

Risks of and from SARS-CoV-2 infection and COVID-19 in people with diabetes: a systematic review of reviews

Running title: Risks of COVID-19 in people with diabetes

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Abstract

Background

This review was commissioned by the World Health Organization and presents a summary of the latest research evidence on the impact of COVID-19 in people with diabetes (PWD).

Purpose

To review the evidence regarding the extent to which PWD are at increased risk of SARS-CoV-2 infection, and/or of suffering its complications including associated mortality.

Data sources

We searched the Cochrane COVID-19 study register, Embase, MEDLINE, and LitCOVID on 3 December 2020.

Study selection

Systematic reviews synthesising data on PWD exposed to SARS-CoV-2 infection, reporting data on confirmed SARS-CoV-2 infection, admission to hospital and/or to ICU with COVID-19, death with COVID-19.

Data extraction

One reviewer appraised and extracted data; data were checked by a second.

Data synthesis

Data from 112 systematic reviews were narratively synthesised and displayed using effect direction plots. Reviews provided consistent evidence that diabetes is a risk factor for severe disease and death from COVID-19. There was less data available on ICU admission, but where available this data also signalled increased risk. Within PWD, higher blood glucose levels both prior to COVID-19 illness and during COVID-19 illness were associated with worse COVID-19 outcomes. Type 1 diabetes was associated with worse outcomes compared to type 2 diabetes. There was no appropriate data for discerning whether diabetes was a risk factor for acquiring SARS-CoV-2 infection.

Limitations

Due to the nature of the review questions, the majority of data contributing to included reviews come from retrospective observational studies. Reviews varied in the extent to which they assessed risk of bias.

Conclusions

There are no data on whether diabetes predisposes to infection with SARS-CoV-2. Data consistently show that diabetes increases risk of severe COVID-19. As both diabetes and worse COVID-19 outcomes are associated with socioeconomic disadvantage, their intersection warrants particular attention.

Introduction

In the context of the COVID-19 pandemic, the World Health Organisation (WHO) and WHO Member States are requesting information and guidance on key topics related to COVID-19 and the virus which causes the disease, SARS-CoV-2. This review of reviews was commissioned to address specific key questions for WHO to provide high-quality, evidence-informed information around COVID-19.

This review presents a summary of the synthesised research evidence on the effects of COVID-19 in people with diabetes (PWD).

At the outset of the pandemic, PWD were assumed to be at increased risk from COVID-19. During 2020, emerging data signalled increased risk of adverse outcomes in PWD, likely dependent on a range of different factors.(1, 2) It is important to establish the risks COVID-19 poses to PWD in order to enable informed decision-making by PWD, their carers, healthcare providers, and policymakers.

Therefore, in this review of reviews, we set out to synthesise the evidence regarding the extent to which PWD are at increased risk of SARS-CoV-2 infection, and/or of suffering its complications including associated mortality. In particular, we set out to analyse evidence on the following questions:

1. Is diabetes associated with increased risk of acquiring SARS-CoV-2?
2. Is diabetes associated with hospitalization with COVID-19?
3. Is diabetes associated with the severity (including ICU admission, death, and other composite measures of severity) of COVID-19 outcomes?
4. Are there differences in outcomes of SARS-CoV-2 infection within the population of people with diabetes?

Methods

A protocol was agreed in advance with the WHO and published online.⁽³⁾ Methods follow a general framework for a suite of reviews commissioned by WHO in respect to their scientific briefs on COVID-19 and selected non-communicable diseases. As pre-specified by WHO, systematic reviews were first identified; primary studies were then to be reviewed only if insufficient systematic reviews were found.

Data sources and searches

We searched the Cochrane COVID-19 study register, Embase, MEDLINE, and LitCOVID on 3 December 2020 for published literature or literature accepted for publication but not yet published, in any language (see Appendix 1 in Supplemental Information for search strategies).

Study selection

Two reviewers screened titles and abstracts, with discrepancies resolved by discussion or referral to a third reviewer. One reviewer screened full texts. We selected systematic reviews (defined as any review in which at least one database was systematically searched) according to the following inclusion criteria, defined using PECO (population; exposure; comparator; outcome):

- Population: people diagnosed with any type of diabetes, with no limitations by age, disease severity, or duration. Excluding people with 'pre-diabetes' (e.g. impaired glycaemic control which does not meet clinical threshold for diabetes diagnosis) and gestational diabetes.
- Exposure: SARS-CoV-2 infection.

- Comparator: Questions 1 to 3 (as above), people without diabetes. Question 4 (as above): people with diabetes, according to the following comparisons as specified in advance by WHO:
 - Type 1 vs type 2 diabetes
 - Controlled vs uncontrolled glycaemia (by HbA1c, whichever definition of control has been used)
 - Previously diagnosed diabetes vs diabetes first diagnosed at COVID-19 diagnosis
 - People treated with metformin vs people not treated with metformin
 - People treated with dipeptidyl peptidase 4-inhibitors (DPP4-i) vs people not treated with DPP4-i
 - People treated with insulin vs people not treated with insulin
 - People with CVD/hypertension/ chronic kidney disease vs people without
 - Low socioeconomic status vs high socioeconomic status
- Outcome: Rates of confirmed SARS-CoV-2 infection; admission to hospital and/or to ICU with COVID-19; death with COVID-19.

Data extraction and quality assessment

One reviewer appraised and extracted data from systematic reviews in relation to the above review questions; data were checked by a second. We included any systematic reviews which met the above criteria. Quality was assessed using the AMSTAR-2 checklist, but focussing only on critical domains, namely: protocol registered before commencement; adequacy of literature search; justification for excluding individual studies; risk of bias from individual studies; appropriateness of meta-analytical methods; consideration of risk of bias when interpreting results;

assessment of presence and likely impact of publication bias.(4) Domains were assessed according to AMSTAR-2 guidance.(4) We considered reviews judged as yes or partial yes for 6 or 7 out of the 7 critical domains of AMSTAR-2 to be higher quality, and those reviews judged as 'no' for at least two critical domains to be of lower quality. Appraisal was not used as a basis for excluding reviews but was used when considering certainty in the findings from the reviews.

Data synthesis and analysis

Data from contributing systematic reviews were narratively synthesised by review question, with effect direction plots used where appropriate. 95% confidence intervals (CIs) and I^2 values are presented alongside all point estimates, where available.

Results

Search results

After removing duplicates, our searches for systematic reviews returned 663 references, 112 of which met our PECO criteria. The most common reason for exclusion at full-text stage was 'wrong patient population' (see Figure 1). As we identified sufficient systematic reviews, we did not search further for primary literature (as per the process set out in our protocol).(3)

Characteristics of included reviews

Of the included reviews: 42 evaluated percentage of PWD in cohorts with COVID-19; 80 evaluated severity of COVID-19 outcomes in PWD compared to people without diabetes, including various definitions of severity, ICU admission (16 references) and/or mortality (56 references); and 45 looked at determinants of risk from COVID-

19 within PWD (note some reviews contributed data on more than one review question). Date of search ranged from March 2020 to November 2020. Supplemental Table 1 lists full citations for the included reviews; Supplemental Table 2 shows key characteristics of included reviews. Unless stated otherwise, reviews did not specify type of diabetes they included.

AMSTAR-2 judgements (conducted for critical domains only) are summarised by domain in Supplemental Table 3 and are provided in more detail in Supplemental Table 4. Five reviews (Tan 2020; Sathish 2020; Espinosa 2020; Mesas 2020; Izcovich 2020) scored yes or partial yes across all seven domains. A further 14 scored yes or partial yes across six domains, and 21 scored yes or partial yes on 5 of the 7 domains. Where systematic reviews provided conflicting answers for the same review question, we prioritised results from the higher scoring reviews. Within the included reviews, included studies were mainly retrospective observational cohort studies in people hospitalised with COVID-19. None of the reviews identified relevant randomized controlled trials.

