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.

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The bidirectional association between diabetes and long-COVID-19 – A systematic review

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ABSTRACT

Some evidence suggests that diabetes may be a risk factor for the development of post-acute sequelae of COVID-19 (PASC). Recent data also indicate that new-onset diabetes may be a complication of COVID-19. Here, we review the existing evidence. Following PRISMA guidelines, we conducted a systematic review through August 8, 2022. We included longitudinal studies reporting on the risk of PASC (i.e., sequelae that extend beyond four weeks after initial infection) in people with and without diabetes, and studies reporting on the risk of new-onset diabetes in people with vs without COVID-19 with a minimum of 4-weeks of follow-up. All studies were published in English. Among 5,532 studies screened, 39 were included in the final review. Among 25 studies reporting on diabetes and PASC, 44 % (n = 11) identified diabetes as a significant risk factor for PASC (increased relative risk ranging from 7 % to 342 %) while 56 % (n = 14) did not. Among 14 studies reporting on new-onset diabetes, 12 (86 %) reported that COVID-19 (vs no COVID) was significantly associated with new-onset diabetes with increased risks ranging from 11 % to 276 %.

COVID-19 survivors may be at increased risk for new-onset diabetes, but whether pre-existing diabetes is also a risk factor for PASC remains unclear.

1. Background

It is estimated that approximately 20–30 % and 50–89 % of non-hospitalized and hospitalized COVID-19 patients, respectively, will suffer from post-acute sequelae of COVID-19 (PASC), also known as long-COVID, four weeks beyond initial symptom onset of COVID-19 [1]. PASC is currently defined by the National Institute of Health (NIH) and the Centers for Disease Control and Prevention (CDC) as "sequelae that extend beyond four weeks after initial infection"[2] and can include several symptoms (e.g., fatigue, shortness of breath, memory loss, anosmia, gastrointestinal distress) [3] and affect multiple organs and systems [4]. Although diabetes has been widely reported as a key risk factor for the development of severe COVID-19 (i.e., hospitalization, intensive care unit admission, and mortality) [5–7] in the acute phase, it is less clear whether it is a risk factor for PASC.

Further, emerging evidence indicates a potential bi-directional relationship between diabetes and COVID-19 such that diabetes may be both a risk factor for COVID-19-related complications and a complication of COVID-19. For example, several studies have suggested that the incidence of both type 1 and type 2 diabetes [8–10] increased in 2020–2021 as compared with pre-COVID years, and a 2021 meta-analysis reported a high proportion of new-onset diabetes in people with COVID-19 [11]. However, these studies do not compare the incidence of new-onset diabetes in people with vs without COVID-19 and

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thus cannot disentangle the causal impact of COVID-19 infection as compared with more broad pandemic factors (i.e., reduced physical activity, weight gain, job loss) on the risk of developing diabetes. One recent study from the US Department of Veterans Affairs reported that in the post-acute phase, people with COVID-19 were 40 % more likely to develop new diabetes compared to matched people without COVID-19 [12].

A detailed assessment of the risk and burden of diabetes in the post-acute phase of COVID-19 is needed to inform post-acute COVID-19 care strategies. Therefore, we conducted a systematic review to examine whether diabetes is: 1) a risk factor for PASC; and 2) a manifestation of PASC.

2. Methods

This review adheres to the Preferring Reporting Items for Systematic Review and meta-Analysis (PRISMA) guidelinesp [13] (Supplementary Table 1) and has been registered with the PROSPERO International Prospective Register of Systematic Reviews (#CRD42022326929).

2.1. Search strategy

A literature search was performed in PubMed and Embase on May 30, 2022 and updated on 9 November 2022. We used medical evidence subject heading (MeSH) related to COVID-19 combined with the operator 'AND' with text word 'diabetes'. The reference lists of included studies were also screened for additional articles.

2.2. Study selection

We included all peer-reviewed full-text research articles published in English that included a longitudinal study design and reported on 1) the risk of PASC in people with vs without diabetes with a minimum of 30-days follow-up after COVID-19 diagnosis, or 2) the risk of new-onset diabetes among people with vs without COVID-19 with a minimum of 30-days follow-up after COVID-19 diagnosis. We included studies of type 1 or type 2 diabetes across all ages (pediatric and adult populations) for both research questions, and included populations with existing additional comorbidities (e.g., kidney disease, hypertension). For the risk of new-onset diabetes in people with vs without COVID-19, a statement pertaining to 'new-onset' or 'incident' diabetes among people previously undiagnosed with diabetes was needed to meet our inclusion criteria. We excluded case reports, editorials and reviews, and clinical trials. All identified articles from the literature search were entered into Covidence for screening. Where two or more studies reported on the same dataset, we included all owing to different study methodologies and COVID-19 waves. Two investigators (JLH and SO) screened the titles, abstracts, and full-text articles for eligibility. Disagreements were discussed until a resolution was reached.

2.3. Quality assessment

The methodological quality of each study was critically appraised by two authors (JLH & SO) using a modified version of the Newcastle-Ottawa tool [14], and conflicts resolved until a consensus was reached. This modified tool, previously utilized in studies of type 2 diabetes incidence [15], includes items to assess the representativeness of the study population, the sample size, completeness of the data, and the method of assessing diabetes status. For the current review, we further tailored the quality assessment to include PASC, Supplementary Table 2. The maximum score was 11 and final scores were defined as low quality (score 0–4), medium (score 5–7), or high (score 8–11) quality.

2.4. Data synthesis and analysis

We extracted the following data from included articles: publication characteristics (i.e., year of publication, author names, PMID, journal source); study characteristics (e.g., study design, country); sample characteristics (e.g., sample size, % diabetes); PASC and diabetes outcomes (e.g., definition, follow-up time); and findings (e.g., rate ratios, odds ratio). Where studies reported counts only, we estimated relative risks and 95 %CI using standard methods [16] as provided in Supplementary Table 3. Data extraction was performed by two authors (JLH and SO). Due to the heterogeneity and relatively limited number of studies, we adopted a qualitative approach to analysis of results and narratively synthesized results of included studies. Estimates of PASC or new-onset diabetes are provided per study and overall patterns across studies described. For patterns of new-onset diabetes, we stratified the results by pediatric and adult populations.

2.5. IRB approval

As this is a review of existing studies, this study was exempt from Institutional Review Board approval.

