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Commentary

Risk of Diabetes Following COVID-19: Translating Evidence Into Clinical and Public Health Actions

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Over the course of the COVID-19 pandemic, epidemiological investigations have explored the risk of various medical conditions following the acute phase of the COVID-19 infection. Although variable definitions and terms have been proposed, this cluster of conditions—encompassing mental health, neurological, metabolic, cardiorespiratory, gastrointestinal, musculoskeletal, coagulative, renal, and dermatological disorders—is commonly referred to as "post-acute sequelae of SARS-CoV-2 infection" or "long-COVID" syndrome (1).

Several studies have reported an increased risk of diabetes, a finding recently confirmed in the investigation of Xie et al (2). In this study, the authors quantified the relative and absolute risk of diabetes in a cohort built using the electronic health records from the U.S. Department of Veterans Affairs: in approximately 4.5 million people without diabetes, the rate of incident diabetes (based on ICD codes or HbA1c) over a median follow-up period of 1 year was, on average, 40% higher in 181 280 people diagnosed with COVID-19 between March 2020 and September 2021 and alive 1 month after the diagnosis than in people without COVID-19 identified in an isotemporal cohort; the rate was 85% higher if the outcome was based on use of a glucose-lowering medication and 46% higher for the composite outcome including either diabetes or use of a glucose-lowering medication. These relative estimates translated into absolute risk differences at 12 months of 13 more people with diabetes per 1000 people (48 and 35 people with incident diabetes in the group with and without COVID-19, respectively), 12 more people using of a glucose-lowering medication (27 and 15), and 18 more people with the composite outcome (58 and 40); the results were similar when a historical cohort (March 2018 to September 2019) was considered as control group: 12, 14, and 18 more people, respectively. Furthermore, the absolute risk difference was progressively higher according to the severity of the COVID-19 infection: compared with the people in the isotemporal cohort, there were 10, 74, and 144 more people with the composite outcome per 1000 nonhospitalized, hospitalized, and intensive care patients, respectively.

As several characteristics associated with the risk of diabetes differ in people with and without COVID-19, to estimate the causal association the authors accounted for confounding using one of the propensity score approaches—the inverse probability weighting—while conducting also numerous analyses to assess the robustness of their findings, including: different cohort definitions or confounding adjustment; missing data imputation; modeling the number of HbA1c measurements during the follow-up (as the surveillance may differ following a diagnosis of COVID-19); and—notably—using both positive (association between COVID-19 and death is expected and was confirmed) and negative (associations between COVID-19 and hearing aid use or acne are not expected and were not observed) outcome controls.

Although the results across all analyses indicated an increased risk of diabetes and aligned with similar previous observations in smaller cohorts with shorter follow-up periods, the persistence of confounding (and other) bias should still be carefully considered, particularly in the context of electronic health records as they pose important challenges related to the quality of the recorded data (nonsystematic collection of information not for research purpose) and to the pre-analytical data processing (3). These biases might have contributed to the large variation in the relative risk of the composite outcome in the 9 sensitivity analyses—from a 20% to a 74% increase in people with COVID-19—making a quantitative interpretation difficult, given the effects of such a variation on the absolute risk. Any decision around alternative screening strategies for diabetes following COVID-19 should primarily account for the individual risk of developing diabetes, which is related to both the pre-infection risk of diabetes and the relative risk of diabetes associated with COVID-19. Moreover, from a public health perspective, the 12-month absolute risk difference in nonhospitalized people was, on average, 10 more people with the composite outcome per 1000 people; using England as an exemplar, the total number of first SARS-CoV-2 infection between June 6, 2021 and June 6 2022, has been 13 772 059 (4): assuming that none of the infections resulted in hospital admission, the

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expected number of extra diabetes diagnosis until June 2023 would be around 138 000 (or greater if accounting for hospitalization). Although breakthrough SARS-CoV-2 infections appear to be associated with a lower risk of long-COVID complications in people vaccinated compared with the infections in those not vaccinated (5), this figure still seems a large overestimation, particularly when contrasted to the average number of new cases of (diagnosed and undiagnosed) diabetes in England during the pre-pandemic years: 55 600 per year between 2015 and 2019 (6). Therefore, differences within and between countries in the epidemiology of COVID-19 and diabetes make these results difficult to translate into actionable information to guide country-specific policies for people with long-COVID.

The results of the study of Xie et al. represent an important step forward in our understanding of the risk of diabetes in the long-COVID syndrome. Whether COVID-19 is the cause of an increased risk of diabetes, however, should be further investigated, as the mechanisms remain unclear and may include previously undiagnosed diabetes, stress hyperglycemia, drug-induced hyperglycemia, or direct or indirect effects of SARS-CoV-2 infection on the pancreatic beta cells (7). Large, prospectively planned observational studies, with standardized procedures for data collection—particularly phenotypical details to differentiate among type 1, type 2, and other forms of diabetes, given their different pathophysiology and the high risk of misclassification in electronic health records—and with longer follow-up periods, as recent data have suggested the transient nature of diabetes in patients with COVID-19 (8), are required. In parallel, similar observational studies investigating the risk of diabetes following other viral infections (i.e., influenza) may further help understand the link between COVID-19 and diabetes. Besides the crucial etiological questions, monitoring the new cases of diabetes during the next years would be instrumental to dynamically guide possible policy changes aiming at identifying diabetes earlier in the disease trajectory and potentially reduce its complications.

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Data Availability

Not applicable.

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