[Is diabetes associated with an increased risk of acquiring SARS-CoV-2 and/or of hospitalisation with COVID-19?](#)

Forty-two reviews reported some data on percentage of PWD within COVID-19 cohorts (Table 1). Six of these were judged to be higher quality (yes or partial yes on at least 6 of 7 AMSTAR-2 critical domains). The most recent search data within this set of reviews was August 2020. As asymptomatic community testing for COVID-19 remains limited, the vast majority of the data comes from hospitalised or at the least symptomatic cohorts. Therefore, questions on acquiring SARS-CoV-2 and hospitalisation with COVID-19 are discussed together here. Few reviews looked at

differences between prevalence of diabetes according to setting, but, as described below, one review indicated higher prevalence of diabetes in hospitalised than non-hospitalised (but symptomatic) cohorts. However, certainty in this finding was limited.(5)

Estimates of percentages of PWD within cohorts of people with COVID-19 were highly heterogeneous but on the whole PWD were over-represented in COVID-19 cases compared to population averages (note, population averages may also be under-representations of true diabetes prevalence due to selective diabetes screening within communities) (Table 2). Estimates from individual studies included in the retrieved systematic reviews ranged from 1.7% to 40% PWD within COVID-19 confirmed cases. The pooled estimates in the systematic reviews of PWD within COVID-19 confirmed cases ranged from 7.7% to 23%. In a cohort of people with obesity and COVID-19 this increased to 30.3%.(6) Estimates of diabetes prevalence from the six higher-quality reviews ranged from 10.8% to 22% when looking at all cases, and from 17% to 20% in subgroups with severe disease.(7-12)

Multiple reviews flagged up the presence of heterogeneity between studies. As acknowledged by the reviewers, some of this heterogeneity will be driven by different practices in recording diabetes status (e.g. on admission with COVID-19 or from previous healthcare records), but other reasons have also been investigated. Kumar 2020 (1) (judged to be higher quality) conducted the most thorough investigation of between-study heterogeneity. Their meta-regression showed that proportion of diabetes in patients with COVID-19 was influenced by age (with studies with higher patient age having higher proportion of diabetes, $p<0.001$), type of composite endpoint (with studies reporting mortality endpoint having higher proportion of diabetes, $p=0.004$), and country of study (with studies outside of China having higher

proportion of diabetes, $p=0.006$)(9). All other reviews which investigated these potential causes of heterogeneity found the same patterns. Desai 2020 and Mantovani 2020 also found percentage of PWD was higher in older compared to younger patients (as would be expected given trends in diabetes prevalence in the general population)(13, 14). Hussain 2020 also found percentage of PWD was higher in studies conducted outside of China and Mantovani 2020 found percentage of PWD was greater in non-Asian than in Asian countries.(14, 15) Barrera 2020, Du 2020, Hartmann-Boyce 2020, Mair 2020, Meng 2020, and Wang 2020 (3) also found the percentage of PWD was higher in patients with severe COVID-19 manifestations, indicating a relationship between diabetes and increased COVID-19 severity which is explored further below(2, 5, 10, 16-18).

Only one review directly compared percentage of PWD in hospitalised versus non-hospitalised cohorts with COVID-19. Mair 2020 found higher rates of diabetes in hospitalised (8%, 95% CI 5 to 10%, 13 studies, n not stated) versus community (4%, 95% CI 1 to 7%, 3 studies, n not stated) cohorts with COVID-19, and concludes that once clinically ill PWD are more likely to be admitted to hospital.(5) However, this finding should be interpreted with caution: the review was judged to have several critical weaknesses according to AMSTAR-2; confidence intervals are compatible with no difference, and between-study heterogeneity does not appear to have been investigated.

Conclusion: Because of a lack of widespread systematic, population-based asymptomatic community testing, data are insufficient to conclude whether or not diabetes predisposes to infection with SARS-CoV-2. Data on prevalence of diabetes in symptomatic/hospitalised COVID-19 cases are heterogeneous, but on the whole suggest PWD are over-represented, particularly in hospitalised cohorts.

Heterogeneity may in part be driven by: age of sample, with older cohorts having a higher prevalence of diabetes and multimorbidity; geographic location, with some indication of lower estimates of prevalence of diabetes in hospitalized COVID patients in Asia compared to outside of Asia; and severity of COVID-19, with estimates higher in severe COVID-19 cohorts. There is some data from an indirect comparison that, once clinically ill with COVID-19, PWD may be more likely to be hospitalised; this is consistent with some studies suggesting PWD appear over-represented in hospitalised cohorts .

[Is diabetes associated with the severity of COVID-19 outcomes?](#)

Eighty reviews evaluated data related to this question. Of these, 15 were considered to be of higher quality (6 or 7 of 7 AMSTAR-2 critical domains as yes or partial yes). The latest search date was August 2020. Where investigated, all of the reviews identified increased risk of mortality and severity of COVID-19 in PWD.

Where data were pooled across studies, outcomes were most commonly calculated as risk ratios (RRs) or odds ratios (ORs), with data given on number of PWD with and without outcome and number of people without diabetes with and without outcome. However, at times effect estimates were extracted from individual studies and numeric data were not available. In addition to possible variation in the way they were calculated, pooled outcomes were subject to some limitations, including statistical heterogeneity and possible publication bias in some instances. Where high statistical heterogeneity or suspected publication bias were detected, this is noted in Table 2, and, where relevant, discussed below. Most analyses were based on unadjusted estimates. However, results of individual studies which provided adjusted estimates are consistent with those from meta-analyses containing unadjusted data.

ICU admission

Sixteen reviews evaluated ICU admission (Table 2). Of these, three were considered to be of higher quality (6 or 7 of 7 AMSTAR-2 critical domains as yes or partial yes). Of those ten that reported pooled effect estimates, five found point estimates indicating increased association of ICU admission with COVID-19 in PWD, with confidence intervals excluding no difference. A further four found point estimates signalling increased association of ICU admission in PWD, but with wide confidence intervals that spanned no difference and are also compatible with a lower rate. One meta-analysis of two studies (n=179) found lower rates of ICU admission in PWD, but here again the confidence intervals were very wide, the difference in risk being compatible with a 94% reduction to a greater than 900% increase.(19)

The two higher quality reviews which evaluated this outcome both found increases in admission in PWD, the 95% CIs being compatible with a 10%-500% increase, and moderate levels of statistical heterogeneity. Fang 2020 compared rates of diabetes in people in ICU versus those not in ICU and found an RR of 1.88 (95% CI 1.10 to 3.23, I²=51%, 5 studies, n=3747).(20) Zhou 2020 (2) conducted the same comparison using pooled data from 4 studies (n=6652) and found an OR of 2.98, 95% CI 1.49 to 5.98, I²=48%).(12)

Mortality

Fifty-six reviews evaluated mortality (death with COVID-19). Of those 34 which reported a pooled estimate, all found a point estimate suggesting increased risk of death with COVID-19 in PWD; 31 of these 34 pooled estimates had confidence intervals ranging from a 1.02 to 5.58 increase.

Nine of the reviews which calculated pooled effect estimates were considered higher quality according to the AMSTAR-2 critical domains; 8 of the 9 detected a statistically significant increase in risk when comparing mortality in PWD to mortality in people without diabetes (in the ninth, Singh 2020(2), the pooled estimate from only 2 studies resulted in wide CIs (RR 1.88, 95% CI 0.89 to 3.73).(9, 12, 20-26) Point estimates for pooled RRs ranged from 1.48 to 1.83, and for ORs ranged from 1.84 to 2.52. Where I^2 values were reported these were in the range of those not considered to indicate significant heterogeneity (<40%) with the exception of Ssentongo 2020 ($I^2=84\%$).(25) Authors of the largest meta-analysis in this group, Izcovich 2020, were also the only ones to use GRADE to evaluate certainty in the evidence and estimate absolute risks. In their meta-analysis of 52 studies (n=30,303), diabetes increased odds of mortality by an OR of 1.84 (95% CI 1.61 to 2.1, $I^2=33\%$).(21) This translated to an absolute estimated increased risk of 5.6% increase in mortality (95% CI 4.3 to 7%). They judged the evidence to be of high certainty. Though some of the contributing studies were judged to be at high risk of bias, sensitivity analysis showed that the pooled estimate was not sensitive to the removal of studies at high risk of bias and/or those which did not report adjusted estimates.

