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Associations of diabetes, hypertension and obesity with COVID-19 mortality: a systematic review and meta-analysis

Chaoyang Li ,[1] Nazrul Islam ,[2,3] Juan Pablo Gutierrez ,[4] Samuel Eloy Gutiérrez-Barreto ,[4] Andrés Castañeda Prado ,[4] Ronald L Moolenaar ,[1] Ben Lacey ,[3] Patricia Richter [1]

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[1]Division of Global Health Protection, Global Health Center, Centers for Disease Control and Prevention, Atlanta, Georgia, USA
[2]Faculty of Medicine, University of Southampton, Southampton, UK
[3]Nuffield Department of Population Health, University of Oxford, Oxford, UK
[4]Center for Policy, Population & Health Research, Universidad Nacional Autónoma de México, Coyoacan, Mexico

Correspondence to
Dr Chaoyang Li; cli@cdc.gov

ABSTRACT

Introduction Despite a growing body of scholarly research on the risks of severe COVID-19 associated with diabetes, hypertension and obesity, there is a need for estimating pooled risk estimates with adjustment for confounding effects. We conducted a systematic review and meta-analysis to estimate the pooled adjusted risk ratios of diabetes, hypertension and obesity on COVID-19 mortality.

Methods We searched 16 literature databases for original studies published between 1 December 2019 and 31 December 2020. We used the adapted Newcastle-Ottawa Scale to assess the risk of bias. Pooled risk ratios were estimated based on the adjusted effect sizes. We applied random-effects meta-analysis to account for the uncertainty in residual heterogeneity. We used contour-funnel plots and Egger's test to assess possible publication bias.

Results We reviewed 34 830 records identified in literature search, of which 145 original studies were included in the meta-analysis. Pooled adjusted risk ratios were 1.43 (95% CI 1.32 to 1.54), 1.19 (95% CI 1.09 to 1.30) and 1.39 (95% CI 1.27 to 1.52) for diabetes, hypertension and obesity (body mass index ≥30 kg/m^2) on COVID-19 mortality, respectively. The pooled adjusted risk ratios appeared to be stronger in studies conducted before April 2020, Western Pacific Region, low- and middle-income countries, and countries with low Global Health Security Index scores, when compared with their counterparts.

Conclusions Diabetes, hypertension and obesity were associated with an increased risk of COVID-19 mortality independent of other known risk factors, particularly in low-resource settings. Addressing these chronic diseases could be important for global pandemic preparedness and mortality prevention.

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WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Early in the COVID-19 pandemic, older people and people with pre-existing non-communicable diseases and related risk factors were found to be at higher risk of severe COVID-19 illness and death. However, estimates of the strength of associations of diabetes, hypertension and obesity with COVID-19 mortality are highly variable, and additional findings, representative of the global context and adjusted for potential confounding effects, are needed.

WHAT THIS STUDY ADDS

⇒ In this comprehensive and rigorous systematic review and meta-analysis, we assessed the strength of adjusted associations of diabetes, hypertension and obesity with COVID-19 mortality using data of 145 observational studies conducted in 26 countries. We estimated that patients with diabetes, hypertension and obesity were at about 43%, 19% and 39% increased risk of COVID-19 mortality, respectively, independent of other known risk factors. Pooled adjusted risk ratios for the association of diabetes, hypertension and obesity with COVID-19 mortality were approximately 33%, 43% and 4%, smaller than the unadjusted risk ratios. The adjusted risk ratios appeared to be stronger in studies conducted before April 2020, in the Western Pacific region, in low- and middle-income countries, and in countries with lower Global Health Security Index scores, when compared with their counterparts.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ Our findings add to the body of evidence that shows the important relationship between underlying chronic diseases and mortality during the COVID-19 pandemic and support the need for further research on pathophysiological mechanisms. Efforts to reduce the prevalence and impact of chronic diseases and improve the function of core health systems are essential to population health in all countries at all times and would especially improve population resilience during times of pandemic threats.

INTRODUCTION

The COVID-19 pandemic has caused over 753.4 million reported cases and over 6.8 million deaths globally as of 1 February 2023.[1] Early in the pandemic, older people, and people with pre-existing non-communicable diseases (NCDs) and related risk factors ('comorbidities'), including hypertension, diabetes and obesity, were found to be at higher risk of severe

COVID-19 illness and death.[2–4] This is not a new phenomenon, as viral respiratory infections (eg, influenza, Severe Acute Respiratory Syndrome or SARS and Middle Eastern Respiratory Syndrome or MERS) have previously been linked with a higher risk of severe outcomes among patients with comorbidities.[5] The US Centers for Disease Control and Prevention defines "higher risk" for severe outcomes as an underlying medical condition or risk factor that has a published meta-analysis or systematic review demonstrating good or strong evidence for an increase in risk for at least one severe COVID-19 outcome.[6] The risk of COVID-19 death increases as the number of comorbid conditions increases. The population-level consequences of COVID-19 illness are compounded by the increasing global burden of NCDs, which increases the potential benefit of reducing this burden through efforts targeted to prevention, early diagnosis, screening and treatment.[7–9] To understand the magnitude of the dual epidemics of COVID-19 and NCDs, it is estimated that 349 million people, or 4% of the global population, are at high risk of severe COVID-19 due to age and pre-existing comorbidities.[10] Moreover, the proportion varies across regions, ranging from 3.0% in Africa to 6.5% in Europe.[10]

Prior to the pandemic, the global prevalence of diabetes was estimated to be 9.3% among adults aged 20–79 years, with an increasing prevalence reaching 19.9% for those aged 65–79 years.[11] Global prevalence of hypertension was estimated to be 31.1% in the adult population.[12] Global prevalence of overweight and obesity combined is estimated to be 39.0% in the adult population, with 12.5% prevalence of obesity alone.[13] Hypertension was identified early in the pandemic as a prevalent comorbidity among severely ill patients.[14] After vaccines became available in 2021, hypertension continued to be an important comorbidity and was associated with a blunted serological response following vaccine administration in hypertensive versus normotensive patients.[15 16] COVID-19 infected individuals with diabetes, a disease associated with chronic inflammation and hyperglycaemia, reportedly have a 2–3 fold increase in mortality from COVID-19 compared with people without diabetes.[3 17 18] An exploratory study of UK medical records found the risk of dying from COVID-19 was almost three times higher for patients with type 1 diabetes and almost twice as high for type 2, versus those without diabetes.[18] Obesity is both a disease and a major risk factor for many adverse health conditions, including diabetes and hypertension.[19] With differences seen by age, race and sex, in populations with a high prevalence of obesity, as much as one-third of hypertension is reportedly due to obesity.[20] During the COVID-19 pandemic, obesity was found to be significantly associated with increased severity in terms of intensive care hospitalisation and mechanical ventilation and higher mortality among COVID-19 patients.[21]

Although, at the time of writing, the SARS-CoV-2 virus is still circulating globally, in many parts of the world, the pandemic is transitioning from response to recovery. Countries and public health decision makers must address common risk factors of NCDs and infectious diseases to decrease the economic burden of disease management and to improve health outcomes as they evaluate the population level impact of COVID-19 on health systems and prepare for the next pandemic.[22 23] Information on the consequences of pre-existing comorbidities has been reported throughout the pandemic, suggesting patterns of vulnerability within populations. Meta-analyses of high-quality studies with wide geographical representativeness are best suited to increase the accuracy of results used to inform health system recovery and strengthening. Therefore, in this study, we conducted a systematic review and meta-analysis to bring together the global evidence on the independent associations of diabetes, hypertension and obesity with mortality in COVID-19 patients and differences in these associations across regions, country-level characteristics and study-level characteristics.

