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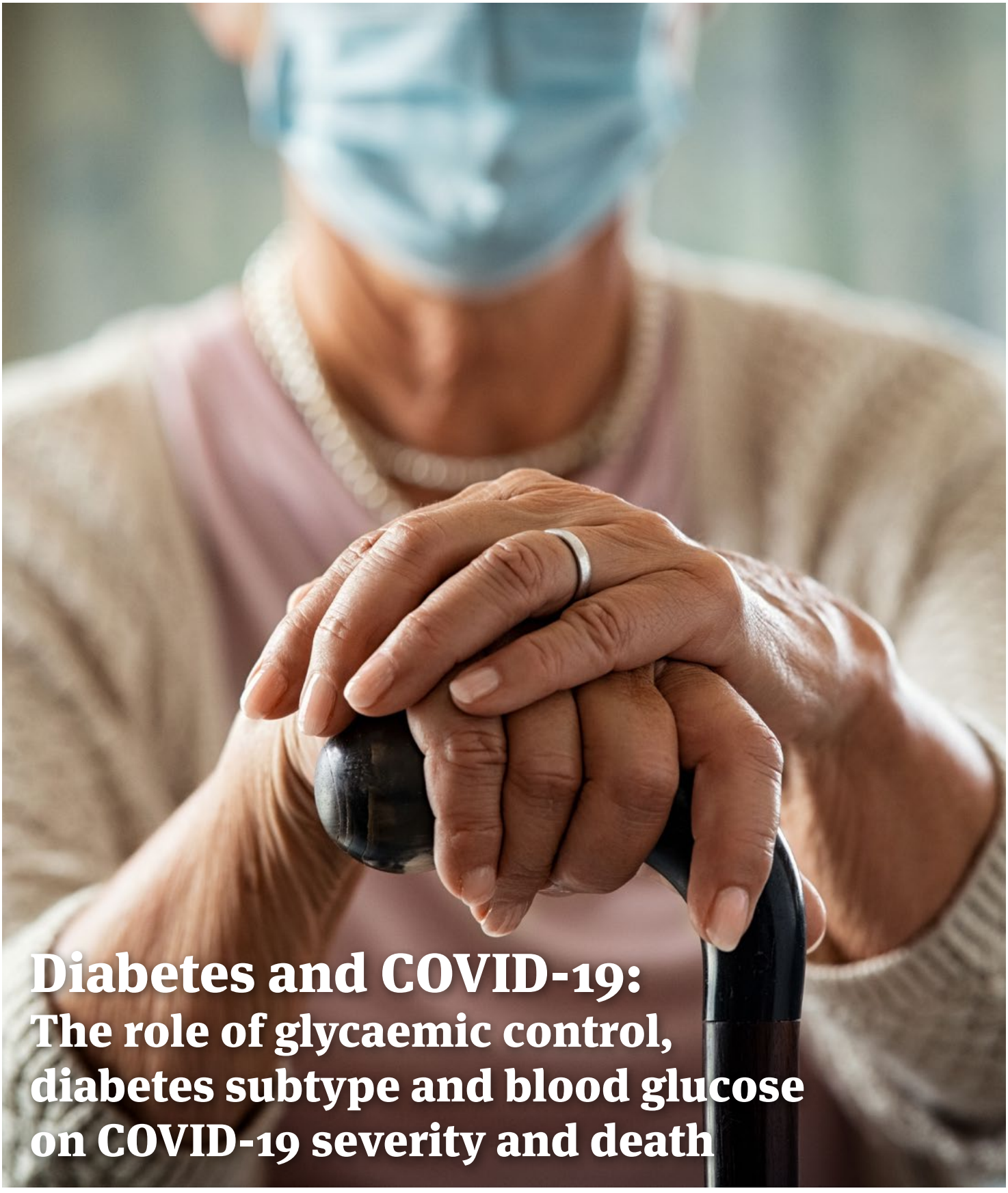