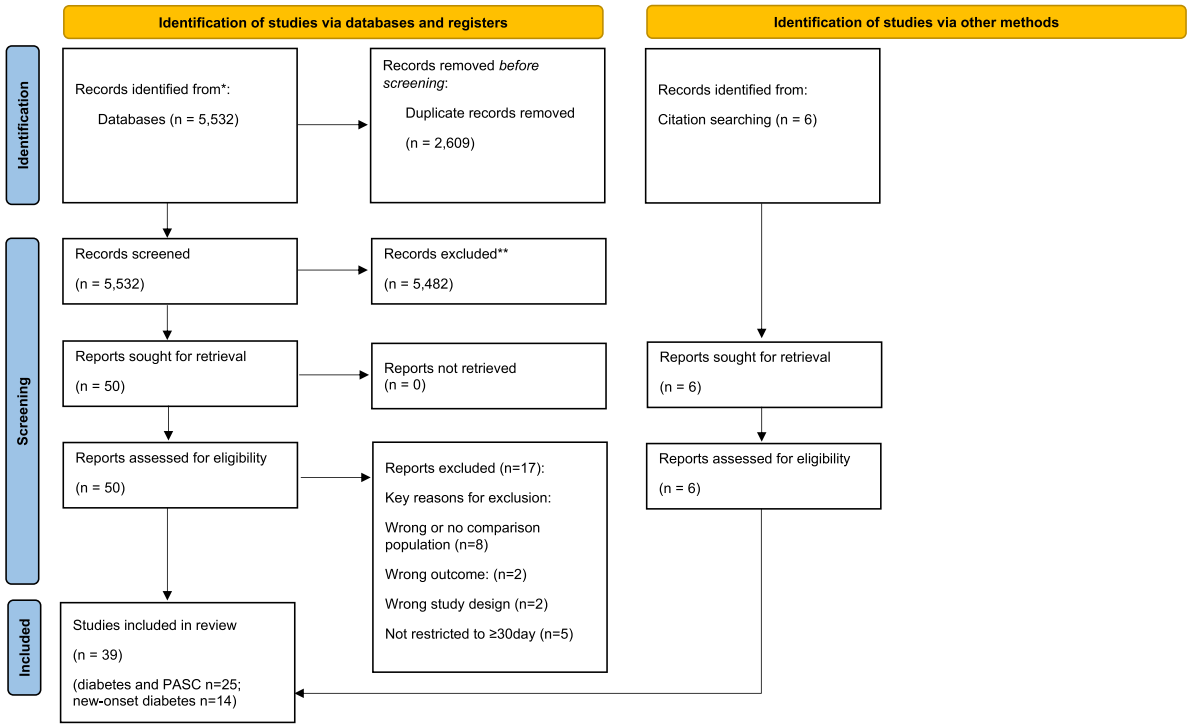
3. Results

The search yielded 8,141 records. After excluding duplicates (n = 2,609), 5,532 records were screened and 39 were included in full text review. An additional six studies were identified from screening of reference lists and included in the review. Of 17 full text articles excluded, eight (47 %) did not include an appropriate comparison population, two (12 %) reported outcomes which were not relevant, two (12 %) were reviews, editorials, or trials, and five (29 %) did not include a minimum of 30-days follow-up. In total, 39 articles met our inclusion criteria: 25 for the assessment of diabetes and PASC, and 14 for the assessment of COVID-19 and incident diabetes, Fig. 1.

3.1. Diabetes and PASC

Twenty-five studies examining diabetes as a risk factor for PASC are summarized in Table 1. PASC was defined with a range of definitions, but commonly included ongoing symptoms such as fatigue, cough, and dyspnea, and follow-up time spanned from 4 weeks to >15 months. Four studies included new diagnosis following a COVID-19 infection, including two studies that examined hospitalization for myocardial infarction or stroke [17]. Supplementary Table 4 includes a detailed summary of PASC definitions. Most studies were from high-income countries (Croatia, Italy, Norway, China, Spain, Germany, Sweden, Switzerland, France, the United Kingdom, and the United States), with seven studies from middle-income countries (India (2 studies), Ghana, Turkey, Iraq, Saudi Arabia, and Bangladesh). The sample sizes of the studies ranged from 74 to 846,987 participants. In total, nine (36 %) studies reported PASC among hospitalized COVID-19 cohorts, nine (36 %) among people with a COVID-19 diagnosis, four (16 %) among a COVID-19 cohort of which a variable portion (13.1 %–71 %) had been hospitalized, one (4 %) study included a cohort of COVID-19 patients with a functioning kidney transplant, one (4 %) included individuals who had confirmed COVID-19 and at least one assessment of high sensitivity for cardiac troponin I, and one (4 %) included social media users with self-reported COVID-19. Eleven studies (44 %) were conducted among people diagnosed with COVID-19 during the first pandemic wave (prior to June 2020), two studies did not report on the COVID-19 diagnosis date, and 12 (48 %) studies included data on COVID-19 cases spanning from 2020 to 2021. All studies ascertained diabetes status using electronic medical record data defined with International Classification of Disease coding, excluding the Chinese study by Chai et al. [18] which used a combination of previous diabetes diagnosis and fasting plasma glucose at admission to ascertain diabetes status.

Only one German study [19] reported risk of PASC in people with type 1 and type 2 diabetes, separately. Twenty-three studies reporting



From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: http://www.prisma-statement.org/

Fig. 1. PRISMA 2020 flow diagram for new systematic reviews which included searches of databases, registers and other sources.

risk of PASC among adults. Two studies, in Bangladesh and India, included children. Specifically, in the Bangladesh study [20], 6.8 % of the study population was ≤ 19 years, and in India [21], 4.1 % of the study population was ≤ 20 years. In both studies, risk of PASC was not reported separately for children and adults.

Overall, 11 (44 %) studies reported that diabetes was a significant risk factor for the development of PASC, while 14 (56 %) studies indicated it was not a significant risk factor. Among the 11 studies indicating diabetes was associated with PASC, 3 (38 %) reported ORs > 4. One such study was among kidney transplant recipients (OR for diabetes vs no diabetes: 4.42 (95 %CI: 1.16–16.8)) [22] and adjusted for several confounding factors; Another examined the association between diabetes, hypertension, and PASC in comparison to people with no comorbidities (unadjusted OR: 4.18 (1.61–10.85));[23] and a multi-omics study reported a strong and significant correlation between type 2 diabetes and at least two PASC-related respiratory symptoms, adjusted for age, gender and severity of COVID-19 [24]. Among the remaining eight positive studies, one study from Bangladesh [20] among people with confirmed COVID-19 reported significant increased risks of impaired mobility, sleep, and pain/discomfort in people with vs without diabetes (RR from 1.31 to 2.00), but did not demonstrate an association with impaired self-care, panic attacks, loss of concentration, or memory loss. In India [21], people with (vs without) diabetes had an increased risk for ongoing cardio-respiratory (OR: 2.29, 95 %CI: 1.97–5.40) and neurological (OR: 2.64, 95 %CIL 1.46–4.77) symptoms, but not abdominal or psychological symptoms. Among hospitalized patients in an India center [25], diabetes was associated with a 96 % (95 %CI: 1.45–2.66) increased for persistent symptoms 6 months after initial diagnosis. In Italy [17], people with diabetes had an increased risk of post-COVID hospitalization for first myocardial infarction or stroke (adjusted IRR: 2.24, 95 %CI: 2.18–4.22), or MACE in people who had been assessed for high sensitivity cardiac troponin I (adjusted HR: 2.35 (1.25–4.43) [26], and three US studies [27–29] demonstrated a 7 %–49 % increased risk of persistent symptoms in people with vs without diabetes. The remaining 14 studies reported a non-significant association between diabetes and a range of PASC including impaired pulmonary function, functional impairment, fatigue, shortness of breath, cough, loss of smell/taste, limitations in activities of daily living, depressive symptoms, poor sleep, and musculoskeletal pain.