METHODS

Search strategy and selection criteria

We conducted this systematic review and meta-analysis according to Conducting Systematic Reviews and Meta-Analyses of Observational Studies of Etiology (COSMOS-E) guidelines[24] and reported our results according to the Meta-analysis Of Observational Studies in Epidemiology checklist.[25] The details of eligibility criteria, study inclusion and exclusion criteria, data sources and search strategy, and study selection were developed with the assistance of an expert medical librarian at the CDC and delineated in our protocol, which was registered at PROSPERO and published previously.[26] In brief, we formulated our study eligibility criteria using the PECOS (Population/Participants, Exposures, Comparators, Outcomes and Study designs) description model.[24] Participants were male and female patients aged 18 years or older with laboratory-confirmed positive COVID-19 by molecular (PCR) or antigen test for COVID-19. Primary exposures were 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 COVID-19 or defined specifically in the study methods), 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 COVID-19 or defined specifically in the study methods), and obesity (defined as having a history of established obesity with a body mass index (BMI)≥30 kg/m^2 prior to the confirmation of COVID-19 or as defined in individual studies). Comparators were patients with no history of preexisting diabetes, hypertension or obesity. The primary outcome was COVID-19 death, defined as people who have had a positive PCR or antigen test for COVID-19, died from a clinically compatible illness or syndrome attributable to COVID-19, and were not due to non-natural causes (eg, accidental, intentional self-harm, homicide).[27 28] Meanwhile, the ICD-10 code U07.1 (COVID-19, virus identified) or U07.2 (COVID-19, virus not identified) was also used to define COVID-19 death. We considered cohort studies, case–control studies and cross-sectional studies

to be eligible. Some randomised controlled trials for COVID-19 treatments and case series were carefully reviewed and considered to be eligible when sufficient data on specified 'exposures', 'comparators' and 'outcomes' were available. For studies labelled as case-series studies, we reassessed these studies and reclassified them to be either cohort studies (if they reported a follow-up time or attempt, or an HR), or cross-sectional studies if they did not.[29]

We searched 16 databases (platforms) including MEDLINE (Ovid), Embase (Ovid), Global Health (Ovid), CAB Abstracts (Ovid), PsycINFO (Ovid), CINAHL (Ebsco), Academic Research Complete (Ebsco), Africa Wide Information (Ebsco), Scopus, PubMed Central, ProQuest Central (Proquest), WHO Virtual Health Library, Homeland Security COVID-19 collection, SciFinder (CAS), Clinical Trials and Cochrane Library for primary or original articles published between December 2019 and December 2020. Our rigorous and broad literature search strategy used key words or terms including, 'novel coronavirus, 2019 coronavirus, coronavirus disease, coronavirus 2019, betacoronavirus, COVID-19, COVID-19, 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 or language. Detailed search strategy and the number of records are presented in online supplemental text 1**.** After careful discussion, we decided not to search the grey literature and the reference lists of the included studies for additional records, because grey literature is not relevant to our research topic, and our literature search of 16 databases is likely to cover all potential original peer-reviewed articles since the start of COVID-19 pandemic in our defined time frame.

The initial search was carried out by the researchers, with technical assistance from an experienced medical librarian from CDC. All references were then collated in EndNote V.20. After the exclusion of duplicates using the function in EndNote V.20, the remaining articles were imported to Covidence Toolkit (a web-based collaboration software platform that streamlines the production of systematic and other literature reviews)[30] for further screening, review, data extraction and risk of bias assessment. For final inclusion, each study was assessed independently by two or more researchers, first by screening the title and abstract, and then through a full-text review. Disagreements on the selection of records between the two researchers were resolved by team discussion or by a third researcher.

Data analysis

Two researchers independently extracted data from each article. This included study-level characteristics such as first author and publication year, geographical location and setting, start and end dates, design, COVID-19 confirmation method, and data collection method. It also included detailed data on study participants, their exposures (diabetes, hypertension and obesity), and outcomes (mortality), and effect estimate measures reported as unadjusted, age-adjusted and age-adjusted and sex-adjusted, and multivariable-adjusted, as well as a list of covariates or potential confounders. Effect measures, including OR, HR,or relative risk (RR) and their 95% CI, were extracted directly from the studies when available. Disagreements in data extraction were resolved by a third researcher. For articles with missing data, we emailed the authors to request the data (eight requests sent and six responses received).

The Newcastle-Ottawa scale (NOS) was adapted to assess the risk of bias (quality) of included studies with a cohort, case–control or cross-sectional design (online supplemental text 2).[31 32] Two researchers independently assessed the quality of studies. Disagreement between the two researchers in the quality assessment was resolved by a third researcher.

Overall pooled risk ratios (PRR) for the association between the exposure variables and the risk of COVID-19 death were conducted according to the type of risk ratio (OR, HR or RR) separately and according to adjustment for potential confounding effects (unadjusted vs multivariable-adjusted risk ratios) for each of the exposure variables (diabetes, hypertension and obesity), respectively. In the subgroup analyses, we combined studies with OR, HR and RR to ensure an adequate number of studies in each subgroup and estimated PRR as we considered HR and OR to be approximate measures of risk ratios given the low COVID-19 mortality rate globally.[33 34]

We applied random-effects meta-analysis using a restricted maximum likelihood method[35 36] and a Hartung-Knapp-Sidik-Jonkman (HKSJ) adjustment to the standard errors to account for the uncertainty in residual heterogeneity.[37–39] We further applied an ad hoc Knapp-Hartung method to ensure that the HKSJ-adjusted SEs were appropriate given the unadjusted SEs.[40 41] To assess the potential effects of geographical locations, socioeconomic factors and healthcare system on the associations between the exposure variables and the risk of COVID-19 death, subgroup analyses (stratified analyses, with ≥3 studies in each subgroup) were conducted by study design (cohort, case–control or cross-sectional), study period (December 2019–April 2020 or May 2020–November 2020), WHO regions (Africa, South-East Asia, Americas, East Mediterranean, Europe, West Pacific inclusive of mainland China and West Pacific exclusive of mainland China), World Bank (WB) income level (high, upper-middle, lower-middle and low),[42] NOS quality assessment score (high=8–9, medium=5–7, low≤5) (Table S3),[31 32] health index score (a measure of the extent to which people are healthy and have access to the necessary services to maintain good health, including health outcomes, health systems, illness and risk factors,

and mortality rates, with a higher score indicating a higher ranking),[43] and Global Health Security Index (GHSI) score (an index of a country's global health security capacity to prevent epidemics, with a higher score indicating a better health security and capability).[44] Meta-regression was conducted to assess the linear relationship between the continuous study-level and country-level indicators and the risk ratios using random-effects method.

Sensitivity analysis was carried out to assess the influence of individual studies on the PRR using influence plots, where one study was excluded at a time to see its effect on the overall estimate. Possible publication bias was assessed by contour-funnel plots and Egger's test.[45–48] The tau-squared (τ^2) statistics were reported as a measure of between-study variance, while the I^2 statistic was reported as the proportion of total variability explained by between-study variance. All statistical analyses were carried out using the statistical software R V.4.2.2 and Stata V.16.1 (StataCorp).

Patient and public involvement

Patients or the public were not involved in the design, conduct, reporting or dissemination plans of our systematic review and meta-analysis. However, many contributing studies did involve patients and community stakeholders in the design and dissemination of their study results.