Diabetes and COVID-19:
The role of glycaemic control, diabetes subtype and blood glucose on COVID-19 severity and death

Acknowledgements

Authors: Diabetes and COVID-19: The role of glycaemic control, diabetes subtype and blood glucose on COVID-19 severity and death

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Introduction

Key messages

- **COVID-19 remains a global health emergency according to WHO, with over 700,000,000 confirmed cases as of the end of 2022.**
- **Among individuals with diabetes who were infected with COVID-19, poor glycaemic control is a risk factor for adverse COVID-19 endpoints. There was a 35-40% increase in the odds of COVID-19 hospitalisation and severe illness among adults with diabetes and haemoglobin A1c levels over or equal to 7% compared to those with haemoglobin A1c less than 7%.**
- **People with diabetes who were admitted to hospital with COVID-19, blood glucose concentrations of more than 10 mmol/L (180 mg/dL) were associated with a three times greater odds of severe illness, including intensive care unit admission, mechanical ventilation or death, and in-hospital mortality.**
- **Studies comparing type 1 and type 2 diabetes yielded heterogeneous results. Many did not adequately control for differences in age and comorbidity levels across diabetes subtypes, and most reported small numbers of events among people with type 1 diabetes which made it difficult to adequately compare risk and yield stable rate estimates.**

Diabetes is a strong risk factor for adverse COVID-19 outcomes.[1] As reported in the 2021 *IDF Diabetes Atlas*, individuals with diabetes experience a substantially greater likelihood of hospitalisation and death as a result of COVID-19 infections compared to those without.[1] Following the onset of the pandemic, three population-based studies from the UK and Sweden demonstrated an early rise in both all-cause and COVID-19 related mortality among people with diabetes, relative to those without diabetes of the same age.[2-4] In these three studies, excess deaths and critical illnesses due to COVID-19 were greater for those with type 1 diabetes than for those with type 2 diabetes. Research also suggests that individuals with diabetes who have poor glycaemic control at the time of infection have a higher risk of adverse outcomes from COVID-19.[5-7] Among the many putative mechanisms that link diabetes and COVID-19, high blood glucose concentrations are thought to cause dysregulation of immune function and may help trigger the catastrophic inflammatory cytokine response to infection, which leads to acute respiratory distress syndrome (ARDS) and septic shock.[8,9]

For this report, we undertook a systematic review to evaluate diabetes-related risk factors for a variety of COVID-19-related endpoints among individuals with diabetes, including hospitalisation, severe COVID-19 illness and mortality. Severe COVID-19 illness was defined as admission to an intensive care unit (ICU), mechanical ventilation (MV), acute respiratory distress syndrome (ARDS) or multiorgan failure, either alone or in combination with other markers of severity, including death. Most studies that examined severe illness reported a composite outcome of ICU admission, MV or death, or a subset thereof. However, a smaller subset of studies defined severity based on the clinical features that would warrant ICU admission or MV, such as signs of ARDS or poor/worsening oxygenation, consistent with the 'severe' or 'critical' categories in the COVID-19 Treatment Guidelines.[10,11]

Overall, 3,799 articles were assessed for relevance, and data from 91 studies were abstracted for analysis.[2,7,12-100] Where possible, results were combined to create summary measures that describe the likelihood of adverse COVID-19 outcomes in relation to glycaemic control, blood glucose levels on admission to hospital, and diabetes subtype. A description of the methodology for this review can be found in Appendix 1.

