.

197. Lovik A, González-Hijón J, Hoffart A, Fawns-Ritchie C, Magnúsdóttir I, Lu Li, *et al*. Elevated symptoms of depression and anxiety among family members and friends of critically ill COVID-19 patients: an observational study of five cohorts across four countries. *Lancet Reg Health Eur* 2023;**33**:100733.

198. Xie Y, Xu E, Al-Aly Z. Risks of mental health outcomes in people with COVID-19: cohort study. *BMJ* 2022;**376**:e068993.

199. de Vries J, Michielsen H, Van Heck GL, Drent M. Measuring fatigue in sarcoidosis: the Fatigue Assessment Scale (FAS). *Br J Health Psychol* 2004;**9**:279–91.

200. *Handgrip Strength Norms*. 1997–2026 URL: www.topendsports.com/testing/norms/handgrip.htm (accessed 20 May 2025).

201. Vu QM, Fitzpatrick AL, Cope JR, Bertolli J, Sotoodehnia N, West TE, *et al*. Estimates of incidence and predictors of fatiguing illness after SARS-CoV-2 Infection. *Emerg Infect Dis* 2024;**30**:539–47. https://doi.org/10.3201/eid3003.231194

202. Aiyegbusi OL, Hughes SE, Turner G, Rivera SC, McMullan C, Chandan JS, *et al*.; TLC Study Group. Symptoms, complications and management of long COVID: a review. *J R Soc Med* 2021;**114**:428–42.

203. Legler F, Meyer-Arndt L, Mödl L, Kedor C, Freitag H, Stein E, *et al*. Long-term symptom severity and clinical biomarkers in post-COVID-19/chronic fatigue syndrome: results from a prospective observational cohort. *EClinicalMedicine* 2023;**63**:102146.

204. van Kessel SAM, Olde Hartman TC, Lucassen PLBJ, van Jaarsveld CHM. Post-acute and long-COVID-19 symptoms in patients with mild diseases: a systematic review. *Fam Pract* 2022;**39**:159–67.

205. Taquet M, Dercon Q, Luciano S, Geddes JR, Husain M, Harrison PJ. Incidence, co-occurrence, and evolution of long-COVID features: a 6-month retrospective cohort study of 273,618 survivors of COVID-19. *PLOS Med* 2021;**18**:e1003773.

206. Hartung TJ, Neumann C, Bahmer T, Chaplinskaya-Sobol I, Endres M, Geritz J, *et al*. Fatigue and cognitive impairment after COVID-19: a prospective multicentre study. *EClinicalMedicine* 2022;**53**:101651.

207. Fernández-de-las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, Palacios-Ceña M, Rodríguez-Jiménez J, de-la-Llave-Rincón AI, *et al*. Fatigue and dyspnoea as main persistent post-COVID-19 symptoms in previously hospitalized patients: related functional limitations and disability. *Respiration* 2022;**101**:132–41.

208. Mazza MG, Palladini M, Villa G, De Lorenzo R, Rovere Querini P, Benedetti F. Prevalence, trajectory over time, and risk factor of post-COVID-19 fatigue. *J Psychiatr Res* 2022;**155**:112–9.

209. Frontera JA, Yang D, Lewis A, Patel P, Medicherla C, Arena V, *et al*. A prospective study of long-term outcomes among hospitalized COVID-19 patients with and without neurological complications. *J Neurol Sci* 2021;**426**:117486.

210. Horwitz LI, Garry K, Prete AM, Sharma S, Mendoza F, Kahan T, *et al*. Six-month outcomes in patients hospitalized with severe COVID-19. *J Gen Intern Med* 2021;**36**:3772–7.

211. Creamer A, Alaee S, Iftikhar H, Ahmed F, Steer H, Sharp C. P175 Clinico-radiological recovery following severe COVID-19 pneumonia. *Thorax* 2021;**76**:A185.

212. Boari GEM, Bonetti S, Braglia-Orlandini F, Chiarini G, Faustini C, Bianco G, *et al*. Short-term consequences of SARS-CoV-2-related pneumonia: a follow up study. *High Blood Press Cardiovasc Prev* 2021;**28**:373–81.

213. König BH, van Jaarsveld CH, Bischoff EW, Schers HJ, Lucassen PL, Olde Hartman TC. Prognostic factors for persistent fatigue after COVID-19: a prospective matched cohort study in primary care. *Br J Gen Pract* 2023;**73**:e340–7.

214. Walker S, Goodfellow H, Pookarnjanamorakot P, Murray E, Bindman J, Blandford A, *et al*. Impact of fatigue as the primary determinant of functional limitations among patients with post-COVID-19 syndrome: a cross-sectional observational study. *BMJ Open* 2023;**13**:e069217.

215. Stapleton T, Norris L, Clancy K, O'Gorman A, Bannan C, Kent B, *et al*. Outcomes of a fatigue management intervention for people with post COVID-19 condition. *Am J Phys Med Rehabil* 2023;**103**:410–7. https://doi.org/10.1097/PHM.0000000000002368

216. Jimeno-Almazán A, Franco-López F, Buendía-Romero A, Martínez-Cava A, Sánchez-Agar JA, Sánchez-Alcaraz Martínez BJ, *et al*. Rehabilitation for post-COVID-19 condition through a supervised exercise intervention: a randomized controlled trial. *Scand J Med Sci Sports* 2022;**32**:1791–801.

217. Sternäng O, Reynolds CA, Finkel D, Ernsth-Bravell M, Pedersen NL, Dahl Aslan AK. Factors associated with grip strength decline in older adults. *Age Ageing* 2015;**44**:269–74.

218. Del Brutto OH, Mera RM, Pérez P, Recalde BY, Costa AF, Sedler MJ. Hand grip strength before and after SARS-CoV-2 infection in community-dwelling older adults. *J Am Geriatr Soc* 2021;**69**:2722–31.

219. Montes-Ibarra M, Oliveira CLP, Orsso CE, Landi F, Marzetti E, Prado CM. The impact of long COVID-19 on muscle health. *Clin Geriatr Med* 2022;**38**:545–57.

220. do Amaral CMSSB, da Luz Goulart C, da Silva BM, Valente J, Rezende AG, Fernandes E, *et al*. Low handgrip strength is associated with worse functional outcomes in long COVID. *Sci Rep* 2024;**14**:2049.

221. Skumlien S, Haave E, Morland L, Bjørtuft O, Ryg MS. Gender differences in the performance of activities of daily living among patients with chronic obstructive pulmonary disease. *Chron Respir Dis* 2006;**3**:141–8.

222. Liljehult MM, von Euler-Chelpin MC, Christensen T, Buus L, Stokholm J, Rosthøj S. Sex differences in independence in activities of daily living early in stroke rehabilitation. *Brain Behav* 2021;**11**:e2223. https://doi.org/10.1002/brb3.2223s

223. Bae S, Malcolm MP, Nam S, Hong I. Association between COVID-19 and activities of daily living in older adults. *OTJR (Thorofare N J)* 2022;**43**:202–10.