RESULTS

Characteristics of included studies

As we focused on synthesising adjusted estimates in this study, data from 145 studies conducted in 26 countries with adjusted risk ratios for the associations of diabetes, hypertension and obesity with COVID-19 mortality contributed to the quantitative analysis. We excluded 1329 studies with various reasons and additional 125 studies due to lack of data for the primary outcome (n=30), or for the primary exposures (n=12), or for adjusted risk ratios (n=83) (figure 1). Among 145 studies, 139 provided results from the fully adjusted models (age, sex, plus one or more comorbidities, complications, or other health risk factors) and 6 from age-adjusted and sex-adjusted models. The geographical distributions of the studies are presented in the map (figure 2). Countries with a large number of studies included the USA (N=40), China (N=23), Italy (N=15), Mexico (N=9), South Korea (N=9) and Spain (N=8). Most of the studies were started between December 2019 and April 2020 (97.2%), had a cohort design (79.3%), reported HR (40.0%) or OR (53.8%), used data from electronic health (medical) records (57.9%), had a high NOS score of 8 or 9 (73.8%), were from high (63.4%) or upper middle-income (32.4%) countries, had a health index score 70 or above (95.6%) and had a GHSI score 33.4 or above (97.2%) (table 1).

The median (ie, centre) and the IQR (defined as the difference between the 25th and 75th percentile) (ie, spread or dispersion) of the sample sizes are similar for diabetes and hypertension. Although the total number of studies for obesity (n=57) is smaller than those for diabetes (n=118) and hypertension (n=99), the median and the spread of the sample sizes in studies for obesity are larger than those for diabetes and hypertension (table 1).

Detailed characteristics of all 145 studies included in the meta-analysis are presented in online supplemental table S3. Because of a large number, details of the total excluded studies with reasons (n=1454) are not presented (available on request).

Meta-analysis

As expected, the overall pooled unadjusted risk ratios were larger than the adjusted risk ratios on COVID-19 mortality for diabetes (2.13, 95% CI 1.80 to 2.52; n=118), hypertension (2.07, 95% CI 1.74 to 2.47; n=99) and obesity (1.46, 95% CI 1.22 to 1.71; n=57) (figure 3). The overall pooled risk estimates using the OR slightly overestimated the risk estimates using HR and risk ratios (RR). The detailed numeric values of overall PRRs were presented in online supplemental table S1. In addition, details of the forest plots for the individual studies were shown in online supplemental figure S1.1 (diabetes), online supplemental file 1.2 (hypertension) and online supplemental figure S1.3 (obesity).

The pooled adjusted risk ratio for the association between diabetes and mortality was 1.43 (95% CI 1.32 to 1.54; n=118) with considerable heterogeneity ($\tau^2 = 0.12$; $I^2 = 0.94$) (table 1). Sensitivity analysis indicated that the exclusion of any one of the studies did not significantly impact the overall PRR (online supplemental figure S2.1). Subgroup analysis showed a lower PRR in countries with a lower health index score, with a higher GHSI score, with a high-income level by WB, in studies with a cohort design, or with a high quality by NOS. In contrast, a higher PRR was observed in countries from the WHO WPR region (figure 4). The detailed numeric value of PRRs by subgroups was presented in online supplemental table S2.1. Meta-regression showed a negative association between the mean age of the participants (p=0.02) and GHSI score (p=0.02) with the risk ratios, and a positive association of health index score (p=0.003) with the risk ratios (table 2). There was no evidence of a funnel plot asymmetry in the association between diabetes and COVID-19 mortality (Egger's test p=0.29) (figure 5).

The pooled adjusted risk ratio for the association between hypertension and mortality was 1.19 (95% CI 1.09 to 1.30; n=99) with considerable heterogeneity ($\tau^2 = 0.12$; $I^2 = 0.91$) (table S1). Sensitivity analysis indicated that the exclusion of any one of the studies did not have any significant impact on the overall PRR (online supplemental figure S2.1). Subgroup analysis showed a lower PRR in studies with high quality, in the WB high

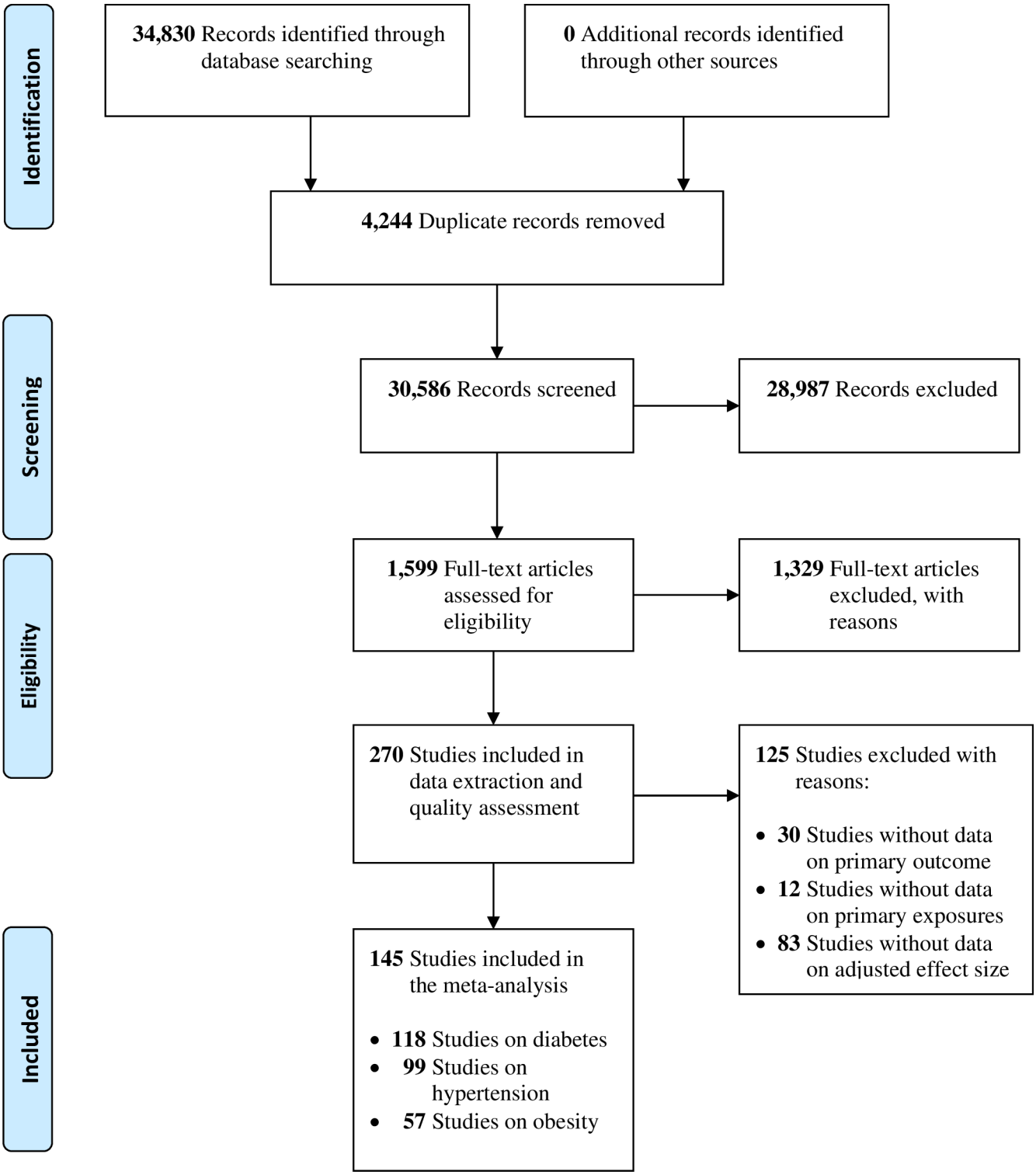

Figure 1 PRISMA flow diagram. PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

income countries, and countries with a higher GHSI score, and a higher PRR in countries from the WHO WPR region (figure 4). Meta-regression showed a negative association of mean age of the participants (p=0.02) and GHSI score (p=0.04) with the risk ratios. There was no evidence of a funnel plot asymmetry in the association between hypertension and COVID-19 mortality (Egger's test p=0.25) (figure 5).