3.2. COVID-19 and new-onset diabetes

The 14 included studies examining new-onset diabetes in people with and without COVID-19 are summarized in Table 2. Overall, nine studies were from the USA, three from the UK (England and Scotland), and two multi-country studies. Seven studies examined total diabetes incidence in adults, two examined type 2 diabetes in adults, one study examined type 2 diabetes in both children and adults, one study examined type 1 and type 2 diabetes separately, and three studies examined type 1 diabetes in children. All studies were conducted from early 2020 (<August 2020) with follow-up time ranging from 30 to 457 days and sample size ranging from 1,476 to 9.3 million.

Overall, 12/14 (86 %) studies reported that COVID-19 was associated with an 11 %–276 % increased risk for incident diabetes, with risk estimates varying depending on comparison population (i.e., non-COVID-19 vs acute upper respiratory infection (AURI)), hospitalization status, and age (i.e., adults vs children). Of the two studies that report no association, one examined any new diabetes diagnosis in 1.85 million people aged < 35 years (i.e., Type 1 diabetes) in Scotland (Hazard Ratio: 0.86, 95 %CI: 0.62–1.21) [30] and the other examined new-onset diabetes 12-months after hospitalization with acute pancreatitis (and with vs without COVID-19 infection) (OR: 0.61 (0.13–2.96) [31].

Of the studies examining new-onset diabetes in adults, all demonstrated an increased risk for new-onset diabetes in people with COVID-19 with some sub-group exceptions. For example, a Veteran's Affair's study by Wander et al. [32] reported an increased risk for new-onset diabetes associated with COVID-19 in men (OR: 1.95 (1.80–2.12), but not women (1.04 (0.82–2.12); Al-Aly reported an increased risk for new-onset type 2 diabetes in non-hospitalized but not hospitalized veterans,

Table 1
Summary of studies included in systematic review of diagnosed diabetes and the post-acute sequelae of COVID-19 (PASC) from Jan 1, 2020 until Nov 9, 2022.

Study characteristics				Sample characteristics				PASC outcome			Findings
First Author	COVID diagnosis date	Country	Study population	Sample size N	Diabetes (%)	Men (%)	Age (years)	PASC definition	Follow-up time	Analysis	Risk estimate (diabetes vs no diabetes) (95 % CI)
Alkwai [45]	Nov 2020–Dec 2020	Saudi Arabia	Social media users with self-reported COVID-19	213	3.8	23.9	90.1 % 18–44	Persistent symptoms	≥3 months	Unadjusted	RR: 0.99 (0.30–1.69)[1]
Akter [20]	Apr 1, 2020–Jun 30, 2020	Bangladesh	Confirmed COVID-19 diagnosis	734	19.9	76	Range: 0 - ≥60	Physical and mental health	4 weeks	Unadjusted	Mobility: RR: 2.00 (1.43–2.76)[2] Self-care: RR: 1.10 (0.64–1.89)[2] Pain/ discomfort: RR: 1.53 (1.22–1.91)[2] Anxiety/ depression: RR: 1.22 (0.89–1.68)[2] Sleep: RR: 1.31 (1.03–1.67)[2] Panic attack: RR: 0.91 (0.56–1.46)[2] Loss of concentration: RR: 1.15 (0.87–1.55)[2] Memory loss: RR: 1.38 (0.99–1.93)[2]
Basic-Jukic [22]	Mar 2020–Jan 2021	Croatia	Kidney transplant recipients with known prior SARS-CoV-2 infection; 77 % hospitalized	104	20.2	66.3	Median [IQR]: 56 [45–65]	Persistent symptoms/ new-onset clinical problem	Median: 64 days [IQR: 50–76]	Adjusted	OR: 4.42 (1.16–16.8)
Bellan [46]	Mar 1–Jun 29, 2020	Italy	Hospitalized COVID-19 patients	238	15.1	59.7	Median [IQR]: 61 [50–71]	Pulmonary function/ physical functioning	3–4 months	Unadjusted	Impaired Pulmonary Function: OR: 2.17 (0.68–6.92) Functional Impairment: OR: 0.95 (0.35–2.60)
Blomberg [47]	Feb 28, 2020–Apr 4, 2020	Norway	79 % hospitalized and 21 % non-hospitalized COVID-19 patients	312	4	49	Median [IQR]: 46 [30–58]	Persistent symptoms	6 months	Adjusted	Total number of PASC symptoms: Unadjusted RR: 1.33 (0.67–2.87) Fatigue: RR: 1.06 (0.91–1.23)
Budhiraja [25]	Mar 2020–Feb 2022	India	Hospitalized COVID-19 patients	5,529	18.1	64.6	Mean (SD): 54.4 (17.0)	Persistent symptoms	1–5 and ≥ 6 months	Adjusted	OR: 1.96 (1.45–2.66)
Cervia [48]	Apr 2020–Aug 2021	Switzerland	66 % mild cases, 34 % severe cases	134	14	56	IQR: 27–74	Persistent symptoms	Median 383 (IQR: 371–397) days	Unadjusted	OR: 2.34 (0.78–8.87)
Chai [18]	Jan 1, 2020–Mar 18, 2020	China	Hospitalized COVID-19 patients	Total: 2545	28.9 [3,4]	No diabetes[4]: 43.6 Diabe-	Range: 0–65	Fatigue, shortness of breath, chest tightness, cough	1 year	Unadjusted	Fatigue: RR: 1.1 (0.7–1.6)[5] Chest tightness: RR: 0.96 (0.7–1.4)[5]

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Table 1 (*continued*)

