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SARS-CoV-2 Infection and Risk of New-Onset Diabetes Mellitus in Adults: A Systematic Review and Stratified Meta-Analysis by Variant Era, Disease Severity, and Vaccination Status

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ADMINISTRATIVE INFORMATION

Support - Self-funded. Supported by University of Hail College of Pharmacy academic resources. No pharmaceutical industry or commercial funding was received for this review.

Review Stage at time of this submission - The review has not yet started.

Conflicts of interest - None declared.

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Amendments - This protocol was registered with the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) on 18 June 2026 and was last updated on 18 June 2026.

INTRODUCTION

Review question / Objective Among adults with laboratory-confirmed SARS-CoV-2 infection, what is the risk of new-onset diabetes mellitus relative to uninfected (or active-comparator) controls, and how does this risk vary by viral variant era, acute disease severity, and vaccination status?

Rationale Multiple primary cohort studies and at least eight prior systematic reviews report an association between SARS-CoV-2 infection and subsequent new-onset diabetes, but most prior pooled estimates were generated from pre-Omicron, largely unvaccinated populations (search cut-offs predominantly mid-2022) and report extreme statistical heterogeneity (I-squared frequently above 90%). Newer large-scale evidence — including a 16-million-person English cohort, a US National COVID Cohort Collaborative variant-era analysis, and a Singapore national study of vaccinated adults — indicates that the association is strongly modified by acute severity, attenuates over time, and is markedly reduced or absent in vaccinated individuals infected during Omicron predominance. No prior review has integrated this contemporary evidence within a formally variant-era- and vaccination-stratified quantitative framework. This review addresses that gap, with explicit attention to surveillance/detection bias and comparator-type effects, to provide an up-to-date and clinically actionable risk estimate.

Condition being studied SARS-CoV-2 infection and risk of new-onset diabetes mellitus.

METHODS

Search strategy MEDLINE/PubMed, Embase, Cochrane CENTRAL, Scopus, Web of Science, with trial-registry and grey-literature checks (ClinicalTrials.gov, WHO ICTRP, medRxiv, conference proceedings), plus backward and forward citation searching of included studies and

prior systematic reviews. Search dates 01 January 2000 through 31 May 2026 (in practice all eligible studies are 2020 onward), with no language restriction at the search stage. Search terms combine controlled vocabulary (MeSH/Emtree) and free text for: SARS-CoV-2; COVID-19; coronavirus; post-acute sequelae; new-onset diabetes; incident diabetes; diabetes mellitus; type 1 diabetes; type 2 diabetes; hyperglycaemia; incidence; cohort.

Participant or population Adults (≥18 years) with laboratory-confirmed SARS-CoV-2 infection and no pre-existing diabetes diagnosis at baseline.

Intervention Confirmed SARS-CoV-2 infection (the exposure of interest), where reported stratified by viral variant era (wild-type/pre-Delta, Delta, Omicron and later), acute disease severity (non-hospitalized, hospitalized, intensive care), and vaccination status at the time of infection.

Comparator Adults without confirmed SARS-CoV-2 infection, including contemporary test-negative controls, historical/pre-pandemic controls, and active comparators (e.g., acute respiratory infection or influenza cohorts). Comparator type will be recorded and analysed as a key effect modifier.

Study designs to be included Prospective cohort studies, retrospective cohort studies, and case-control studies (quantitative designs only).

Eligibility criteria Inclusion: adults (≥18 years) with laboratory-confirmed SARS-CoV-2 infection; no pre-existing diabetes diagnosis at baseline; an uninfected or active-comparator control group; incident diabetes outcome with a risk estimate reported or calculable.Exclusion: studies restricted to participants with pre-existing diabetes at baseline; paediatric-only samples (<18 years); case reports and case series without a comparator; conference abstracts without extractable data; mechanistic, animal, or in-vitro studies; qualitative studies; and any retracted publication.

