Associations of Diabetes, Hypertension, and Obesity with COVID-19 Mortality in the Global Context:

A Systematic Review and Meta-Analysis of 145 Observational Studies

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WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Early in the COVID-19 pandemic, older people, and people with pre-existing noncommunicable 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 pathophysiologic 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.

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 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 Dec 1, 2019, to Dec 31, 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 (BMI $\geq$ 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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Keywords Diabetes, hypertension, obesity, COVID-19 mortality, systematic review, meta-analysis, global context, observational studies

Introduction

The COVID-19 pandemic has caused over 753.4 million reported cases and over 6.8 million deaths globally as of February 1, 2023.[1] Early in the pandemic, older people, and people with pre-existing noncommunicable 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 (e.g., influenza, SARS, and MERS) have previously been linked with a higher risk of severe outcomes among patients with comorbidities.[5] The U.S. 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 COVID-19 outcome. The risk of COVID-19 death increases as the number of comorbid conditions increases.[6] The population level consequences of COVID-19 illness are compounded by the increasing global burden of non-communicable diseases, 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 to 79 years, with an increasing prevalence reaching 19.9% for those aged 65 to 79 years.[11] Global prevalence of hypertension was estimated to be 31.1% in the adult population.[12] Global prevalence of overweight ($25 \leq \text{BMI} < 30$ kg/m^2) and obesity

(BMI ≥ 30 kg/m^2) 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 serologic response following vaccine administration in hypertensive versus normotensive patients.[15 16] COVID-19 infected individuals with diabetes, a disease associated with chronic inflammation and hyperglycemia, reportedly have a two- to three-fold increase in mortality from COVID-19 compared to people without diabetes.[3 17 18] An exploratory study of U.K. 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 (a body mass index ≥ 30 kg/m^2) was found to be significantly associated with increased severity in terms of intensive care hospitalization 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 geographic 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 COSMOS-E guidelines[24] and reported our results according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) 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 (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 (polymerase chain reaction, 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 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 (e.g., 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 randomized 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 labeled 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 a hazard ratio), 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 1st, 2019 and December 31st, 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, 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, or language. Detailed search strategy and the number of records are presented in **Supplementary 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 20. After the exclusion of duplicates using the function in EndNote 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, geographic 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- and age- and sex-adjusted, and multivariable-adjusted, as well as a list of covariates or potential confounders. Effect measures, including odds ratio (OR), hazard ratio (HR), or relative risk (RR), and their 95% confidence intervals (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 (8 requests sent and 6 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 (**Supplementary 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 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 pooled risk ratio (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 (REML) 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 standard errors were appropriate given the unadjusted standard errors.[40 41] To assess the potential effects of geographical locations, socioeconomic factors, and health care 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 through April 2020 or May 2020 through November 2020), WHO regions (Africa, Southeast 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),[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 (Stata Corp).

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 synthesizing 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 1,329 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) (**Fig. 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- and sex-adjusted models. The geographic distributions of the studies are presented in the map (**Fig. 2)**. Countries with a large number of studies included the United States (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)**.

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	1,000	1,336	1,157	2,015
	Interquartile range (IQR)	5,053	6,953	6,964	10,117
	95-<1,000	72 (49.7%)	52 (44.1%)	46 (46.5%)	24 (42.1%)
	1,000-<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					
	Hazard ratio (HR)	58 (40.0%)	48 (40.7%)	35 (35.4%)	23 (40.4%)
	Odds ratio (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%)
	Americas - US	40 (27.6%)	31 (26.3%)	29 (29.3%)	18 (31.6%)
	Americas - Outside US	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%)
	Southeast 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%)

Note: * The number of studies for each of the three comorbidities doesn't 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; WHO = World Health Organization.