Study characteristics				Sample characteristics				PASC outcome			Findings
First Author	COVID diagnosis date	Country	Study population	Sample size N	Diabetes (%)	Men (%)	Age (years)	PASC definition	Follow-up time	Analysis	Risk estimate (diabetes vs no diabetes) (95 % CI)
						tes[5]: 56.7					Cough: RR: 0.98 (0.6–1.6)[5] Shortness of breath: RR: 1.2 (0.8–1.7)[5]
Crankson [23]	Mar 2020–Aug 2021	Ghana	Hospitalized COVID-19 patients	2,334	5.4	60.1	Range: 30–59	Persistent symptoms	4 weeks	Unadjusted	OR: 4.18 (1.61–10.85)[6]
Fernández-de-Las-Peñas [49]	Mar 1, 2020–May 31, 2020	Spain	Hospitalized COVID-19 patients	435	33	62.1	Mean (SD): 70.2 (13.2)	Persistent symptoms	Mean: 7.2 ± 0.6 months	Matched	Number of symptoms: RR: 1.06 (0.92–1.24) Fatigue: OR: 1.45 (0.93–2.25) Dyspnea: OR: 0.97 (0.64–1.47) Musculoskeletal Pain: (OR: 0.95 (0.76–1.18) Anxiety: OR: 1.30 (0.77–2.20) Depressive Symptoms: OR: 1.31 (0.79–2.17) Poor Sleep Quality: OR: 1.34 (0.89–2.03) Limitations in Occupational Activities: OR: 0.73 (0.40–1.35) Limitations in Leisure Activities: OR: 1.34 (0.87–2.06) Limitations in Activities of Daily Living: OR: 1.05 (0.67–1.65) Limitations in Basic Activities of Daily Living: OR: 1.04 (0.63–1.71)
Ioannou [29]	Feb 1, 2020–Apr 30, 2020	USA	Veterans with diagnosed COVID-9 = 19	198,601	34.2	89.1	Mean (SD): 60.4 (17.7)	ICD-10 diagnoses specific to COVID-19	≥3 months	Adjusted	Unadjusted OR: 1.37 (1.33–1.40) Adjusted OR: 1.07 (1.04–1.11)
Jones [50]	Aug 7, 2020–Jan 22, 2021	UK	Self-diagnosed, clinician-diagnosed, or test-confirmed COVID-19	3,151	21.1	35	Median (IQR: 52 (40–61)	Persistent symptoms	≥4 weeks	Adjusted	OR: 1.07 (0.78–1.45)
Loosen [19]	Mar 1, 2020–Mar 31, 2021	Germany	Confirmed COVID-19 diagnosis	50,402	People with T1D: 0.7 People with	45.5	Mean (SD): 48.8 (19.3)	ICD-10 diagnoses	Range: 90–183 days	Adjusted	People with T1D: OR: 1.00 (0.59–1.69)

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Table 1 (*continued*)

Study characteristics				Sample characteristics				PASC outcome			Findings
First Author	COVID diagnosis date	Country	Study population	Sample size N	Diabetes (%)	Men (%)	Age (years)	PASC definition	Follow-up time	Analysis	Risk estimate (diabetes vs no diabetes) (95 % CI)
					T2D: 10.0						Women with T1D: OR: 0.98 (0.45–2.11) Men with T1D: OR: 0.99 (0.48–2.05) People with T2D: OR: 0.93 (0.79–1.10) Women with T2D: OR: 0.80 (0.64–1.02) Men with T2D: OR: 1.10 (0.87–1.41)
Mechi [51]	May 20, 2020–Jun 1, 2021	Iraq	Hospitalized COVID-19 patients	112	37.5	66.1	People with DM: mean (SD): 60 (10) People without DM: mean (SD): 45 (12)	Persistent symptoms	≥9 months	Unadjusted	RR: 1.12 (0.96–1.29)[7]
Messin [52]	Mar 2020	France	Hospitalized COVID-19 patients	74	8.1	40.5	Mean (SD): 52.3 (18)	Persistent symptoms	≥6 months	Unadjusted	RR: 1.18 (0.79–1.57)[8]
Nesan [21]	Jun 1, 2020–Nov 10, 2020	India	Hospitalized COVID-19 patients	1354	9.7	73	Range: ≤10 - ≥60	Cardio-respiratory, abdominal, psychological, neurological, renal	≥3 months	Adjusted	General symptoms: OR: 0.77 (CI: 0.53–1.11) Cardio-respiratory symptoms: OR: 2.29 (CI: 1.97–5.40) Abdominal symptoms: OR: 0.89 (CI: 0.46–1.72) Psychological symptoms: OR: 1.02 (CI: 0.70–1.50) Neurological symptoms: OR: 2.64 (CI: 1.46–4.77) Renal symptoms: OR: 0.79 (CI: 0.38–1.61)
Nguyen [53]	Early 2020	France	PCR-confirmed COVID-19 patients who reported smell and/or taste disorders during the acute phase upon admission	605	5	36.2	Mean (SD): 40.0 (13.3)	Persistent loss of smell and/or taste	≥6 months	Unadjusted	OR: 0.72 (0.29–1.79)

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Table 1 (*continued*)

Study characteristics				Sample characteristics				PASC outcome			Findings
First Author	COVID diagnosis date	Country	Study population	Sample size N	Diabetes (%)	Men (%)	Age (years)	PASC definition	Follow-up time	Analysis	Risk estimate (diabetes vs no diabetes) (95 % CI)
Peghin [54]	Mar 2020–May 2020	Italy	Confirmed COVID-19 inpatient and outpatients	599	5.5	31.6	≥18 years	Persistent symptoms	Mean (SD): 187 (22) days	Unadjusted	RR: 1.14 (0.75–1.53)[9]
Pfaff [27]	Not available	USA	Confirmed COVID-19 diagnosis	846,981	9.9	40.8	≥18 years	ICD-10 diagnosis	45–365 days	Unadjusted	All patients: OR: 1.49 (1.13–1.96) Hospitalized patients: OR: 1.16 (0.84–1.58)
Profili [17]	<March 1, 2020	Italy	Confirmed COVID-19 diagnosis	92,304	9.96	46.3	Range: 45–97	First hospitalization for myocardial infarction or stroke	≤6 months	Adjusted	Myocardial infarction: RR: 2.7[10] Stroke: RR: 2.5[10] Myocardial infarction or stroke: IRR: 2.24 (2.18–4.22
Rinaldi [26]	Mar 2021–Jan 2022	Italy	Confirmed COVID-19 and ≥ 1 assessment of high sensitivity cardiac troponin I (hs-cTnI)	701	17.4	59.8	Mean (SD): 66.4 (14.4)	MACE	Median (IQR): 270 (165–380) days	Adjusted	Unadjusted HR: 4.04 (2. 26–7.20) Adjusted HR: 2.35 (1.25–4.43)
Su [24]	Not reported	USA	71 % hospitalized	209	22.4	50	Mean (SD): 56 (18)	Respiratory viral, gastrointestinal, neurologic and anosmia/ dysgeusia	2–3 months	Adjusted	Diabetes was significantly correlated with respiratory viral (defined as at least 2 respiratory symptoms)[11]
Sudre [55]	Mar 25, 2020–Jun 30, 2020	UK, USA, Sweden	Incident COVID-19 cases; 13.9 % hospitalized	4,182	2.9	28.5	Median [IQR]: 42 [32–53]	Persistent symptoms	4 weeks	Propensity score	18–49 years[12]: OR: 1.5 (0.5–4.2) 50–69 years[12]: OR: 0.5 (0.3–1.1) ≥70 years[12]: OR: 1.8 (0.4->7.0)
Yaksi [56]	Jan 1, 2021–Feb 28, 2021	Turkey	Hospitalized patients with confirmed COVID-19	133	38.3	51.9	Mean (SD): 65.7 (13.1)	Persistent symptoms	4 weeks	Unadjusted	OR: 1.98 (0.80–4.86)
Yoo [28]	Apr 2020–Feb 2021	USA	Adults with laboratory confirmed SARS-CoV-2 infection	1,038	37.9	50.4	Median [IQR]: 60 [37–83]	Persistent symptoms	≥30 days	Adjusted	OR: 1.39 (1.02–1.88)

