Association of COVID-19 with diabetes: a systematic review and meta-analysis

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Emerging evidence suggests that coronavirus disease-2019 (COVID-19) may lead to a wide range of post-acute sequelae outcomes, including new onset of diabetes. The aim of this meta-analysis was to estimate the incidence of newly diagnosed diabetes in survivors of COVID-19. We searched MEDLINE, Scopus, Cochrane Central Register of Controlled Trials and the World Health Organization Global Literature on Coronavirus Disease and clinical trial registries for studies reporting the association of COVID-19 and diabetes. Search dates were December 2019–October 16, 2022. Two investigators independently assessed studies for inclusion. Risk of bias was assessed using the Newcastle–Ottawa Scale. We estimated the effect of COVID-19 on incident diabetes by random-effects meta-analyses using the generic inverse variance method. We identified 8 eligible studies consisting of 4,270,747 COVID-19 patients and 43,203,759 controls. Median age was 43 years (interquartile range, IQR 35–49), and 50% were female. COVID-19 was associated with a 66% higher risk of incident diabetes (risk ratio, 1.66; 95% CI 1.38; 2.00). The risk was not modified by age, sex, or study quality. The median risk of bias assessment was 7. In this systematic review and meta-analysis, COVID-19 was associated with higher risk for developing new onset diabetes among survivors. Active monitoring of glucose dysregulation after recovery from severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection is warranted.

Methods

This study is being reported following Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) 2020. This study was deemed exempt by the Penn State Institutional Review Board.

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Data sources and searches. We searched MEDLINE, Scopus, Cochrane Central Register of Controlled Trials and the World Health Organization Global Literature on Coronavirus Disease and clinical trial registries for studies reporting the association of COVID-19 and diabetes without language restriction. Search dates were December 2019–October 16, 2022. The following Medical Subject Headings and keyword search terms were used: ['diabetes' OR type 2 diabetes OR type 1 diabetes OR ‘type 1 diabetes mellitus’ OR ‘type 2 diabetes mellitus’ OR ‘diabetes mellitus'] AND ['SARS-CoV-2' OR 'COVID-19' OR ‘severe acute respiratory syndrome coronavirus-2’ OR ‘coronavirus disease 2019’].

Study selection. Participant (P) Exposure (E) Comparator [C], Outcome (O) Study type (S) [PECOS] criteria was used to select studies12:

Participants Persons of all ages and sex included in studies that investigated incident diabetes in survivors of COVID-19.

Exposure COVID-19.

Comparison Non-COVID-19 group.

Outcome of interest Diabetes.

Study type Observational studies.

Pairs of independent investigators (YZ and DMB) screened the titles and abstracts of all citations and screened the full-text version of eligible studies. Disagreements in the included papers were resolved by discussion and if necessary, a third investigator (PS) was consulted.

Data extraction and quality assessment. Two investigators (YZ and DMB) worked independently to extract study the following date: authors, publication year, country of the study, study design, study-level descriptive statistics (mean (SD)/median (IQR) age in years, proportion (%) female), sample size, number with diabetes, number with COVID-19, outcome assessment, follow-up time, number of controls, risk ratio and 95% confidence interval. Newcastle–Ottawa Scale for observational studies was used to evaluate the risk of bias13. Studies with fewer than 5 stars were considered low quality; 5 to 7 stars, moderate quality; and more than 7 stars, high quality.

