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Diabetes, obesity, hypertension and risk of severe COVID-19: a protocol for systematic review and meta-analysis

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ABSTRACT

Introduction Previous evidence from several countries, including China, Italy, Mexico, UK and the USA, indicates that among patients with confirmed COVID-19 who were hospitalised, diabetes, obesity and hypertension might be important risk factors for severe clinical outcomes. Several preliminary systematic reviews and meta-analyses have been conducted on one or more of these non-communicable diseases, but the findings have not been definitive, and recent evidence has become available from many more populations. Thus, we aim to conduct a systematic review and meta-analysis of observational studies to assess the relationship of diabetes, obesity and hypertension with severe clinical outcomes in patients with COVID-19.

Method and analysis We will search 16 major databases (MEDLINE, Embase, Global Health, CAB Abstracts, PsycINFO, CINAHL, Academic Research Complete, Africa Wide Information, Scopus, PubMed Central, ProQuest Central, WHO Virtual Health Library, Homeland Security COVID-19 collection, SciFinder, Clinical Trials and Cochrane Library) for articles published between December 2019 and December 2020. We will follow the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2016 guidelines for the design and reporting the results. We will include observational studies that assess the associations of pre-existing diabetes, obesity and hypertension in patients with COVID-19 with risk of severe clinical outcomes such as intensive care unit admission, receiving mechanical ventilation or death. Stata V.16.1 and R-Studio V.1.4.1103 statistical software will be used for statistical analysis. Meta-analysis will be used to estimate the pooled risks and to assess potential heterogeneities in risks.

Ethics and dissemination The study was reviewed for human subjects concerns by the US CDC Center for Global Health and determined to not represent human subjects research because it uses data from published studies. We plan to publish results in a peer-reviewed journal and present at national and international conferences.

PROSPERO registration number CRD42021204371.

Strengths and limitations of this study

- This will be a rigorous and comprehensive systematic review and meta-analysis to assess the effects and relations of diabetes, obesity and hypertension with risk of severe COVID-19.
- Using a broad literature search strategy with inclusion of 16 electronic databases will allow identification of eligible studies available from different sources and wide geographic representativeness.
- The title and abstract screening, full-text review, data extraction and risk of bias assessment will be performed by two reviewers independently to minimise errors and potential bias in study selection.
- Different types of study design, various measurements of exposures and effect sizes, and wide range of sample sizes will be the major sources of heterogeneity and challenges in analysis and interpretation.
- Recall bias might be possible due to the use of self-reported data on the history of diabetes, obesity and hypertension in the individual studies.

INTRODUCTION

The pandemic of COVID-19 has caused over 79.2 million reported cases and over 1.7 million deaths globally as of 27 December 2020.[1] Several case-series studies from China,[2 3] Italy,[4] Mexico,[5] UK[6] and the USA[7–9] reported that among patients with confirmed COVID-19 who were hospitalised, those with pre-existing non-communicable diseases (NCDs), including hypertension, diabetes, obesity, cardiovascular disease, chronic obstructive pulmonary disease/asthma, cancer and kidney disease had a higher proportion of severe outcomes than those without these comorbidities. These findings suggest that NCDs might be important risk factors of severe clinical complications and outcomes in patients with COVID-19. Given the global burden of these conditions, it is likely that the COVID-19 pandemic has been substantially exacerbated by pre-existing NCDs.[10]

Diabetes, obesity and hypertension have been among the most prevalent NCDs reported in hospitalised patients with COVID-19 with severe clinical outcomes.[2–9] To date, some systematic reviews and meta-analyses have

been conducted to synthesise published estimates for the impact of diabetes,[11–32] obesity[33–46] and hypertension[12 13 27 47–52] on the risk of severe clinical outcomes from COVID-19. However, there are limitations in geographic locations, numbers, types and sample sizes of the original studies included, high risk of biases, inconsistent definitions of outcome measures and inconsistent use of effect size measures in published meta-analyses. In addition, because diabetes, obesity and hypertension coexist in many people, uncertainty remains about the independent effect of each of these conditions as well as their synergistic effects in combination on risk of severe clinical outcomes in patients with COVID-19.