Acronyms: CI = confidence interval; DM = diabetes mellitus; FBG = fasting blood glucose; HR = hazard ratio; ICD = international classification of disease; IRR: incident rate ratio; MACE = major adverse cardiac events; OR = odds ratio; PASC: post-acute sequela of COVID-19; RR = rate ratio; TIA = transient ischemic attack; T1D = type 1 diabetes; T2D = type 2 diabetes; UK = United Kingdom; USA = United States of America.

[1]RR and CI calculated using count in Table 1 of original manuscript by Alkwai et al.

[2]RR and CI calculated using count in Table 4 of original manuscript by Akter et al.

[3]Denied history of diabetes and have a FBG of < 7 mmol/L.

[4]History of diabetes or FBG ≥ 7 mmol/L.

[5]Sequelae RR and CI calculated using counts from Table 1 and Table 3 of original manuscript by Chai et al.

[6]Odds Ratio compared people with hypertension and diabetes to people with no comorbidities.

[7]RR and CI calculated using counts in Table 1 of original manuscript by Mechi et al.

[8]RR and CI calculated using counts in Table 1 of original manuscript by Messin et al.

[9]RR and CI calculated using counts in Table 1 of original manuscript by Peghin et al.

[10]Calculated using adjusted rates in Table 2a of original manuscript by Profili et al.

[11]ln(odds ratio) reported though precise estimates not available from Fig. 1D in original manuscript by Su et al.
[12]OR values estimated visually from Extended Data Fig. 3 of original manuscript by Sudre et al.

and for new-onset type 2 but not new-onset type 1 diabetes [33]; Hernandez-Romieu et al. [34] reported a 87 % and 125 % increased risk of new-onset diabetes in hospitalized and mechanically ventilated COVID-19 patients (vs no COVID-19), but a decreased risk for new-onset diabetes in non-hospitalized COVID-19 patients (prevalence ratio: 0.90 (0.85–0.96)).

Among studies that stratified by COVID-19 severity (i.e., not hospitalized, hospitalized), greater severity was generally associated with higher diabetes risk. For example, in a study of US veterans by Xie et al. [12], non-hospitalized COVID-19 patients had a 25 % (95 %CI: 21 %–29 %) increased risk of diabetes relative to people without non-COVID-19 patients, which increased to 173 % and 276 % in patients hospitalized, and admitted to the intensive care unit (ICU), respectively. However, in a similar study of US veterans by Al-Aly [33], an increased risk for type 2 diabetes was seen in non-hospitalized COVID-19 patients, but not hospitalized patents. In another US study [35], risk of new-onset diabetes increased from 70 % to 266 % in non-hospitalized and hospitalized COVID-19 patients, respectively, as compared with historical non-COVID-19 populations (i.e., data from pre-2020).

Risk of new-onset diabetes also appears to decrease with increasing time from COVID-19 infection. For example, one study from the United Kingdom [36] examined risk of new-onset diabetes at varying follow-up times. In the 5–12 weeks from index date, the increased risk of new-onset diabetes in people with vs without COVID-19 was 81 % (95 % CI:51 %–119 %), which decreased to 7 % (−1 % to 16 %) and become non-significant at 13–52 weeks from index date [36]. In a multi-country study, risk of new-onset diabetes at 30–89 days following COVID-19 infection was 26 % (16 %–36 %), which decreased to 11 % (2 %–21 %) at ≥ 90 days following infection [37]. Finally, in a second study of US veterans, Wander et al. demonstrated a 156 % increased risk for new-onset diabetes in men with vs without COVID-19 within 120 days from infection, but this decreased to 95 % when the study included the total follow-up time (i.e., 456 days) [32].

Among two studies, risk estimates also varied depending on the comparison population. For example, Daugherty et al. [35] examined the risk of new-onset diabetes in people with COVID-19 compared to people without COVID-19 in 2020, without COVID-19 in 2019 (arguably a true non-COVID population) and in people with AURI. Risk estimates were 83 %, 80 % and 39 %, respectively [35]. In Xie et al. a veterans-based study, risk of new-onset diabetes was 40 % (95 %CI: 36–44) in people with COVID-19 vs a 2020 contemporary cohort of people without COVID-19. This risk decreased slightly to 35 % (31 %–39 %) when the comparison was a historical cohort of people without COVID-19 from 2018 to 2020.

In children, Barrett et al. [38] reported that COVID-19 increased the risk of new-onset diabetes in US people aged < 18 years by 31 %–166 % across two insured populations. Risk estimates were lower when the comparison population was AURI (Hazard Ratio: 2.66 (1.98–3.56) vs non-COVID-19 (2.16 (1.64–2.86). In Scotland [30], no increased risk was observed in people with vs without COVID-19 aged < 35 years, and in another US study, non-hospitalized and hospitalized children aged < 20 years with COVID-19 had a 27 % and 114 % increased risk of diabetes as compared to people without COVID-19, respectively [34]. Finally, in another US study, new-onset diabetes was increased in children aged 10–18 years at 3 months (HR: 2.40 (1.62–3.56)) and 6 months (HR: 2.18 (1.57–3.03), but not in children aged 0–9 years. [39].