Data synthesis and analysis. The primary outcome was incident diabetes in survivors of COVID-19. For studies without measures of associations, a generalized linear mixed model was used to calculate the RR using the number of events and the sample size of each study group14. One study Barret et al. (2022) used two different national databases and reported separate results. Therefore, in this circumstance, we separated the effect estimates from Barret et al. study into two studies as one with IQVIA database and the second one with HealthVerity9. A study by McKeigure and colleagues reported two separate RRs for diabetes associated with COVID-19 at various time points, therefore, a fixed-effects model was utilized to pool the estimate within the study before conducting the random-effect meta-analysis. The pooled RR estimate for diabetes risk from each study was weighted by the inverse of its variance (inter-study plus intra-study variances). Pooled inter-study variance (heterogeneity) was estimated by DerSimonian and Laird (DL) random-effects method15. Heterogeneity among studies was evaluated using Cochran’s Q and the I² indicator expressed as percent low (25%), moderate (50%), and high (75%)16. Egger’s linear regression and Begg’s rank tests were employed to quantitatively evaluate publication bias17,18 and qualitatively with funnel plots. Statistical significance was set at p < 0.05. All statistical analyses were performed with R software version 3.6.2 (R Foundation for Statistical Computing, Vienna, Austria) using Metafor R packages.

Results

Identified studies. Figure 1 summarizes study selection process. A total of 853 studies were screened. The exclusion process yielded 8 studies3,5,9,19–23 conducted in 3 countries. Barret et al. was reported in this meta-analysis as two independent studies3. The baseline characteristics of the studies included in the systematic review are presented in Table 1. Included studies consisted of patients 47,474,506 participants, with median age of 43 years (IQR 35–49), and 50% were female. The median study quality was 7 (range 5–9).

Association of COVID-19 and incident diabetes. Of the 8 studies that characterized the risk of incident diabetes among survivors of COVID-19, the pooled point estimates was 1.66 (95% CI 1.38; 2.00, Fig. 2), implying a 66% higher risk of diabetes. The between-study variation was high ($I^2 = 94$, p < 0.0001). The risk was not modified by age, sex and study quality (Supplemental Table 1). However, when studies were stratified by geographic region, the risk was higher in studies from the United States 1.77 (95% CI 1.41; 2.22, Fig. 3), compared to those in Europe 1.33 (95% CI 1.14; 1.56).

Publication bias and study heterogeneity. Funnel plot of the included studies (Fig. 4) indicated asymmetry suggesting lack of publication bias. Quantitative analysis of publication bias with Egger’s test ($p = 0.053$) and Begg’s test ($p = 0.06$) were non-significant. Duval and Tweedie’s trim and fill test was conducted to balance the funnel plots and adjust for potential publication bias14. The analysis showed that if publication bias existed, 2 additional studies will be needed to eliminate bias and the overall effect of COVID-19 on incident diabetes changed from 1.66 (95% CI 1.38; 2.00 to 1.51 (1.21; 1.88, Fig. 5). Next, we performed influence sensitivity analyses by excluding and replacing one study at a time from the meta-analysis and calculated the RR for the remaining studies25. No substantial change from any of the pooled RR was observed when other studies were removed.
in turn, indicating that no individual study had a considerable influence on the pooled estimate. The plots for the analysis estimates are provided in Fig. 6.

Discussion

Principal findings. In this systematic review and meta-analysis of 8 cohort studies including over 47 million participants, COVID-19 was associated with a 66% higher risk of diabetes compared to the controls without COVID-19. The risk was not modified by age, sex, and study quality. The risk of bias assessment was low.

Our findings are consistent with the previous meta-analysis that assessed the proportion of COVID-19 survivors with incident diabetes. A 2021 study by Sathish and colleagues assessed a total of 3711 COVID-19 patients with 492 cases of newly diagnosed diabetes from eight studies10. In the random-effects meta-analysis model, the estimated pooled proportion of incident diabetes was 14.4% (95% CI 5.9–25.8%). They, however, noted a high degree of heterogeneity (I² 98.6%, p < 0.001). The weaknesses of the above study, however, included a lack of a control group and a very small study sample size.