The median (i.e., center) and the interquartile range (IQR, defined as the difference between the 25th and 75th percentile) (i.e., 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 **Supplementary Table S3**. Because of a large number, details of the total excluded studies with reasons (n=1,454) are not presented (available upon 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, 2.52; n=118), hypertension (2.07, 95% CI: 1.74, 2.47; n=99), and obesity (1.46, 95% CI: 1.22, 1.71; n=57) (**Fig. 3**). The overall pooled risk estimates using the odds ratios (OR) slightly

overestimated the risk estimates using hazard ratios (HR) and risk ratios (RR). The detailed numeric values of overall pooled risk ratios were presented in **Supplementary Table S1**. In addition, details of the forest plots for the individual studies were shown in **Supplementary Fig S1.1** (diabetes), **Fig S1.2** (hypertension), and **Fig 1.3** (obesity).

The pooled adjusted risk ratio for the association between diabetes and mortality was 1.43 (95% CI: 1.32, 1.54; n=118) with considerable heterogeneity (I^2=94%) (**Fig. 3**). Sensitivity analysis indicated that the exclusion of any one of the studies did not significantly impact the overall pooled risk ratio (**Supplementary Fig. 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 (**Fig. 4**). The detailed numeric value of pooled risk ratios by subgroups was presented in Supplementary **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) (**Fig. 5 A**).

Table 2 – Meta-Regression Analysis* on the Effect Estimates for the Associations of Diabetes, Hypertension, and Obesity with COVID-19 Mortality by Study- and Country-Level Indicators

Study- or Country-Level Indicators	Diabetes		Hypertension		Obesity	
	β (95% CI)†	*P*-value‡	*β* (95% CI)	*P*-value	*β* (95% CI)	*P*-value
Mean, age, y	-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**

Note: * Meta-regression was conducted to assess the linear relationship between the explanatory variables (continuous study-level and country-level indicator) and the outcome variables (effect estimates) using a random-effect method.

† The regression coefficient *(β)* and 95% confidence interval (CI) describe how the outcome variable (the effect estimate) changes with a unit increase in the explanatory variable (the potential effect modifier).

‡ The statistical significance (*P*-value) of the regression coefficient is a test of whether there is a linear relationship (*P*-value < 0.05) between the explanatory variable and the outcome variable.

NOS = Newcastle-Ottawa Scale; GHSI = Global Health Security Index.

The pooled adjusted risk ratio for the association between hypertension and mortality was 1.19 (95% CI: 1.09, 1.30; n=99) with considerable heterogeneity (I^2=91%) (**Fig. 3**). Sensitivity analysis indicated that the exclusion of any one of the studies did not have any significant impact on the overall pooled risk ratio (Supplementary **Fig. S2.2**). Subgroup analysis showed a lower PRR in studies with high quality, in the WB high income countries, and countries with a higher GHSI score, and a higher PRR in countries from the WHO WPR region (**Fig. 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) (**Fig. 5 B**).

The pooled adjusted risk ratio for the association between obesity and mortality was 1.39 (95% CI: 1.27, 1.52); n=57) with considerable heterogeneity (I^2=96%) (**Fig. 3**). Sensitivity analysis indicated that the exclusion of any one of the studies did not significantly impact the overall pooled risk ratio (Supplementary **Fig. S2.3**). Due to the small number of studies reporting adjusted obesity-COVID-19 mortality associations, some 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 (**Fig. 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) (**Fig. 5 C**). There was a suggestion of missing studies in the middle left-hand-side of the contour-funnel plot (i.e., small studies with high standard error), broadly in the non-significance region (white area where P>0.1), making publication bias plausible. The detailed numeric value of pooled risk ratios for the subgroup analyses were presented in **Supplementary 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 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 summarize 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 relative risk estimates adjusted for multiple confounders reported in recently published meta-analyses with inclusion of studies published as of 2022.[2 51 56 57] 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 meta-analyses.[53 58-61] 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 to those with normal BMI (18.5 ≤ BMI < 25 kg/m^2) or without obesity.[60] When BMI was modeled 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,[60] whereas a continuous BMI measure was not associated with the risk of COVID-19 mortality in another study.[61] 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 (i.e., the US and most of the western world).[13 62 63] 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 relative risk in published meta-analyses.[53 58-60]