Other measures of severity

30 reviews evaluated 'severity' as a construct in and of itself; of these 10 were considered higher quality. Severity was a broad definition – in some reviews, it was not defined, or authors relied on categorisations from original study authors. In other reviews, severity was a composite score derived from set criteria, most commonly including elements such as ICU admission, mortality, oxygen levels, acute respiratory distress syndrome (ARDS), and the need for mechanical ventilation. More detail can be found in Table 2.

Of the 20 reviews which calculated a pooled estimate for severity, all found point estimates suggesting increased risk of severe disease in PWD compared to risk in people without diabetes. In 19 of 20, this effect was statistically significant (the one estimate which did not detect a statistically significant difference contained 4 studies (total n not reported) and found an OR of 2.07, 95% CI 0.89 to 4.82).(27) Point estimate ORs ranged from 1.66 to 3.68; RRs ranged from 1.50 to 2.96. I^2 values tended to indicate moderate statistical heterogeneity, but with some variation. The 10 higher quality reviews all found statistically significant increases equating to, on average, over a doubling in risk of severe disease in PWD compared to people without diabetes.(9, 20-22, 24, 26, 28-31) Again, Izcovich 2020 was the largest analysis and also used GRADE to evaluate certainty and calculate absolute risks. In their meta-analysis of 97 studies (n=21,381), in which severity was defined as reported by study authors or on the basis of ARDs or the requirement of ICU or invasive mechanical ventilation, they found a pooled OR of 2.51 (95% CI 2.2 to 2.87, $I^2=32\%$) and judged the evidence to be of high certainty. Estimated absolute risks were a 13.2% increase in severe COVID-19 disease (95% CI 11 to 15.5%) in PWD compared to people without diabetes.(21)

Conclusion: There is consistent evidence across many systematic reviews that diabetes increases risks of severe COVID-19 disease including ICU admissions and of death with COVID-19. Most data are from retrospective cohort studies in people hospitalised with COVID-19. The largest review used GRADE to evaluate certainty and judged the evidence to be of high certainty regarding increased risk of severe COVID-19 and increased risk of death with COVID-19 in PWD; restricting analyses to studies at low risk of bias also showed increased risk for both outcomes in PWD. Estimates for severe disease suggest a greater than doubling increase in risk; for

death, estimates suggest a slightly less than 2-fold increase in risk. There is some evidence of between-study heterogeneity, suggesting magnitude of increase may vary by study population/characteristics. Data on ICU admission was more limited, with fewer reviews reporting this as an outcome, but again suggested increased risk in PWD.

Are there differences in outcomes of SARS-CoV-2 infection within the population of people with diabetes?

Systematic reviews which contained analyses or data regarding our pre-specified characteristics *within people with diabetes* are discussed below. Only one review contained any data on socioeconomic status; Boddu 2020 reported on data from a UK cohort study which found that within PWD (as well as in the general population without diabetes) COVID-19 outcomes were worse in people from less-advantaged groups.(32) There was no data on ethnicity beyond analyses cited above which looked at country in which research was conducted (this was not one of our pre-specified outcomes, but may inform future research needs).

Type of diabetes

The majority of studies in this field, and hence of reviews aggregating those studies, do not delineate between diabetes type. To some extent, this may be due to issues with recording diabetes status in hospital. Regardless, it is an area that warrants better reporting. Two reviews contained some data explicitly comparing risks in type 1 versus type 2 diabetes; both were judged to have two or more critical weaknesses according to AMSTAR-2 and neither conducted meta-analyses. No reviews explicitly considered differential risks in other types of diabetes (note, this was not something we set out to investigate). Both Apicella 2020 and Boddu 2020 cited data from a

large UK cohort study (n=61,414,47) which used population data collected from medical records independent of COVID-19 status.(32-34) Adjusted for age, sex, deprivation, ethnicity, and geographical region, compared with people without diabetes, the risk of in-hospital COVID-19-related death was markedly higher in people with type 1 diabetes than with type 2 (type 1 OR 3.51 (95% CI 3.16–3.90); type 2 OR 2.03 (1.97–2.09)).(34)

Newly diagnosed diabetes

Two reviews contained some data on diabetes diagnosed at time of COVID-19 infection. Sathish 2020, judged to be of higher quality, conducted a meta-analysis of eight studies (n=3700) to estimate prevalence of newly diagnosed diabetes in hospitalised COVID-19 patients.(35) They estimated a pooled proportion of 14.4% (95% CI 5.9 to 25.8%) but data were highly heterogeneous ($I^2=98\%$). Of note, this area may also be particularly prone to publication bias, as reports with higher-than expected levels of newly diagnosed diabetes may be more likely to be written and subsequently published. Boddu 2020, which was judged to have two or more critical weaknesses according to AMSTAR-2, did not conduct meta-analysis but notes that SARS-CoV-2 can trigger severe diabetic ketoacidosis at presentation in people with new-onset diabetes.(32) The authors note that at present there is no evidence that SARS-CoV-2 induces diabetes on its own accord. Acute infection, stress and steroids can all also raise blood glucose. Distinguishing between new diabetes *caused* by COVID-19 and newly diagnosed diabetes which was already present prior to COVID-19 infection but was exacerbated and/or detected due to measurements taken at hospital also is a challenge. A global registry of patients with COVID-19-related diabetes (covidien.e-dendrite.com) has been set up to monitor this.

Glucose control

Eight systematic reviews contained some data on glucose control; all were judged to have two or more critical weaknesses according to AMSTAR-2.(2, 32, 33, 36-40). A major challenge for this characteristic is temporality; glucose at admission may be an inappropriate proxy for glucose control over time.

Chen 2020 set out to assess the impact of COVID-19 on blood glucose, meaning measures were those when admitted with COVID-19. The authors pooled data from three studies (n=222) in PWD comparing blood glucose or glycated haemoglobin (HbA1c) levels between patients classed as having severe versus mild disease (definition not provided)(36). The pooled mean difference (MD) in blood glucose was 2.21 mmol/L (95% CI 1.30 to 3.13, $I^2=0\%$), indicating a statistically significantly greater elevation in blood glucose in patients with severe disease. HbA1c, representing longer-term glucose control, was also higher in patients with severe disease, but the estimate was also compatible with no difference (MD 0.29%, 95% CI -0.59 to 1.1.6, $I^2=68\%$) when pooling the two small studies providing data (n=179). Lee 2020 set out to determine the effects of hyperglycaemia on complications of COVID-19, and did not specify at which points these measures were taken. They pooled results from 8 studies (including 681 PWD) and found that hyperglycaemia was associated with worse COVID-19 prognosis in both PWD and people without diabetes.(38) Pooled results showed an increased association of admission to ICU (OR 2.7, 95% CI 0.98 to 7.35, I^2 NR) and of death with COVID-19 (OR 7.2, 95% CI 2.7 to 19.2, I^2 NR) in PWD with hyperglycaemia compared to those with 'controlled blood glucose' (not defined).