3.3. Quality assessment

Using the modified Newcastle-Ottowa Scale, the quality of studies examining diabetes and PASC ranged from 4 to 11. Four studies were deemed low quality (score 1–4) owing to a small sample size, poor characterization of PASC, and crude analysis, ten were deemed moderate (score 5–7), and 11 were deemed high quality (score 8–11), Supplementary Table 5. Among the 14 studies examining COVID-19 and incident diabetes, 11 were scored as high-quality with scores ranging from 8 to 10, one study was moderate quality with a score of 7, and one was deemed low quality (score 5).

4. Discussion

In this systematic review of the bi-directional relationship between diabetes and PASC, our findings are twofold. First, we report that COVID-19 survivors may be at increased risk for new-onset diabetes. This risk appears to increase in a graded fashion according to the severity of the initial infection (i.e., hospitalized vs not hospitalized), is greater than what is observed for other acute respiratory infections, but declines with increasing time from infection. Diabetes, therefore, may arguably be considered as a component of the multifaceted PASC diagnosis and post-acute care strategies might consider the integration of diabetic screening and management. Second, whether pre-existing diabetes is a risk factor for the development of PASC remains unclear due, in part, to the heterogeneity of studies with regard to PASC definitions, populations at risk, small sample sizes, and short follow-up times. Regardless, careful monitoring of people with diabetes for development of PASC should be strongly considered.

The mechanisms underpinning the bi-directional association between diabetes and PASC are not entirely clear. The association between diabetes and severe COVID-19 (i.e., hospitalization, intensive care unit admission, and mortality) in the acute phase [5–7] is thought to be explained, in part, by the virus' tropism for islet β-cells that express ACE2 receptors resulting in impaired production and secretion of insulin and subsequently worsening hyperglycemia, ketoacidosis, and hyperosmolarity [6]. It is possible that this same mechanism increases the risk both for PASC as well as new-onset diabetes. Other possible explanations include autonomic dysfunction, hyperactivated immune response or autoimmunity, and persistent low-grade inflammation leading to insulin resistance [12]. It is also possible that people with COVID-19 have been differentially exposed to social, economic, and environmental changes that occurred during the pandemic (i.e., lockdowns, job loss) that might have indirectly contributed to the increased risks of diabetes. Future research should consider the use of multi-level and multi-factorial models that consider the complex interplay between diabetes, COVID-19, comorbidities, and the social determinants of health.

In the case of new-onset diabetes, it is worth considering that the detection of new-onset diabetes in COVID-19 patients could be a case of undiagnosed prediabetes, diabetes, or pre-existing hyperglycemia. For instance, certain population groups who do not routinely access healthcare services, including those living in remote, and rural regions, may be diagnosed with diabetes as they receive in-hospital COVID-19 testing and treatment. This notion is supported by studies that demonstrate declining risk of new-onset diabetes further out from COVID-19 infection. For example, Rezel-Potts et al. report an increased risk for post-acute new-onset diabetes at 13–52 weeks post COVID-19 infection in people with vs without COVID-19, but this becomes non-significant at 13–52 weeks [36]. Whether detection bias is the whole story remains unknown. Studies with longer term follow-up, that stratify by time since infection, are needed to tease this out.

In our study, we did not perform a meta-analysis owing to the heterogeneity of included studies. However, a recent meta-analysis published in May 2022 reported a pooled risk estimate for incident diabetes in people with vs without COVID-19, despite high heterogeneity estimates (I^2 reported = 94 %) [40]. In this review, Banerjee et al. [40] report a 59 % (95CI: 40 %–81 %) higher risk of developing incident diabetes in the post-acute COVID-19 phase versus healthy controls among 5,787,027 subjects from four observational studies, and a 22 %

Table 2
Summary of studies included in systematic review of COVID-19 and new-onset diabetes from Jan 1, 2020 until Nov 9, 2022.

Study characteristics					Sample characteristics				Diabetes Outcome			Analysis		Findings
First Author	Cohort Name	COVID-19 diagnosis date	Country	Study population	Sample size N	COVID-19 (%)	non-COVID comparator	Men (%)	Age (years)	Diabetes Type	Diabetes Definition	Follow-up time	Adjusted	Risk estimate (95 %CI)
Al-Aly [33]	Veterans Affairs	Mar 1, 2020 – Nov 30, 2020	USA	Non-hospitalized VA members	5.1 million	1.5	Non-COVID; non-hospitalized	90.4	Median (IQR): COVID patients: 60.9 (47.6–71.6) Non-COVID patient: 66.7 (51.9–73.9)	Type 1/ Type 2	ICD code: not specified	Median (IQR): COVID-19 patients: 126 (81–203) days Non-COVID-19 patients: 130 (82–205)	Propensity score	Type 1 diabetes HR: 1.22 (0.91–1.64) Type 2 diabetes: HR: 1.44 (1.30–1.60)
				Hospitalized VA members	27,651	49	Hospitalized with influenza	94.0	Median (IQR): COVID patients: 70.3 (60.7–75.7) Influenza patient: 70.1 (63.0–77.0)			Median (IQR): COVID-19 patients: 126 (81–203) days Non-COVID-19 patients: 130 (82–205)		Type 1 diabetes HR: 0.70 (0.49–1.01) Type 2 diabetes: HR: 1.14 (0.96–1.34)
Ayoubkhani [57]	N/A	<31 Aug 2020	England	Hospitalized COVID-19 patients and general population with at least one GP visit (1 Jan 2019–30 Sept 2020)	287,160	16.6	Non-COVID-19	46.7	Mean (SD): 64.5 (19.2)	Type 1/ Type 2	ICD code: not specified	30–253 days	Matched	Overall COVID vs non COVID: RR: 3.5 (2.9–4.3)[1]
Barrett [38]	IQVIA	Mar 1, 2020 – Feb 26, 2021	USA	Closed payor system; 0.7 % hospitalized with COVID-19	1.7 million	4.8	1) Non-COVID-19; 2) ARI	49.9	Mean (SD): 12.3 (4.3)	All	ICD-10-CM: E08–E13	>30 days	Matched	1) COVID vs non-COVID-19: HR: 2.66 (1.98–3.56) 2) COVID-19 vs ARI: HR 2.16 (1.64–2.86)
	HealthVerity	Mar 1, 2020 – Jun 28, 2021		Closed payor system; 0.9 % hospitalized with COVID-19	878,878	50	Non-COVID-19	49.9	Mean (SD): 12.7 (4.3)					HR: 1.31 (1.20–1.44)
Daugherty [35]	United Health	<1 Apr 2020	USA	Insured population; continuous enrolment	9.25 million	3	1) non-COVID 2020; 2) non-COVID 2019; 3) ARI	50.2	Mean (SD): 42.4 (13.6)	Type 2	ICD-10-CM: E11	median (IQR): 95 (42–135)	Propensity score	COVID-19 vs non-COVID 2020: HR: 1.83 (1.60–2.10) COVID-19 vs non COVID 2019: HR: 1.80 (1.57–2.06) COVID-19 vs ARI: HR: 1.39 (1.22–1.58) Not hospitalized