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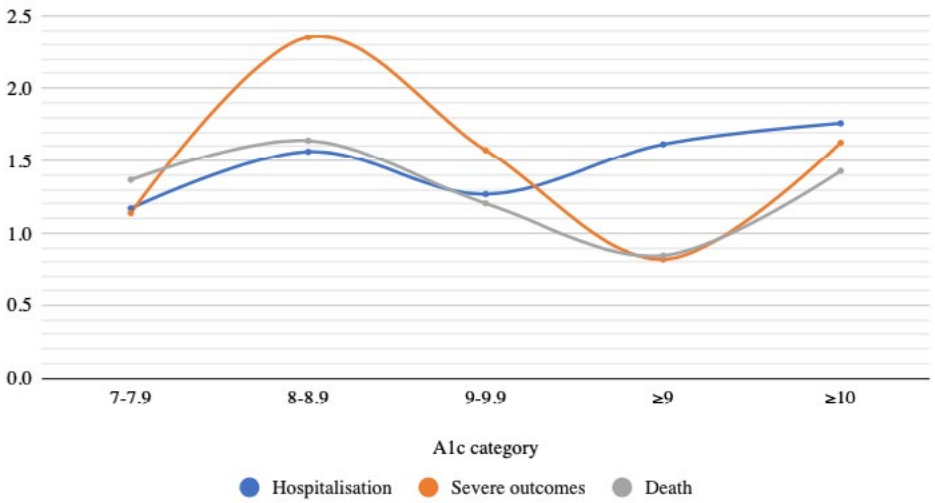
Glycaemic control in patients with diabetes and COVID-19

Table 1 summarizes results from 52 studies that evaluated the impact of glycaemic control on COVID-19 outcomes in patients with diabetes diagnosed with COVID-19 in community settings (N=18) or during hospitalisation (N=34). Glycaemic control, as measured by haemoglobin A1c levels, was a risk factor for all adverse outcomes following COVID-19 infection.[2,12-62] For instance, adults with diabetes and COVID-19 whose most recent A1c level was greater than 7% had a higher likelihood of hospitalisation than those with optimal A1c levels (less than 6.5 or 7%), evidenced by significant findings in 8 out of 10 studies.[12-21] Individuals who had A1c levels above this range had, on average, a 56% increase in the likelihood of being hospitalised for COVID-19, based on unadjusted (crude) analyses,[15-21] and a 35% increase in the likelihood of hospitalisation after adjusting for differences in age, sex, the presence of comorbidities, or other confounding factors.[12-19]

Similar findings were noted for COVID-19 severity and death.[2,13-17,21-62] In unadjusted analyses, having an elevated A1c level in the moderate to high range (7-10%, Table 1) was a risk factor for adverse outcomes from COVID-19, with a 65% and 72% greater risk of severe illness and death compared to individuals who had lower A1c levels.[2,15,21-42] In contrast, having a very high A1c level (›9 or ›10% depending on the study) was not a risk factor for disease severity or death in unadjusted analyses.[2,21,22,37-44] As depicted in Figure 1, the relationship between A1c and severe outcomes was not linear.[17,39,45-54] Adjustments for age, sex, and/or other relevant factors eliminated differences in findings across A1c categories to some extent. The adjusted odds of severe illness increased significantly by 40% among individuals with both moderate to high (7-10%) and very high A1c (›9 or ›10%) levels compared to those with optimal glycaemic control (Table 1).[13,14,22-24,47,57] Additionally, after adjusting for confounding factors, the relationship between A1c and mortality from COVID-19 was no longer apparent overall, nor in subgroup analyses comparing moderate to high or very high A1c concentrations with lower A1c levels (Table 1).[13-15,23,42,44,47]

These adjusted analyses may have accounted for factors, such as age and body mass index, that could modify the relationship between A1c and severe COVID-19 related illness.[1,101] In addition, young individuals with type 1 or type 2 diabetes are more likely to develop diabetic ketoacidosis (DKA) in the context of COVID-19, particularly if they have poor glucose control at the time of infection.[102,103] Such individuals will require close monitoring in an ICU setting for their metabolic abnormalities, even if their pulmonary disease is mild. Younger adults are also far more likely to survive COVID-19 than older adults.[1] These factors could contribute to observed differences in the association between A1c and severe illness (which includes ICU admission) and COVID-19-related mortality. Finally, it is possible that healthcare providers are more likely to admit individuals with poor glucose control to hospital in the setting of COVID-19 for management of hyperglycaemia, or because of their perceived risk for adverse outcomes, even in the absence of DKA or severe illness.[1]

Figure 1: Unadjusted Odds of COVID-19-Related Outcomes in Hospitalised or Outpatient Populations with Diabetes and Covid-19, by A1c Level Comparison Group †



For comparison arms comprised of a discrete range of A1c values, the mid-point of the range was used to assign the study findings to a given A1c category. Comparison arms that included a broad range of values were assigned to the next category above the upper threshold, unless otherwise indicated. For example, ≥7% was assigned to 8-8.9% and ≥ 8% to 9-9.9%.