To accurately estimate the relationships of diabetes, obesity and hypertension with the risk of death and other severe illnesses/conditions in patients with COVID-19, meta-analyses of high-quality studies with wider geographic representativeness are needed. Furthermore, it would be valuable to identify subgroups among people with different demographic and socioeconomic characteristics and those with pre-existing diabetes, obesity and hypertension who are particularly at risk for severe COVID-19, such as those with poor glycaemic control or blood pressure control and use of certain medications.

METHODS

We will conduct a systematic review and meta-analysis that will comply with the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols 2015 guidelines for the design and reporting of the results (online supplemental material 1).[53] The protocol has been registered in the PROSPERO database (https://www.crd.york.ac.uk/PROSPERO).

Eligibility criteria

We will formulate our study eligibility criteria using the **PECOS** (**P**opulation, **E**xposure, **C**ontrol/**C**omparator, **O**utcome(s), and **S**tudy design) description model.[54]

- **P**opulation (patients or participants)
  - Male and female patients aged 18 years or older with laboratory-confirmed COVID-19.
- **E**xposure
  - Primary measures
    - Diabetes: defined as having a history of diagnosed diabetes by self-report or medical record or use of blood glucose lowering medications prior to the confirmation of COVID19 or defined specifically in the study methods.
    - Obesity/overweight (based on body mass index, BMI): defined as having a history of established overweight (25≤BMI<30 kg/m^2) or obesity (BMI≥30 kg/m^2) prior to the confirmation of COVID-19 or as defined in individual studies. BMI or fat mass as continuous variables will also be assessed.
    - Hypertension: defined as having a history of diagnosed hypertension by self-report or medical record or use of blood pressure medications prior to the confirmation of COVID19 or defined specifically in the study methods.
  - Secondary measures
    - Type of diabetes: Type 1 and Type 2.
    - Use of metformin, insulin or dipeptidyl peptidase 4 (DPP-4) inhibitors, among patients with a history of diagnosed diabetes.
    - Glycemic control, i.e., hemoglobin A1c (glycated hemoglobin, A1c, or HbA1c) < 7% (53 mmol/mol), among patients with a history of diagnosed diabetes.
    - Obesity categories: Class 1 – BMI 30 to < 35 kg/m^2, Class 2 – BMI 35 to < 40 kg/m^2, Class 3 – BMI ≥40; or as defined in individual studies.
    - Stages of hypertension prior to COVID-19 infection: stage 1 hypertension – systolic blood pressure (SBP) 130 to 139 mm Hg or diastolic blood pressure (DBP) 80 to 89 mm Hg; stage 2 hypertension – SBP ≥140 mm Hg or DBP ≥90 mm Hg; or as defined in individual studies.
    - Use of angiotensin-converting enzyme inhibitors (ACEI) or angiotensin II receptor blocker (ARB), among patients with a history of diagnosed hypertension.
    - Blood pressure control prior to COVID-19 infection: SBP/DBP <130/80mm Hg, among patients with a history of diagnosed hypertension; or as defined in individual studies.

  While diabetes, obesity, and hypertension are defined as a binary or ordinal variable in most primary studies, continuous measures such as fasting glucose or hemoglobin A1c levels, BMI, or systolic or diastolic blood pressure may also be reported in some studies. Therefore, primary studies with binary, ordinal, or continuous variables are eligible for our meta-analysis.
- **C**ontrol/**C**omparator
  - Primary measures
    - Patients with no history of preexisting diabetes, obesity, or hypertension.
  - Secondary measures
    - No use of metformin, insulin, or DPP-4 inhibitors, among patients with a history of diagnosed diabetes
    - Poor glycaemic control, that is, HbA1c≥7%, among patients with a history of diagnosed diabetes.
    - No use of ACEI or ARB, among patients with a history of diagnosed hypertension.
    - Poor blood pressure control, that is, SBP/DBP≥130/80 mm Hg, among patients with a history of diagnosed hypertension.
- **O**utcomes/endpoints of severe COVID-19[55 56]
  - Primary outcome variable
    - COVID-19 deaths.
  - Secondary outcome variables
    - Intensive care unit admission.