224. Pizarro-Pennarolli C, Sánchez-Rojas C, Torres-Castro R, Vera-Uribe R, Sanchez-Ramirez DC, Vasconcello-Castillo L, *et al*. Assessment of activities of daily living in patients post COVID-19: a systematic review. *PeerJ* 2021;**9**:e11026.

225. Goździewicz L, Tobis S, Chojnicki M, Chudek J, Wieczorowska-Tobis K, Idasiak-Piechocka I, *et al*. Long-term impairment in activities of daily living following COVID-19 in residents of long-term care facilities. *Med Sci Monit* 2023;**29**:e941197. https://doi.org/10.12659/MSM.941197

226. Edemekong P, Bomgaars DL, Sukumaran S, Schoo C. *Activities of Daily Living*. Treasure Island, FL: StatPearls Publishing; 2023.

227. Belli S, Balbi B, Prince I, Cattaneo D, Masocco F, Zaccaria S, *et al*. Low physical functioning and impaired performance of activities of daily life in COVID-19 patients who survived hospitalisation. *Eur Respir J* 2020;**56**:2002096.

228. Chen S, Jones LA, Jiang S, Jin H, Dong D, Chen Xi, *et al*. Difficulty and help with activities of daily living among older adults living alone during the COVID-19 pandemic: a multi-country population-based study. *BMC Geriatr* 2022;**22**:181.

229. Frutos ML, Cruzado DP, Lunsford D, Orza SG, Cantero-Téllez R. Impact of social isolation due to COVID-19 on daily life activities and independence of people over 65: a cross-sectional study. *Int J Environ Res Public Health* 2023;**20**:4177.

230. Fettes L, Bayly J, de Bruin LM, Patel M, Ashford S, Higginson IJ, Maddocks M. Relationships between prolonged physical and social isolation during the COVID-19 pandemic, reduced physical activity and disability in activities of daily living among people with advanced respiratory disease. *Chron Respir Dis* 2021;**18**:147997312110358.

231. Liu H, Wang M. Socioeconomic status and ADL disability of the older adults: cumulative health effects, social outcomes and impact mechanisms. *PLOS ONE* 2022;**17**:e0262808.

232. Lima-Costa MF, Mambrini JVM, Peixoto SV, Malta DC, Macinko J. Socioeconomic inequalities in activities of daily living limitations and in the provision of informal and formal care for noninstitutionalized older Brazilians: National Health Survey, 2013. *Int J Equity Health* 2016;**15**:137.

233. Ferioli M, Prediletto I, Bensai S, Betti S, Daniele F, Di Scioscio V, *et al*. The role of 6MWT in COVID-19 follow up. *Euro Respir J* 2021;**58**:OA4046.

234. Wong AW, López-Romero S, Figueroa-Hurtado E, Vazquez-Lopez S, Milne KM, Ryerson CJ, *et al*. Predictors of reduced 6-minute walk distance after COVID-19: a cohort study in Mexico. *Pulmonology* 2021;**27**:563–5.

235. Saunders S, Mayhew A, Kirkwood R, Nguyen K, Kuspinar A, Vesnaver E, *et al*. Factors influencing mobility during the COVID-19 pandemic in community-dwelling older adults. *Arch Phys Med Rehabil* 2023;**104**:34–42.

236. Liu K, Zhang W, Yang Y, Zhang J, Li Y, Chen Y. Respiratory rehabilitation in elderly patients with COVID-19: a randomized controlled study. *Complement Ther Clin Pract* 2020;**39**:101166.

237. Curci C, Pisano F, Bonacci E, Camozzi DM, Ceravolo C, Bergonzi R, *et al*. Early rehabilitation in post-acute COVID-19 patients: data from an Italian COVID-19 Rehabilitation Unit and proposal of a treatment protocol. *Eur J Phys Rehabil Med* 2020;**56**:633–41. https://doi.org/10.23736/S1973-9087.20.06339-X

238. Zheng B, Daines L, Han Q, Hurst JR, Pfeffer P, Shankar-Hari M, *et al*. Prevalence, risk factors and treatments for post-COVID-19 breathlessness: a systematic review and meta-analysis. *Eur Respir Rev* 2022;**31**:220071.

239. Zheng B, Vivaldi G, Daines L, Leavy OC, Richardson M, Elneima O, *et al*.; PHOSP-COVID Study Collaborative Group. Determinants of recovery from post-COVID-19 dyspnoea: analysis of UK prospective cohorts of hospitalised COVID-19 patients and community-based controls. *Lancet Regional Health Eur* 2023;**29**:100635.

240. Daines L, Zheng B, Elneima O, Harrison E, Lone NI, Hurst JR, *et al*. Characteristics and risk factors for post-COVID-19 breathlessness after hospitalisation for COVID-19. *ERJ Open Res* 2023;**9**:00274–2022.

241. Roozbeh F, Saeedi M, Alizadeh-Navaei R, Hedayatizadeh-Omran A, Merat S, Wentzel H, *et al*. Sofosbuvir and daclatasvir for the treatment of COVID-19 outpatients: a double-blind, randomized controlled trial. *J Antimicrob Chemother* 2021;**76**:753–7.

242. Li J, Xia W, Zhan C, Liu S, Yin Z, Wang J, *et al*. A telerehabilitation programme in post-discharge COVID-19 patients (TERECO): a randomised controlled trial. *Thorax* 2022;**77**:697–706.

243. Chest H. *Managing Breathlessness with Long COVID*. 2021. URL: www.chss.org.uk/documents/2021/05/managing-breathlessness-with-long-covid.pdf (accessed 20 May 2025).

244. Clegg A, Young J, Iliffe S, Rikkert MO, Rockwood K. Frailty in elderly people. *Lancet* 2013;**381**:752–62.

245. McDermid RC, Stelfox HT, Bagshaw SM. Frailty in the critically ill: a novel concept. *Crit Care* 2011;**15**:301.

246. Kojima G, Taniguchi Y, Iliffe S, Jivraj S, Walters K. Transitions between frailty states among community-dwelling older people: a systematic review and meta-analysis. *Ageing Res Rev* 2019;**50**:81–8.

247. Ferrara MC, Zarcone C, Tassistro E, Rebora P, Rossi E, Luppi F, *et al*.; STORM Long-COVID Team. Frailty and long-COVID: is COVID-19 responsible for a transition in frailty status among older adults who survived hospitalization for COVID-19? *Aging Clin Exp Res* 2022;**35**:455–61.

248. D'Ascanio L, Pandolfini M, Cingolani C, Latini G, Gradoni P, Capalbo M, *et al*. Olfactory dysfunction in COVID-19 patients: prevalence and prognosis for recovering sense of smell. *Otolaryngol Head Neck Surg* 2021;**164**:82–6.

249. Shamsundara M, Jayalakshmi L. Anosmia: an effect of COVID-19 infection-review. *Indian J Otolaryngol Head Neck Surg* 2023;**75**:815–21.

250. Carfì A, Bernabei R, Landi F; Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. *JAMA* 2020;**324**:603–5.

251. Park JW, Wang X, Xu RH. Revealing the mystery of persistent smell loss in long COVID patients. *Int J Biol Sci* 2022;**18**:4795–808.

