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Rising diabetes diagnosis in long COVID

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A few reports have raised the possibility that COVID-19 could increase the risk of type 2 diabetes.[1,2] In *The Lancet Diabetes & Endocrinology,* Xie and Al-Aly[3] offer further evidence for the increased risk of diabetes beyond the first 30 days of infection (post-acute phase) by analysing the US Department of Veterans Affairs national health-care records of those who survived the first 30 days after a positive COVID-19 test. These data raise important questions about the relationship between COVID-19 and diabetes concerning causality, biological mechanisms, and implications for clinical care and public health.

Incidence of diabetes and antihyperglycaemic medication use was compared between 181 280 COVID-19 survivors, 4 118 441 contemporary controls without COVID-19 infection from the same year, and 4 286 911 historical controls from 2017. Diabetes was defined by International Classification of Diseases-10 diagnosis codes or an HbA_{1c} of more than 6·4% (46 mmol/mol). The authors used inverse probability weighted survival analyses, including predefined and algorithmically selected high dimensional variables and reported two measures of risk; hazard ratio (HR) and burden per 1000 people at 12 months.

People who survived the first 30 days of SARS-CoV-2 infection exhibited an increased risk (hazard ratio [HR] 1·40, 95% CI 1·36–1·44) and excess burden (13·46, 95% CI 12·11–14·84) of incident diabetes per 1000 people at 12 months, compared with contemporary controls. COVID-19 survivors also had an increased risk (HR 1·85, 95% CI 1·78–1·92) and excess burden (12·35, 11·36–13·38) of incident antihyperglycaemic use. Results were consistent when historical controls were used. The association between COVID-19 and diabetes was consistent across strata of several potential confounders, namely, age, sex, race, BMI, diabetes risk score, steroid use, and area deprivation scores. The authors also did a full range of sensitivity analyses, including accounting for missing data with multiple imputation. Furthermore, an exposure–response relationship between severity of the acute infection, as shown by the care setting (non-hospitalised, hospitalised, or admitted to intensive care), and diabetes incidence was found. Notably, even those with mild, non-hospitalised COVID-19 had an excess 1-year burden of 8·28 per 1000 persons (95% CI 6·97–9·62). However, a major weaknesses of the study is the inclusion of a study population that was predominantly White and male. Furthermore, socioeconomic factors imposed by COVID-19 were not taken into account and there was no assessment for differential diabetes testing between cases and controls. Nevertheless, these data warrant further multipronged investigations.

Carefully designed multi-ethnic prospective epidemiological studies of long-term COVID-19 consequences (eg, incidence of diabetes types and associated conditions) across demographic and socioeconomic factors are needed to confirm or refute the findings from Xie and Al-Aly.[3] Studies should use standardised approaches to accurately measure exposure to SARS-CoV-2 infection (eg, antigen and antibody tests) and diabetes (eg, using oral glucose tolerance tests). Factors postulated to influence long-term complications of COVID-19 should also be measured, including severity of infection, viral load, and the presence of antibodies signalling auto-immune attack.[4] Variables that might help explain potential mechanisms for any association between COVID and diabetes should also be collected (eg, multiple point insulins, C-peptides, pancreatic and hepatic ectopic fat, and body composition), as well as co-occurring conditions, such as cardiovascular events,[5] that could share disease mechanisms with diabetes pathogenesis. Studies should examine the extent that biological effects of SARS-CoV-2 infection are specific to diabetes or generalised by similar mechanisms across multiple systems.

Mechanistic studies will also be needed to explore the SARS-CoV-2 and diabetes connection. Among the most intriguing of hypotheses to explain the COVID-19 and diabetes connection is that SARS-CoV-2 virus might infect and replicate in the pancreas, injuring exocrine and endocrine cells.[6,7] Analysis of autopsy samples suggests that COVID-19 infection could lead to beta cell transdifferentiation mediated by the eIF2 signalling pathway.[8] Other potential mechanisms, which the authors mention, are also worthy of investigation, including autonomic dysfunction, immune response or induced autoimmunity, and low grade inflammation.[3] All of these factors should be considered within a

real-world context of preadmission diabetes, steroid-induced diabetes, and sources of stress hyperglycaemia.[9]