Information sources MEDLINE/PubMed, Embase, Cochrane CENTRAL, Scopus, Web of Science (plus ClinicalTrials.gov, WHO ICTRP, and medRxiv for grey literature).

Main outcome(s) Incidence of new-onset diabetes mellitus (any type; type 1 vs type 2 distinguished where reported) following SARS-CoV-2 infection, expressed as hazard ratio, risk ratio, odds ratio, incidence rate ratio, or cumulative incidence ratio.

Additional outcome(s) Risk stratified by (a) viral variant era; (b) acute disease severity; (c) vaccination status; (d) diabetes type (T1DM vs T2DM); (e) comparator type; and (f) follow-up window. Persistence of risk over time and excess absolute burden where reported.

Data management Two reviewers (A.S.A., B.A.A.) will independently screen titles/abstracts and full texts using Rayyan, with disagreements resolved by consensus or third-party adjudication. Data will be extracted into a pre-piloted standardized form capturing study identifiers, design, data source and country, population characteristics, exposure and comparator definitions, effect-measure type, follow-up duration, outcome ascertainment method (ICD code vs laboratory vs medication), diabetes type, variant era, severity and vaccination strata, adjusted effect estimates with confidence intervals, and risk-of-bias items. Retraction status of every included record will be checked against the Retraction Watch database and Crossref before extraction.

Quality assessment / Risk of bias analysis Risk of bias will be assessed using ROBINS-I (Risk Of Bias In Non-randomised Studies of Interventions/ Exposures) as the primary tool for cohort studies, supplemented by the Newcastle-Ottawa Scale; the overall certainty of evidence for each outcome stratum will be rated using GRADE for observational evidence, with explicit consideration of surveillance/detection bias and residual confounding.

Strategy of data synthesis A structured narrative synthesis (reported per SWiM guidance) will form the backbone. Where studies within a pre-specified stratum are sufficiently homogeneous, a random-effects (DerSimonian-Laird and/or REML) meta-analysis will pool comparable effect estimates; strata are defined by comparator type, follow-up window, acute severity, variant era, vaccination status, and diabetes type. Effect-measure types (HR, RR, OR, IRR, cumulative incidence ratio) will not be pooled together unless transformation is justified. Heterogeneity will be quantified with I-squared and tau-squared; if within-stratum I-squared exceeds 75%, that stratum will default to narrative synthesis without pooling. Meta-regression on candidate moderators, leave-one-out and subgroup sensitivity analyses, small-study-effect assessment (Egger's test/funnel plots where ≥10 studies), and E-value / quantitative bias analysis for surveillance bias and unmeasured confounding are planned.

Subgroup analysis Viral variant era; acute disease severity; vaccination status; diabetes type (T1DM vs T2DM); comparator type (test-negative vs historical vs active comparator); geographic region; and follow-up window.

Sensitivity analysis Restriction to studies using laboratory-confirmed diabetes definitions; restriction to active-comparator designs; restriction to studies with ≥6 months follow-up; leave-one-out analysis; and exclusion of studies at critical/serious ROBINS-I risk of bias.

Language restriction No language restriction at the screening stage; non-English full texts will be translated where feasible.

Country(ies) involved Saudi Arabia.

Other relevant information Infectious Disease; Endocrinology; Epidemiology

Keywords SARS-CoV-2; COVID-19; new-onset diabetes; incident diabetes; type 2 diabetes; variant era; vaccination status; disease severity; systematic review; meta-analysis.

Dissemination plans Peer-reviewed publication in an infectious disease, endocrinology, diabetology, or epidemiology journal; open-access preferred. Findings may also be presented at relevant scientific meetings.

Contributions of each author

Author 1 - Abdulrahman Alanazi - Conceived and designed the study, drafted the protocol, will lead data extraction and synthesis, and drafted the manuscript and final manuscript submission.
Email: aas2@hotmail.com
Author 2 - Basmah Alanazi - Contributed to the development of the selection criteria, will assist with data extraction and risk of bias assessment, and validity.
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