252. Grund S, Bauer JM. Malnutrition and sarcopenia in COVID-19 survivors. *Clin Geriatr Med* 2022;**38**:559–64.

253. Promislow DEL. A geroscience perspective on COVID-19 mortality. *J Gerontol A Biol Sci Med Sci* 2020;**75**:e30–3.

254. Pan American Health Organisation. *Policy Brief: The Impact of COVID-19 on Older Persons*. URL: www.paho.org/en/documents/policy-brief-impact-covid-19-older-personsv04.03.24 (accessed 20 May 2025).

255. Cocuzzo B, Wrench A, O'Malley C. Effects of COVID-19 on older adults: physical, mental, emotional, social, and financial problems seen and unseen. *Cureus* 2022;**14**:e29493. https://doi.org/10.7759/cureus.29493

256. Pérez-Rodríguez P, Díaz de Bustamante M, Aparicio Mollá S, Arenas MC, Jiménez-Armero S, Lacosta Esclapez P, *et al*. Functional, cognitive, and nutritional decline in 435 elderly nursing home residents after the first wave of the COVID-19 Pandemic. *Eur Geriatr Med* 2021;**12**:1137–45.

257. Masoudi M, Maasoumi R, Bragazzi NL. Effects of the COVID-19 pandemic on sexual functioning and activity: a systematic review and meta-analysis. *BMC Public Health* 2022;**22**:189.

258. Kaynar M, Gomes ALQ, Sokolakis I, Gül M. Tip of the iceberg: erectile dysfunction and COVID-19. *Int J Impot Res* 2022;**34**:152–7.

259. Harirugsakul K, Wainipitapong S, Phannajit J, Paitoonpong L, Tantiwongse K. Erectile dysfunction after COVID-19 recovery: a follow-up study. *PLOS ONE* 2022;**17**:e0276429.

260. Marciniak E, Górniak A, Hanke W. Long lasting symptoms of dyspnea, cough and fatigue after COVID-19: narrative review of epidemiological studies. *Med Pr* 2021;**72**:711–20.

261. Hickie I, Davenport T, Wakefield D, Vollmer-Conna U, Cameron B, Vernon SD, *et al*.; Dubbo Infection Outcomes Study Group. Post-infective and chronic fatigue syndromes precipitated by viral and non-viral pathogens: prospective cohort study. *BMJ* 2006;**333**:575.

262. Clauw DJ, Häuser W, Cohen SP, Fitzcharles MA. Considering the potential for an increase in chronic pain after the COVID-19 pandemic. *Pain* 2020;**161**:1694–7.

263. El-Tallawy SN, Perglozzi JV, Ahmed RS, Kaki AM, Nagiub MS, LeQuang JK, Hadarah MM. Pain management in the post-COVID era: an update: a narrative review. *Pain Ther* 2023;**12**:423–48.

264. Kemp HI, Corner E, Colvin LA. Chronic pain after COVID-19: implications for rehabilitation. *Br J Anaesth* 2020;**125**:436–40.

265. Kim J, Thomsen T, Sell N, Goldsmith AJ. Abdominal and testicular pain: an atypical presentation of COVID-19. *Am J Emerg Med* 2020;**38**:1542.e1–3.

266. Mao L, Jin H, Wang M, Hu Y, Chen S, He Q, *et al*. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurol* 2020;**77**:683–90.

267. Yong SJ. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. *Infect Dis* 2021;**53**:737–54.

268. Üçeyler N, Burgmer M, Friedel E, Greiner W, Petzke F, Sarholz M, *et al*. Ätiologie und pathophysiologie des fibromyalgiesyndroms. *Der Schmerz* 2017;**31**:239–45.

269. Afari N, Ahumada SM, Wright LJ, Mostoufi S, Golnari G, Reis V, Cuneo JG. Psychological trauma and functional somatic syndromes. *Psychosom Med* 2014;**76**:2–11.

270. Agrawal U, Bedston S, McCowan C, Oke J, Patterson L, Robertson C, *et al*. Severe COVID-19 outcomes after full vaccination of primary schedule and initial boosters: pooled analysis of national prospective cohort studies of 30 million individuals in England, Northern Ireland, Scotland, and Wales. *Lancet* 2022;**400**:1305–20.

271. Tran VT, Perrodeau E, Saldanha J, Pane I, Ravaud P. Efficacy of first dose of covid-19 vaccine versus no vaccination on symptoms of patients with long covid: target trial emulation based on ComPaRe e-cohort. *BMJ Med* 2023;**2**:e000229.

272. Martono M, Fatmawati F, Mulyanti S. Risk factors associated with the severity of COVID-19. *Malaysian J Med Sci* 2023;**30**:84–92.

273. Guy's and St Thomas' NHS Foundation Trust. *Coronavirus (COVID-19) Recovery*. URL: www.guysandstthomas.nhs.uk/health-information/coronavirus-covid-19-recovery#:~:text=After%20you%20test%20positive%20for,to%20feel%20a%20bit%20better (accessed 5 February 2024).

274. The World Health Organization. *Coronavirus Disease (COVID-19): Post COVID-19 Condition*. URL: www.who.int/news-room/questions-and-answers/item/coronavirus-disease-(covid-19)-post-covid-19-condition (accessed 5 February 2024).

275. Al-Thaqafy MS, Batahaf R, Bahakeem R, Batarjee R, Mubaraki W, Alsaedi A, *et al*. Factors affecting confirmed COVID-19 patient's recovery time at King Abdulaziz Medical City, Jeddah. *Cureus* 2023;**15**:e34130. https://doi.org/10.7759/cureus.34130

276. Kaso AW, Hareru HE, Kaso T, Agero G. Time to recovery from Covid-19 and its associated factors among patients hospitalized to the treatment center in South Central Ethiopia. *Environ Chall (Amst)* 2022;**6**:100428.

277. Kassie MZ, Gobena MG, Alemu YM, Tegegne AS. Time to recovery and its determinant factors among patients with COVID-19 in Assosa COVID-19 treatment center, Western Ethiopia. *Pneumonia* 2023;**15**:17.

278. Dessie AM, Feleke SF, Anley DT, Anteneh RM, Demissie ZA. Assessment of factors affecting time to recovery from COVID-19: a retrospective study in Ethiopia. *Adv Public Health* 2022;**2022**:1–7.

279. Mateu L, Tebe C, Loste C, Santos JR, Lladós G, López C, *et al*. Determinants of the onset and prognosis of the post-COVID-19 condition: a 2-year prospective observational cohort study. *Lancet Reg Health Eur* 2023;**33**:100724.

280. Sant Fruchtman C, Fischer FB, Monzón Llamas L, Tavakkoli M, Cobos Muñoz D, Antillon M. Did COVID-19 policies save the same effect on COVID-19 incidence among women and men? Evidence from Spain and Switzerland. *Int J Public Health* 2022;**67**:1604994. https://doi.org/10.3389/ijph.2022.1604994

281. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, *et al*. Factors associated with COVID-19-related death using OpenSAFELY. *Nature* 2020;**584**:430–6.