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Table 1: Association between A1c level (%) and odds of adverse COVID-19-related outcomes in hospitalised and outpatient populations (N=174,280)

Outcome, Comparison Group	Unadjusted Odds Ratio (95% CI)	No. Studies	Adjusted Odds Ratio (95% CI)*	No. Studies
Hospitalisation				
Increased A1c † ≥7%	**1.56** (1.32-2.08)	5	**1.35** (1.21-1.55)	4
Moderate to high A1c† 7.0-9.9%	**1.56** (1.35-1.99)	5	**1.26** (1.09-1.54)	4
Very high A1c † ≥9 or 10%	**1.61** (0.99-3.32)	3	**1.44** (1.33-1.55)	2
Per 1%	**1.24** (1.13-1.37)	3	**1.13** (1.07-1.20)	4
Severe COVID-19 outcomes **				
Increased A1c † ≥7%	**1.53** (0.98-2.69)	16	**1.41** (1.20-1.73)	7
Moderate to high A1c† 7.0-9.9%	**1.65** (1.01-3.06)	16	**1.4** (1.18-1.75)	5
Very high A1c † ≥9 or 10%	**1.19** (0.82-1.78)	7	**1.4** (1.27-1.67)	3
Per 1%	**1.18** (0.88-1.65)	6	**1.13** (1.07-1.21)	9
COVID-19 mortality				
Increased A1c † ≥7%	**1.53** (1.07-2.39)	17	**1.03** (0.95-1.12)	9
Moderate to high A1c† 7.0-9.9%	**1.72** (1.18-2.72)	15	**1.12** (0.81-1.63)	7
Very high A1c † ≥9 or 10%	**0.92** (0.68-1.31)	7	**1.12** (0.82-1.65)	6
Per 1%	**0.99** (0.96-1.03)	8	**1.1** (0.80-1.58)	3

* Adjusted for age, sex, +/- presence of comorbidities, or other confounding factors
† Reference category = ≤ 6.5% or < 7.0% or ≤ 7.0% depending on the study
** Intensive care unit admission, mechanical ventilation or death

Blood glucose on admission in hospitalised patients with diabetes and COVID-19

Based on 42 studies of inpatient populations with COVID-19 [7,24,27,35-38,44,47,50-53,61-89], blood glucose concentrations at the time of hospital admission were significantly associated with adverse outcomes (Table 2).The magnitude of this association was reduced after adjustment for relevant covariates, and the risk of adverse COVID-19 endpoints remained significant only for those with very high glucose levels. Modest elevation in blood glucose (e.g. 7-10 mmol/L) resulted in a non-significant increase in mortality, while blood glucose levels higher than 10 mmol/L were associated with two to three times greater odds of death compared to individuals with lower glucose levels on admission.

There were inconsistencies across studies with respect to how diabetes was determined

There were inconsistencies across studies with respect to how diabetes was determined. Studies that based the diagnosis of diabetes on blood glucose levels at the time of hospitalisation may have captured non-diabetes cases presented to hospitals with stress hyperglycaemia. This misclassification of diabetes status among non-diabetes cases may have diminished the magnitude of the association between higher glucose levels and adverse outcomes, given that diabetes is associated with higher risk of severe adverse outcomes from COVID-19.[1] While most studies examined glucose levels at presentation, some assessed blood glucose concentrations that had been averaged over 48 to 72 hours, and thus reflected treatments received during the initial hospital stay. Individuals admitted to critical care units are more likely to receive an insulin infusion, which could lead to lower average glucose values among critically ill patients than among those treated outside of a critical care unit. This could result in a higher frequency of adverse outcomes among those with lower glucose levels.[104,105] Lastly, the findings could have been affected by treatment with dexamethasone for severe COVID-19, which can lead to substantial elevations in blood glucose levels during hospitalisation.[106,107]