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Table 2 (*continued*)

Study characteristics					Sample characteristics				Diabetes Outcome			Analysis		Findings
First Author	Cohort Name	COVID-19 diagnosis date	Country	Study population	Sample size N	COVID-19 (%)	non-COVID comparator	Men (%)	Age (years)	Diabetes Type	Diabetes Definition	Follow-up time	Adjusted	Risk estimate (95 %CI)
														COVID-19 vs non-COVID 2020: RR: 1.70[2] Hospitalized COVID-19 vs non-COVID 2020: RR: 3.66[2]
Hernandez-Romieu [34]	PCORnet	Mar – Dec 2020	USA	Adults (≥20 years) who had undergone a PCR test for COVID-19	1.79 million	12.2	Negative COVID-19 test	40	≥20	Type 2	ICD-10-CM: E11	31–150 days	Unadjusted	Non-hospitalized positive COVID test vs negative COVID test: PR: 0.9 (99 % CI: 0.85–0.96) Hospitalized positive COVID test vs negative COVID test: PR: 2.03 (99 % CI: 1.87–2.19) Mechanically ventilated positive COVID test vs negative COVID test: PR: 2.25 (99 % CI: 1.82–2.77)
				Children (<20 years) who had undergone a PCR test for COVID-19	338,024	10.6		50	<20					Non-hospitalized positive COVID test vs negative COVID test: PR: 1.27 (99 % CI: 1.75–2.14) Hospitalized positive COVID test vs negative COVID test: PR: 2.14 (99 % CI: 1.13–4.06)
Horberg [58]	KPMAS	Jan 2020–Dec 2020	USA	Insured adults (>18 years); continuous enrolment	98,411	28.6	Non-COVID-19	42.7	≥18	All	CCS 49 and 50	30–120 days	Matched	RR: 1.20 (1.03–1.38)
Kendall [39]	TriNetX	Mar 2020–Dec 2021	USA	Insured population	1.09 million	28.9	ARI	50	0–18	Type 1	ICD-10 code E10	3 and 6 months	Matched	*3 months* 0–18 years: HR: 2.10 (1.48–3.00) 0–9 years: HR: 1.75

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Table 2 (*continued*)

Study characteristics					Sample characteristics				Diabetes Outcome			Analysis		Findings
First Author	Cohort Name	COVID-19 diagnosis date	Country	Study population	Sample size N	COVID-19 (%)	non-COVID comparator	Men (%)	Age (years)	Diabetes Type	Diabetes Definition	Follow-up time	Adjusted	Risk estimate (95 %CI)
														(0.92–3.32) 10–18 years: HR: 2.40 (1.62–3.56) *6 months* 0–18 years: HR: 1.83 (1.36–2.44) 0–9 years: HR: 1.73 (1.02–2.94) 10–18 years: HR: 2.18 (1.57–3.03)
McKeigue [30]	REACT-SCOT	Mar 1, 2020–Nov 22, 2021	Scotland	<35 years	1.85 million	19.7	Non-COVID-19	50	0–35	Type 1	ICD-10 (E10-E14), outpatient code, or medication	≥30 days	Matched	HR: 0.86 (0.62–1.210
Nayar [31]	COVIDPAN	Mar 1, 2020–Jul 23, 2020	Multi-country	Patients hospitalized with acute pancreatitis	1,476	8.0	Non-COVID-19	52.3	Mean (SD): 54.5 (18.1)	All	Not reported	12 months	Adjusted	OR: 0.61 (0.13–2.96)
Rezel-Potts [36]	CPRD Aurum	Jan 2020–Feb 2021	UK	Family Practices	857,300	50	Non-COVID-19	44.0	Median (IQR): 35 (22–50)	All	ICD codes, diabetic medication, or HbA1c ≥ 48 mmol/mol	Range 5–52 weeks	Matched and adjusted	5–12 weeks from index date: RR: 1.27 (1.11–1.46) 13–52 weeks from index date: RR: 1.07 (0.99–1.16)
Wander [32]	VHA	Mar 2020 –Mar 2021	USA	US Veterans; 2 % hospitalized with COVID	2.8 million	4.6	Non-COVID-19	86.0	Mean (SD): 59.0 (17.1)	All	Abnormal laboratory values (e.g., HbA1c) or ICD-10 E08-E13 or antihyperglycemic medication	COVID-19 group: mean 193 days [range 32–456]; non-COVID-19 group: mean 239 days [range 32–457])	Adjusted	Men 120 days: OR: 2.56 (2.32–2.83) Men total time: OR: 1.95 (1.80–2.12) Women 120 days: OR: 1.21 (0.88–1.68) Women total time: OR: 1.04 (0.82–2.12) Hospitalized men 120 days: OR: 1.42 (1.22–1.65) Hospitalized men total time: OR: 1.32 (1.16–1.50)

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Table 2 (*continued*)

Study characteristics					Sample characteristics				Diabetes Outcome			Analysis		Findings
First Author	Cohort Name	COVID-19 diagnosis date	Country	Study population	Sample size N	COVID-19 (%)	non-COVID comparator	Men (%)	Age (years)	Diabetes Type	Diabetes Definition	Follow-up time	Adjusted	Risk estimate (95 %CI)
Xie [12]	VHA	Mar 1, 2020–Sept 30, 2021	USA	US Veterans who survived 30 days; 8.3 % of COVID-19 patients hospitalized and 2.3 % admitted to ICU	contemporary cohort: 4.5 million; historical cohort; 4.3 million	4.2	Contemporary control: Non-COVID-19 who used the VHA services in 2019; Historical cohort: used the VHA services in 2017	COVID-19: 88.1; contemporary control: 88.8; historical control: 88.7	Mean (SD): COVID-19: 60.6 (17.0); contemporary control: 61.5 (17.1); historical control: 61.5 (17.1)	All	ICD-10 codes (E08.X to E13.X) or a HbA1c measurement of>6·4%	Median (IQR): COVID-19: 352 (244–406); contemporary control: 352 (245–406); historical control: 352 (245–406) days	Propensity Score	Hospitalized women 120 days: OR: 0.72 (0.34–1.52) Hospitalized women total time: OR: 0.80 (0.44–1.45) COVID-19 vs contemporary control: HR 1.40 (1.36–1.44) COVID-19 vs contemporary control non-hospitalized: HR 1.25 (1.21–1.29) COVID-19 vs contemporary control hospitalized: HR 2.73 (2.50–2.99) COVID-19 vs contemporary control ICU admission: HR 3.76 (3.24–4.37) COVID-19 vs historical control: HR 1.35 (1.31–1.39) COVID-19 vs historical control non-hospitalized: HR 1.21 (1.17–1.25) COVID-19 vs historical control hospitalized: HR 2.66 (2.43–2.91)