Potential pathophysiological mechanisms of new-onset diabetes among COVID-19 survivors are complex and not fully understood. SARS-CoV-2 binds to angiotensin-converting enzyme 2 and transmembrane serine protease 2 receptors, which are expressed in key metabolic organs and tissues, including pancreatic beta cells, adipose tissue, the small intestine, and the kidneys28–30. Furthermore, it has been demonstrated that SARS-CoV-2 infection attenuates pancreatic insulin levels and secretion and induces β cell apoptosis31,32. Thus, it is plausible that SARS-CoV-2 may cause pleiotropic alterations of glucose metabolism that could lead to incident diabetes or facilitate a rapid transition from the prediabetes state to full-blown diabetes. SARS-CoV-2 is not the only virus associated with diabetes. A significant number of other viruses are associated with type 1 diabetes through molecular mimicry, including Coxsackievirus B, rotavirus, mumps virus, and cytomegalovirus33–35. Furthermore, findings from prospective studies have demonstrated a temporal association between hepatitis C virus and type 2 diabetes36.

Clinical implications of our findings and recommendations. Given the extraordinary number of COVID-19 survivors globally, the modest increase in diabetes risk could correspond to a drastic rise in the number of people diagnosed with the disease worldwide. Therefore, active monitoring of glucose dysregulation after recovery from severe COVID-19 infection is warranted. Additionally, there is a need for studies that determine various social determinants of health associated with new onset diabetes. These factors would be critical to developing effective prevention and management strategies for the disease. Lastly, future research could also focus on employing genomics data to stratify acute COVID-19 patients and predict phenotypes of patients at an increased risk of COVID-19-induced diabetes and uncover novel disease mechanisms.

Limitations. Our study has some limitations worth noting. First, a high degree of heterogeneity was observed, which could have been caused by pooling studies from different sociodemographic populations. Nevertheless, a random effects model was invoked to derive plausible estimates. Second, it is also a possibility that
Table 1. Meta-analysis characteristics of included cohort studies reporting COVID-19 and risk of diabetes.

| Author (year) | Sample size, N | Female, N (%) | Outcome (diabetes assessment) | Country | Study design | Mean age (y) | Total Cases, N | Follow-up periods | Median follow-up time (D) | Reported effect sizes | Covariates in the fully-adjusted model | Quality score | COVID-19 patients | Controls |
|---------------|----------------|---------------|-------------------------------|---------|--------------|--------------|----------------|-------------------|--------------------------|----------------------|----------------------------------------|--------------|------------------|---------|
| Balfe et al. (2022) | 7,178,535 (5,863 patients) | 52,731 (45.4%) | ICD-10 codes (E11-E14) | Germany | Retrospective cohort study | 42.6 | 104 | March 2020 to January 2021 | 144 | OR: 1.10 (1.05, 1.15) | Age, sex, smoking status, BMI, hypertension, hyperlipidaemia, depression, diabetes history, smoking status | 3 | 5,863 | 5,863 |
| Barret et al. (2022) | 485,021 | 285,628 (30.14%) | ICD-10 codes (E08-E13) | USA | Retrospective cohort study | 52.3 | 200 | March 2020 to February 2021 | NA | HR: 1.31 (1.20, 1.44) | Matched on age, sex, and month of encounter | 3 | 485,021 | 485,021 |
| Barret et al. (2022) | 462,478 | 440,024 (50.1%) | ICD-10 codes (E08-E13) | USA | Retrospective cohort study | 52.7 | 101 | March 2020 to June 2021 | NA | HR: 1.31 (1.20, 1.44) | Age, sex, and month of encounter | 3 | 462,478 | 462,478 |
| Xie et al. (2022) | 1,849,411 | 924,706 (50%) | ICD-10 codes (E08-E13) | USA | Cohort study | 39 | 27,292,879 | 13,755,616 (54.1%) | ICD-10 codes US | 9,247,505 | 4,607,112 (49.8%) | ICD-10 codes US | 2,777,768 | 376,274 (13.5%) | 120,288 (49.8%) | NA US |
| | | | | | | | | | | | | | | | | | 46,480,150 | 31,840,150 |
| Wunder et al. (2022) | 2,777,768 | 196,274 (13.34%) | ICD-10 codes (E08-E13) | USA | Retrospective cohort study | 59 | 515 | March 2019 to March 2021 | 120 | OR: 1.40 (1.36, 1.44) | Age, sex, ethnicity, BMI, smoking status | 3 | 2,777,768 | 2,777,768 |
| | | | | | | | | | | | | | | | | 72,651,830 | 40,851,830 |
| Daugherty et al. (2022) | 9,247,505 | 6,987,122 (49.9%) | ICD-10 codes | USA | Retrospective cohort study | 42.4 | 1,884 | January 2020 to October 2020 | 80 | HR: 2.47 (1.14, 5.37) | Frequently score matching with age, sex, race, socioeconomic status, area and region, primary care physician, nephrologist | 3 | 9,247,505 | 9,247,505 |
| Qudah et al. (2022) | 27,292,879 | 13,755,616 (54.1%) | ICD-10 codes | USA | Retrospective cohort study | 45.6 | 336 | December 2019 to July 2021 | NA | OR: 1.42 (1.38, 1.46) | Age, gender, race, ethnicity, marital status, region, and US geographical region | 3 | 27,292,879 | 27,292,879 |
| Kondal et al. (2022) | 192,285 | 104,285 (54.01%) | ICD-10 codes | USA | Retrospective cohort study | 9.3 | 120 | January 2020 to November 2021 | NA | OR: 1.36 (1.32, 1.40) | Frequently score matching with age, sex, ethnicity, and family history of diabetes | 3 | 192,285 | 192,285 |
| Mikkonen et al. (2022) | 4,808,031 | 2,769,286 (59.8%) | ICD-10 codes (E08-E13) | USA | Retrospective cohort study | 39.4 | 204 | March 2020 to November 2021 | NA | OR: 1.21 (1.18, 1.24) | Age, sex, and number of vaccine doses at least 14 days before | 3 | 4,808,031 | 4,808,031 |

