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Author contributions

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Competing interests

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Understanding and tracking the impact of long COVID in the United Kingdom

To the Editor — There is now a rich body of knowledge on acute COVID-19, but much less is known about the risk factors, clinical presentation, duration and management of persistent or new symptoms following recovery from initial infection, often termed long COVID¹. Post-infection follow-up data show that a significant proportion of hospitalized and non-hospitalized patients experience persistent symptoms and organ dysfunction^{2–4}.

The UK Office for National Statistics (ONS) estimates that the number of people in the UK that are self-reporting symptoms lasting more than 4 weeks currently stands at 1.1 million (1.7% of the population)³, while the real-time assessment of community transmission (REACT) study in England estimated the overall number of people who reported at least one symptom lasting for 12 or more weeks as more than 2 million by February 2021 (ref. ⁵). Patients globally have reported a range of new, returning

and/or ongoing symptoms, including (but not limited to) fatigue, shortness of breath, altered smell and taste, cough, myalgia, cognitive impairment and diarrhea following COVID-19 infection⁶. Of great concern are data from imaging studies that report single or multiple organ impairment, even in non-hospitalized patients⁷.

To build greater understanding of long COVID, a wide range of nationally funded studies has been launched in the UK (see Fig. 1 and Table 1). The post-hospitalisation

Fig. 1 | Timeline of major funded epidemiological studies on long COVID in the UK. *PHOSP-COVID has ethical approval for 25-year follow-up and REACT-LC for 20-year follow-up, with plans highlighting how each study will evolve, ask new questions and seek further resources. #REACT-LC is funded from February 2021 but the timeline of the project starts in May 2020 with the use of the first baseline data from REACT participants, which form the sampling for follow-up.

Table 1 | Summary of major funded epidemiological studies on long COVID in the UK

Study	Aim	Design and cohort	Population	SARS-Cov-2 serology	Place of care for acute COVID-19
TLC: Therapies for long COVID in non-hospitalized individuals	To develop a new Symptom Burden Questionnaire™ for long-COVID phenotype symptom clusters with laboratory-confirmed SARS-CoV-2 infection compared to test-negative controls, identify potential therapies, develop a supportive remotely delivered intervention for patients with long COVID in the community, and establish a trial platform for further intervention studies.	Using electronic GP records in partnership with the CPRD, the team will identify and recruit thousands of non-hospitalized patients with long COVID who have had symptoms for 12 weeks or longer.	4,000 patients with a positive SARS-CoV-2 RT-PCR result and 1,000 matched controls recruited from primary care.	No.	Non-hospitalized.
CIS: The COVID-19 infection survey	To provide national estimates of SARS-CoV-2 prevalence and incidence over time.	Repeated cross-sectional surveys of representative households across the UK, identified either by one adult from the household having participated in existing surveys conducted by ONS or the Northern Ireland Statistics and Research Agency and providing consent for future contact regarding research, or by the household being randomly selected from a commercially available source such as AddressBase or equivalent databases (including those in the devolved administrations).	Randomly sampled households (children and adults aged 2+ years) from all parts of the UK; as the CIS began in April 2020, more than 476,000 individuals from over 236,000 households have participated.	Yes.	Hospitalized and non-hospitalized.
CLoCk: The children & young people with long COVID study	To describe the clinical phenotype of post-COVID symptomatology in CYP with laboratory-confirmed SARS-CoV-2 infection compared to test-negative controls, produce an operational research definition of long COVID in CYP and establish the prevalence of long COVID in CYP.	Second-generation surveillance system; patient demographic service. A longitudinal cohort of SARS-CoV-2 positives aged 11–17 years compared with age-, sex- and region-matched SARS-CoV-2 test-negative controls ('cohort-analytic' study), identified by Public Health England.	>17,000 11–17 years old (with 18–20-year old extension planned); half COVID-19 test positive and half matched controls that are COVID-19 test negative.	No.	Non-hospitalized.
Longitudinal Health and Wellbeing National Core Study	To understand the health, social and economic impacts of the COVID-19 pandemic by uniting established population cohorts and national anonymized electronic health records to inform policy.	Parallel and complementary analysis of national anonymized electronic health records (~59 million people), and 12 well-established population cohort studies (~60 million).	Whole population (for anonymized electronic health records), geographically distributed population samples for cohorts.	Partial.	Hospitalized and non-hospitalized.
CONVALESCENCE: Coronavirus post-acute long-term effects: constructing an evidence base	To define the sub-phenotypes of long COVID, identify predictors and mechanisms, understand long-term health (physical and mental) and socioeconomic consequences, and clarify and improve GP adherence to NICE diagnosis and management guidelines.	Linked to Longitudinal Health and Wellbeing National Core Study. In addition, a sub-study of 800 participants (200 with long COVID and evidence of SARS-CoV-2 infection (cases), 200 each of 3 control groups: (1) symptoms of long COVID but no evidence of infection; (2) evidence of infection but no long COVID; (3) neither long COVID nor history of COVID-19 infection) recruited for in-depth phenotyping.	As for the National Core Study, the sub-study participants were recruited from population cohorts.	Yes for sub-study.	Hospitalized and non-hospitalized.