As compared to the number of original studies included for diabetes and hypertension, we identified fewer studies for obesity, with several possible reasons. First,

obesity was not recognized as a risk factor for COVID-19 mortality at the early stage of the pandemic,[64 65] therefore few studies reported results for obesity in the countries at the early pandemic.[64 65] 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 synthesize data in meta-analyses. For example, whereas many studies used BMI $\geq$ 30 kg/m^2 to define obesity (i.e., overall obesity or unclassified obesity), a few studies used BMI as classified categories (i.e., 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: $\geq$ 40 kg/m^2) or a continuous scale.[61] Fourth, missing data on BMI in electronic health (medical) record systems are common.[66] 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 pro-inflammatory response, and cytokine storm might play critical roles in the severity and mortality of COVID-19 in patients with diabetes, hypertension, and obesity.[67-69] Emerging

evidence showed that SARS CoV-2 infection could increase the risk of developing new onset diabetes among survivors.[70 71] The relationship between SARS CoV-2 infection and new onset diabetes is complex, however, and not only is acquiring the virus associated with more severe outcomes, [2 56] but a large and increasing body of epidemiologic evidence shows an increase in diabetes incidence following infection.[70 71] This is consistent with laboratory evidence showing that the virus infects and can kill pancreatic beta cells.[72]

The elevated mortality risk among COVID-19 patients with comorbidities, particularly among those with uncontrolled diabetes or hypertension, suggests a correlation between pre-pandemic levels of control and the impact of these conditions on COVID-19 outcomes.[73 74] Countries with better healthcare quality often have a higher proportion of individuals with controlled diabetes and hypertension. This could imply that variations in pre-pandemic 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.[75] As the first country where the outbreak occurred, China had the strongest associations, followed by South Korea, European region, East Mediterranean region, Southeast 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.[76] As the pandemic progressed, individuals affected later on received more informed care, especially regarding treating individuals with comorbidities.[77-79] 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.[80] 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 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 World Health Organization (WHO) 2005 International Health Regulations (IHR).[44] Our result was in contrast with discrepant findings between the GHSI ranking and the actual response of countries based on COVID-19 performance indicators (total cases, total deaths, recovery rate, and total tests) in 37 Organization for Economic Cooperation and Development countries[81] and lack of association between GHSI score and COVID-19 mortality rates in top 36 countries ranked by GHSI score.[82] In both studies, countries with a lower GHSI score were not included; therefore, the generalizability of those findings were limited. It is possible that community mitigation interventions and public health measures play an important role in outbreak spreading or responses.[83 84]

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)[85]. 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 recognize the importance of ensuring the provision of essential health services before, during, and after an emergency to foster overall health system resilience.[86]

The major strengths of this systematic review and meta-analysis were its comprehensiveness and rigor. 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 minimize 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

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 standardized scoring method, the NOS score for the individual study assessed in our study might differ from that in other similar analyses. Our 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 minimize 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 publicized 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.[87]

Although diabetes, hypertension, and obesity have been linked clinically with mechanistic and cellular plausibility,[88 89] 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 to those with only one chronic condition.[90] As diabetes, hypertension, and obesity are inter-related and increasingly prevalent conditions globally,[11-13] integration of communicable and noncommunicable disease 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 suggest 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 react to emergencies but can proactively adapt so they are prepared to provide quality health care 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.

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Associations of Diabetes, Hypertension, and Obesity with COVID-19 Mortality in the Global Context:

A Systematic Review and Meta-Analysis of 145 Observational Studies

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WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Early in the COVID-19 pandemic, older people, and people with pre-existing noncommunicable 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 pathophysiologic 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.

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 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 Dec 1, 2019, to Dec 31, 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 (BMI $\geq$ 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.