some individuals in the control groups could have had undetected mild or asymptomatic COVID-19 because they had not been tested. Such non-differential misclassification of the exposure may underestimate the strength of the association of COVID-19 with the onset of diabetes. Lastly, due to the limited number of studies included in the present meta-analysis, we did not categorize the risk by the type of diabetes such as type 1 and type 2.
| Study, Pub Year, Country | Risk Ratio | RR  | 95% CI | Weight |
|--------------------------|------------|-----|--------|--------|
| Rathmann et al, 2022, Germany | 1.28 | [1.05; 1.57] | 11.7% |
| Barrett et al, 2022, US | 1.31 | [1.20; 1.44] | 13.1% |
| Xie et al, 2022, US | 1.40 | [1.36; 1.44] | 13.4% |
| Qeadan et al, 2022, US | 1.42 | [1.38; 1.46] | 13.4% |
| McKeigue et al, 2022, UK | 1.42 | [1.11; 1.82] | 10.9% |
| Kendall et al, 2022, US | 1.83 | [1.37; 2.45] | 10.2% |
| Wander et al, 2022, US | 2.40 | [2.18; 2.64] | 13.0% |
| Daugherty et al, 2021, US | 2.47 | [1.14; 5.37] | 4.1% |
| Barrett et al, 2022, US | 2.66 | [1.98; 3.57] | 10.1% |

Overall (Random−Effect Model)

Heterogeneity: $I^2 = 94\%$, $p < 0.0001$

Risk Ratio 1.66 [1.38; 2.00] 100.0%

Figure 2. Forest plot for the overall pooled estimate for the association of COVID-19 and incident diabetes. Effect size values represent risk ratio and corresponding 95% CI. Blue squares and their corresponding lines are the point estimates of each study and 95% confidence intervals (95% CI). Maroon diamonds represent the pooled estimate (width denotes 95% CI). Heterogeneity ($I^2 = 94\%$, $p$ for heterogeneity < 0.0001; 8 studies).

