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The bidirectional complexity of multiple long-term conditions and Long COVID

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Long COVID is a heterogeneous complex condition diagnosed in people with ongoing symptoms at least 12 weeks after SARS-CoV-2 infection, and occurs irrespective of the acute illness severity. Long Covid is a patient derived term. There have been challenges in defining long COVID with a number of definitions both for research and clinical practice **(1)** which have not been universally agreed, with different terminologies being used in different settings including Post Covid Condition (PCC), Post Covid Syndrome (PCS), and Post Acute COVID-19 Sequelae (PACS). Furthermore, these definitions were only used in approximately one third of 295 studies published on long COVID. **(1)** The early definitions mostly use a temporal

criterion but without further clinical characteristics. The most recent definition includes the type of symptoms and newly emerged long-term conditions but does not include pre-existing conditions or severity of impact **(2**). A new report detailing all the health effects that constitute long COVID concludes that long COVID is a complex long-term condition that can result in more than 200 health effects across multiple body systems. These include a wide range of symptoms, but also new emerging long-term conditions such as heart disease, diabetes and kidney disease.**(3)**

Multiple organs can be involved and therefore long COVID is considered a complex multisystem disease and a risk factor for development of multiple long-term conditions (or multimorbidity). Multiple long-term conditions are defined as cooccurrence of at least two chronic conditions in the same individual**.(4)**There is a bidirectional association of long-COVID and multiple long-term conditions. Having multiple long-term conditions is a risk factor for developing long COVID and long COVID is associated with development of new long-term conditions.

A recent population-based longitudinal UK cohort study using data from 1,554,040 individuals with confirmed SARS-CoV-2 infection found that odds for long COVID increased in a multitude of pre-existing long-term conditions, including mental health conditions. **(5)** Another large database study found that a large number of comorbidities, including physical and mental health conditions, were associated with persistent symptoms at 12 weeks following SARS-Co-V2 infection.**(6)** Over 12 months follow up, in a propensity score-matched commercial insurance cohort, people with long COVID experienced two or more times increased risk of cardiac arrhythmias, ischemic stroke, coronary artery disease, heart failure, chronic obstructive pulmonary disease, and asthma and pulmonary embolism, compared to people who did not contract COVID-19.**(7)**

Multiple long-term conditions are highly prevalent and associated with individuals having reduced quality of life, increased psychological needs, greater healthcare needs and increased mortality. The prevalence of multiple long-term conditions is 14.8% in the general population and increases with age, with nearly a third of people aged over 60 years having multiple long-term conditions with cardiometabolic

diseases, depression, hypertension and osteoarthritis being the most prevalent.**(8)** A nationwide long COVID in Scotland Study reported a crude prevalence of 12.8% at 12 months. **(9)** Although this is similar to the prevalence of multiple long-term conditions, the new incidence of long-term conditions in long COVID occurs at a far younger age than normal.**(10)**Where multiple long-term conditions are more common in middle aged or elderly population and in deprived populations, the prevalence of long COVID in the working age group and in deprived populations and its impact on the workforce is concerningly high. Multiple long-term conditions and COVID-19 are also more prevalent in ethnic minority populations **(8, 11)**however, the studies on prevalence of long COVID have yielded mixed results, possibly due to translational and cultural issues.**(12)**

Similar to long COVID, there have been challenges in operationalizing the definition of multiple long-term conditions. One systematic review of 566 studies reported that the number of conditions included as a measure of multiple long-term conditions ranged from two to 285 (median 17 conditions).(13) In view of these large variations in reporting, a Delphi consensus study had agreement on 24 conditions to always include and 35 conditions to usually include in multiple long-term research and care. The consensus also had agreement that the included chronic conditions had to have persisted long-term (longer than 6-12 months), should be currently active, permanent in their effects, requiring current treatment in care or therapy, and requiring surveillance or relapsing conditions requiring ongoing care.**(14)**

Finally, both multiple long-term conditions and long COVID are challenging for health service delivery, both for primary and specialist care. Most international guidelines have service models and recommendations based on single diseases and there are potential similarities in the service models for both long COVID and multiple long-term conditions that include involvement of multidisciplinary teams in complex decision making. **(15)** However, once a long-term condition is diagnosed in long COVID, it is labelled as that long-term condition and not as long COVID. This poses a clinical problem as it does not take into account that other long-term conditions might already exist, that more may occur, and that the individual has long COVID with possibly a plethora of symptoms that need medical attention and management.

We suggest that for clinical services and management of long COVID, a clinical definition is needed incorporating a diagnostic classification with axes for a) current manifest long COVID symptoms and organ involvement, b) pre-existing long-term conditions, c) newly occurred long-term conditions, d) severity of impact. Identifying adults with Long Covid living with MLTC would direct healthcare services to facilitate clinical multidisciplinary teams to identify and address patient needs appropriately: an essential step towards an integrated care approach guided by complex decision making.

Conflict of interest

KK was Chair of the ethnicity subgroup of the UK Scientific Advisory Group for Emergencies (SAGE) and is a member of SAGE. KK is Director for Centre for Ethnic Health Research, University of Leicester, UK.

KK (Chair), AB and RAE are members of the National Long Covid Research Group that informs the CMO for England.

KK has acted as a consultant, speaker or received grants for investigator-initiated studies for Astra Zeneca, Bayer, Novo Nordisk, Sanofi-Aventis, Servier, Lilly and Merck Sharp & Dohme, Boehringer Ingelheim, Oramed Pharmaceuticals, Pfizer, Roche, Daiichi-Sankyo, Applied Therapeutics, Embecta and Nestle Health Science.

AB has acted as a consultant or speaker for Astra Zeneca, Pfizer and Shionogi and investigator-initiated studies from Astra Zeneca.

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