The pooled adjusted risk ratio for the association between obesity and mortality was 1.39 (95% CI 1.27 to 1.52; n=57) with considerable heterogeneity ($\tau^2 = 0.06$; $I^2 = 0.96$) (table S1). Sensitivity analysis indicated that the exclusion of any one of the studies did not significantly impact the overall PRR (online supplemental figure S2.3). Due to the small number of studies reporting adjusted obesity-COVID-19 mortality associations, some

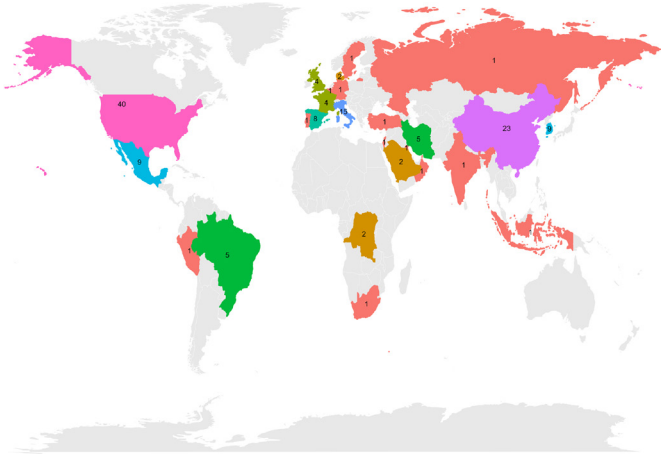

Figure 2 Number and distribution of studies included in the meta-analysis by country. Colours in the map indicate the various number of studies included in the meta-analysis by country (n=143). Studies conducted in multiple countries (n=2) were not shown in this map.

subgroup analyses could not be conducted. Subgroup analysis showed a higher PRR in studies from the EUR region than from the AMR region, and in studies conducted in April or earlier than those conducted in May or later in 2020 (figure 4). Meta-regression showed a negative association of GHSI score (p=0.001) with the risk ratios. There was evidence of a funnel plot asymmetry in the association between obesity and COVID-19 mortality (Egger's test p=0.002) (figure 5). There was a suggestion of missing studies in the middle left-hand side of the contour-funnel plot (ie, small studies with high SE), broadly in the non-significance region (white area where p>0.1), making publication bias plausible. The detailed numeric value of PRRs for the subgroup analyses is presented in online supplemental table S2.

DISCUSSION

In this systematic review and meta-analysis, we estimated that persons with diabetes, hypertension and obesity were at about 43%, 19% and 39% increased risk of COVID-19 mortality, respectively, independent of other known risk factors. Our results showed that pooled adjusted risk ratios for the association of diabetes, hypertension and obesity with COVID-19 mortality were approximately 33%, 43% and 4% smaller than their unadjusted risk ratios. Moreover, the pooled adjusted risk ratios appeared to be stronger in studies conducted before April 2020, in the Western Pacific region, in low- and middle-income countries, and in countries with a lower GHSI score, when compared with the counterparts.

It is noteworthy to mention that the lower adjusted risk ratios for diabetes and hypertension on COVID-19 mortality than their unadjusted estimates as observed in this study confirm that unadjusted risk ratio could overestimate the real associations, as age, sex, health risk factors and other comorbidities and complications could be related to both the exposure measures and COVID-19 mortality. Across a number of published systematic reviews and meta-analyses, the majority reported the unadjusted estimates that failed to consider possible confounding effects and thus likely biased the strength or direction of the associations.[49–53] As reported in a recent umbrella meta-analysis,[49] the pooled unadjusted risk ratios for diabetes, hypertension and obesity with COVID-19 mortality were 2.09, 2.50 and 2.18, respectively, which were similar to the pooled unadjusted risk ratios in this study. In other umbrella meta-analyses, pooled unadjusted risk ratios for diabetes and hypertension on COVID-19 mortality were 1.87 and 1.79, respectively.[50 51] The pooled unadjusted risk ratios for obesity on COVID-19 mortality ranged from 0.89 to 3.52.[52 53] Umbrella reviews, which are reviews of previously published systematic reviews and meta-analyses, could be a cost-effective way to summarise information available on a specific topic.[54 55] However, umbrella reviews might suffer from reliance on studies and reviews lacking in quality or data. Indeed, as shown in a recent umbrella meta-analysis, the majority of published systematic reviews and meta-analyses on the association between obesity and mortality in patients with COVID-19 presented critically low quality and very low certainty of the evidence.[53]

Our results on the pooled adjusted risk ratios for diabetes and hypertension in relation to COVID-19 mortality are consistent with the summary RR estimates adjusted for multiple confounders reported in recently published meta-analyses with inclusion of studies published as of 2022.[2 50 51 56] Therefore, our findings provide further evidence and support on the independent effects and highlighted importance of possible confounding effects for the association of diabetes and hypertension with COVID-19 mortality.

The association between BMI and COVID-19 mortality appeared to be inconsistent in published studies.[21 53 57–59] Persons with unclassified obesity (BMI≥30 kg/m^2) or those with class III obesity (BMI≥40 kg/m^2) were at risk of COVID-19 mortality, whereas those with obesity classes I (30≤BMI<35 kg/m^2) or II (35≤BMI<40 kg/m^2) were not at risk of COVID-19 mortality, as compared with those with normal BMI (18.5≤BMI<25 kg/m^2) or without obesity.[58] When BMI was modelled as a continuous measure, conflicting reports were found such that every 5 units (kg/m^2) increment in BMI increased the risk of COVID-19 mortality in one study,[58] whereas a continuous BMI measure was not associated with the risk of COVID-19 mortality in another study.[59] As observed in our analysis, most original studies on obesity and the risk of COVID-19 mortality were conducted in the countries with the highest level of obesity (ie, the USA and most of the western world).[13 60 61] Our results on the pooled adjusted risk ratios for obesity (BMI≥30 kg/m^2) and the risk of COVID-19 mortality are consistent with the summary RR in published meta-analyses.[21 53 57 58] Nevertheless, caution is warranted when interpreting the associations between obesity as measured by BMI and COVID-19 mortality across different populations because