The remaining six reviews did not conduct meta-analyses relevant to this question, but all described an association between higher blood glucose and worse COVID-19

outcomes, citing individual studies to support these assertions.(2, 32, 33, 37, 39, 40)

As infection and steroids can in themselves raise blood glucose levels, determining the direction of association between high blood glucose when hospitalised with COVID-19 and worse COVID-19 outcomes is challenging. A number of reviews also cited data from large (mainly UK-based) population-based cohort studies which used last-measured HbA1c, taken prior to COVID-19 infection, providing a better picture of longer-term blood glucose control and its impact on COVID-19 risk. These studies also found significant associations between higher HbA1c (defined as >10% (86 mmol/mol)) and worse COVID-19 outcomes, including ICU admission and ARDS.(1, 34)

[Selected medications](#)

We focussed on metformin, DPP4-i, and insulin. No systematic reviews identified studies which evaluated the relationship between insulin-treated versus non-insulin treated diabetes and COVID-19 outcomes.

Two reviews, both of which were considered to have two or more critical weaknesses according to AMSTAR-2, considered DPP4-i; neither conducted formal analyses. Apicella 2020 noted that though there is speculation that DPP4-i could, hypothetically, reduce virulence (by acting as a co-receptor for a subset of coronaviruses and hence interfering with binding), there is no clinical evidence of this.(33) They cite two studies which found no associations between glucose-lowering drugs (as prescribed/taken prior to COVID-19 illness) and COVID-19 outcomes in PWD hospitalised with COVID-19. Flaherty 2020 also sounds a note of possible optimism regarding the role of DPP4-ias possible receptors for SARS-CoV-2, but calls for further research to investigate their role.(41)

Four reviews, all of which were considered to have two or more critical weaknesses according to AMSTAR-2, considered the role of metformin in COVID-19 outcomes. Three of these conducted meta-analyses, all of which found a clinically and statistically significant association between metformin use prior to COVID-19 diagnosis and reduction in death with COVID-19:

- Hariyanto 2020 pooled 5 studies, and found an RR of 0.54 (95% CI 0.32 to 0.90, $I^2=54\%$, $n=6937$) for metformin use in PWD. The authors caution that confounding was not taken into account in most studies, and that none of the studies stated the dose or duration of metformin treatment in their samples.(42) In addition, all five studies were retrospective.
- Kow 2020 pooled 5 studies ($n=8121$), all of which were in PWD, and four of which are identified by the authors as reliable given their large-scale and adjustments for multiple confounding factors. They found an OR of 0.62 (95% CI 0.43 to 0.89, $I^2=29\%$).(43)
- Lukito 2020 pooled 9 studies ($n=10,233$), including both PWD and people without diabetes. They tested sensitivity between non-adjusted and adjusted models and found that regardless of model used, metformin was associated with a reduction in death with COVID-19 (non-adjusted model (OR 0.45, 95% CI 0.25 to 0.81; $I^2=63.9\%$; adjusted model (OR 0.64, 95% CI 0.43 to 0.97; $I^2=52.1\%$)). However, there was some indication of small study effects.(44)

Of note, metformin is consistently shown to be associated with lower mortality in a range of conditions (e.g. breast cancer (45), not just COVID-19). These associations are not presumed to be causal and these findings should not be immediately interpreted as suggesting that metformin has a protective effect in COVID-19 illness without further investigation. Flaherty 2020 did not conduct meta-analyses but

suggests metformin be discontinued in PWD with severe COVID-19 to reduce risk of developing lactic acidosis.(41) Though at first glance this seems to contradict the findings above, which relate – where specified – to pre-hospital use of metformin, not to the use of metformin when hospitalised with severe disease.

[Selected co-morbidities](#)

We focus here on PWD with concurrent cardiovascular disease, hypertension, or chronic kidney disease. Considering the high prevalence of these co-morbidities in PWD, there was a notable paucity of data in this area.

Three reviews considered co-morbidities relevant to our review. All were considered to have two or more critical weaknesses according to AMSTAR-2. Only one conducted a meta-analysis which included investigation of co-morbidities. Huang 2020 evaluated the impact of diabetes on a composite poor outcome in people with COVID-19 pneumonia and found a statistically and clinically significant association (13 studies, n=3561, see Table 2).(46) They used meta-regression to test whether the association between diabetes and worse outcomes was impacted by age, gender, cardiovascular disease, hypertension, and COPD. In unadjusted models, gender, cardiovascular disease, and co-morbid COPD did not statistically significantly influence the relationship with poor outcome within PWD. However, but the association with composite poor outcome was influenced by age (weaker association in studies with median age >55, p=0.003) and prevalence of co-morbid hypertension (weaker association in populations with greater hypertension prevalence, p<0.001). In studies where prevalence of co-morbid hypertension was >25%, the RR was 1.93 (95% CI 1.48 to 2.52, I²=58%), compared to 3.06 in studies with prevalence of co-morbid hypertension <25% (95% CI 2.19 to 4.26; I²=33%). However, in multivariable meta-regression including both age and co-morbid

hypertension, the association was attenuated for both co-morbid hypertension ($p=0.107$, RRs not reported) and age ($p=0.334$) suggesting the observed differences are probably dependent on each other.

The other two reviews provide very little data. Barerra 2020 reports an unadjusted RR from one study of 22 people showing a high point estimate for risk of severe COVID-19 in PWD with hypertension, but due to the small sample size, CIs are very wide (RR 10, 95% CI 0.94 to 105.2).(16) Boddu 2020 cites the same large UK, population-based cohort study mentioned above(34) and observes that the relationship between diabetes and COVID-19 mortality is particularly pronounced in older age groups with pre-existing renal or cardiac disease.(32) They interpret the low absolute risk of in-hospital death with COVID-19 in PWD under 40 years old as indication that co-morbidities may contribute significantly to increased risk of death with COVID-19 in PWD. Of note, in Haddon 2020, adjusting for previous hospital admissions with coronary heart disease, cerebrovascular disease, or heart failure somewhat attenuated the observed increase in risk of death with COVID-19 in PWD, but a clear increase in risk remained for both types of diabetes (type 1 OR 2.86, 95% CI 2.58 to 3.18; type 2 OR 1.80, 95% CI 1.75 to 1.86).(34)

Conclusions:

- Individual studies, including a very large population based study in the UK, show that type 1 diabetes is associated with higher risks of COVID-19 mortality than type 2 diabetes. We did not find any meta-analyses evaluating this.

- There is no evidence of differences in risk between new-onset and pre-existing diabetes during COVID-19. Whether COVID-19 causes new-onset diabetes is unclear and is under investigation, including in a global registry.
- Higher blood glucose levels, both in the immediate and longer-term, are associated with worse COVID-19 outcomes. As high blood glucose can be caused by infection and/or steroids to treat said infection, it is difficult to determine the causal relationship between worse COVID-19 outcomes and measures of blood glucose control taken when ill with COVID-19. However, general practice and national health services databases using HbA1c measured prior to COVID-19 show a clear association between glucose control and COVID-19 outcomes, with higher HbA1C prior to illness increasing risk from said illness. In the literature HbA1c of 10% (86 mmol/mol) or 7.5% (58 mmol/mol) are commonly used as cut-offs for defining 'high'.
- Metformin use prior to hospitalisation with COVID-19 was associated with a clinically meaningful reduction in the risk of death with COVID-19, as evidenced in three meta-analyses, but these were all judged to have critical weaknesses and none included studies which could establish causality. The use of metformin is cautioned against while patients are hospitalised with severe disease due to concerns over inducing lactic acidosis. Data on DPP4-i and insulin use are lacking in the context of COVID-19.
- There is very little evidence regarding the role of co-morbidities in increasing risk of worse outcomes from COVID-19 in PWD.

Discussion

This overview of reviews provides consistent evidence from multiple meta-analyses that diabetes is a risk factor for severe disease and death from COVID-19. There was less data available on ICU admission as an outcome, but where available this data also signalled increased risk in PWD. Within PWD, higher blood glucose levels were associated with worse COVID-19 outcomes. Type 1 diabetes was associated with worse outcomes than type 2, but this data comes from individual studies; we did not find any meta-analyses evaluating this.