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Table 2 (*continued*)

Study characteristics					Sample characteristics				Diabetes Outcome			Analysis		Findings
First Author	Cohort Name	COVID-19 diagnosis date	Country	Study population	Sample size N	COVID-19 (%)	non-COVID comparator	Men (%)	Age (years)	Diabetes Type	Diabetes Definition	Follow-up time	Adjusted	Risk estimate (95 %CI)
														COVID-19 vs COVID-19 vs historical control ICU admission: HR 3.66 (3.15–4.25)
Xie [59]	VHA	Mar 1, 2020–Mar 15, 2021	USA	US Veterans who survived 30 days	4.4 million	4.1	General VHA users	90.5	Median (IQR) 67.1 (53.1–74.5)	All	ICD-10 code E08-13 or HbA1c > 6.5 % or use of antihyperglycemics	6-months	Unadjusted	HR: 1.39 (1.33–1.44)
Zhang [37]	n/a	Jan 1, 2020–Mar 30, 2021	Multi-country	Hospitalized patients	580,287	13.0	Non-COVID-19 hospitalized patients	With COVID-19: 74.0 Without COVID-19: 76.0	≥18 years	Type 2	ICD codes	≥30 days	Unadjusted	No increased diabetes risk, RR not reported
				Non-hospitalized patients	2.2 million	15.9	Non-COVID-19 hospitalized patients	With COVID-19: 64.0 Without COVID-19: 59.0						Mid-stage (30–89 days post infection): RR: 1.26 (1.16–1.36) Late stage (≥90 days): RR: 1.11 (1.02–1.21)

Abbreviations: ARI = Acute Respiratory Infection; AURI = Acute Upper Respiratory Infection; CCS = Certified Coding Specialist; CI = Confidence Interval; GP = General Practitioner; HR = Hazard Ratio; ICU = Intensive Care Unit; IRR: Incident Rate Ratio; KPMAS = Kaiser Permanente Mid Atlantic Sites; OR = Odds Ratio; PR = Prevalence Ratio; RR = Relative Risk; UK = United Kingdom; USA = United States of America; VHA: Veterans' Health Administration.

[1]Risk estimate calculated using values from Supplementary Table 2 of original manuscript by Ayoubkhani et al.

[2]Risk estimates calculated using values from Supplementary Table 4d of original manuscript by Daugherty et al.

(14 %–31 %) and 52 % (36 %–70 %) increase in new-onset diabetes among mild and moderate-severe COVID-19 cases, respectively, as compared with non-COVID-19 ARI comparisons across three studies. In the current review, we include data from an additional eight studies. Though the conclusions between the current and earlier review are similar, we caution researchers against pooling of risk estimates when heterogeneity is high as it can lead to misleading interpretations of the available data. In particular, studies included in this review differed by methods of detecting new-onset diabetes (i.e., ICD codes vs HbA1C and use of hyperglycemic medication, and type 1 vs type 2), comparison populations (i.e., non-COVID-19, general population, or ARI), follow-up time, and analytical methods (i.e., propensity score, matching, adjustment). This issue is highlighted when studies using the same study population, but differing methodologies produce different results. For example, using the Veterans Health Administration (VHA) data, Al-Aly [33] showed an increased risk for type 2 diabetes in non-hospitalized, but not hospitalized patients, while the study by Xie et al. [12] using the same data demonstrated a graded increased risk whereby patients hospitalized with COVID-19 and admitted to the ICU had a greater risk than non-hospitalized COVID-19 patients. These differences are likely to be explained primarily by the different comparison populations used in these two studies. In Al-Aly, people hospitalized with COVID-19 are compared to a historical cohort hospitalized with influenza, while in the Xie et al. study, they are compared to a non-hospitalized population.

Given the large and growing number of people infected with COVID-19 (562 million people globally as of July 20, 2022[41]), identifying people at high risk of COVID-19-related complications, including PASC and new-onset diabetes, to manage and prevent complications is of high importance. The findings from this review underscore the importance of COVID-19 prevention strategies, including vaccination, in addition to screening for and managing PASC. Prevention should include screening and monitoring for signs of diabetes following COVID-19 infection. In addition, it may be important to identify people with diabetes as high-risk for PASC to allow for additional screening, monitoring, and possible prevention and treatment. For example, poorly controlled diabetes increases the risk of severe COVID-19 and is associated with increased morbidity and mortality [42]. Regular monitoring of glucose levels, coupled with the use of glucose-lowering agents as appropriate [43], may therefore help in reducing and managing PASC risk.

This review examines diabetes as a risk factor for PASC (long COVID) and incident diabetes as a key complication of COVID. The key strength of this review is in the systematic approach to the search strategy which includes two databases (Embase and Pubmed), and broad search terms to attempt to capture all published data on diabetes and COVID-19. Key limitations include the possible exclusion of relevant studies not published in English, the heterogeneity of studies, particularly with respect to PASC definitions, limiting our ability to pool risk estimates across studies, and possible misclassification of diabetes status due to undiagnosed cases. As the evidence base builds, researchers are encouraged to adopt rigorous approaches to assess and define PASC, and carefully document the association between diabetes and PASC to enable meaningful comparisons between studies. This includes the use of validated algorithms for identifying people with diabetes in administrative data [44], refining PASC definitions as per NIH and CDC guidelines [2], and the use of appropriate comparison groups (i.e., people without diabetes rather than people without comorbidities).

5. Conclusion

The conclusions of this systematic review are twofold. First, among 14 studies, 86 % report that COVID-19 survivors may be at increased risk for new-onset diabetes and thus careful monitoring of high-risk individuals (i.e., those with pre-diabetes or those hospitalized with COVID-19) for the development of diabetes may be advised. Second, among 25 studies, whether pre-existing diabetes is also a risk factor for PASC remains unclear with 44 % indicating diabetes is a PASC risk factor, and 56 % indicating it is not. More high-quality studies across multiple populations and settings are needed to determine if diabetes is indeed a risk factor for PASC. In the meantime, careful monitoring of people with diabetes for development of PASC may be advised.

6. Contribution statement

JLH conceptualized the paper, conducted the literature review, extracted data, and wrote the paper. SO screened studies for eligibility, extracted data, and reviewed the final manuscript. MKA, IO, DJM, and REP provided intellectual input, and reviewed the final manuscript. JLH is the guarantor of this work and takes responsibility for final responsibility for the decision to submit for publication.

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.diabres.2022.110202.

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