  - Receiving mechanical ventilation (or intubation).
  - Severe or critical illnesses/conditions as specified in published articles
  - A composite endpoint/outcome (death, intensive care unit admission, mechanical ventilation, or other severe or critical illnesses/conditions) as specified in published articles
  - A composite endpoint/outcome (death, intensive care unit admission, receiving mechanical ventilation, or other severe or critical illnesses/conditions) as specified in published articles
- Study design

We will consider cohort studies, case–control studies and cross-sectional studies to be eligible and exclude studies without data on the 'exposure', 'control/comparator' and 'outcome(s)' as defined above. Some randomised controlled trials (RCTs) for COVID-19 treatments and case series will be carefully reviewed and may be considered when sufficient data on specified 'exposures', 'comparators' and 'outcomes' are available in these studies.

Study inclusion and exclusion criteria

Our inclusion criteria are in line with the eligibility criteria as specified above. Original or primary studies that focus on diabetes, obesity and hypertension as major independent variables (eg, risk factors, predictors, determinants, comorbidities and clinical characteristics or features) will be considered. If multiple articles that are based on the same data source and that report the same results are identified, only the most recent or comprehensive article shall be included. The exclusion criteria are: (1) studies that solely focus on paediatric population, pregnant women, and those with other medical conditions; (2) studies that do not include diabetes, obesity or hypertension as a primary exposure variable but only as covariates or confounders or elements in a scoring system or index or nomogram; (3) non-peer reviewed articles.

Data sources and search strategy

We will search 16 databases (platforms) including (1) MEDLINE (Ovid), (2) Embase (Ovid), (3) Global Health (Ovid), (4) CAB Abstracts (Ovid), (5) PsycInfo (Ovid), (6) CINAHL (Ebsco), (7) Academic Research Complete (Ebsco), (8) Africa Wide Information (Ebsco), (9) Scopus, (10) PubMed Central, (11) ProQuest Central (Proquest), (12) WHO Virtual Health Library, (13) Homeland Security COVID-19 collection, (14) SciFinder (CAS), (15) Clinical Trials and (16) Cochrane Library for primary or original articles published between December 2019 and December 2020. We will include all potential studies that present diabetes, obesity and hypertension in patients with COVID-19 and their health effects on severe clinical outcomes of COVID-19 (including risk ratio (RR), hazard ratio (HR) and odds ratio (OR)). We will use a rigorous and broad literature search strategy using the key words or terms including "novel coronavirus, 2019 coronavirus, coronavirus disease, coronavirus 2019, betacoronavirus, COVID-19, COVID19, nCoV, novel CoV, CoV 2, CoV2, sarscov2, sars-cov, sarscov, 2019nCoV, 2019-nCoV, severe acute respiratory syndrome or pneumonia outbreak or pandemic" and "diabetes, obesity/overweight, hypertension, comorbidity, chronic disease, noncommunicable disease, cardiovascular disease, metabolic, predictor, risk factor or determinant" with no limitations on age, sex, publication type and language.

Study selection

The initial search will be carried out by the reviewers, with technical assistance from a qualified and experienced medical librarian from CDC. All references will be collated in EndNote 20. After exclusion of duplicates using the function in EndNote 20, the remaining articles will be imported to Covidence Toolkit[57] for further review, screening, data extraction and risk of bias assessment.

- Title and abstract screening: titles and abstracts retrieved using the search strategy will be screened by two reviewers, in parallel and independently, to identify studies that potentially meet the inclusion criteria and exclude the obviously non-relevant studies that meet exclusion criteria as outlined in the Study inclusion and exclusion criteria section. Non-relevant studies will be decided at the two reviewers' discretion (or in the case of disagreement by a third reviewer) and should identify studies that are discernibly not relevant to the study question. Studies excluded at this phase will be counted to allow completion of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram. The reviewers will be overly inclusive at this phase to reduce the chance of omitting relevant studies. When an abstract is not available and the title cannot be used to assess its relevance, the study will be retained for full text review.
- Full-text review: retained studies will be further reviewed by two reviewers in parallel and independently. The purpose at this phase is to more closely assess studies based on inclusion and exclusion criteria. The full-text or PDF files of these potentially eligible studies will be retrieved through EndNote 20 or hand search and will be assessed for eligibility. A more detailed coding scheme for exclusion reasons will be developed and recorded for completion of the PRISMA flow diagram. Any disagreement between the two reviewers over the eligibility of specific studies will be resolved through consensus or by a third reviewer. For all the excluded references, the exclusion reasons will be recorded in Covidence and a Microsoft Excel spreadsheet.