Due to the nature of the review questions, the majority of data contributing to included reviews comes from retrospective observational studies. Reviews varied in the extent to which they assessed risk of bias. In the one review which used the GRADE framework to evaluate certainty, the authors judged the evidence on the association between diabetes and increased risk of worse outcomes and death from COVID-19 to be of high certainty.⁽²¹⁾ Though the majority of studies contributing to these analyses were judged to be at high risk of bias, results remained consistent when removing studies at high risk of bias and those which did not provide adjusted estimates.

We were unable to reach any firm conclusions on whether PWD were more likely to be infected with SARS-CoV-2. This is unsurprising and reflects limited data, especially a lack of widespread community asymptomatic testing for both SARS-CoV-2 and diabetes. Additionally, other complex issues may be at play which determine whether or not someone is tested. This includes country-level variations in testing capacity but also individual-level considerations. For example, it may be that PWD are more likely to get tested than others (if they feel or are a priori perceived as

more vulnerable), but given links between deprivation and diabetes, it may also be that PWD are less likely to be tested, given reports from healthcare providers that some symptomatic patients are refusing to be tested or isolate because they cannot afford to miss work. As with all overviews of reviews, a further limitation to this work is that lack of data availability for some outcomes and associations may be due to the fact that this evidence has yet to be included in a systematic review, as opposed to reflecting a lack of primary studies.

There are of course other well-established differences in risks for COVID-19 outcomes beyond those investigated here. It is worth noting that risk factors which exist in the wider population also exist in PWD – e.g. older age, deprivation, obesity, non-white ethnicity, and being male all confer greater risk both within and outside PWD.⁽¹⁾ Some of these risk factors for COVID-19 severity are also risk factors for diabetes.⁽²⁾ To the extent to which reviews and individual studies have been able to adjust for these, associations have only been somewhat attenuated. In a nationwide analysis in England – arguably the largest study of its type to contribute data on COVID-19 risks in PWD – authors adjusted for age, sex, deprivation, ethnicity and geographic region and still found increased ORs for in-hospital COVID-19 related death of approximately 2-fold for people with type 2 diabetes and greater than 3-fold for people with type 1 diabetes.⁽¹⁾ As both diabetes and worse COVID-19 outcomes are associated with socioeconomic disadvantage, their intersection is likely to further exacerbate existing health disparities. This warrants increased research and syntheses in this area. The consistent data found in this overview of systematic reviews showing increased risks from SARS-CoV-2 in PWD should inform policy and practice moving forward.

A note regarding paediatric populations

Age was not a pre-specified characteristic for this review due to clear evidence that COVID-19 risk increases with age. Risk of severe disease in children and adolescents from COVID-19 is low in the general population, and none of the systematic reviews suggested otherwise in children and adolescents with diabetes. Though a lack of evidence typically connotes uncertainty, if COVID-19 posed a substantial risk to children and adolescents with diabetes, it may be reasonable to assume that evidence would have started to emerge by now. D'Annunzio 2020, which focusses on type 1 diabetes, notes that, at present, COVID-19 infection in children and adolescents with type 1 diabetes is clinically different as compared to adults, without increased morbidity and mortality.(47) They state that there are no reports suggesting diabetes is a comorbidity associated with poor COVID-19 outcomes in children and adolescents, and advise that – as with any suspected infection in a PWD - careful glycaemic management is required.

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References

Tables

Table 1. Prevalence of diabetes in people with COVID-19¹

First author/Year	Prevalence
Abdi 2020	14.5% (95% CI 10.4 to 19.9)
Bajgain 2020	17.40% (95% CI not reported)
Baradaran 2020	10% (95% CI not reported)
Barrera 2020	Across all studies: 12% (95% CI 10 to 15) Severe COVID-19 only: 18% (95% CI 16 to 20)
Bennett 2020	9.2% (95% CI not reported)
Del Sole 2020	10.1% (95% CI not reported)
Desai 2020	In studies in patients with a mean age >50 years: 13.2% (95% CI 9.7 to 17.1) In studies in patients with mean age <50 years: 9.0% (95% CI 5.1 to 13.5)
Du 2020	In all COVID-19 patients: 10% (95% CI 7 to 15) In severe patients: 17% (95% CI 14 to 20) In non-severe patients: 6% (95% CI 5 to 8) In patients dying with COVID-19: 30% (95% CI 13 to 46) In patients surviving COVID-19: 8% (95% CI 2 to 15)
Emami 2020	7.87% (95% CI 6.57 to 9.28)
Espinosa 2020**	22% (95% CI 21 to 23)
Fadini 2020	10.3% (95% CI not reported) ²
Faghir-Gangi 2020	14% (95% CI 11 to 17)
Gold 2020	9.65% (95% CI 6.83 to 13.48)
Guler 2020	7.7% (95% CIs not reported)
Hu 2020	7.7% (95% CI 6.1 to 9.3)
Hussain 2020	Overall: 15% (95% CI 12 to 18) In US only: 21% (95% CI 6 to 35) In China only: 14% (95% CI 12 to 16)
Kaur 2020	12.80% (95% CI not reported)
Khan 2020	25.2% (95% CI not reported)
Khateri 2020 **	14% (95% CI not reported)
Kumar 2020 (1) **	11.2% (95% CI 9.5 to 13.0) ³
Liu 2020 (1)	10.0% (95% CI 8.0 to 12.0)
Liu 2020 (2)	8.5% (95% CI 5.5 to 11.4)
Mair 2020	8% hospitalised; 4% non-hospitalised (95% CI not reported)
Mantovani 2020	Overall: 14.34% (95% CI 12.62 to 16.06) Patients aged >60 years: 23.30% (95% CI 19.65 to 26.94)

¹ Data represent pooled prevalence unless indicated otherwise. ** considered higher quality (judged as yes or partial yes for at least 6 of 7 critical AMSTAR-2 domains)

² For comparison, the review states nationwide prevalence of diabetes in China in 2013 was 10.9% overall and 12.3% among people aged 40–59

³ Meta-regression showed: proportion of diabetes in patients with COVID-19 was influenced by age (with studies with higher patient age having higher proportion of diabetes, $p < 0.001$), type of composite endpoint (with studies reporting mortality endpoint having higher proportion of diabetes, $p = 0.004$), and country of study (with studies outside of China having higher proportion of diabetes, $p = 0.006$). There was no influence of number of patients in studies or quality score of studies.

First author/Year	Prevalence
	Patients aged<60 years:8.79% (95% CI 7.56 to 10.02) Non-Asian countries: 23.34% (95% CI 16.40 to 30.28) Asian countries: 11.06% (95%CI 9.73 to 12.39)
Matsushita 2020	The prevalence of diabetes ranged from 5% to 58% (pooled results not reported)
Meng 2020 **	Overall: 12.55% (95% CI not provided) Severe patients: 20.50% (95% CI not provided)
Miller 2020	14.40% (95% CI not provided)
Nandy 2020	13% (95% CI 10 to 17)
Patel 2020 (1)	10% (95% CI not provided)
Patel 2020 (2)	15.4% (95% CI 12 to 19.4)
Pinedo-Torres 2020 **	10.8% (95% CI 5.9 to 16.6)
Sacks 2020	Pooled result not presented; report range within China of 5% to 20%
Sales-Peres 2020	30.3% (95% CI not provided; in people who also had obesity)
Sanyaolu 2020	Report range: 9.4% to 23.8%
Sayed 2020	Report range: 1.7% to 39.7%
Tadic 2020	Report range: 3% to 21%
Tian 2020	23.80% (95% CI not provided)
Venkata 2020	23% (95% CI not provided)
Wang 2020 (3)	Overall: 9% (95% CI 6 to 12) In moderately severe COVID patients: 7% (95% CI 4 to 10) In severe COVID patients: 17% (95% CI 13 to 21)
Zaki 2020	Report range: 12% to 22%
Zhou 2020 (2) **	In severe or fatal COVID-19 cases: 17% (95% CI 15 to 20%)