Table 2: Association between blood glucose (BG) level (mmol/L) on admission and odds of adverse COVID-19-related outcomes in hospitalised patients (N=17,335)

Outcome, Comparison Group	Unadjusted Odds Ratio (95% CI)	No. Studies	Adjusted Odds Ratio (95% CI)*	No. Studies
Severe COVID-19 outcomes **				
Increased BG † ≥6 mmol/L	**2.3** (1.0-6.64)	14	**1.93** (0.85-5.36)	7
Moderate to high BG † 6-11 mmol/L	-	-	-	-
Very high A1c † >10 or 11 mmol/L	**2.27** (1.14-5.14)	10	**2.82** (1.15-7.53))	6
Per 1 mmol/L increase	**1.06** (0.92-1.31)	7	**1.15** (0.96-1.42)	7
COVID-19 mortality			**7**	
Increased BG † ≥6 mmol/L	**2.87** (1.55-6.14)	15	**2.76** (1.00-9.08)	15
Moderate to high BG † 6-11 mmol/L	**1.7** (1.23-2.46)	4	**1.19** (0.38-5.73)	4
Very high A1c † >10 or 11 mmol/L	**3.22** (1.70-7.02)	12	**3.17** (1.16-9.96)	13
Per 1 mmol/L increase	**1.05** (0.99-1.11)	4	**1.09** (1.01-1.54)	9

* Adjusted for age, sex, +/- presence of comorbidities, or other confounding factors
† Reference category < 6.0 or < 7.8 mmol/L in most studies, <4.0 mmol/L in two studies
** Intensive care unit admission, mechanical ventilation or death

Type 1 versus type 2 diabetes

From a review of 19 studies that compared the rate of adverse COVID-19 endpoints among individuals with type 1 or type 2 diabetes, the findings appeared to be quite heterogeneous.[2,13,35,36,38,54,88-100] In three out of six studies, type 2 diabetes was associated with greater unadjusted odds of hospitalisation than type 1 diabetes,[54,89,96] whereas the remaining studies reported nonsignificant findings.[13,90,95] Most studies found no significant association between diabetes subtype and COVID-19 severity or death, and some studies reported opposite results.[13,91,96]

These comparisons were limited by an extremely small number of outcome events in those with type 1 diabetes. Furthermore, few studies accounted for the broad difference in age and comorbidity status across diabetes subtypes. The only propensity score-matched study on this topic was conducted using population-based data from Turkey[13] where individuals with type 1 diabetes had a two to three times greater likelihood of critical illness and death.

These associations persisted after adjusting for differences in A1c and both microvascular and macrovascular complications. A large study, which captured 25% of admissions for COVID-19 in the United States, reported an excess risk of ICU admission for type 1 diabetes compared to type 2 diabetes, but similar mortality in these two diabetes subtypes.[91] In this study, models that adjusted for the presence of DKA (which can occur in both individuals with type 1 and type 2 diabetes who have COVID-19)[102] eliminated any differences in ICU risk between diabetes subtypes, but uncovered a greater mortality risk among those with type 2 diabetes. Discordant findings across studies may also reflect a tendency in some countries for younger adults to be admitted to critical care units due to the triaging of cases when intensive care unit beds were in short supply during the first and second waves of the pandemic;[108,109] as well as the higher proportion of COVID-19 deaths in the community among older adults living in alternate care settings, who were more likely to have type 2 diabetes.[110]

Overall, this review noted a strong relationship between the acute and chronic measures of glycaemia and COVID-19 severity. While higher glucose concentrations are thought to exacerbate the inflammatory response to COVID-19, the reasons for observed associations are likely to be more complex. Blood glucose levels serve as a marker of disease severity for a variety of acute illnesses due to the negative impact of counterregulatory hormones (e.g. adrenaline) on insulin sensitivity and secretion. Therefore, there may be an element of reverse causality whereby individuals who have severe COVID-19 outcomes experience greater elevations in glucose due to their acute illness. Because this phenomenon (stress hyperglycaemia) occurs in both individuals with and without diabetes, careful ascertainment of diabetes status at the time of infection is essential to disentangle the effects of acute illness on the association between glucose and COVID-19 severity.