Table 1 Characteristics of the studies included in the meta-analysis

Characteristic		Studies, n (%)*			
		Total	Diabetes	Hypertension	Obesity
Overall		145 (100.0%)	118 (100.0%)	99 (100.0%)	57 (100.0%)
Total N					
Study period					
Start date	December 2019–April 2020	141 (97.2%)	114 (96.6%)	96 (97.0%)	55 (96.5%)
	May 2020–November 2020	4 (2.8%)	4 (3.4%)	3 (3.0%)	2 (3.5%)
End date	February 2020–April 2020	84 (57.9%)	65 (55.1%)	47 (47.5%)	31 (54.4%)
	May 2020–November 2020	61 (42.1%)	53 (44.9%)	52 (52.5%)	26 (45.6%)
Sample size					
	Median	1000	1336	1157	2015
	IQR	5053	6953	6964	10 117
	95 to <1000	72 (49.7%)	52 (44.1%)	46 (46.5%)	24 (42.1%)
	1000 to <10 000	47 (32.4%)	41 (34.7%)	33 (33.3%)	19 (33.3%)
	≥10 000	26 (17.9%)	25 (21.2%)	20 (20.2%)	14 (24.6%)
Mean or median age (years)					
	<60	62 (42.8%)	56 (47.5%)	47 (47.5%)	28 (49.1%)
	≥60	83 (57.2%)	62 (52.5%)	52 (52.5%)	29 (50.9%)
Male (%)					
	<50	41 (28.3%)	36 (30.5%)	24 (24.2%)	12 (21.1%)
	≥50	104 (71.7%)	82 (69.5%)	75 (75.8%)	45 (78.9%)
Study design					
	Cohort	115 (79.3%)	90 (76.3%)	78 (78.8%)	44 (77.2%)
	Cross-sectional	28 (19.3%)	27 (22.9%)	21 (21.2%)	12 (21.1%)
	Case–control	2 (1.4%)	1 (0.8%)	0 (0.0%)	1 (1.8%)
Type of effect estimate					
	HR	58 (40.0%)	48 (40.7%)	35 (35.4%)	23 (40.4%)
	OR	78 (53.8%)	63 (53.4%)	60 (60.6%)	30 (52.6%)
	Relative risk (RR)	9 (6.2%)	7 (5.9%)	4 (4.0%)	4 (7.0%)
Data source					
	Electronic health (medical) records	84 (57.9%)	63 (53.4%)	57 (57.6%)	26 (45.6%)
	Administrative, registry, surveillance systems	49 (33.8%)	45 (38.1%)	34 (34.3%)	27 (47.4%)
	Other†	12 (8.3%)	10 (8.5%)	8 (8.1%)	4 (7.0%)
NOS score					
	8–9	107 (73.8%)	84 (71.2%)	71 (71.7%)	42 (73.7%)
	5–7	34 (23.4%)	31 (26.3%)	26 (26.3%)	15 (26.3%)
	<5	4 (2.8%)	3 (2.5%)	2 (2.0%)	0 (0.0%)
Funding source					
	Industry funded	2 (1.4%)	1 (0.8%)	2 (2.0%)	1 (1.8%)
	Independently funded	68 (46.9%)	57 (48.3%)	46 (46.5%)	24 (42.1%)
	None or NA	45 (31.0%)	37 (31.4%)	28 (28.3%)	20 (35.1%)
	Not reported	30 (20.7%)	23 (19.5%)	23 (23.2%)	12 (21.1%)
WHO region					
	Africa	3 (2.1%)	2 (1.7%)	3 (3.0%)	1 (1.8%)

Continued

Table 1 Continued

Characteristic		Studies, n (%)*			
	Americas—USA	40 (27.6%)	31 (26.3%)	29 (29.3%)	18 (31.6%)
	Americas—outside USA	15 (10.3%)	15 (12.7%)	12 (12.1%)	14 (24.6%)
	East Mediterranean	9 (6.2%)	9 (7.6%)	5 (5.1%)	2 (3.5%)
	Europe	42 (29.0%)	32 (27.1%)	27 (27.3%)	20 (35.1%)
	South-East Asia	3 (2.1%)	2 (1.7%)	3 (3.0%)	0 (0.0%)
	Western Pacific—inclusive mainland China	23 (15.9%)	18 (15.3%)	15 (15.2%)	0 (0.0%)
	Western Pacific—exclusive mainland China	9 (6.2%)	8 (6.8%)	4 (4.0%)	2 (3.5%)
	Worldwide	1 (0.7%)	1 (0.8%)	1 (1.0%)	0 (0.0%)
WB income level					
	High	93 (64.1%)	73 (61.9%)	63 (63.6%)	42 (73.7%)
	Upper middle	47 (32.4%)	41 (34.7%)	31 (31.3%)	14 (24.6%)
	Lower middle	4 (2.8%)	3 (2.5%)	4 (4.0%)	1 (1.8%)
	Worldwide	1 (0.7%)	1 (0.8%)	1 (1.0%)	0 (0.0%)
Health Index Score					
	≥80	66 (45.5%)	51 (43.2%)	41 (41.4%)	21 (36.8%)
	70–79	72 (49.7%)	62 (52.5%)	51 (51.5%)	35 (61.4%)
	<70	5 (3.4%)	3 (2.5%)	5 (5.1%)	1 (1.8%)
GHSI score					
	Most prepared (≥66.7)	46 (31.7%)	35 (29.7%)	34 (34.3%)	20 (35.1%)
	More prepared (33.4–66.6)	95 (65.5%)	79 (66.9%)	61 (61.6%)	36 (63.2%)
	Least prepared (0–33.3)	2 (1.4%)	2 (1.7%)	2 (2.0%)	1 (1.8%)

*The number of studies for each of the three comorbidities does not sum up to the total number of studies because many studies have data available for two or more comorbidities: diabetes only=29, hypertension only=14, obesity only=11, both diabetes and hypertension=45, both diabetes and obesity=6, both hypertension and obesity=3, all three comorbidities=38.
†Other types of data source include paper medical records, manual data collection and unspecified medical charts or records.
GHSI, Global Health Security Index; NOS, Newcastle-Ottawa Scale; WB, World Bank.

of the ethnic differences in BMI and its associations with disease risks.[62–64]

As compared with the number of original studies included for diabetes and hypertension, we identified fewer studies for obesity, with several possible reasons. First, obesity was not recognised as a risk factor for COVID-19 mortality at the early stage of the pandemic,[65 66] therefore, few studies reported results for obesity in the countries at the early pandemic.[65 66] Second, countries with a lower prevalence of obesity might be less likely to report data due to insufficient number of deaths by obesity status. It is evident in this study that few studies on obesity were identified in Asia and Africa. Third, various BMI scales used in the studies could make it difficult to compare results across studies or countries and synthesise data in meta-analyses. For example, whereas many studies used BMI≥30 kg/m^2 to define obesity (ie, overall obesity or unclassified obesity), a few studies used BMI as classified categories (ie, underweight: <18.5 kg/m^2, normal weight: 18.5 to <25 kg/m^2, overweight: 25 to <30 kg/m^2, obesity class I: 30 to <35 kg/m^2, obesity class II: 35 to <40 kg/m^2 and obesity class III: ≥40 kg/m^2) or a continuous scale.[59] Fourth, missing data on BMI in electronic health (medical) record systems are common.[67] Fifth, it is possible that insignificant or negative results for obesity, particularly in small studies, might not be published or reported as suggested by the possible publication bias detected in our analysis.