Table 2. Association between diabetes and severe outcomes with COVID-19⁴

First author/Year	ICU admission and direction of effect		Mortality and direction of effect		Other measures of severity
Abdi 2020	NR		Death rate higher among patients with both diabetes and COVID-19. No pooled data.		Severe symptoms higher in both diabetes and COVID-19
Aggarwal 2020	NR		Diabetes in people not surviving COVID-19 versus those surviving COVID-19: OR: 2.03 [95%CI: 1.29-3.20] 4 studies, 307/618 died of which 96 (15.5%) had DM. I ² =0%	↑↑	Diabetes in COVID-19 severe disease: OR: 2.03 [95%CI: 1.29-3.45] . 12 studies. 754/265 (10.3%) have DM explored/explained.
Apicella 2020	Reports estimates from 3 other reviews, all of which are included here. No new data.		Reports data from 2 other reviews, both of which are included here. No new data. Also reports data from large primary studies in type 1 and 2 diabetes (Barron et al): N=23804, 32% T2D, OR 2.03 (1.97, 2.09); 1.5% T1D, OR 3.5 (3.15, 3.89)		NR
Awortwe 2020	Risk difference for ICU vs non-ICU 0.01 (-.33;0.34) , p value 0.98, I ² =84.8 (n studies/participants NR)	↑	Risk difference for surviving COVID-19 vs. not surviving: 0.14 [0.08; 0.19] , p value (<00000.1), I ² =21%. (n studies/participants NR)	↑↑	Risk difference for severe disease: 0.08 (0.02 to 0.14) , p value 0.000001, I ² =84.8 (n studies/participants NR)
Bajgain 2020	NR		66 fatal, 172 non-fatal with diabetes. In studies showing only fatal cases: 33.2% fatality for diabetes and Covid-19		NR
Barrera 2020	Unadjusted RR, 3 studies, N=8890, RR 1.96 (1.19, 3.22) , I ² =80%	↑↑	Unadjusted RR, 4 studies, N=2058, RR 2.78 (1.39, 5.58) , I ² =75%	↑↑	Unadjusted RR for severe disease (defined): 1.50, 95% CI 1.00 to 2.00 , 12 studies, n=1991
Chidambaram 2020	NR		PWD in those who died versus those who survived: RR 1.59 [1.41–1.78] . 27 studies, n=16263, I ² =23	↑↑	PWD in severe versus non-severe disease: 2.09, 95% CI 1.66 to 2.62 , 12 studies, n=7552
Chowdhury 2020	NR		Only reports data from Barron et al primary studies: 3.50 (3.15–3.89) greater odds of dying in hospital with COVID-19 in PWD compared with those without diabetes. Attenuated to 2.86 when adjusted for previous hospital admissions with coronary heart disease, cerebrovascular disease, or heart failure.		NR
Costa 2020	NR		Report results from 3 individual studies (no synthesis), all of which show greater risk in PWD. Cite Chinese CFR of 7.3% in PWD compared to 2.3% in total population.		NR
de Almeida-Pititto 2020	NR		10 studies, 4247 patients, 532 PWD. Compared diabetes rate in people who died versus people who survived. OR 2.50 (95% CI 1.74–3.59) . Random	↑↑	Severity (defined as need for mechanical ventilation or death): 2.50 (95% CI 1.74 to 3.59) , 10 studies, 4247 patients, 532 PWD. Compared diabetes rate in people who died versus people who survived.

⁴ NR not reported. ** higher quality (6 or 7 yes or partial yes on AMSTAR-2). Bold=pooled estimates. ↑ increased risk in PWD, not statistically significant; ↑↑ statistically significant increased risk in PWD; ↓ lower risk in PWD, not statistically significant

⁵ Severity as per definitions of individual study authors unless otherwise specified

First author/Year	ICU admission and direction of effect		Mortality and direction of effect		Other measures of effect
			effects model ($I^2=50.72$). No publication bias was detected.		OR 2.35 (95% CI 1.80-3.00) model ($I^2=34.78$), with no publication bias detected
Del Sole 2020	NR		NR		Severity (ARDS, ICU admission) (95% CI 2.09 to 7.72)
Deravi 2020	NR		NR		Narrative only. "Individuals with diabetes mellitus and hypertension had higher risks for the late onset of coronavirus, and the severity of SARS, MERS and COVID-19."
Deshmukh 2020	NR		Narrative only. "These reports indicate that severe or critically ill COVID-19 patients with concurrent hypertension, diabetes and cardiovascular disease have a significantly higher risk of mortality and require special attention during their hospitalization."		NR
Du 2020	Diabetes was not found to be significantly associated with admission to ICU (RR = 1.16, 95%CI: 0.15-9.11). 2 studies, n=1631. $I^2=78\%$. Suspected publication bias.	↑	Compared with patients without diabetes, the risk of death (RR = 3.16, 95%CI: 2.64-3.78 , $I^2=34\%$) was higher in COVID-19 patients with diabetes. No evidence of publication bias. 4 studies, n=46,654	↑↑	Compared with patients without diabetes, the risks of severe cases (RR = 3.16, 95%CI: 1.76-2.56 , $I^2=34\%$) were higher in COVID-19 patients with diabetes. No evidence of publication bias. 7 studies, n=46,654
Espinosa 2020**	NR		19% prevalence of PWD within deaths with COVID-19, 95% CI (16-22), number of studies NS, no comparisons made		17% prevalence of PWD within deaths with COVID-19, 95% CI (16-22), number of studies NS, no comparisons made
Fadini 2020	NR		NR		Narrative only. "Based on the results, we can conclude that diabetes increases the risk of SARS-CoV-2 infection and the outcome of this new disease."
Fang 2020**	5 studies, 3747 total cases, RR 1.88 (1.10-3.23) , $I^2=51\%$. Calculated as rates of diabetes in people in ICU versus those not in ICU.	↑↑	Using 10 studies, with 4748 cases, the RR of death with COVID-19 and co-morbid diabetes is as follows: RR 1.75 (1.27-2.41) , $I^2=23\%$	↑↑	Severity (American Thoracic Society) for community-acquired pneumonia, New Coronavirus Pneumonia Control Guidelines of China (2.36) . Data from 23 studies. Statistically and clinically significant risk for ARDS and invasive pneumonia found in pooled data
Figliozi 2020**	NR		NR		"Adverse prognosis" for COVID-19 infection, hospitalization and/or use of mechanical ventilation, progression of the disease (1.64 to 3.33, $I^2=80\%$)
Flaherty 2020	NR		NR		Narrative only. "Patients with diabetes had a 50% greater chance of dying from COVID-19 than non-diabetic individuals"
Gold 2020	NR		Diabetes was more prevalent among fatal cases [24.89% (95%CI: 18.80%, 32.16%)] compared to total cases [9.65% (95%CI: 6.83%, 13.48%)]		NR