282. Dessie ZG, Zewotir T. Mortality-related risk factors of COVID-19: a systematic review and meta-analysis of 42 studies and 423,117 patients. *BMC Infect Dis* 2021;**21**:855.

283. Grima P, Guido M, Zizza A. Clinical characteristics and risk factors associated with COVID-19 mortality in a non-Intensive Care Unit. *J Prev Med Hyg* 2023;**64**:E3–8.

284. Cancarevic I, Nassar M, Daoud A, Ali H, Nso N, Sanchez A, *et al*. Mortality rate of COVID-19 infection in end stage kidney disease patients on maintenance hemodialysis: a systematic review and meta-analysis. *World J Virol* 2022;**11**:352–61.

285. Lv F, Gao X, Huang AH, Zu J, He X, Sun X, *et al*. Excess diabetes mellitus-related deaths during the COVID-19 pandemic in the United States. *EClinicalMedicine* 2022;**54**:101671.

286. Yan Y, Yang Y, Wang F, Ren H, Zhang S, Shi X, *et al*. Clinical characteristics and outcomes of patients with severe COVID-19 with diabetes. *BMJ Open Diabetes Res Care* 2020;**8**:e001343.

287. Zakerkish M, Fooladi MS, Shahbazian HB, Ahmadi F, Peyman Payami S, Dargahi-Malamir M. Assessment of mortality rate, need for ICU admission and ventilation in COVID-19 patients with diabetes mellitus. *Qatar Med J* 2022;**2022**:9. https://doi.org/10.5339/qmj.2022.9

288. Gao X, Lv F, He X, Zhao Y, Liu Y, Zu J, *et al*. Impact of the COVID-19 pandemic on liver disease-related mortality rates in the United States. *J Hepatol* 2023;**78**:16–27.

289. Barnard S, Fryers P, Fitzpatrick J, Fox S, Waller Z, Baker A, *et al*. Inequalities in excess premature mortality in England during the COVID-19 pandemic: a cross-sectional analysis of cumulative excess mortality by area deprivation and ethnicity. *BMJ Open* 2021;**11**:e052646.

290. Feldman JM, Bassett MT. Variation in COVID-19 mortality in the US by race and ethnicity and educational attainment. *JAMA Netw Open* 2021;**4**:e2135967.

291. Nab L, Parker EPK, Andrews CD, Hulme WJ, Fisher L, Morley J, *et al*.; OpenSAFELY Collaborative. Changes in COVID-19-related mortality across key demographic and clinical subgroups in England from 2020 to 2022: a retrospective cohort study using the OpenSAFELY platform. *Lancet Public Health* 2023;**8**:e364–77.

292. Finn A, Tanzer JR, Jindal A, Selvaraj V, Collins B, Dapaah-Afriyie K. Readmission risk after COVID-19 hospitalization: a moderation analysis by vital signs. *South Med J* 2022;**115**:842–8.

293. Ramos-Martínez A, Parra-Ramírez LM, Morrás I, Carnevali M, Jiménez-Ibañez L, Rubio-Rivas M, *et al*. Frequency, risk factors, and outcomes of hospital readmissions of COVID-19 patients. *Sci Rep* 2021;**11**:13733.

294. Donnelly JP, Wang XQ, Iwashyna TJ, Prescott HC. Readmission and death after initial hospital discharge among patients with COVID-19 in a large multihospital system. *JAMA* 2021;**325**:304–6.

295. Nematshahi M, Soroosh D, Neamatshahi M, Attarian F, Rahimi F. Factors predicting readmission in patients with COVID-19. *BMC Res Notes* 2021;**14**:374.

296. Loo WK, Hasikin K, Suhaimi A, Yee PL, Teo K, Xia K, *et al*. Systematic review on COVID-19 readmission and risk factors: future of machine learning in COVID-19 readmission studies. *Front Public Health* 2022;**10**:898254. https://doi.org/10.3389/fpubh.2022.898254

297. Verna EC, Landis C, Brown RS, Mospan AR, Crawford JM, Hildebrand JS, *et al*. Factors associated with readmission in the United States following hospitalization with coronavirus disease 2019. *Clin Infect Dis* 2022;**74**:1713–21.

298. Gore V, Li Z, Drake CB, Heath JL, Raiszadeh F, Daniel J, Fagan I. Coronavirus disease 2019 and hospital readmissions. *Med Care* 2022;**60**:125–32.

299. Kirsch JA, Slutske WS, McCarthy DE, Smith SS, Williams BS, Piasecki TM, *et al*. Factors associated with 60-day readmission among inpatients with COVID-19 at 21 United States health systems. *J Med Virol* 2023;**95**:e28972. https://doi.org/10.1002/jmv.28972

300. Green H, Yahav D, Eliakim-Raz N, Karny-Epstein N, Kushnir S, Shochat T, *et al*. Risk-factors for re-admission and outcome of patients hospitalized with confirmed COVID-19. *Sci Rep* 2021;**11**:17416.

301. Günster C, Busse R, Spoden M, Rombey T, Schillinger G, Hoffmann W, *et al*. 6-month mortality and readmissions of hospitalized COVID-19 patients: a nationwide cohort study of 8,679 patients in Germany. *PLOS ONE* 2021;**16**:e0255427.

302. Menditto VG, Fulgenzi F, Bonifazi M, Gnudi U, Gennarini S, Mei F, Salvi A. Predictors of readmission requiring hospitalization after discharge from emergency departments in patients with COVID-19. *Am J Emerg Med* 2021;**46**:146–9.

303. Evans RA, Dube S, Lu Y, Yates M, Arnetorp S, Barnes E, *et al*. Impact of COVID-19 on immunocompromised populations during the Omicron era: insights from the observational population-based INFORM study. *Lancet Reg Health Eur* 2023;**35**:100747.

304. Puebla Neira D, Watts A, Seashore J, Polychronopoulou E, Kuo YF, Sharma G. Smoking and risk of COVID-19 hospitalization. *Respir Med* 2021;**182**:106414.

305. The Cochrane Collaboration. *9.5.2 Identifying and Measuring Heterogeneity*. URL: https://handbook-5-1.cochrane.org/chapter_9/9_5_2_identifying_and_measuring_heterogeneity.htm (accessed 16 January 2024).

306. Aben B, Kok RN, de Wind A. Return-to-work rates and predictors of absence duration after COVID-19 over the course of the pandemic. *Scand J Work Environ Health* 2023;**49**:182–92.

307. Norman BC, Jackson JC, Graves JA, Girard TD, Pandharipande PP, Brummel NE, *et al*. Employment outcomes after critical illness: an analysis of the bringing to light the risk factors and incidence of neuropsychological dysfunction in ICU survivors cohort*. *Crit Care Med* 2016;**44**:2003–9.

308. Myhren H, Ekeberg O, Stokland O. Health-related quality of life and return to work after critical illness in general intensive care unit patients: a 1-year follow-up study. *Crit Care Med* 2010;**38**:1554–61.

309. Jacobsen PA, Andersen MP, Gislason G, Phelps M, Butt JH, Køber L, *et al*. Return to work after COVID-19 infection: a Danish nationwide registry study. *Public Health* 2022;**203**:116–22.

