# Cardiometabolic syndrome — an emergent feature of Long COVID?

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Large-scale clinical studies on the post-infectious impacts of SARS-CoV-2 have suggested that patients who have recovered from acute infection have increased risk for cardiometabolic syndrome-associated morbidities such as diabetes, chronic kidney disease and heart failure. Initial studies have taken the first steps towards unravelling the molecular processes that may be driving these findings, including the role of immune and inflammatory factors, but a comprehensive aetiology remains unclear. Given that cardiometabolic syndrome progression in patients with Long COVID may pose a significant global health and economic burden post pandemic, there is an emergent need to identify therapeutic targets and treatment options.

SARS-CoV-2, the virus that causes COVID-19, has, in the two-and-a-half years since first reports of human infection, been estimated to have infected in excess of 200 million people, demonstrating an overall mortality rate of 2.5%[1]. Although rising levels of immunity, development of new therapies, and the rapid formulation and distribution of vaccines have greatly reduced the death rate from COVID-19, disease burden has remained high in part owing to the emergence of several highly transmissible variant strains of SARS-CoV-2 (REF.[1]). Furthermore, as growing proportions of the population recover from acute infection, COVID-19 has proven to cause a persistent symptomology that can last from weeks to years. Colloquially referred to as 'Long COVID' or 'post-acute sequelae of SARS-CoV-2 infection', this syndrome of persistent symptomology has been found to affect up to 60% of individuals who have recovered from acute infection[1]. Given the continued spread of SARS-CoV-2 variants and the vast number of individuals who contracted the initial pandemic strains, it is likely that millions of people worldwide will be impacted by the long-term consequences of this pandemic[1].

## Long COVID

Early investigations into Long COVID showed that the condition has a very heterogeneous clinical presentation, with renal, pulmonary, cardiovascular, gastrointestinal, neuroaffective and/or cognitive manifestations being reported[1]. In an effort to better define the phenomenon, studies utilizing massive clinical datasets have leveraged population-scale metrics to ascertain which disease manifestations have a clear linkage to prior SARS-CoV-2 infection. Some of the best examples of the use of such large-scale data can be seen in a recent series of studies that looked to define the post-infection sequelae of SARS-CoV-2 through analysis of the US Department of Veterans Affairs electronic health database[2–5]. With access to the health records of nearly five million patients, which included more than 70,000 patients who had been previously infected with SARS-CoV-2, the authors were able to compare medical resource usage and mortality rates in those with previous SARS-CoV-2 infection against non-infected patients or a separate group of patients who were documented as being recently recovered from influenza virus infection[3].

These efforts demonstrated an increased use of medical resources and higher mortality rates among the SARS-CoV-2 recovered group compared with the other cohorts. The disease manifestations reported among patients with previous SARS-CoV-2 infection included an array of symptomologies encompassing nearly every organ system and represented much of the previously reported Long COVID literature in the inclusion of increased neurobehavioral, cognitive, gastrointestinal, renal, pulmonary and cardiovascular abnormalities[3]. Among the many complications associated with Long COVID, cardiometabolic syndrome (CMS)-associated manifestations were some of the most prevalent[2–5].

## Cardiometabolic syndrome and COVID-19

CMS is a group of interacting clinical abnormalities that often develop into diabetes, cardiovascular diseases and chronic renal failure — complications that show increased likelihoods ranging from 40% (diabetes) to 200% (end-stage kidney disease) among individuals previously infected with SARS-CoV-2 (REFS[2–6]). CMS is defined by increased central adiposity, triglycerides, blood pressure and fasting glucose metrics, as well as reduced levels of high-density lipoprotein (HDL)-cholesterol[6]. The syndrome also often presents concomitantly with increased inflammation, endothelial

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dysfunction, microalbuminuria, coagulation abnormalities and dysfunction of the renin–angiotensin–aldosterone system, which regulates blood pressure and fluid balance. Although the specific mechanisms by which these risk factors contribute to CMS are generally unclear, substantial evidence has implicated impaired insulin signalling as a core mediator of the disease process[6].