First author/Year	ICU admission and direction of effect		Mortality and direction of effect		Other measures of severity
Guler 2020	NR		Narrative only, discusses increased risk as per Costa 2020 (cite increased CFR in PWD)		NR
Guo 2020	NR		NR		Severity (indication of severe COVID-19: respiratory rate ≥ 30 breaths/min, or $\text{SpO}_2 \leq 93\%$ or $\text{PaO}_2/\text{FiO}_2 \leq 300$ mmHg, or any complication (respiratory failure, organ dysfunction, and or multiple organ dysfunction syndrome, or death). Nine studies, pooled RR 2.96 (95% CI: 1.44, 6.11) , $I^2=23\%$. No evidence of publication bias.
Hartmann-Boyce 2020			Narrative only, cite data showing higher risk of death across individual studies		Narrative only. "...current evidence suggests that COVID-19 is associated with a higher risk of death in PWD."
Hu 2020	NR		No comparisons. Within PWD, the risks of severity and mortality rate ranged from 12.6 to 23.5% and from 2.0 to 4.4%, with pooled estimates at 18.0 and 3.2%, respectively.		No comparisons. The risk of severe cases (not defined but including cardiac injury) in diabetic patients was 27.0 to 61.9%.
Huang 2020	RR 1.47 [0.38, 5.67] , $p=0.57$; $I^2=63\%$. 10 studies, $n=1985$	↑	RR 2.12 [1.44, 3.11] , $p<0.001$; $I^2=72\%$. 10 studies, $n=1985$	↑↑	Severe COVID-19 ((1) respiratory rate ≥ 30 breaths per min); (2) $\text{SpO}_2 \leq 93\%$; (3) ratio of partial pressure of oxygen (PaO_2) to fractional oxygen inspired air (fraction of oxygen inspired air) ≤ 300 mmHg; (4) critical complication (respiratory failure, shock, and or multiple organ dysfunction/failure): $p<0.001$; $I^2=45\%$, 13 studies. Composite poor outcome (severe COVID-19, acute respiratory syndrome (ARDS), need for mechanical (ICU) care, and disease-related death): RR 1.88 [1.18, 3.03] , $p<0.001$. Qualitatively symmetric funnel plot for the association between poor outcome.
Hussain 2020	RR 1.88 (1.20- 2.93) . 5 studies, $n=7484$, $I^2=75\%$. Calculated as rates of diabetes in people in ICU compared to those not in ICU.	↑↑	Mortality risk was found to be significantly higher in COVID-19 patients with diabetes as compared to COVID-19 patients without diabetes with a pooled risk ratio of 1.61 (95% CI: 1.16-2.25) . $I^2=93\%$. 11 studies, $n=7093$.	↑↑	NR
Izcovich 2020**	NR		13.6% with diabetes, 7.9% without. OR 1.84 (95% CI 1.61 to 2.1) . $n=30303$, 52 studies, $I^2=33\%$. High certainty evidence according to GRADE. Estimated absolute risks: 5.6% increase in mortality. Between 4.3% more and 7% more.	↑↑	"Severe COVID-19 defined as reported by primary care requirement, invasive ventilation, or ARDs): OR 2.51 (2.14 to 2.91) . 52 studies. $I^2 = 32\%$. High certainty evidence according to GRADE. 13.2% increase severe COVID-19. Between 11% more and 15% more.
Javanmardi 2020	NR		No comparison. 26% (21-31%) of diabetes in those dying with COVID-19.		NR

First author/Year	ICU admission and direction of effect		Mortality and direction of effect		Other measures of severity
Khan 2020	NR		Not calculated for diabetes specifically. For all immune and metabolic disorders (OR = 2.46, 95% CI = 2.03-2.85)		NR
Kumar 2020 (1)**	NR		Presence of diabetes was found to be significantly associated with mortality due to COVID-19 (OR 1.90 (95% CI: 1.37-2.64) , I ² =32%). 9 studies, total n not reported.	↑↑	Severity of disease: 2 defined criteria (16 studies) versus no requirement for ventilation requirement (2 studies); progressive disease (2 studies); responsive disease (1 study). No ARDS (1 study). Presence of diabetes found to be significantly associated with COVID-19 (OR 2.75 (95% CI: 1.85-4.14) , I ² =63%. Total n not reported)
Kumar 2020 (2)	NR		NR		Composite: 'severe clinical course' requiring ICU care; or 2. development of respiratory failure, or need for mechanical ventilation, or critical groups according to the national and treatment guidelines by the National Health Commission of the People's Republic of China (not surviving.). OR 3.12 (95% CI: 1.85-5.21) , I ² =48%; 14 studies.
Li 2020 (1)	NR		Non-survivors of COVID-19 were significantly more likely to have diabetes than survivors (24.8%, 95% CI 18.7-32.0 vs. 13.9%, 95 % CI 10.5-18.1, p=0.003)		NR
Li 2020 (3)	Diabetes accounted for 11.7% of ICU/severe cases, but 4.0% of non-ICU/severe cases		NR		"The result indicated that the presence of diabetes in ICU/severe cases was statistically significant (OR 5.57 , I ² =67%. 5 studies)
Liu 2020 (1)	NR		NR		"Increased risk of death (OR 1.93 , 95% CI 1.93 to 3.52 , I ² =67%, reported)
Lu 2020	NR		OR 2.63, 95% CI 1.45, 4.76 . 5 studies, n=2307. I ² NR	↑↑	NR
Luo 2020**	NR		In-hospital mortality OR 2.09, 95% CI: 1.80-2.42 (do not report total n, studies, or I ² for this analysis as part of larger analysis (124 studies))	↑↑	OR 2.54, 95% CI: 1.85-3.52 , I ² =67%. 124 studies, n, studies, or I ² for this analysis (124 studies)
Mahumud 2020	NR		NR		Chronic comorbid conditions (hypertension, diabetes, chronic kidney disease, respiratory conditions) were identified in 10.5% of patients
Mantovani 2020	NR		"Pre-existing diabetes was significantly associated with a ~three-fold greater risk of in-hospital mortality associated with COVID-19" (n=15 studies included random-effects OR 2.68, 95% CI 2.09-3.44 ; I ² =46.7%). Publication bias judged unlikely	↑↑	Severe disease: "Patients with pre-existing diabetes had an approximately three-fold greater risk of severe/critical illness compared to their counterparts without diabetes" (22 studies; OR 2.57 ; I ² =41.5%). Publication bias judged unlikely

First author/Year	ICU admission and direction of effect		Mortality and direction of effect		Other measures of severity
Mehraeen 2020	NR		OR 1.34; 95% CI 1.10 to 1.64 (114 studies, 310,494 participants, I ² NR)	↑↑	NR
Mesas 2020**	NR		OR 2.12, 95% CI 1.79, 2.52 , I ² =77.9. 38 studies, n=25498	↑↑	NR
Miller 2020	NR		In meta-regression, “each 1% increase in DM prevalence was associated with a 1.5% absolute increase in the mortality rate (P<.001)”	↑↑	NR
Moula 2020	NR		Comparing mortality in PWD versus those without diabetes, RR 1.59, 95% CI 1.25 to 2.02 ; 28 studies, total n not reported, I ² not reported	↑↑	NR
Mudatsir 2020**	NR		NR		OR 2.10, 95% CI 1.33 to 3.41 (95% CI defined). 17 studies, I ² =93.6%
Nandy 2020	NR		“Patients with diabetes mellitus had a higher risk of mortality than non-diabetic patients” (OR 2.28 95 CI 1.40 to 5.55)	↑↑	NR
Noor 2020	NR		The prevalence of mortality among COVID-19 patients with diabetes was 49%. RR 1.87, 95% CI 1.23 to 2.84	↑↑	NR
Pal 2020	NR		In-hospital mortality rate: 45% in PWD		NR
Palaodimos 2020	NR		PWD compared to people without diabetes: OR 1.65, 95% CI 1.35 to 1.96 ; I ² =77.4%, 14 studies. Possible presence of publication bias	↑↑	NR
Parohan 2020	NR		OR 2.41, 95% CI 1.05 to 5.51 , I ² =93.6%,	↑↑	NR
Parveen 2020	OR 0.78, 95% CI 0.06 to 9.34 ; I ² =75.9%. 2 studies, 179 patients, 49 ICU admissions	↓	Odds of survival: 2 studies, 465 patients, 167 deaths. “The pooled estimate (OR 0.56, 95% CI 0.35 to 0.90 ; I ² =0.0%) suggested that diabetes was significantly lower in the survivors”	↑↑	3 studies, 1374 patients having respiratory distress, 100 beats/minute in a respiratory rate of <93%, a mean oxygen partial pressure of 100 mmHg, a mean oxygen concentration (FiO ₂) of 0.21. “The pooled estimate of the association between diabetes and mortality was OR 1.66; 95% CI: 1.20–2.11 ”
Patel 2020 (2)	NR		Meta-regression model: Mortality odds ratio 1.02 (0.94–1.11) -age adjusted for diabetes	↑	“Diabetes was not found to be a need for invasive mechanical ventilation”
Pinedo-Torres 2020**	ICU admission, 1 study, N=138, prevalence 57.97% (95% CI 25.36 -111.03)		Death, 2 studies, N=716, prevalence 96.33% (95% CI 61.36 -137.66), I ² 0%		NR
Plasencia-Urizarri 2020**	NR		NR		Severe clinical presentation, OR 2.79 to 4.47 . 13 studies, I ² =93.6%
Qui 2020	NR		“The pooled prevalence of diabetes in COVID-19 death patients was estimated to be 22.2% (95% CI 19.30 ~ 25.10%). The heterogeneity of the study was low (I ² = 28.4%, P = 0.1519)”		NR
Radwan 2020	NR		NR		“Severity” (intensive care unit admission)