310. Goda G, Soltas E. *The Impacts of COVID-19 Illnesses on Workers*. National Bureau of Economic Research; 2022. URL: www.nber.org/system/files/working_papers/w30435/w30435.pdf (accessed 12 May 2024).

311. Westerlind E, Palstam A, Sunnerhagen KS, Persson HC. Patterns and predictors of sick leave after Covid-19 and long Covid in a national Swedish cohort. *BMC Public Health* 2021;**21**:1023.

312. Cutler DM. The costs of long COVID. *JAMA Health Forum* 2022;**3**:e221809.

313. Bakker C, van der Linden S. Health related utility measurement: an introduction. *J Rheumatol* 1995;**22**:1197–9.

314. Torres-Rueda S, Sweeney S, Bozzani F, Naylor NR, Baker T, Pearson C, *et al*. Stark choices: exploring health sector costs of policy responses to COVID-19 in low-income and middle-income countries. *BMJ Glob Health* 2021;**6**:e005759.

315. Violato M, Pollard J, Lloyd A, Roope LSJ, Duch R, Becerra MF, Clarke PM. The COVID-19 pandemic and health-related quality of life across 13 high- and low-middle-income countries: a cross-sectional analysis. *PLOS Med* 2023;**20**:e1004146.

316. Fink G, Tediosi F, Felder S. Burden of Covid-19 restrictions: national, regional and global estimates. *EClinicalMedicine* 2022;**45**:101305.

317. Mao Z, Li X, Jit M, Beutels P. COVID-19-related health utility values and changes in COVID-19 patients and the general population: a scoping review. *Qual Life Res* 2024;**33**:1443–54. https://doi.org/10.1007/s11136-023-03584-x

318. Van Wilder L, Devleesschauwer B, Clays E, Van der Heyden J, Charafeddine R, Scohy A, De Smedt D. QALY losses for chronic diseases and its social distribution in the general population: results from the Belgian Health Interview Survey. *BMC Public Health* 2022;**22**:1304.

319. Feinstein AR. Biases introduced by confounding and imperfect retrospective and prospective exposure assessments. In Bate R, editor. *What Risk?* Butterworth-Heinemann; 1997. pp 37–48.

320. Higgins J, Savović J, Page M, Elbers RG, Sterne JAC. Assessing risk of bias in a randomized trial. In Higgins JPT, Thomas J, Chandler J, Cumpston M, Li T, Page MJ, *et al*., editors. *Cochrane Handbook for Systematic Reviews of Interventions (updated August 2023)*. Cochrane; 2023.

321. Viswanathan M, Berkman ND. Development of the RTI item bank on risk of bias and precision of observational studies. *J Clin Epidemiol* 2012;**65**:163–78.

322. Helbok R, Chou SHY, Beghi E, Mainali S, Frontera J, Robertson C, *et al*.; GCS-NeuroCOVID Consortium. NeuroCOVID: it's time to join forces globally. *Lancet Neurol* 2020;**19**:805–6.

323. *International Statistical Classification of Diseases and Related Health Problems 10th Revision*. URL: https://icd.who.int/browse10/2019/en (accessed 17 October 2023).

324. Berkman LF, Glass T, Brissette I, Seeman TE. From social integration to health: Durkheim in the new millennium. *Soc Sci Med* 2000;**51**:843–57.

325. Huber M, Knottnerus JA, Green L, van der Horst H, Jadad AR, Kromhout D, *et al*. How should we define health? *BMJ* 2011;**343**:d4163.

326. Ammar A, Chtourou H, Boukhris O, Trabelsi K, Masmoudi L, Brach M, *et al*. COVID-19 home confinement negatively impacts social participation and life satisfaction: a worldwide multicenter study. *Int J Environ Res Public Health* 2020;**17**:6237.

327. The World Health Organization. *Active Ageing. A Policy Framework*. 2026. URL: https://iris.who.int/bitstream/handle/10665/67215/WH0?sequence=102.01.24 (accessed 20 May 2025).

328. Ammar A, Trabelsi K, Brach M, Chtourou H, Boukhris O, Masmoudi L, *et al*. Effects of home confinement on mental health and lifestyle behaviours during the COVID-19 outbreak: Insight from the ECLB-COVID19 multicenter study. *Biol Sport* 2021;**38**:9–21.

329. Ammar A, Mueller P, Trabelsi K, Chtourou H, Boukhris O, Masmoudi L, *et al*.; ECLB-COVID19 Consortium. Psychological consequences of COVID-19 home confinement: The ECLB-COVID19 multicenter study. *PLOS ONE* 2020;**15**:e0240204.

330. The British Medical Association. *The Impact of the Pandemic on Population Health and Health Inequalities*. 2024. URL: www.bma.org.uk/advice-and-support/covid-19/what-the-bma-is-doing/the-impact-of-the-pandemic-on-population-health-and-health-inequalities (accessed 20 May 2025).

331. Kluge HHP, Wickramasinghe K, Rippin HL, Mendes R, Peters DH, Kontsevaya A, Breda J. Prevention and control of non-communicable diseases in the COVID-19 response. *Lancet* 2020;**395**:1678–80.

332. Basu S. Non-communicable disease management in vulnerable patients during Covid-19. *Indian J Med Ethics* 2020;**05**:103–5.

333. Bain SC, Czernichow S, Bøgelund M, Madsen ME, Yssing C, McMillan AC, *et al*. Costs of COVID-19 pandemic associated with diabetes in Europe: a health care cost model. *Curr Med Res Opin* 2021;**37**:27–36.

334. Kapinos KA, Peters RM, Murphy RE, Hohmann SF, Podichetty A, Greenberg RS. Inpatient costs of treating patients with COVID-19. *JAMA Netw Open* 2024;**7**:e2350145.

335. Bots SH, Peters SAE, Woodward M. Sex differences in coronary heart disease and stroke mortality: a global assessment of the effect of ageing between 1980 and 2010. *BMJ Glob Health* 2017;**2**:e000298.

336. Feltcher M, Evans L, Parry-Williams L, Ashton K, Green L. *The Impact of the COVID-19 Pandemic on Women, Employment and Health Inequalities*. 2023. URL: https://phwwhocc.co.uk/wp-content/uploads/2023/12/Impacts-of-COVID-on-Women-Explanatory-Note-Eng-FINAL.pdf (accessed 20 May 2025).

337. McGowan VJ, Bambra C. COVID-19 mortality and deprivation: pandemic, syndemic, and endemic health inequalities. *Lancet Public Health* 2022;**7**:e966–75.

338. Thompson K, van der Kamp D, Vader S, Pijpker R, den Broeder L, Wagemakers A. Experiences of resilience during the COVID-19 pandemic: a qualitative study among high and low socio-economic status individuals in the Netherlands. *SSM – Qual Res Health* 2023;**4**:100322.

339. Quan D, Luna Wong L, Shallal A, Madan R, Hamdan A, Ahdi H, *et al*. Impact of race and socioeconomic status on outcomes in patients hospitalized with COVID-19. *J Gen Intern Med* 2021;**36**:1302–9.