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

Methods We searched 16 literature databases for original studies published between Jan 1, 2020, to Dec 31, 2020. We used the adapted Newcastle-Ottawa Scale to assess the risk of bias. Pooled risk ratios were estimated according to the type of risk ratio (OR, HR, or RR) and adjustment for potential confounding effects separately. 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 for diabetes (1.43, 95% CI 1.32 to 1.54), hypertension (1.19, 95% CI 1.09 to 1.30), and obesity (1.39, 95% CI 1.27 to 1.52) on COVID-19 mortality were about 33%, 43%, and 4% smaller than the unadjusted risk ratios. There was considerable heterogeneity for pooled risk ratios of diabetes (I^2=94%), hypertension (I^2=91%), and obesity (I^2=96%) associated with COVID-19 mortality. The pooled adjusted risk ratios appeared to be stronger in studies conducted before April 2020, the 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. This association was more

~~pronounced in low-resource settings, highlighting the importance of addressing these chronic diseases for global pandemic preparedness and prevention of severe outcomes.~~

PROSPERO registration number CRD42021204371**.**

Keywords Diabetes, hypertension, obesity, COVID-19 mortality, systematic review, meta-analysis, global context, observational studies

Introduction

The COVID-19 pandemic has caused over 753.4 million reported cases and over 6.8 million deaths globally as of February 1, 2023.[1] Early in the pandemic, older people, and people with pre-existing noncommunicable 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 (e.g., influenza, SARS, and MERS) have previously been linked with a higher risk of severe outcomes among patients with comorbidities.[5] The U.S. 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 COVID-19 outcome. The risk of COVID-19 death increases as the number of comorbid conditions increases.[6] The population level consequences of COVID-19 illness are compounded by the increasing global burden of non-communicable diseases, 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 to 79 years, with an increasing prevalence reaching 19.9% for those aged 65 to 79 years.[11] Global prevalence of hypertension was estimated to be 31.1% in the adult population.[12] ~~Global prevalence of obesity is estimated to be 39.0% in the adult~~

~~population~~ Global prevalence of overweight (25 ≤ BMI < 30 kg/m^2) and obesity (BMI ≥ 30 kg/m^2) 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 serologic response following vaccine administration in hypertensive versus normotensive patients.[15 16] COVID-19 infected individuals with diabetes, a disease associated with chronic inflammation and hyperglycemia, reportedly have a two- to three-fold increase in mortality from COVID-19 compared to people without diabetes.[3 17 18] An exploratory study of U.K. 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 (a body mass index ≥ 30 kg/m^2) was found to be significantly associated with increased severity in terms of intensive care hospitalization 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 geographic 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 COSMOS-E guidelines[24] and reported our results according to the Meta-analysis Of Observational Studies in Epidemiology (MOOSE) 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 (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 (polymerase chain reaction, 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 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 a death resulting from a clinically compatible illness in a person with lab-confirmed COVID-19)~~, 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 (e.g., 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 randomized 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 labeled 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 a hazard ratio), 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 1st, 2019 and December 31st, 2020 ~~(i.e., prior to widespread vaccination programs for coronavirus, which may affect the associations)~~. Our rigorous and broad literature search strategy used 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, or language. Detailed search strategy and a number of records are presented in **Supplementary 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 20. After the exclusion of duplicates using the function in EndNote 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, geographic 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- and age- and sex-adjusted, and multivariable-adjusted, as well as a list of covariates or potential confounders. Effect measures, including odds ratio (OR), hazard ratio (HR), or relative risk (RR), and their 95% confidence intervals (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 (8 requests sent and 6 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 (**Supplementary 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 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 pooled risk ratio (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 (REML) 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 standard errors were appropriate given the unadjusted standard errors.[40 41] To assess the potential effects of geographical locations, socioeconomic factors, and health care 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 through April 2020 or May 2020 through November 2020), WHO regions (Africa, Southeast 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),[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 (Stata Corp).

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 synthesizing 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 1,329 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) (**Fig. 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- and sex-adjusted models. The geographic distributions of the studies are presented in the map (**Fig. 2)**. Countries with a large number of studies included the United States (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 (~~95.2%~~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)**.

