Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

Diabetes after SARS-CoV-2 infection

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The COVID-19 global pandemic represents a unique opportunity to better understand the post-viral and post-infectious condition. More than 2 years into the pandemic, a large body of evidence makes it clear that infection with SARS-CoV-2 can lead to post-acute sequelae in the pulmonary and broad array of extrapulmonary organ systems—collectively referred to by the umbrella term of long COVID.[1,2] Evidence also suggests that the myriad clinical abnormalities of long COVID might extend to new onset diabetes.[3]

A US Center of Disease Control (CDC) analysis of a large electronic health-care database of 353 164 adults with COVID-19 and 1 640 776 controls with no evidence of infection, suggested that people with COVID-19 had an increased risk of new onset type 1 diabetes and type 2 diabetes.[4] Furthermore, a German cohort study of 35 865 people with COVID-19 showed higher risk of newly diagnosed type 2 diabetes than an equal number of matched controls with acute upper respiratory tract infections.[5]

I also investigated whether there was an association between new-onset diabetes and COVID-19. Together with my colleague Yan Xie, we used data from the US Department of Veterans Affairs to characterise the risk and 12-month burden of diabetes in 181 280 people with SARS-CoV-2 infection versus two control groups: 4 118 441 contemporary controls who were enrolled during the same time but did not get infected with SARS-CoV-2 and 4 286 911 historical controls from before the pandemic.[3] Our findings suggested that compared with both the contemporary and historical controls, people with SARS-CoV-2 had increased risk of incident diabetes and incident use of antihyperglycemic therapy in the post-acute phase.[3] Interestingly, compared with non-infected controls, the increased risk of diabetes (>99% was type 2 diabetes) was evident even in people who had very low baseline (pre-COVID-19) risk of diabetes according to traditional risk factors including age, race, sex, body-mass index, hypertension, and hyperlipidaemia). Among people with COVID-19, the risk of diabetes increased in a graded fashion according to baseline risk of diabetes (ie, the traditional baseline characteristics that predict the risk of developing diabetes in an individual). The main limitation of our study was that the participants were mostly White males. Our findings, along with the findings of others, suggest the possible coexistence of two pathways that should be investigated in mechanistic studies: (1) COVID-19 leading to de novo disease in people who might have otherwise not developed diabetes, and (2) COVID-19 as an amplifier of baseline risks and accelerant of disease development.

Due to paucity of studies, the evidence base of new onset diabetes following COVID-19 in children is far less well developed. In an analysis of two large health-care databases, researchers from the US CDC suggested that, compared with non-infected controls, people younger than 18 years with SARS-CoV-2 infection had increased risk of a diabetes diagnosis in the post-acute phase of COVID-19; they also showed that COVID-19 was associated with higher risk of diabetes than pre-pandemic acute respiratory infections and that non–SARS-CoV-2 respiratory infection was not associated with an increased risk for diabetes.[6] However, this study did not differentiate between type 1 and type 2 diabetes.

The evidence for increased risk of diabetes after SARS-CoV-2 infection is not universally consistent. A Scottish study in people younger than 35 years documented a 20% increase in the incidence of type 1 diabetes during the pandemic in general, and increased risk of type 1 diabetes within, but not beyond, the first 30 days of SARS-CoV-2 infection.[7] Another study of 428 650 people (median age 35 years) with COVID-19 and matched controls showed a net increase in incidence of diabetes in the first 4 weeks after COVID-19, which remained elevated from 5 to 12 weeks but not from 13 to 52 weeks.[8]

Most of these studies on COVID-19 and diabetes were conducted before vaccines were available and when reinfections were uncommon. However, recent evidence from a US Department of Veterans Affairs study involving more than 13 million individuals suggests that compared with non-infected controls, both unvaccinated and vaccinated individuals with SARS-CoV-2 infection are at increased risk of diabetes and that the risk of diabetes in the post-acute phase of COVID-19 was not significantly different in people who had a SARS-CoV-2 infection after vaccination than unvaccinated individuals.[9] A new study of more than 5 million people (also from the US Department

of Veterans Affairs) suggests that reinfections with SARS-CoV-2 (compared with no reinfection) could contribute additional risks of acute and post-acute sequelae including increased risk of diabetes in both phases of the disease.[10]