The data presented by Xie and Al-Aly[3] have major implications for clinical policy and public health. If COVID-19 is indeed a risk factor for diabetes in the post-acute phase of infection, screening and management of dysglycaemia should be an integral part of clinical guidelines for COVID-19 diagnosis and follow-up. The long-term implications of SARS-CoV-2 infection increasing diabetes risk are profound. The rates of type 2 diabetes, and associated non-communicable diseases, are already growing, as shown on the diabetes atlas by the International Diabetes Federation. With large and growing numbers of people worldwide infected with SARS-CoV-2 (434 154 739 cumulative cases by Feb 28, 2022),[10] any COVID-19-related increases in diabetes incidence could lead to unprecedented cases of diabetes worldwide—wreaking havoc on already over-stretched and under-resourced clinical and public health systems globally, with devastating tolls in terms of deaths and suffering.

The potential connection between COVID-19 and diabetes highlights that infectious diseases (eg, SARS-CoV-2) and chronic diseases (eg, diabetes) cannot be viewed in siloes. When we emerge out of the pandemic, the much-neglected non-communicable diseases, such as type 2 diabetes, will continue their relentless trajectory, possibly in an accelerated manner, as the leading burdens of global health.

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1 Barrett CE, Koyama AK, Alvarez P, et al. Risk for newly diagnosed diabetes >30 days after SARS-CoV-2 infection among persons aged <18 Years—United States, March 1, 2020–June 28, 2021. *MMWR Morb Mortal Wkly Rep* 2022; **71:** 59–65.
2 Montefusco L, Ben Nasr M, D'Addio F, et al. Acute and long-term disruption of glycometabolic control after SARS-CoV-2 infection. *Nat Metab* 2021; **3:** 774–85.
3 Xie Y, Al-Aly Z. Risks and burdens of incident diabetes in long COVID: a cohort study. *Lancet Diabetes Endocrinol* 2022; published online March 21. https://doi.org/10.1016/S2213-8587(22)00044-4.
4 Su Y, Yuan D, Chen DG, et al. Multiple early factors anticipate post-acute COVID-19 sequelae. *Cell* 2022; published online Jan 25. https://doi.org/10.1016/j.cell.2022.01.014.
5 Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. *Nat Med* 2022; published online Feb 7. https://doi.org/10.1038/s41591-022-01689-3.
6 Müller JA, Groß R, Conzelmann C, et al. SARS-CoV-2 infects and replicates in cells of the human endocrine and exocrine pancreas. *Nat Metab* 2021; **3:** 149–65.
7 van der Heide V, Jangra S, Cohen P, et al. Limited extent and consequences of pancreatic SARS-CoV-2 infection. *Cell Rep* 2022; **38:** 110508.
8 Tang X, Uhl S, Zhang T, et al. SARS-CoV-2 infection induces beta cell transdifferentiation. *Cell Metab* 2021; **33:** 1577–91.
9 Khunti K, Del Prato S, Mathieu C, Kahn SE, Gabbay RA, Buse JB. COVID-19, hyperglycemia, and new-onset diabetes. *Diabetes Care* 2021; **44:** 2645–55.
10 WHO. WHO coronavirus (COVID-19) dashboard. https://covid19.who.int/ (accessed Feb 15, 2022).

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Levothyroxine treatment in euthyroid women positive for thyroid peroxidase antibodies and recurrent pregnancy loss

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Miscarriage matters. For couples who have a miscarriage, it is a devastating experience with major physical and psychological consequences that are often under—estimated or even trivialised.[1] Combined with the major health-economic effect on a population level, this makes research into miscarriage prevention and care a high priority.[1,2] Both the individual and population-based consequences of miscarriage are magnified for the approximate 2% of all women trying to conceive who have recurrent pregnancy losses. There are no proven effective preventative interventions for women with recurrent pregnancy losses;[2] this can often lead to a no other option scenario in which treatments are started despite an absence of or scarce evidence for their efficacy. Of the known risk factors for miscarriage is seropositivity for thyroperoxidase antibodies (TPO-Abs), which has been associated with a 1·85–4-times higher risk of recurrent miscarriage, even in women who are euthyroid.[3] TPO-Abs are clinically non-functioning IgG antibodies that reflect thyroid autoimmunity used for diagnosing autoimmune hypothyroidism. It has been hypothesised that the underlying mechanism for the higher risk of miscarriage could be either a relative thyroid hormone shortage,