340. House of Commons Health and Social Care and Science and Technology Committees. *Sixth Report of the Health and Social Care Committee and Third Report of the Science and Technology Committee of Session 2021–22*. Coronavirus: *Lessons Learned* to *Date*. 2021. URL: https://committees.parliament.uk/publications/7496/documents/78687/default/ (accessed 20 May 2025).

Appendix 1 Search strategy

The core search strategy consisted of coronavirus (COVID-19) terms (see lines 1–11 below) and a relevant study design filter to locate systematic reviews and meta-analyses for step 1 (see search strings) and another filter to identify randomised controlled trials for step 2 [(37)]. Our searches were peer reviewed in accordance with PRESS guidelines (38).

1. coronavirus/ or betacoronavirus/ or betacoronavirus 1/ or middle east respiratory syndrome coronavirus/ or sars virus/
2. coronavirus infections/ or severe acute respiratory syndrome/
3. (coronavirus$ or corona virus$ or OC43 or NL63 or 229E or HKU1 or HCoV$ or ncov$ or covid$ or sars-cov$ or sarscov$ or Sars-coronavirus$ or Severe Acute Respiratory Syndrome Coronavirus$).mp.
4. 1 or 2 or 3
5. (20191$ or 202$).dp. or 20191117 : 20301231.(ep).
6. 4 and 5
7. sars-cov-2/ or covid-19/
8. (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus$ or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus$ or corona virus or Pandemi$2)) or ((covid or covid19 or covid-19) and (outbreak or crisis or pandemic$2)) or (coronavirus$ and pneumonia)).mp.
9. COVID-19.rx,px,ox. or severe acute respiratory syndrome coronavirus 2.os.
10. 7 or 8 or 9
11. 6 or 10

Step 1: Search strings

Cochrane Database of Systematic Reviews Issue 7 of 12 July 2021 (last searched 15 July 2021) *n* = 42

#1 MeSH descriptor: [Coronavirus] this term only
#2 MeSH descriptor: [Betacoronavirus] this term only
#3 MeSH descriptor: [Betacoronavirus 1] this term only
#4 MeSH descriptor: [Middle East Respiratory Syndrome Coronavirus] this term only
#5 MeSH descriptor: [Middle East Respiratory Syndrome Coronavirus] this term only
#6 MeSH descriptor: [Coronavirus Infections] this term only
#7 MeSH descriptor: [Coronavirus Infections] this term only
#8 (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*):ti,ab,kw (Word variations have been searched)
#9 {or #1-#8} with Cochrane Library publication date from Oct 2019 to present
#10 MeSH descriptor: [COVID-19] this term only
#11 MeSH descriptor: [SARS-CoV-2] explode all trees
#12 ("2019-ncov" or ncov19 or ncov-19 or "2019-novel CoV" or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) near/2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemi*)) or ((covid or covid19 or covid-19) and (outbreak or crisis or pandemic*)) or (coronavirus* and pneumonia)):ti,ab,kw
#13 {or #9-#12}
#14 #9 OR #13

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations, Daily and Versions(R) 1946 to 13 July 2021 ("NOT Children" filter added; last searched 15 July 2021) (*n* = 3547)

1. coronavirus/ or betacoronavirus/ or betacoronavirus 1/ or middle east respiratory syndrome coronavirus/ or sars virus/
2. coronavirus infections/ or severe acute respiratory syndrome/
3. (coronavirus$ or corona virus$ or OC43 or NL63 or 229E or HKU1 or HCoV$ or ncov$ or covid$ or sars-cov$ or sarscov$ or Sars-coronavirus$ or Severe Acute Respiratory Syndrome Coronavirus$).mp.
4. 1 or 2 or 3
5. (20191$ or 202$).dp. or 20191117 : 20301231.(ep).
6. 4 and 5
7. sars-cov-2/ or covid-19/
8. (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus$ or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus$ or corona virus or Pandemi$2)) or ((covid or covid19 or covid-19) and (outbreak or crisis or pandemic$2)) or (coronavirus$ and pneumonia)).mp.
9. COVID-19.rx,px,ox. or severe acute respiratory syndrome coronavirus 2.os.
10. 7 or 8 or 9
11. 6 or 10
12. meta-analysis/ or "systematic review"/
13. systematic reviews as topic/
14. exp meta-analysis as topic/
15. (meta analy$ or metaanaly$ or meta synthes$).ti.
16. (systematic adj3 (review$1 or overview$1)).ti.
17. or/12-16
18. exp animals/ not humans.sh.
19. 17 and 11
20. 19 not 18
21. exp Adolescent/
22. exp Child/
23. exp Infant/
24. exp Minors/
25. exp Pediatrics/
26. exp Puberty/
27. exp Schools/
28. (baby$ or babies or infant$ or infancy or neonat$ or newborn$ or postmatur$ or prematur$ or preterm$).ti.
29. (boy$ or girl$ or teen$).ti.
30. (child$ or kid or kids or preschool$ or school age$ or schoolchild$ or toddler$).ti.
31. (elementary school$ or high school$ or highschool$ or kindergar$ or nursery school$ or primary school$ or secondary school$).ti.
32. minors$.ti.
33. (paediatric$ or peadiatric$ or pediatric$).ti.
34. (prepubescen$ or pubescen$ or pubert$).ti.
35. (youth or adolescen$).ti.
36. or/21-35
37. 20 not 36

EMBASE 1980 to 2021 Week 27 (last searched 15 July 2021) (*n* = 6812)

1. betacoronavirus/ or coronavirinae/ or betacoronavirus 1/ or middle east respiratory syndrome coronavirus/ or sars-related coronavirus/
2. coronavirus infection/ or severe acute respiratory syndrome/

3. (coronavirus$ or corona virus$ or OC43 or NL63 or 229E or HKU1 or HCoV$ or ncov$ or covid$ or sars-cov$ or sarscov$ or Sars-coronavirus$ or Severe Acute Respiratory Syndrome Coronavirus$).mp.
4. 1 or 2 or 3
5. (20191$ or 202$).dp.
6. limit 5 to dd= 20200118-20200626
7. 5 or 6
8. 4 and 7
9. exp severe acute respiratory syndrome coronavirus 2/ or coronavirus disease 2019/
10. (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus$ or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus$ or corona virus or Pandemi$2)) or ((covid or covid19 or covid-19) and (outbreak or crisis or pandemic$2)) or (coronavirus$ and pneumonia)).mp.
11. 9 or 10
12. 8 or 11
13. evidence based medicine/ or exp meta analysis/ or "systematic review"/
14. exp meta analysis/ or "systematic review"/
15. methodology/ or "meta analysis (topic)"/ or "systematic review (topic)"/
16. (meta analy$ or metaanaly$).ti.
17. (systematic adj3 (review$1 or overview$1)).ti.
18. or/13-17
19. (exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
20. 18 not 19
21. 12 and 20
22. exp *adolescence/
23. exp *adolescent/
24. exp *child/
25. *high school/
26. *kindergarten/
27. *middle school/
28. exp *newborn/
29. *nursery school/
30. exp *pediatrics/
31. *primary school/
32. exp *puberty/
33. *school/
34. adoles*.ti.
35. (baby* or babies or infant* or infancy or neonat* or newborn* or postmatur* or prematur* or preterm*).ti.
36. (boy* or girl* or teen*).ti.
37. (child* or kid or kids or preschool* or school age* or schoolchild* or toddler*).ti.
38. (elementary school* or high school* or highschool* or kindergar* or nursery school* or primary school* or secondary school*).ti.
39. minors*.ti.
40. (paediatric* or peadiatric* or pediatric*).ti.
41. (prepubescen* or pubescen* or pubert*).ti.
42. or/22-41
43. 21 not 42

CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; 1982 to present) ('Limiters – Publication Year: 2019-2021'; last searched 15 July 2021) (*n* = 1181)

S1 (MH "Coronavirus") OR (MH "Coronavirus Infections") OR (MH "Severe Acute Respiratory Syndrome") OR (MH "SARS Virus")

S2 TI (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*) OR AB (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*)
S3 S1 OR S2
S4 (MH "COVID-19") OR (MH "COVID-19 Pandemic") OR (MH "SARS-CoV-2")
S5 TI (("2019-ncov" or ncov19 or ncov-19 or "2019-novel CoV" or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) N2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemi*)) or ((covid or covid19 or covid-19) and (outbreak or crisis or pandemic*)) or (coronavirus* and pneumonia))) OR AB (("2019-ncov" or ncov19 or ncov-19 or "2019-novel CoV" or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) N2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemi*)) or ((covid or covid19 or covid-19) and (outbreak or crisis or pandemic*)) or (coronavirus* and pneumonia)))
S6 S4 OR S5
S7 S3 OR S6
S8 (MH "Scoping Review") OR (MH "Systematic Review")
S9 (MH "Meta Analysis") OR (MH "Meta Synthesis")
S10 TI ((systematic N3 (review* or overview*))) OR TI (meta analy* or metaanaly* or meta synthes*)
S11 S8 OR S9 OR S10
S12 S7 AND S11

APA PsycArticles Full Text (last searched 15 July 2021) (*n* = 109)

1. coronavirus/ or severe acute respiratory syndrome/
2. (coronavirus$ or corona virus$ or OC43 or NL63 or 229E or HKU1 or HCoV$ or ncov$ or covid$ or sars-cov$ or sarscov$ or Sars-coronavirus$ or Severe Acute Respiratory Syndrome Coronavirus$).mp.
3. limit 2 to yr="2019 -Current"
4. (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus$ or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus$ or corona virus or Pandemi$2)) or ((covid or covid19 or covid-19) and (outbreak or crisis or pandemic$2)) or (coronavirus$ and pneumonia)).mp.
5. 1 or 3 or 4
6. "systematic review"/ or "literature review"/ or meta analysis/
7. (meta analy$ or metaanaly$ or meta synthes$).ti.
8. (systematic adj3 (review$1 or overview$1)).ti.
9. 6 or 7 or 8
10. 5 and 9

Web of Science – Book Citation Index – Science (BKCI-S), Book Citation Index – Social Sciences and Humanities (BKCI-SSH), Conference Proceedings Citation Index – Science (CPCI-S), Emerging Sources Citation Index (ESCI), Science Citation Index Expanded (SCI-EXPANDED) (last searched 15 July 2021) (*n* = 2863)

#1 TS=(coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*) and 2019 or 2020 or 2021 (Publication Years)
#2 TS=("2019-ncov" or ncov19 or ncov-19 or "2019-novel CoV" or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or "covid 2019" or ((novel or new or nouveau) NEAR/2 (CoV or nCoV or covid or coronavirus* or "corona virus" or pandemi*)) or ((covid or covid19 or "covid-19") and (outbreak or crisis or pandemic*)) or (coronavirus* and pneumonia))
#3 (#1) OR #2

#4 TI=((meta analy* or metaanaly* or meta synthes*))
#5 TI=((systematic near/3 (review* or overview*)))
#6 #4 OR #5

WHO Global Index Medicus (last searched 15 July 2021) (*n* = 119, *n* = 400)

Updated 15 July 2021_PRECIOUS_final search Search strategy is pre-written by World Health Organization Global Index Medicus

((("2019-2020" OR 2019 OR da:202*) ("New Coronavirus" OR "Novel Coronavirus" OR "Nuevo Coronavirus" OR "Novo Coronavirus" OR "Coronavirus disease" OR "Enfermedad por Coronavirus")) OR (2019-ncov OR covid19 OR covid-19 OR covid2019 OR covid-2019 OR "COVID 2019") OR ((srag-cov-2 OR sars2 OR sars-cov-2 OR coronavirus OR mh:betacoronavirus OR mh:"Coronavirus infections") AND (tw:2019 OR da:202*) AND NOT da:201*) OR ((srag-cov-2 OR sars2 OR sars-cov-2 OR coronavirus* OR mh:betacoronavirus OR mh:"Coronavirus infections") AND (tw:2019 OR da:202*) AND NOT da:201*) OR ("Coronavirus 2" da:202*) OR (wuhan market virus) OR (virus mercado wuhan) OR "Wuhan Coronavirus" OR "Coronavirus de Wuhan") AND NOT (ti:"Middle East respiratory syndrome" OR ti:mers-cov OR mh:"Middle East Respiratory Syndrome Coronavirus") AND (type_of_study:("systematic_reviews" OR "policy_brief" OR "overview"))

WHO COVID-19 Global literature on coronavirus disease

db:("COVIDWHO") AND type_of_study:("systematic_reviews" OR "overview")

LitCovid-19 (www.ncbi.nlm.nih.gov/research/coronavirus/; last searched 15 July 2021) *n* = 4110;

LitCovid-19 (www.ncbi.nlm.nih.gov/research/coronavirus/)

Chen Q, Allot A, Lu Z. Keep up with the latest coronavirus research. Nature. 2020 Mar;579(7798):193. doi: 10.1038/d41586-020-00694-1. PMID: 32157233.

systematic review OR systematic overview OR meta-analysis OR meta-synthesis

Epistemonikos: Database of the best Evidence-Based Healthcare (www.epistemonikos.org/; last searched; 15 July 2021) *n* = 4840;

(title:((title:((coronavirus* OR corona virus* OR HCoV* OR ncov* OR covid* OR sars-cov* OR sarscov* OR sars-coronavirus*)) OR abstract:((coronavirus* OR corona virus* OR HCoV* OR ncov* OR covid* OR sars-cov* OR sarscov* OR sars-coronavirus*)))) OR abstract:((title:((coronavirus* OR corona virus* OR HCoV* OR ncov* OR covid* OR sars-cov* OR sarscov* OR sars-coronavirus*)) OR abstract:((coronavirus* OR corona virus* OR HCoV* OR ncov* OR covid* OR sars-cov* OR sarscov* OR sars-coronavirus*)))))

Added to Database: From: 1-11-2019 to 15-7-2021 Publication Type: systematic Review.