Data extraction

Two reviewers will summarise the results of selected studies using the Extraction 2.0 template in the Covidence Toolkit in parallel and independently. The spreadsheets

will be compared between two reviewers to ensure validity and accuracy of data extraction.

The following information will be extracted:

- Basic information
  - First author, year, journal of publication, study location, study design, sample size.
  - Patient demographic and socioeconomic characteristics: age, sex, socioeconomic status.
- Total number of patients and number of patients with and without pre-existing or comorbid diabetes, obesity, or hypertension.
  - Diabetes: total N, n with diabetes, type 1 diabetes, type 2 diabetes.
    - Use of metformin, insulin, or DPP-4 inhibitors: yes versus no.
    - Glycaemic control, that is, HbA1c<7%: yes versus no, or measured HbA1c where available.
  - Obesity or overweight: total N, n with overweight (25≤ BMI<30 kg/m^2), class 1 obesity (30≤BMI<35 kg/m^2, class 2 obesity (35≤BMI<40 kg/m^2), class 3 obesity (BMI ≥40 kg/m^2); data on measured BMI or fat mass will be recorded where available.
  - Hypertension: total N, n with hypertension (≥130 mm Hg systolic or ≥80 mm Hg diastolic), stage 1 hypertension (130–139 mm Hg systolic or 80–89 mm Hg diastolic), stage 2 hypertension (≥140 mm Hg systolic or ≥90 mm Hg diastolic).
    - Use of ACEI or ARB: yes versus no.
    - Blood pressure control, that is, systolic blood pressure (SBP)/diastolic blood pressure (DBP)<130/80 mm Hg: yes versus no, or measured blood pressure where available.
- Data on the outcomes and effect size measures
  - Outcome event counts by exposure groups.
  - Effect sizes (RR, HR, OR) where reported (appropriately adjusted estimates would be preferred over the unadjusted, if both were reported) along with the SEs.
  - Lower and upper 95% CIs where reported.
  - P-value where reported.

Risk of bias and quality assessment

Each selected article will be reviewed by two reviewers independently for the risk of bias and quality assessment using the standardised Newcastle-Ottawa Scale (NOS).[58] The NOS is a tool for assessing quality and risk of bias for observational studies. For each study, we will report an overall risk of bias assessment and evaluate each of the domains proposed by NOS. The NOS uses a star system to assess the risk of bias for a study in three domains: selection, comparability and exposure or outcome. Age will be considered as the most important factor controlled for in the study. At least one additional factor from the following list will also be considered: sex, socioeconomic status, other demographic characteristics, smoking status, alcohol use, cardiometabolic biomarkers or other comorbidities. Studies with a score of eight stars or higher will be considered to have a low risk of bias or a high quality. The average score for each article across two reviewers will be calculated and used in the meta-regression or subgroup analysis.

Data synthesis and statistical analysis

All statistical analyses will be carried out using the statistical software packages Stata V.16.1 (Stata Corp) and R-Studio V.1.4.1103. For binary or ordinal exposure variables, meta-analysis will be used to estimate the pooled RR, HR and OR with 95% CIs. For continuous exposure variables, meta-analysis will be used to estimate pooled effect sizes by certain unit increases as defined in published studies (eg, 1 unit or 5 units) in the continuous scales. The I^2 statistic and Cochran's Q test will be used to assess statistical heterogeneity among the reported results in the selected studies.