First author/Year	ICU admission and direction of effect		Mortality and direction of effect		Other measures of s
					(ICU) admission, mec death): OR 2.46, 95% CI 1.85 to 3.21 , n=1885, I ² =31%
Rod 2020	NR		NR		No synthesis, but dia main predictors of CO
Roncon 2020	"PWD had a significant increased risk of ICU admission" (OR: 2.79, 95 % CI 1.85 to 4.22 , p < 0.0001, I ² =46 %), 4 studies	↑↑	"PWD had higher mortality risk" (OR 3.21, 95 % CI 1.82–5.64 , p < 0.0001, I ² =16 %), 4 studies	↑↑	NR
Sacks 2020	Narrative only, cites mixed evidence of increased risk		Narrative only, cites consistent evidence of increased risk		NR
Sayed 2020	NR		China observational report (1023 deaths/4462 confirmed cases) overall CFR 2.3%, CRF in people with diabetes 7.3%; USA 1122 patients in 88 hospitals, 38.5% had either DM or uncontrolled hyperglycaemia had "a more than 4 times higher mortality rate compared to no diabetes/hyperglycaemia"		NR
Sepandi 2020	NR		Type 2 OR: 2.42 (95% CI 1.06 to 5.52) , 9 studies, I ² =90%. Number of participants NS.	↑↑	NR
Shang 2020			28 studies. "COVID-19 patients with DM had higher mortality rate compared with those non-diabetic patients (28.5 vs. 13.3%, p<0.01). COVID-19 patients with DM had a higher risk of death (pooled OR 2.21, 95% CI 1.83 to 2.66 , p<0.001; I ² 50%,p<0.01)." No evidence of publication bias.	↑↑	"COVID-19 patients w infection rate compa diabetic patients (21 DM was found to be significantly greater r infection (pooled OR 2.78 ,p<0.001; I ² =39% evidence of publicati
Shoar 2020	NR		OR 1.7, 95% CI 1.04 to 2.78 , I ² =47%. N studies/participants not reported for this analysis, 12 studies (n=3257) included overall	↑	NR
Singh 2020 (1)	NR		No new analyses; cites existing studies finding increased risk		NR
Singh 2020 (2)**	NR		Estimated pooled RR of mortality from COVID-19 if you have a comorbidity compared to if you do not. RR 1.83 95% CI 0.89,3.73 p-value 0.100, 2 studies, total n not stated, I ² 0%		RR 2.11 (95% CI 1.40 to 3.31) (not stated), I ² =84.6% detected
Singh 2020 (3)	NR		Increased risk of mortality in patients with comorbidities however this is a literature review with no pooled effect data		NR
Ssentongo 2020**	NR		Risk of mortality in PWD compared to people without diabetes: RR 1.48 (95% CI 1.02 to 2.15) , 16 studies, I ² =84%, n not reported	↑↑	NR

First author/Year	ICU admission and direction of effect		Mortality and direction of effect		Other measures of effect
Tadic 2020	Narrative only, cites studies finding increased risk of admission to ICU		"In most of the studies exists the trend toward higher prevalence of diabetes among non-survivors, but in majority of studies, it did not reach statistical significance due to the small sample size"		NR
Tan 2020**	Prevalence of Diabetes within COVID patients admitted to ICU/HDU: 26.6% (22.7-30.8), $I^2=84$, $P<0.01$		NR		NR
Tian 2020	NR		"Of 1103 that died from COVID-19, 31.2% had diabetes. Of 3212 that survived COVID-19, 21.2% had diabetes." OR 1.97 (95% CI 1.67 to 2.31) . 12 studies. $I^2=0\%$	↑↑	NR
Varikasuvu 2020**	NR		"Diabetic proportions were 259/879 and 429/3292 in mortal and survival groups of COVID-19...diabetes related significantly with COVID-19 disease mortality (OR 2.52, 95% CI 1.93 to 3.30 , $Z = 6.79$, $p < 0.00001$, $I^2 = 31\%$, $p = 0.08$)" 22 studies	↑↑	"The diabetic proportion was 931/6203 in severe and 1558/10703 in non-severe COVID-19 cases... diabetes related significantly with COVID-19 disease mortality (OR 2.52, 95% CI 1.69 to 2.86 , $Z = 5.12$, $p < 0.0001$)" Severe non-severe
Wang 2020 (2)**	NR		NR		1558 patients with COVID-19. Risk of exacerbation: 3.66 , $I^2=39$
Wu 2020	NR		OR 1.75 (95% CI 1.31 to 2.36) . 6 studies, $n=1471$, $I^2=5\%$	↑↑	NR
Xu 2020	NR		NR		Narrative only, states that patients may develop severe COVID-19
Yanai 2020	NR		NR		"Metabolic syndrome was significantly associated with COVID-19 to SARS-CoV-2 infection in COVID-19."
Yang 2020	NR		NR		Diabetes in "severe" group: OR 2.07, 95% CI 1.12 to 3.86 , total n not reported,
Zaki 2020	NR		NR		"Diabetes, hypertension, and obesity possess an apparent association with severity"
Zhao 2020 (1)	NR		NR		NR
Zhao 2020 (2)	RR 1.26; 95% CI 0.11 to 14.42 ; $I^2=80\%$) 2 studies, $n=179$	↑	NR		NR
Zheng 2020	NR		NR		Diabetes incidence significantly higher in "critical/mortal" patients compared to "non-critical" OR 3.68, 95% CI 1.12 to 12.45 , 10 studies, $I^2=45\%$, total $n=1014$
Zhou 2020 (1)	NR		"The death group had significantly higher proportions of patients with diabetes (OR 2.51, 95% CI 1.86 to 3.35 , $I^2=87.32\%$)."	↑↑	NR

First author/Year	ICU admission and direction of effect		Mortality and direction of effect		Other measures of s
Zhou 2020 (2)**	4 studies recorded ICU admission (a sample of 6652 patients, 1138 (17.1%) of whom were classified as admitted to the ICU). Regarding diabetes, OR (95% CI), 2.98 (1.49, 5.98) , $I^2=48$.	↑↑	5 studies compared the rates of comorbidities in survivors versus non-survivors, with a sample of 3436 patients, 1624 (47.3%) of whom died. In subgroup analysis based on severe clinical outcomes associated with COVID-19, 4 studies used for diabetes (n not reported). OR 2.08 (95% CI 1.38 to 3.15) , $I^2=0.0\%$	↑↑	NR

Figure legends

Figure 1. PRISMA diagram of study flow

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