Step 2: Search strings

Cochrane Database of Systematic Reviews Issue 9 of 12 July 2021 (last searched 15 September 2021) (*n* = 7339)

#1 MeSH descriptor: [Coronavirus] this term only
#2 MeSH descriptor: [Betacoronavirus] this term only
#3 MeSH descriptor: [Betacoronavirus 1] this term only
#4 MeSH descriptor: [Middle East Respiratory Syndrome Coronavirus] this term only

#5 MeSH descriptor: [Coronavirus Infections] this term only
#6 (coronavirus* or corona virus* or OC43 or NL63 or 229E or HKU1 or HCoV* or ncov* or covid* or sars-cov* or sarscov* or Sars-coronavirus* or Severe Acute Respiratory Syndrome Coronavirus*):ti,ab,kw
#7 {or #1-#6}
#8 MeSH descriptor: [COVID-19] this term only
#9 MeSH descriptor: [SARS-CoV-2] explode all trees
#10 ("2019-ncov" or ncov19 or ncov-19 or "2019-novel CoV" or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) near/2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemi*)) or ((covid or covid19 or covid-19) and (outbreak or crisis or pandemic*)) or (coronavirus* and pneumonia)):ti,ab,kw
#11 {or #8-#10}
#12 #7 OR #11

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review and Other Non-Indexed Citations, Daily and Versions(R) (last searched 25 August 2021) (Ovid) (*n* = 8373)

1 sars-cov-2/ or covid-19/
2 (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus$ or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus$ or corona virus or Pandemi$2)) or ((covid or covid19 or covid-19) and (outbreak or crisis or pandemic$2)) or (coronavirus$ and pneumonia)).mp.
3 COVID-19.rx,px,ox. or severe acute respiratory syndrome coronavirus 2.os.
4 1 or 2 or 3
5 randomized controlled trial.pt.
6 controlled clinical trial.pt.
7 randomized.ab.
8 placebo.ab.
9 clinical trials as topic.sh.
10 random$.ab.
11 trial.ti.
12 5 or 6 or 7 or 8 or 9 or 10 or 11
13 exp animals/ not humans.sh.
14 12 not 13
15 4 and 14

EMBASE (Ovid) (last searched 25 August 2021) (*n* = 9901)

1 exp severe acute respiratory syndrome coronavirus 2/ or coronavirus disease 2019/
2 (2019-ncov or ncov19 or ncov-19 or 2019-novel CoV or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus$ or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) adj2 (CoV or nCoV or covid or coronavirus$ or corona virus or Pandemi$2)) or ((covid or covid19 or covid-19) and (outbreak or crisis or pandemic$2)) or (coronavirus$ and pneumonia)).mp.
3 1 or 2
4 Clinical Trial/
5 Randomized Controlled Trial/
6 controlled clinical trial/
7 multicenter study/
8 Phase 3 clinical trial/
9 Phase 4 clinical trial/
10 exp RANDOMIZATION/

11 Single Blind Procedure/
12 Double Blind Procedure/
13 Crossover Procedure/
14 PLACEBO/
15 randomi?ed controlled trial$.tw.
16 rct.tw.
17 (random$ adj2 allocat$).tw.
18 single blind$.tw.
19 double blind$.tw.
20 ((treble or triple) adj blind$).tw.
21 placebo$.tw.
22 Prospective Study/
23 or/4-22
24 Case Study/
25 case report.tw.
26 abstract report/ or letter/
27 Conference proceeding.pt.
28 Conference abstract.pt.
29 Editorial.pt.
30 Letter.pt.
31 Note.pt.
32 or/24-31
33 23 not 32
34 3 and 33

CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature; 1982 to present; last searched 14 November 2021) (*n* = 12,916)

S1 (MH "COVID-19") OR (MH "COVID-19 Pandemic") OR (MH "SARS-CoV-2")
S2 TI (("2019-ncov" or ncov19 or ncov-19 or "2019-novel CoV" or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) N2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemi*)) or ((covid or covid19 or covid-19) and (outbreak or crisis or pandemic*)) or (coronavirus* and pneumonia))) OR AB (("2019-ncov" or ncov19 or ncov-19 or "2019-novel CoV" or sars-cov2 or sars-cov-2 or sarscov2 or sarscov-2 or Sars-coronavirus2 or Sars-coronavirus-2 or SARS-like coronavirus* or coronavirus-19 or covid19 or covid-19 or covid 2019 or ((novel or new or nouveau) N2 (CoV or nCoV or covid or coronavirus* or corona virus or pandemi*)) or ((covid or covid19 or covid-19) and (outbreak or crisis or pandemic*)) or (coronavirus* and pneumonia)))
S3 S1 OR S2
S4 (MH "Clinical Trials+")
S5 PT Clinical trial
S6 TX clinic* n1 trial*
S7 TX ((singl* n1 blind*) or (singl* n1 mask*)) or TX ((doubl* n1 blind*) or (doubl* n1 mask*)) or TX ((tripl* n1 blind*) or (tripl* n1 mask*)) or TX ((trebl* n1 blind*) or (trebl* n1 mask*))
S8 TX randomi* control* trial*
S9 (MH "Random Assignment")
S10 TX random* allocat*
S11 TX placebo*
S12 (MH "Placebos")
S13 (MH "Quantitative Studies")
S14 TX allocat* random*
S15 S4 OR S5 OR S6 OR S7 OR S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14
S16 S3 AND S15

Clinical trial registers*

US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov (www.clinicaltrials.gov) (*n* = 2470)

Simple search function: In condition: Covid19 or long Covid or Covid-19

***World Health Organization International Clinical Trials Registry Platform (apps.who.int/trialsearch) search strategy**

Multiple attempts to search this database were made between 15 July and 30 August 2021.However, the platform was unstable due to the volume of COVID-19 related studies. We were finally able to download an excel file dated 16 August 2021 which contained the contents of the WHO ICTRP database and searched this file for relevant studies.

Pre-prints MedRxiv (*n* = 5105 records, of which 156 were potentially relevant)

www.medrxiv.org

Simple search function: Covid-19 or long Covid

Open repository datasets (*n* = 6044 records, of which 27 were potentially relevant) (date of last search: 25 August 2021)

Simple search function: Covid, Covid-19, SARS-COV-2, long Covid

- https://figshare.com
- https://zenodo.org
- https://datamendeley.com
- https://dataverse.harvard.edu

Personal networks, funding agencies, citation tracking (backward and forward) (date of last search: 15 November 2021; potentially relevant studies 91)

Personal networks including members of the PRECIOUS collaboration were asked to identify any potentially relevant study that met the selection criteria.

We also conducted supplementary searches of the following funding agencies for potentially relevant studies:

- www.nihr.ac.uk
- https://reporter.nih.gov
- https://cihr-irsc.gc.ca/e/193.html
- https://ukcdr.org.uk/data-tool/covid-19-research-project-tracker-by-ukcdr-glopid-r/ (downloaded excel file data 29 October 2021).

We also searched the reference list of all studies that were invited to contribute data and used Google Scholar (https://scholar.google.com) for forward citation tracking of included record.

EME
HSDR
HTA
PGfAR
PHR

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