The pooled estimations will include direct or adjusted effects controlling at least for age and one additional potential confounder such as sex, socioeconomic status, other demographic characteristics, smoking status, alcohol use, cardiometabolic biomarkers or other comorbidities in the main analysis and in the stratified analysis. When the number of studies with each of the effect size estimates is sufficient, pooled effect sizes will be estimated by the types of the effect size measures separately in the subgroup analyses. A pooled OR may be converted to a pooled RR in 'Summary of Findings' tables to facilitate interpretation and communication of the results using the methods recommended in the Cochrane Handbook.[59] Alternatively, when the baseline risks or rates of severe COVID-19 or death in the comparator (control or unexposed) group are available in individual studies, the ORs and HRs could be converted to RRs before data synthesis using the methods proposed by Grant and VanderWeele.[60 61]

Subgroup analysis and meta-regression

If adequate data are available, we will conduct subgroup analyses or meta-regression analyses to evaluate the potential impact of the following covariates on the results: age (<50 years, 50–64 years, ≥65 years), sex (males vs females), socioeconomic status (high income, middle income, low income), geographic locations (African Region, Region of the Americas, South-East Asian Region, European Region, Eastern Mediterranean Region, Western Pacific Region-Mainland China, Western Pacific Region-outside Mainland China), types of study design (cohort study, case–control study, cross-sectional study), sample sizes (<200, 200–<500, 500–<1000, ≥1000) and risk of bias assessment scoring (<5, 5–7, ≥8). While the directions of results may be uncertain for some of these subgroup categories, we would anticipate that being in the subgroup of older ages, men or low income would have larger effects than their counterparts.

Sensitivity analysis

Sensitivity analysis will be carried out to assess the influence of individual studies on the estimated effect size using influence plots, where one study will be excluded at a time to see its effect on the overall estimate. To examine the robustness of pooled data, sensitivity analysis will be conducted between

low and high risk of bias, as assessed by the NOS. We will report and emphasise the confidence intervals instead of p values.

Assessment of publication bias

We will examine possible publication bias by creating and examining a funnel plot. Egger *et al*'s linear regression test and/or the tests proposed by Harbord *et al* and Peters *et al* will be used to test funnel plot asymmetry[62–64] when the number of studies is adequate.

Rating the quality of evidence

The quality of evidence for our overall study and the major outcomes will be assessed in accordance with the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system.[65 66] The GRADE approach categorises the quality of evidence into four levels: 'high', 'moderate', 'low' and 'very low'. The initial quality of evidence will be high for RCTs and will be low for observational studies in the GRADE rating system. The quality of evidence can be downgraded from a higher level to lower level based on risk of bias, inconsistency, indirectness, imprecision and publication bias. The quality of evidence can be upgraded from a lower level to a higher level based on having a large magnitude of effect and evidence of a dose–response, and assessment of all plausible residual confounding.[66]

Addressing missing data

When detailed participant's summary data or effect size estimates are initially unavailable or not in the required formats in the articles or in the supplementary materials, we will contact the authors to obtain relevant data or clarification. We will also contact the authors to request additional data if relevant information on study settings (fasting, or non-fasting state for blood glucose levels, potential overlapping populations, etc) is missing in the article.

Patient and public involvement

Patients and the public will not be involved in this systematic review and meta-analysis. However, once our findings are disseminated, they will be shared through peer-reviewed publications, at conferences and on social networks.

Ethics and dissemination

The study was reviewed for human subjects concerns by the CDC Center for Global Health, and determined to not represent human subjects research because it uses data from previously published studies. We plan to publish the findings in open-access peer-reviewed journals and present at international and national conferences.

Progress and amendments

The literature search was conducted in October 2020 and updated in January 2021; the title and abstract screening was performed between January 2021 and June 2021; the full-text review of identified articles is currently ongoing. We anticipate completing data collection, synthesis, and reporting by June 2022. The protocol for this study will be amended as necessary and will be reported in the final publication of the findings for transparency.

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Contributors Full access to all the data in the study and take responsibility for the integrity of the data: CL, NI, JPG, BL, RLM, PR. Conception and design: BL, PR, NI, BL, RLM, JPG. Literature search: BL, PR, NI, BL, RLM, JPG. Acquisition of data: CL, NI, JPG, BL, RLM, PR. Drafting of protocol: Li, PR. Critical revision of manuscript for important intellectual content: CL, NI, JPG, BL, RLM, PR. Statistical expertise: NI, CL. Administrative, technical or material support: PR. Study supervision: RLM, PR.

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