A major methodological challenge in studying the post-acute and long-term health effects of SARS-CoV-2 infection—and a main reason for the discordance in evidence—is how to best disentangle the causal effects of the infection itself from other changes that might relate to both exposure and outcomes. For example, increased health-care use following SARS-CoV-2 infection and changes due to the pandemic itself (without SARS-CoV-2 infection) including effects of lockdowns, social isolation, loss of employment, and other factors that might have differentially affected people with SARS-CoV-2 infection might influence the risk of health outcomes (including diabetes). Although, for obvious ethical reasons, randomly exposing people to SARS-CoV-2 versus placebo is not possible, leveraging large-scale observational data and advances in causal inference methodologies to emulate a target trial are indeed feasible and should be actively pursued. The target trial emulation approach might be especially helpful to approximate—by design—a matched comparison between people with COVID-19 and non-infected controls, and estimate the causal effects of COVID-19 exposure. A trial emulation approach would first specify the causal question and lay out the protocol components of the ideal randomised trial that—if conducted—would randomise exposure and answer the causal question. This step would be then followed by specification of the emulation strategy including specification of the target population, eligibility (inclusion and exclusion) criteria, follow up, outcome, causal estimate, and a detailed analysis plan to estimate the causal contrast of interest. Although conceptualisation of an infection as a treatment in a randomised controlled trial might be perceived as unusual, the target trial emulation approach will further elevate the scientific rigor of large epidemiological analyses and enhance the ability to infer the causal long-term health effects of SARS-CoV-2 infection. Additionally, prospective controlled studies with detailed assessment of pre-COVID-19 health status and protocolised longitudinal health assessments are also useful to characterise the health trajectories of people with SARS-CoV-2 infection. Although, these studies might be less powered because they generally include far fewer participants than large observational studies.

Robust research agendas to better understand long COVID (and all its components including the increased risk of diabetes), prevent it, and treat it are urgently needed. Several pressing strategic considerations and research questions will need to be answered in the near future (panel).

Panel: **Strategic considerations and urgent research priorities to address knowledge gaps in long COVID and more broadly infection-associated chronic illnesses**

Strategic considerations for governments to address the challenge of long COVID and to prepare for future pandemics

- Prioritise research funding of post-viral and infection-associated chronic illnesses
- Investment in real-world data systems that integrate a broad array of data sources and leverage advanced methodologies in causal inference is needed to address in near real-time major knowledge gaps and to devise public health policies
- Surveillance systems for infectious diseases must incorporate longitudinal surveillance with appropriate controls to monitor for development of post-acute and chronic sequelae

Urgent research priorities

- Experimental studies to elucidate the biological mechanisms of diabetes following SARS-CoV-2 infection and other viral infections
- Large well-powered prospective cohort studies with carefully curated controls, adaptive design (to dynamically adapt to the changes in the pandemic) and robust assessment of health status at regular time intervals after infection
- Studies integrating both protocolised prospective collection of health information and routinely collected health data (eg, from wearable health trackers, electronic health records, and other data sources)
- Studies evaluating genetic, environmental, and other susceptibility factors of post-viral disease (including risk of diabetes after SARS-CoV-2 infection)
- Studies with both historical controls (pre-pandemic era) and contemporary (pandemic era) controls that disentangle the effects of the pandemic (effects of lockdowns and behavioural, environmental, and other changes) from those of SARS-CoV-2 infection on the epidemiology of diabetes
- Long-term comparative analyses of the risks of diabetes following SARS-CoV-2 versus other viral infections (eg, seasonal influenza) would help contextualise the risk of diabetes following SARS-CoV-2 within the broader post-viral condition
- Longitudinal studies to understand health trajectories and outcomes of people with diabetes following COVID-19, including response to treatment, health resource use, and downstream health outcomes
- Studies looking at whether antivirals or other therapeutics during the acute or post-acute phase of COVID-19 reduce the risk of diabetes (or other post-acute sequelae)
- Longer term studies to determine if diabetes and other cardiometabolic sequelae in people with COVID-19 might remit with time or whether they morph into chronic conditions
- Studies evaluating the effect of SARS-CoV-2 variants (and subvariants) and new vaccines and boosters as well as the effect of repeated infections on the epidemiology on post-acute sequelae including diabetes
- The effect of new onset diabetes (and other chronic diseases) on health systems, the economy, and society at large

The broad implications of SARS-CoV-2 infection on human health are becoming increasingly clear. Before the pandemic, the global burden of diabetes was high and rising; the possible increased incidence of diabetes due to the pandemic could further compound the already staggering pre-pandemic burden. In turn, this could lead to substantial ramifications on health systems, health-care costs, life expectancy and economic indicators such as employment and labour participation. More broadly, the multifaceted long-term consequences of SARS-CoV-2 infection (including the risk of diabetes) should be reflected in the global discussion about non-communicable diseases.

Long after the pandemic ends (and we must admit that it has not yet ended), millions of people around the world will still bear its scars. Chronic conditions, including diabetes, require lifelong care and can affect people's lives, livelihood, the economy, and societal wellbeing. A silverlining of this pandemic is the opportunity to more broadly understand the post-viral condition, which has been marginalised and understudied for more than a century. Long COVID, including the possible burden of diabetes, must be further investigated, understood and considered in every health-care and health policy decision we make now and going forward.

I declare no competing interests.

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