Our pooled adjusted risk ratios suggest that patients with diabetes and obesity had about a 40% increased risk for COVID-19 mortality and those with hypertension about a 20% increased risk, independent of other known risk factors. While mechanisms for the increased risk of COVID-19 mortality in individuals with diabetes, hypertension and obesity remain elusive, our findings provide further motivation to support research on the underlying pathophysiology. Available laboratory and clinical studies suggest that overexpression of ACE2 in adipose tissue, impaired immune function, increased proinflammatory response and cytokine storm might play critical roles in the severity and mortality of COVID-19 in patients with diabetes, hypertension and obesity.[68–70] Emerging evidence showed that SARS CoV-2 infection could increase the risk of developing new onset diabetes among survivors.[71 72] The relationship between SARS CoV-2 infection and new onset diabetes is complex, however,

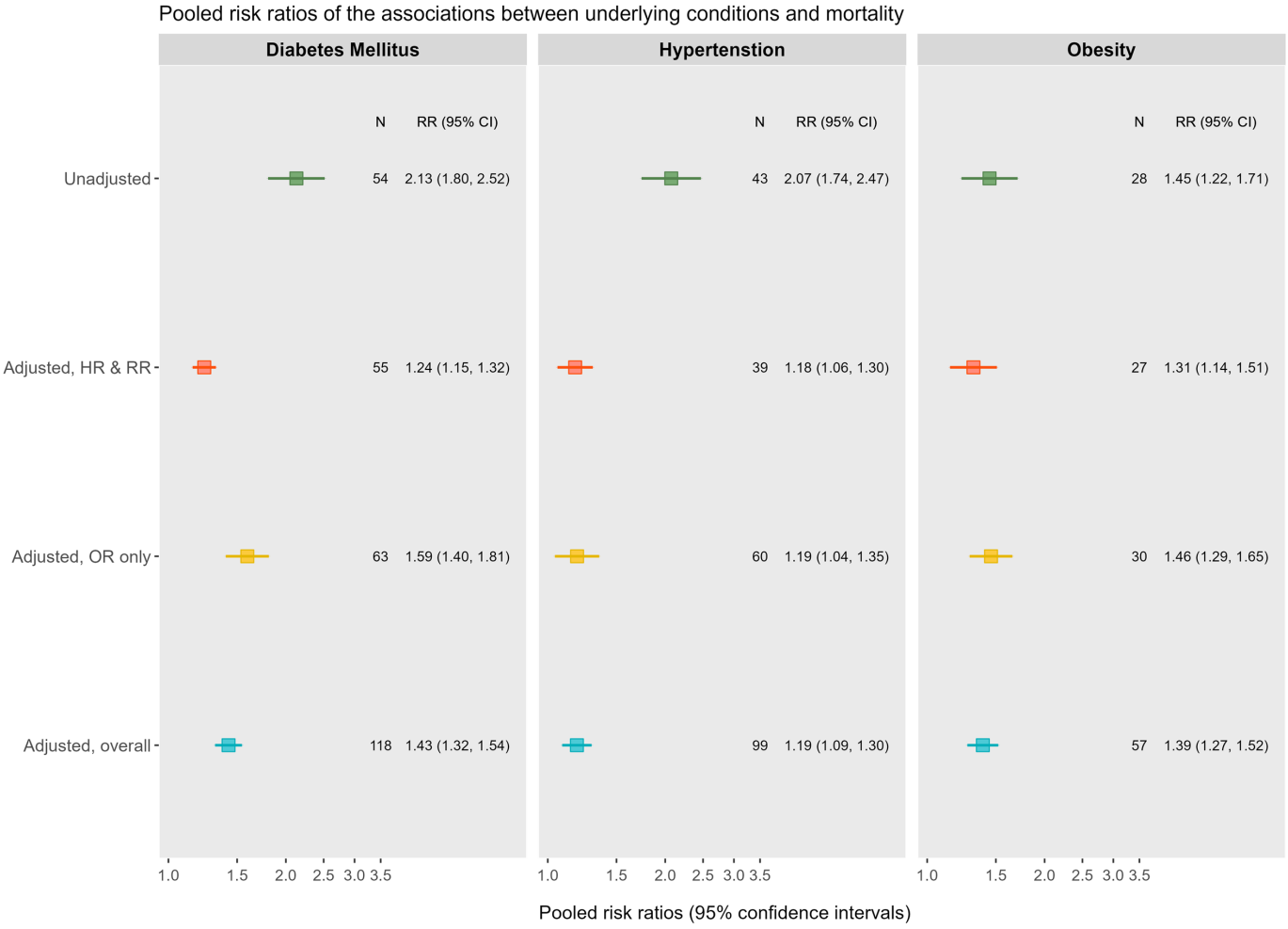

Figure 3 Overall pooled adjusted risk ratios for the associations of diabetes, hypertension and obesity with COVID-19 mortality. HR, hazard ratio. OR, odds ratio. RR, relative risk or risk ratio.

and not only is acquiring the virus associated with more severe outcomes,[2 50] but a large and increasing body of epidemiological evidence shows an increase in diabetes incidence following infection.[71 72] This is consistent with laboratory evidence showing that the virus infects and can kill pancreatic beta cells.[73]

The elevated mortality risk among COVID-19 patients with comorbidities, particularly among those with uncontrolled diabetes or hypertension, suggests a correlation between prepandemic levels of control and the impact of these conditions on COVID-19 outcomes.[74 75] Countries with better healthcare quality often have a higher proportion of individuals with controlled diabetes and hypertension. This could imply that variations in prepandemic control levels across countries play a role in COVID-19 mortality rates among those with comorbidities.

Although the differences in the strength of associations of diabetes, hypertension and obesity with COVID-19 mortality we observed across regions were lower than anticipated given the known differences in the control of these chronic conditions and quality of health services, they are still intriguing and appeared to be related to the timeline of COVID-19 spreading and virus strain mutations across countries or regions.[76] As the first country where the outbreak occurred, China had the strongest associations, followed by South Korea, European region, East Mediterranean region, South-East Asian region, followed by North America. One of the explanations for this could be improved knowledge of treating COVID-19 patients. Our study included articles published in the entire year of 2020, covering the initial months of the pandemic. Potential differences in the treatment of COVID-19 might be attributed to the evolving understanding of the condition and the identification of effective therapeutic options.[77] As the pandemic progressed, individuals affected later on received more informed care, especially regarding treating individuals with comorbidities.[78–80] Another explanation could be the notion of a'quality penalty' imposed by overburdened healthcare services occurred early in the pandemic, where the benefits of treatment at high-quality facilities are diminished when the system is overwhelmed.[81] Other factors, sometimes outside of pandemic preparedness efforts, such as adequacy and resiliency of healthcare systems could act as effect modifiers on the strength of observed association across countries or regions.

One of the interesting results in our study is the inverse association between the higher GHSI score and the lower