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	1,000	1,336	1,157	2,015
	Interquartile range (IQR)	5,053	6,953	6,964	10,117
	95-<1,000	72 (49.7%)	52 (44.1%)	46 (46.5%)	24 (42.1%)
	1,000-<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					
	Hazard ratio (HR)	58 (40.0%)	48 (40.7%)	35 (35.4%)	23 (40.4%)
	Odds ratio (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%)
	Americas - US	40 (27.6%)	31 (26.3%)	29 (29.3%)	18 (31.6%)
	Americas - Outside US	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%)
	Southeast 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%)

Note: * The number of studies for each of the three comorbidities doesn't 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; WHO = World Health Organization.

The median (i.e., center) and the interquartile range (IQR, defined as the difference between the 25th and 75th percentile) (i.e., 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 **Supplementary Table S3**. Because of a large number, details of the total excluded studies with reasons (n=1,454) are not presented (available upon 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, 2.52; n=118), hypertension (2.07, 95% CI: 1.74, 2.47; n=99), and obesity (1.46, 95% CI: 1.22, 1.71; n=57) (**Fig. 3**). The overall pooled risk estimates using the odds ratios (OR) slightly overestimated the risk estimates using hazard ratios (HR) and risk ratios (RR). The detailed numeric values of overall pooled risk ratios were presented in **Supplementary Table S1**. In addition, details of the forest plots for the individual studies were shown in **Supplementary Fig S1.1** (diabetes), **Fig S1.2** (hypertension), and **Fig 1.3** (obesity).

The pooled adjusted risk ratio for the association between diabetes and mortality was 1.43 (95% CI: 1.32, 1.54; n=118) with considerable heterogeneity (I^2=94%) (**Fig. 3**). Sensitivity analysis indicated that the exclusion of any one of the studies did not significantly impact the overall pooled risk ratio (**Supplementary Fig. 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 (**Fig. 4**). The detailed numeric value of pooled risk ratios by subgroups was presented in Supplementary **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) (**Fig. 5 A**).

Table 2 – Meta-Regression Analysis* on the Effect Estimates for the Associations of Diabetes, Hypertension, and Obesity with COVID-19 Mortality by Study- and Country-Level Indicators

Study- or Country-Level Indicators	Diabetes		Hypertension		Obesity	
	β (95% CI)†	*P*-value‡	*β* (95% CI)	*P*-value	*β* (95% CI)	*P*-value
Mean, age, y	-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**

Note: * Meta-regression was conducted to assess the linear relationship between the explanatory variables (continuous study-level and country-level indicator) and the outcome variables (effect estimates) using a random-effect method.

† The regression coefficient *(β)* and 95% confidence interval (CI) describe how the outcome variable (the effect estimate) changes with a unit increase in the explanatory variable (the potential effect modifier).

‡ The statistical significance (*P*-value) of the regression coefficient is a test of whether there is a linear relationship (*P*-value < 0.05) between the explanatory variable and the outcome variable.

NOS = Newcastle-Ottawa Scale; GHSI = Global Health Security Index.

The pooled adjusted risk ratio for the association between hypertension and mortality was 1.19 (95% CI: 1.09, 1.30; n=99) with considerable heterogeneity (I^2=91%) (**Fig. 3**). Sensitivity analysis indicated that the exclusion of any one of the studies did not have any significant impact on the overall pooled risk ratio (Supplementary **Fig. S2.2**). Subgroup analysis showed a lower PRR in studies with high quality, in the WB high income countries, and countries with a higher GHSI score, and a higher PRR in countries

from the WHO WPR region (**Fig. 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) (**Fig. 5 B**).

The pooled adjusted risk ratio for the association between obesity and mortality was 1.39 (95% CI: 1.27, 1.52); n=57) with considerable heterogeneity (I^2=96%) (**Fig. 3**). Sensitivity analysis indicated that the exclusion of any one of the studies did not significantly impact the overall pooled risk ratio (Supplementary **Fig. S2.3**). Due to the small number of studies reporting adjusted obesity-COVID-19 mortality associations, some 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 (**Fig. 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) (**Fig. 5 C**). There was a suggestion of missing studies in the middle left-hand-side of the contour-funnel plot (i.e., small studies with high standard error), broadly in the non-significance region (white area where P>0.1), making publication bias plausible. The detailed numeric value of pooled risk ratios for the subgroup analyses were presented in **Supplementary 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 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 summarize 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 relative risk estimates adjusted for multiple confounders reported in recently published meta-analyses with inclusion of studies published as of 2022.[2 51 56 57] 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 meta-analyses.[53 58-61] 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 to those with normal BMI (18.5 ≤ BMI < 25 kg/m^2) or without obesity.[60] When BMI was modeled 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,[60] whereas a continuous BMI measure was not associated with the risk of COVID-19 mortality in another study.[61] 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 (i.e., the US and most of the western world).[13 62 63] 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 relative risk in published meta-analyses.[53 58-60]