After adjusting for confounding factors, the risk of adverse COVID-19 outcomes was generally similar for those with type 1 and type 2 diabetes. However, several studies pointed to worse outcomes, particularly higher rates of ICU admission for those with type 1 diabetes, for reasons that have not been fully elucidated. Prevention and early treatment of COVID-19, and of DKA in the setting of COVID-19, may help to mitigate the excess risk of adverse COVID-19 outcomes in people with diabetes who have less glucose control. However, further research is needed to understand the optimal methods for doing so.

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Appendix 1: Diabetes and COVID-19 research methods

This systematic review was undertaken to examine the association between key diabetes-related risk factors and adverse COVID-19 related outcomes. The Cochrane Handbook for Systematic Reviews was used to develop the study design, and the protocol was registered with PROSPERO: the International Prospective Register of Systematic Reviews (registration #CRD42021236875).[1-2] A comprehensive search of the published peer-reviewed literature was conducted by a senior information specialist working at St. Michael's Hospital in Toronto, Canada in February 2021 in preparation for the 2021 *IDF Diabetes Atlas*, and updated again in May 2022. In response to the large influx of COVID-19 research, the updated May 2022 search included keywords for specific risk factors of interest (glycated haemoglobin/A1c, blood glucose level at the time of hospital admission, and diabetes subtype) and 15 possible outcomes, including hospitalisation, critical illness and death. Using the systematic review software, Covidence,[3] studies were independently assessed for relevance by two reviewers, starting with title and abstracts, before moving on to full-text review. Disagreements were resolved by consensus.

Articles were eligible for inclusion if the study sample consisted of adults with confirmed COVID-19 based on validated diagnostic testing (or clinical guidelines if the study preceded the availability of rt-PCR testing), and at least 20 members of the sample with established diabetes. In addition, the study had to provide data that would allow for a comparison of COVID-19-related hospitalisations, critical illness or deaths, according to A1c level, blood glucose concentration at the time of hospital admission, or diabetes subtype. Articles that restricted their sample to specialised groups, such as organ transplant recipients or people admitted with diabetic ketoacidosis, were excluded.

Key information was extracted from each study, including measures of the effects associated with a given risk factor. These consisted primarily of odds ratios (ORs) and 95% confidence intervals (95% CI). If unavailable, ORs were calculated using crude numbers of individuals per group who did or did not have an event, using the formula by Higgins et al. outlined in the Cochrane Handbook for Systematic Reviews.[4] Where possible, ORs from individual articles were statistically pooled based on derived weights that reflect the number of outcome events observed in a given study relative to the total number of events observed across all studies. Some studies reported ORs for different comparison arms separately (e.g. A1c categories for those with an A1c of 7.0-7.9%, 8.0-8.9%, and ≥9% versus <7% computed separately), therefore, the number of events occurring in each comparison arm (but not within referent groups) were used to determine a given study's sample weight to avoid double counting. For continuous analyses, sample weights were based on the number of outcome events in the overall study. Therefore, if a study contributed 100 outcome events among a total of 1,000 events across all studies, that study would account for 10% of the pooled OR and, therefore, the calculated weight would be 0.1. Pooled ORs were derived for each outcome of interest and stratified based on whether or not analyses adjusted for one or more confounders, and based on the magnitude of elevation in A1c or blood glucose. Research findings related to diabetes subtype were summarised qualitatively and not combined due to heterogeneity across studies.

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