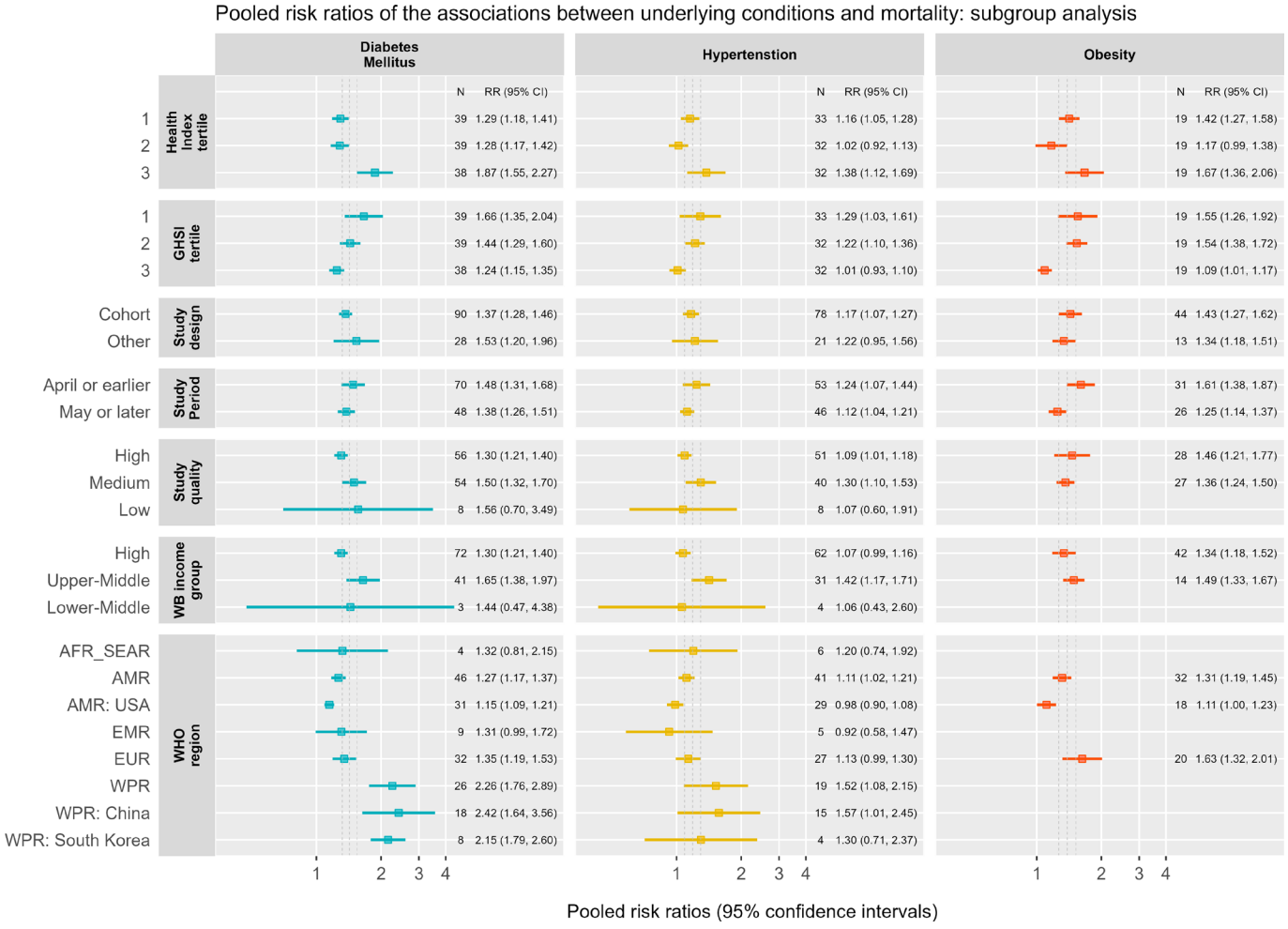

Figure 4 Pooled adjusted risk ratios for the associations of diabetes, hypertension and obesity with COVID-19 mortality by subgroups. GHSI, Global Health Security Index. AFR, Africa. AMR, Americas. EMR, Eastern Mediterranean. EUR, Europe. SEAR, South-East Asia. USA, United States of America. WB, World Bank. WHO, World Health Organization. WPR, Western Pacific.

strength in the associations of diabetes, hypertension and obesity with COVID-19 mortality. The GHSI is the first comprehensive assessment of countries' preparedness for infectious disease outbreaks such as COVID-19 based on the health security and related capabilities of 195 States Parties to the WHO 2005 International Health Regulations (IHR).[44] Our results were consistent with findings reported by others that higher country GHSI scores were associated with reduced deaths from communicable diseases (a composite of diarrhoeal disease, HIV, lower respiratory infection, meningitis and tuberculosis)[82] and that greater levels of preparedness were associated with lower excess COVID-19 mortality after accounting for under-reporting and age structure.[83] Collectively, these findings suggest that GHSI could be a measure for the capacity of overall healthcare system readiness, emergency medical response and critical care for illness that can progress in severity such as COVID-19 when risk is amplified by comorbidities such as diabetes, hypertension and obesity. Indeed, based on the global experience of COVID-19, the Monitoring and Evaluation Framework of the IHR was updated in 2021 to integrate health systems strengthening and health equity. Previously focused mainly on infection prevention and control, the updates recognise the importance of ensuring the provision of essential health services before, during and after an emergency to foster overall health system resilience.[84]

The major strengths of this systematic review and meta-analysis were its comprehensiveness and rigour. It involved searching 16 literature bases and obtaining a large number of eligible studies. While the majority of articles found in our literature review are in English, eight articles in Chinese, French, Italian, Persian, Russian, Spanish and Turkish were also identified, translated into English, and reviewed by two or more researchers to minimise possible omission of published original studies. The large number of studies enabled us to assess variations in subgroups by study-level and country-level characteristics as well as across all seven WHO regions. There were also several limitations in this study. First, all original studies included in this study were observational studies; therefore, the presence of information bias is possible, particularly due to the inclusion of studies relying on self-reports and retrospective data. However, the recall bias would be

Table 2 Meta-regression analysis* on the effect estimates for the associations of diabetes, hypertension and obesity with COVID-19 mortality by study-level and country-level indicators

Study-level and country-level indicators	Diabetes		Hypertension		Obesity	
	β (95% CI)†	P value‡	β (95% CI)	P value	β (95% CI)	P value
Mean, age, years	−0.01 (−0.02 to −0.001)	**0.02**	−0.01 (−0.02 to −0.001)	**0.03**	−0.00 (−0.01 to 0.01)	0.34
Men, %	−0.00 (−0.01 to 0.001)	0.23	−0.00 (−0.01 to 0.01)	0.74	−0.00 (−0.01 to 0.01)	0.43
Study starting date, month	−0.03 (−0.09 to 0.02)	0.20	−0.03 (−0.08 to 0.03)	0.30	−0.03 (−0.08 to 0.02)	0.28
NOS score	−0.03 (−0.10 to 0.04)	0.37	−0.02 (−0.10 to 0.06)	0.64	0.01 (−0.09 to 0.11)	0.85
Health Index Score, 2019	0.02 (0.01 to 0.04)	**0.003**	0.01 (−0.01 to 0.02)	0.21	0.00 (−0.02 to 0.02)	0.71
GHSI score, 2019	−0.01 (−0.01 to −0.001)	**0.02**	−0.01 (−0.01 to −0.001)	**0.04**	−0.01 (−0.02 to −0.001)	**0.001**

*Meta-regression was conducted to assess the linear relationship between the explanatory variables (continuous study-level and country-level indicators) and the outcome variables (effect estimates) using a random-effects method.
†The regression coefficient (β) and 95% CI describe how the outcome variable (the effect estimate) changes with a unit increase in the explanatory variable (potential moderation effect).
‡The statistical significance (p value) of the regression coefficient is a test of whether there is a linear relationship between the explanatory variable and the outcome variable. Bold values indicate $P<0.05$.
NOS, Newcastle-Ottawa Scale; GHSI, Global Health Security Index.

expected to be minimal as data from electronic health (medical) records were used for most studies included in this meta-analysis. Second, although we focused on the use of adjusted risk ratios in our meta-analyses, residual confounding might be possible because some unobserved variables might not have been included in the original studies. Third, our meta-analyses relied on the adjusted risk ratios available in studies that used different sets of covariates, which might have contributed to the variations observed. Fourth, about half of the studies used OR as the risk measure, which could overestimate the associations. However, OR can be used approximately as an approximate measure of risk given the low mortality rate for COVID-19.[33 34] Fifth, we adapted the NOS tool as a method to assess the quality or risk of bias of included studies. Due to the lack of a universally standardised scoring method, the NOS score for the individual study assessed in our study might differ from that in other similar analyses. The scores were produced by two researchers independently, and disagreement between two independent researchers was resolved by group discussion or by a third researcher, which would be expected to minimise the possibility of bias in quality assessment. Finally, our findings were limited to the studies published at the early phase of COVID-19 pandemic with highly publicised Alpha (B.1.1.7), Beta (B.1.351) and Gamma (P.1) variants of SARS-CoV-2 virus by the end of 2020. Future studies would be helpful to examine these associations in the later phases of COVID-19 pandemic with Delta (B.1.617.2) variant that hit hard in the spring of 2021 and Omicron (BA.1) variant that was identified in late November 2021 and overtook Delta as the dominant variant.[85]