Continued

Table 1 | Summary of major funded epidemiological studies on long COVID in the UK (continued)

Study	Aim	Design and cohort	Population	SARS-Cov-2 serology	Place of care for acute COVID-19
REACT-long COVID: Real-time assessment of community transmission	To characterize the genetic, biological, social and environmental determinants, and their inter-relationships, that underpin progression to long COVID, and to understand the natural history and long-term sequelae post SARS-CoV-2 infection.	Prospective study of 120,000+ participants in the REACT-1 and REACT-2 community prevalence studies (among more than 2 million), including detailed phenotyping and omic profiles from >10,000 participants with prior SARS-CoV-2 infection. NHS record linkage follow-up of whole cohort (with consent). Nested qualitative study of patient experience and detailed symptom profiles.	Random sample of the population in England aged 5+ years. Sub-cohort of >10,000 adults with prior SARS-CoV-2 infection, detailed phenotyping and whole-genome sequencing. Survey follow-up and data linkage for 120,000+ participants aged 5+ years.	Yes.	Community based.
PHOSP-COVID: The post-hospitalisation COVID-19 study	To understand and improve long-term outcomes for survivors of hospitalization with COVID-19.	Prospective longitudinal cohort study recruiting patients aged 18+ years who were discharged from 1 of 70+ NHS hospitals across England, Northern Ireland, Scotland and Wales following admission to a medical assessment or ward for confirmed or clinician-diagnosed COVID-19.	Aim to recruit 10,000 adults discharged from hospital with COVID-19; 3,000 for careful in-clinic phenotyping and samples for storage in a biobank for current use or for other future studies or collaborators.	Yes.	Hospitalized only.
STIMULATE-ICP: Symptoms, trajectory, inequalities and management: understanding long COVID to address and transform existing integrated care pathways	A programme of work focused on current long COVID care in the UK.	Mixed methods study of current long COVID care in the UK to evaluate trajectory of illness, cost and effectiveness. A cluster randomized trial, recruiting >4,500 people with long COVID, testing effectiveness of repurposed drugs by measuring the effects of 3 months of treatment, including symptoms, mental health and outcomes such as returning to work. It will also assess the use of MRI scans to help diagnose potential organ damage, as well as enhanced rehabilitation through an app to track their symptoms.	Adults.	Yes for those who had a test as part of routine care.	Non-hospitalized.
OpenPROMPT: Using OpenSAFELY and patient reported outcome measures from a smartphone app to quantify the health and economic costs of long COVID	To explore the health and economic impacts of long COVID for those who are not hospitalized.	Cohort study of participants recruited through the Airmid smartphone app, and then submitting health-related quality of life data through the app. Data will be linked to the OpenSAFELY data platform.	Adults in primary care, recruited through a smartphone app.	Yes for those who had a test as part of routine care.	Non-hospitalized.

CPRD, Clinical practice research datalink; RT-PCR, reverse transcription-polymerase chain reaction; CYP, children and young people; NICE, The National Institute for Health and Care Excellence; NHS, National Health Service; MRI, magnetic resonance imaging.

COVID-19 study (PHOSP-COVID) was the first such study, securing £8.4 million in July 2020 from UK Research and Innovation (UKRI), and aims to understand and improve long-term outcomes for people who survive hospitalization with COVID-19.

Another study that started early in the pandemic was the REACT programme, which was commissioned by the Department of Health and Social Care in April 2020. The REACT studies are nationally representative prevalence surveys of SARS-CoV-2 in the community in England. REACT was then extended to include REACT-long COVID (REACT-LC) in February 2021 via the National Institute for Health Research (NIHR) and UKRI funding. REACT-LC aims to characterize the genetic, biological, social and environmental determinants, and the corresponding inter-relationships, that underpin progression to long COVID, and to understand the natural history and long-term sequelae after SARS-CoV-2 infection. In early 2021, the NIHR and UKRI funded four research studies (totalling £18.5 million) to better understand and address longer-term effects of SARS-CoV-2 infection on physical and mental health. In summer 2021, NIHR funded a further 15 projects (totalling £19.6 million) to improve the diagnosis of long COVID, as well as treatment, rehabilitation and recovery.

From this cohort of funded projects, as well as other key national projects, nine major epidemiology-focused long COVID studies are currently running in the UK (see Fig. 1 and Table 1). These studies cover population epidemiology, symptomatology, phenotyping, operational definition, health impacts post-hospitalization, determinants, mechanisms and consequences of the long-term effects, and genetic, biological, social and environmental signatures and pathways. Researchers on these studies have formed the National Long COVID Research working group, to share key findings and promote rapid knowledge exchange and efficient timely research. Key outputs of the group are shared with the Chief Medical Officer for England. An example of this knowledge exchange in action is an open science repository platform⁸ that the National Long COVID working group has formed to collate and index the latest research on long COVID.