| Study, Pub Year, Country | Risk Ratio | RR  | 95% CI | Weight |
|--------------------------|------------|-----|--------|--------|
| Barrett et al, 2022, US | 1.31 | [1.20; 1.44] | 13.1% |
| Xie et al, 2022, US | 1.40 | [1.36; 1.44] | 13.4% |
| Qeadan et al, 2022, US | 1.42 | [1.38; 1.46] | 13.4% |
| Kendall et al, 2022, US | 1.83 | [1.37; 2.45] | 10.2% |
| Wander et al, 2022, US | 2.40 | [2.18; 2.64] | 13.0% |
| Daugherty et al, 2021, US | 2.47 | [1.14; 5.37] | 4.1% |
| Barrett et al, 2022, US | 2.66 | [1.98; 3.57] | 10.1% |

Overall (Random−Effect Model)

Heterogeneity: $I^2 = 96\%$, $p < 0.0001$

Risk Ratio 1.77 [1.41; 2.22] 77.4%

Figure 3. Forest plot of studies stratified by geographic regions.
Figure 4. Funnel plots to assess potential for small-study publication bias. Symmetrical inverted funnel plot suggested absence of publication bias.

Figure 5. Funnel plots from trim and fill analysis. Duval & Tweedie trim and fill analytical method suggests that the adjusted effect estimates would fall in the range of 1.21 to 1.88, and 2 studies were added.

| Study, Pub Year, Country | Risk Ratio   | RR   | 95% CI      | P-value | Tau2  | Tau  | I²  |
|-------------------------|--------------|------|-------------|---------|-------|------|-----|
| Omitting Xie et al, 2022, US | 1.71         | 1.38; 2.11 | < 0.01      | 0.0763  | 0.2762| 95%  |
| Omitting Barrett et al, 2022, US | 1.57         | 1.32; 1.86 | < 0.01      | 0.0494  | 0.2223| 94%  |
| Omitting Barrett et al, 2022, US | 1.72         | 1.40; 2.11 | < 0.01      | 0.0709  | 0.2662| 99%  |
| Omitting Daugherty et al, 2021, US | 1.63         | 1.36; 1.98 | < 0.01      | 0.0887  | 0.2621| 99%  |
| Omitting Wander et al, 2022, US | 1.55         | 1.31; 1.82 | < 0.01      | 0.0418  | 0.2046| 74%  |
| Omitting Rathmann et al, 2022, Germany | 1.72        | 1.40; 2.11 | < 0.01      | 0.0703  | 0.2652| 99%  |
| Omitting Qeadan et al, 2022, US | 1.70         | 1.36; 2.11 | < 0.01      | 0.0773  | 0.2780| 99%  |
| Omitting Kendall et al, 2022, US | 1.65         | 1.33; 2.03 | < 0.01      | 0.0770  | 0.2775| 99%  |
| Omitting McKeege et al, 2022, UK | 1.70         | 1.36; 2.09 | < 0.01      | 0.0788  | 0.2771| 95%  |

Random effects model  1.66 [1.38; 2.00]  < 0.01  0.0680  0.2609  94%

Figure 6. Influence and outlier (leave-one-out meta-analysis) analysis for the association of COVID-19 and incident diabetes. The results of our outlier and influence analysis show the recalculated pooled point estimate ranged from 1.55 to 1.72 when one study was omitted each time.
Conclusions. In this systematic review and meta-analysis, COVID-19 was a risk factor for developing new onset diabetes among survivors. Active monitoring of glucose dysregulation after recovery from severe acute respiratory syndrome coronavirus 2 infection is warranted.

Data availability
All data generated for this study are included in this manuscript.

Received: 12 July 2022; Accepted: 11 November 2022
Published online: 23 November 2022

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Author contributions
Designed research (project conception, development of overall research plan, and study oversight): P.S. and D.M.B. Data extraction: Y.Z., P.S., and D.M.B. Analyzed data: P.S. and D.M.B. Performed statistical analysis: P.S. Wrote the first draft of the manuscript: P.S. and D.M.B. Review and editing: P.S., L.W., V.M.C. and D.M.B. All authors have read and approved the final manuscript.

Competing interests
The authors declare no competing interests.

Additional information
Supplementary Information The online version contains supplementary material available at https://doi.org/10.1038/s41598-022-24185-7.
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