Interestingly, many of the hallmark signs of CMS are shared risk factors for enhanced SARS-CoV-2-associated disease. Obesity, diabetes and hypertension — all of which are end-stage disease products of CMS — are also strong predictors of COVID-19-induced hospitalization[1–5]. Moreover, studies of SARS-CoV-2 pathogenesis have shown that SARS-CoV-2 and the systemic inflammatory response that it induces are able to dysregulate many of the pathways implicated in cardiometabolic disease. Despite being largely confined to the airways, SARS-CoV-2 infection results in extensive chemokine expression and the production of inflammatory viral RNA, prior to inducing death of host cells[7]. Infiltrating and resident immune cells detect this viral material and release additional proinflammatory cytokines that enter the circulation, generating a unique response in all tissues thereafter[1,7].

One example of how this can contribute to cardiometabolic dysregulation has been demonstrated in the pancreas. Here, the presence of viral RNA has been observed in islet cells concomitant with cellular release of cytokines and chemokines. Notably, these proinflammatory signals accompany decreased pancreatic release of insulin and a noted transdifferentiation of insulin-producing pancreatic β-cells — mimicking the pathological changes that are seen during diabetes development[8]. So far, it is still unclear to what extent this phenotype is driven by direct viral infection of pancreatic islet cells or by a cellular response to circulating cytokines and/or viral RNA.

Altered insulin signalling has also been demonstrated to occur in adipocytes during SARS-CoV-2 infection. Similar to observations in the pancreas, viral RNA could be readily detected in adipose tissues. This occurred in conjunction with increased levels of insulin resistance and altered signalling of pathways downstream of adiponectin, a hormone that regulates insulin sensitivity[9]. These data provide further mechanistic insight into how SARS-CoV-2 infection can cause systemic insulin dysregulation and thus potentially contribute to CMS progression[7–9].

A similar phenomenon is also observed for cardiovascular abnormalities present following acute SARS-CoV-2 infection. SARS-CoV-2 viral material has been detected in a subset of cardiac tissue from individuals who died from COVID-19, a result that can be phenocopied in the hamster model[10]. In response to infection with SARS-CoV-2, cardiomyocyte-mediated chemokine induction results in the infiltration of monocytes and other mononuclear cells, culminating in damage to the cardiac tissue[10].

Together, these studies show that SARS-CoV-2 and the inflammatory environment it creates have a distinct ability to dysregulate processes and organs involved in cardiometabolic homeostasis, and that in individuals who already have alterations to these processes, COVID-19 is likely to exacerbate pathological abnormalities.

Currently, it remains unclear whether the Long COVID-linked increase in CMS-associated diseases is a result of damage to associated tissues during acute infection or an indirect response to the sustained inflammation thought to be a key player in Long COVID progression. In both cases, it is likely that virus-mediated immune dysregulation has a key role in pathogenesis. Whatever the cause, CMS-associated diseases are expected to represent a significant burden on the human population, and they should thus be recognized as a distinct and emergent feature of Long COVID[2–5].

Given these data suggesting that SARS-CoV-2 infection is a risk factor for persistent symptomology and CMS progression, it would seem prudent to continue public health interventions to abrogate viral transmission. Furthermore, as the world now grapples with how to address the rapidly rising number of patients with Long COVID, it is important to prepare our health systems for an increased incidence of CMS-associated diseases over the coming months and years. This looming public health crisis will demand expansion of both health service and social service capabilities, as the necessary medical attention and reduced work capacity may be significant. In addition, there is a crucial need for more research into the specific mechanistic drivers of CMS progression in patients with COVID-19, both during active infection and following viral clearance. This will inevitably demand further elucidation of the role of immune and inflammatory factors in these processes. Identification and therapeutic targeting of the pathological processes driving this biology will be imperative for developing appropriate care regimens for both patients with Long COVID and patients with CMS-associated diseases moving forward.


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**Competing interests**
The authors declare no competing interests.