There are a wide range of outstanding research priorities, including defining long COVID, identifying its pathogenesis, describing its clinical presentation and health impacts, characterizing the longer-term burden and predictive risk factors and developing clinical interventions. The primary areas of knowledge that the

studies outlined in Table 1 will advance are: the prevalence and phenotyping of symptom clusters (TLC, CIS, CONVALESCENCE, REACT-LC and PHOSP-COVID; see Table 1 for full study names), identification of the short- and long-term mental and physical health sequelae of long COVID (TLC, CIS, CLoCk, PHOSP-COVID, CONVALESCENCE, REACT-LC, STIMULATE-ICP and OpenPROMPT), prevalence, phenotyping and operational research definition of long COVID in children and young people (CLoCk), the immunological causes and consequences of long COVID (TLC and REACT-LC), identifying mechanisms that underpin the development of long COVID (TLC, CONVALESCENCE and REACT-LC), and identifying and trialling potential therapies and interventions to treat and manage long COVID (TLC, PHOSP-COVID and STIMULATE-ICP). The CLoCk study is the largest study of long COVID specifically in children that we know of globally, uniquely uses child-reported symptoms, a control group and standardized measures, and is longitudinal and based on a national cohort.

A particular strength of several of the studies (TLC, CLoCk, CONVALESCENCE and the REACT cohort follow-up) is the use of control groups, which allows comparison of symptom profiles and burden in individuals with confirmed SARS-CoV-2 infection compared to those without infection who may experience symptoms due to comorbidities, and because some reported long-COVID symptoms are non-specific and prevalent in the general population⁹. There is a huge burden of ill health from long COVID in the UK and globally. People living with long COVID were the first to identify and describe long COVID¹⁰. The research community have joined patient researchers in their efforts to improve understanding of long COVID, including its symptoms, health impacts, pathophysiology and treatments. Patient and public involvement is a feature of all the studies described above, with research teams working with patient partners from diverse backgrounds, as well as engaging with national long-COVID support groups. Multidisciplinary research collaboration with patients at the core, as well as co-producing the research as equal partners, is crucial for developing a comprehensive approach to unraveling the complexity and heterogeneity of long COVID. This co-production will be fundamental in the development of targeted therapeutic approaches and to inform health service provision to meet the large unmet need from long COVID. □

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Author contributions

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Pseudonymization of healthcare data in South Korea

To the Editor — In many parts of the world, there is a growing interest in how best to utilize healthcare data while providing adequate privacy safeguards. Achieving this balance is both a technical matter and a regulatory and procedural matter. Recent experiences in South Korea have emphasized the role of pseudonymized personal information and provide useful insights for the rest of the world.

Korea's main data privacy law, the Personal Information Protection Act (PIPA), has a generally similar structure to the EU's General Data Protection Regulation (GDPR). The PIPA has been construed to impose a strong requirement for consent¹. In 2020, Korea amended the PIPA and introduced the concept of pseudonymized data². Under the amended Korean law, as in the GDPR³, pseudonymized data are still considered statutorily defined personal information. Unlike other types of personal information, however, pseudonymized data can be used without obtaining the data subjects' consent.

The use of pseudonymized data is limited to scientific research purposes, statistical purposes and archiving purposes in the public interest. The amended PIPA also introduced a scheme for the combination of pseudonymized data, which can be carried out by designated expert agencies⁴. Data combination could take place not only between datasets containing healthcare data but also between datasets containing healthcare data and other types of data.

With the PIPA amendment in place, Korea's Ministry of Health and Welfare, together with the Personal Information Protection Commission, issued a healthcare data guideline for utilizing healthcare data in January 2021. Separately, by late 2020,

Fig. 1 | An illustration of the utilization of pseudonymized and combined data. In this example, datasets held by two hospitals are pseudonymized and combined. Data combination takes place at an expert agency, and subsequent analysis can be conducted at this expert agency. If approved by the expert agency, the hospitals involved could extract the combined data to their research facilities for further analysis. IRB, institutional review board; DRB, data review board.

three agencies with expertise in healthcare data had been designated as expert agencies for the purpose of assessing the overall pseudonymization and data combination process, with more to be designated.

The Healthcare Data Guideline provides substantive as well as procedural safeguards applicable to the process of pseudonymizing healthcare data⁵. In terms of procedural safeguards, an important new concept was introduced: in order to utilize pseudonymized healthcare data, approval by a data review board (DRB) is now required. This is in addition to and separate from the existing requirement of institutional

review board (IRB) approval. IRBs already have an existing mandate to review issues related to data privacy, and this mandate remains in place. The additional, mandatory DRB reflects the growing significance of considering privacy when utilizing healthcare data.

When pseudonymizing healthcare data, different statistical and technical measures are needed depending on the categories of individual data elements: i.e., depending on whether they are identifiers, quasi-identifiers or other attributes. For identifiers, the basic principle is to delete them or to substitute them with serial