Although diabetes, hypertension and obesity have been linked clinically with mechanistic and cellular plausibility,[86 87] few studies have assessed the effects of the combination of these three comorbidities on the risk of COVID-19 mortality perhaps due to insufficient sample size. A large study from Mexico reporting all possible combinations of three comorbidities suggested that patients having two or three comorbidities could have increased risk for COVID-19 mortality compared with those with only one chronic condition.[88] As diabetes, hypertension and obesity are inter-related and increasingly prevalent conditions globally,[11–13] integration of communicable and NCD prevention and treatment services could be a strategic measure to lessen the impact of future pandemics.[7–9]

CONCLUSION

Our systematic review and meta-analysis suggests that patients with diabetes and those with obesity had about a 40% increased risk for COVID-19 mortality, while those with hypertension had a 20% increased risk, independent of other known risk factors for COVID-19 mortality. Our findings motivate further research into the underlying pathophysiology of the associations. The independent associations of diabetes, hypertension and obesity with COVID-19 mortality support the need for intervention and management of these chronic conditions to mitigate the risk of mortality from respiratory pathogens and other infectious agents. The significant differences in the strength of associations across countries or regions and by the GHSI scores highlight the importance of readiness and preparedness of healthcare systems, medical resources, clinical care provision and capacity. Healthcare systems need to be integrated and resilient enough that they can not only

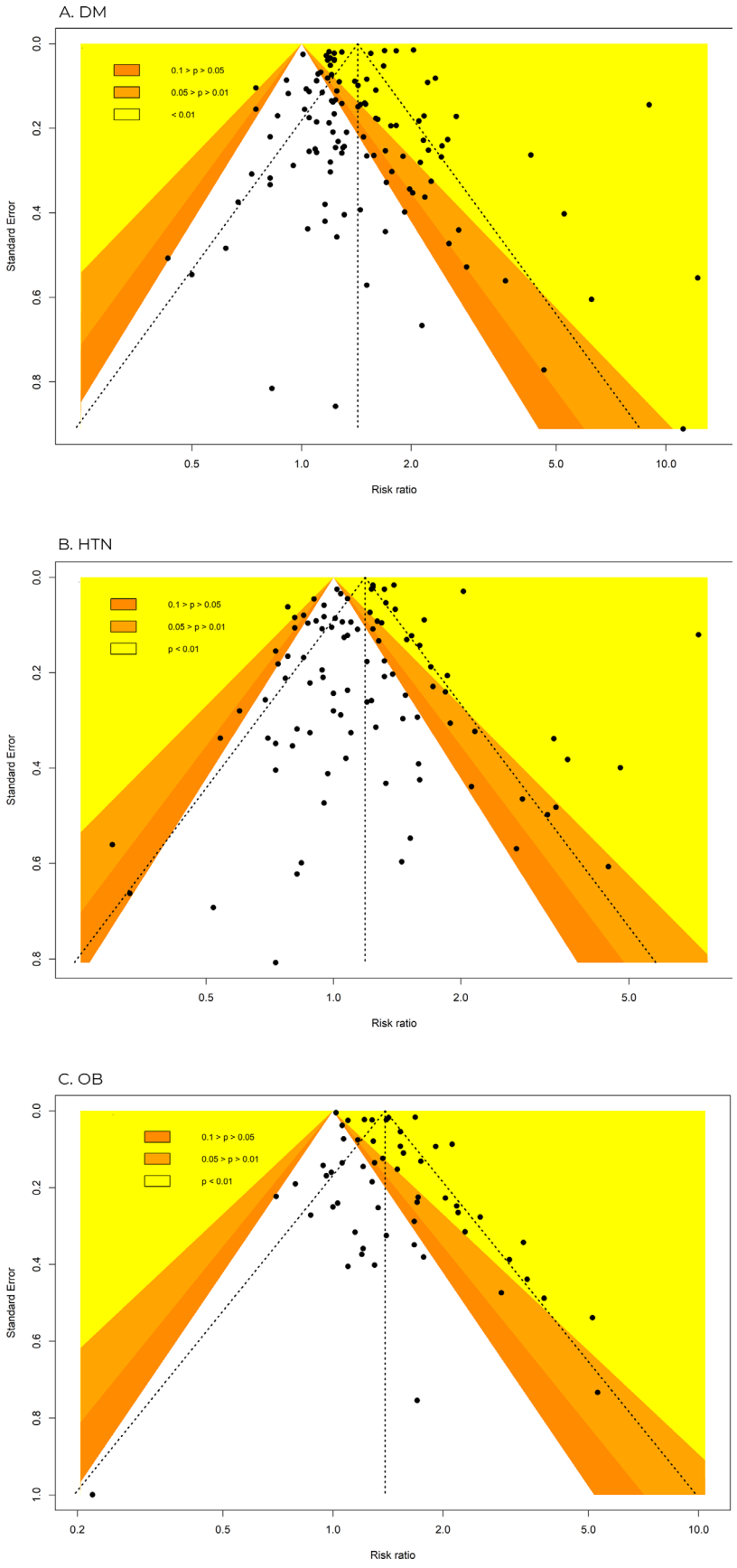

Figure 5 Contour-funnel plots of meta-analyses for the associations of diabetes (DM, A), hypertension (HTN, B), and obesity (OB, C) with COVID-19 mortality. Yellow region = $P<0.01$, light orange region = $0.01 \leq P<0.05$, dark orange region = $0.05 \leq P<0.1$, white region = $P \geq 0.1$. The vertical dashed line represents the overall pooled risk ratio. The diagonal dashed lines show the expected 95% confidence intervals around the overall pooled risk ratio. Each dot represents the effect size of a study.

react to emergencies but can proactively adapt so they are prepared to provide quality healthcare in every situation. Addressing the increasing burden of diabetes, obesity and hypertension is important both for the prevention of NCDs and for the resilience of populations in the face of pandemics, particularly those in low- and middle-income countries where healthcare access and resources can vary greatly.

Twitter Juan Pablo Gutierrez @gutierrezjp

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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, SEG-B, ACP, RLM, BL and PR. Conception and design: CL, NI, JPG, RLM, BL and PR. Literature search: CL, NI, JPG, SEG-B, ACP, RLM and PR. Acquisition of data: CL, NI, JPG, SEG-B, ACP, RLM and PR. Drafting of protocol: CL, NI, JPG, RLM, BL and PR. Critical revision of the manuscript for important intellectual content: CL, NI, JPG, SEG-B, ACP, RLM, BL and PR. Statistical expertise: NI and CL. Administrative, technical or material support: PR. Study supervision: PR. Guarantor for the overall content: CL and PR.

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ORCID iDs
Chaoyang Li http://orcid.org/0000-0001-7422-8110
Nazrul Islam http://orcid.org/0000-0003-3982-4325
Juan Pablo Gutierrez http://orcid.org/0000-0002-0557-5562
Samuel Eloy Gutiérrez-Barreto http://orcid.org/0000-0003-3598-1358
Andrés Castañeda Prado http://orcid.org/0000-0002-0197-6764
Ronald L Moolenaar http://orcid.org/0000-0002-3157-8222
Ben Lacey http://orcid.org/0000-0003-0139-2934
Patricia Richter http://orcid.org/0000-0003-2370-314X

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