As compared to the number of original studies included for diabetes and hypertension, we identified fewer studies for obesity, with several possible reasons. First, obesity was not recognized as a risk factor for COVID-19 mortality at the early stage of the pandemic,[64 65] therefore few studies reported results for obesity in the countries at the early pandemic.[64 65] 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 synthesize data in meta-analyses. For example, whereas many studies used BMI $\geq$ 30 kg/m^2 to define obesity (i.e., overall obesity or unclassified obesity), a few studies used BMI as classified categories (i.e., 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: $\geq$ 40 kg/m^2) or a continuous scale.[61] Fourth, missing data on BMI in electronic health (medical) record systems are common.[66] 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 pro-inflammatory response, and cytokine storm might play critical roles in the severity and mortality of COVID-19 in patients with diabetes, hypertension, and obesity.[67-69] Emerging evidence showed that SARS CoV-2 infection could increase the risk of developing new onset diabetes among survivors.[70 71] The relationship between SARS CoV-2 infection and new onset diabetes is complex, however, and not only is acquiring the virus associated with more severe outcomes, [2 56] but a large and increasing body of epidemiologic evidence shows an increase in diabetes incidence following infection.[70 71] This is consistent with laboratory evidence showing that the virus infects and can kill pancreatic beta cells.[72]

The elevated mortality risk among COVID-19 patients with comorbidities, particularly among those with uncontrolled diabetes or hypertension, suggests a correlation between pre-pandemic levels of control and the impact of these conditions on COVID-19 outcomes.[73 74] Countries with better healthcare quality often have a higher proportion of individuals with controlled diabetes and hypertension. This could imply that variations in pre-pandemic 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.[75] As the first country where the outbreak occurred, China had the strongest associations, followed

by South Korea, European region, East Mediterranean region, Southeast 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.[76] As the pandemic progressed, individuals affected later on received more informed care, especially regarding treating individuals with comorbidities.[77-79] 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.[80] 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 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 World Health Organization (WHO) 2005 International Health Regulations (IHR).[44] Our result was in contrast with discrepant findings between the GHSI ranking and the actual response of countries based on COVID-19 performance indicators (total cases, total deaths, recovery rate, and total tests) in 37 Organization for Economic Cooperation and Development countries[81] and lack of association between GHSI score and COVID-19 mortality rates in

top 36 countries ranked by GHSI score.[82] In both studies, countries with a lower GHSI score were not included; therefore, the generalizability of those findings were limited. It is possible that community mitigation interventions and public health measures play an important role in outbreak spreading or responses.[83 84]

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)[85]. 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 recognize the importance of ensuring the provision of essential health services before, during, and after an emergency to foster overall health system resilience.[86]

The major strengths of this systematic review and meta-analysis were its comprehensiveness and rigor. 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 minimize 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 expected to be minimal as data from electronic medical records were used for the majority of 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~~Finally~~, 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 standardized scoring method, the NOS score for the individual study assessed in our study might differ from that in other similar analyses. Our 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 minimize 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 publicized 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.[87]

Although diabetes, hypertension, and obesity have been linked clinically with mechanistic and cellular plausibility,[88 89] 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 to those with only one chronic condition.[90] As diabetes, hypertension, and obesity are inter-related and increasingly prevalent conditions globally,[11-13] integration of communicable and noncommunicable disease 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 suggest 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 react to emergencies but can proactively adapt so they are prepared to provide quality health care 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.

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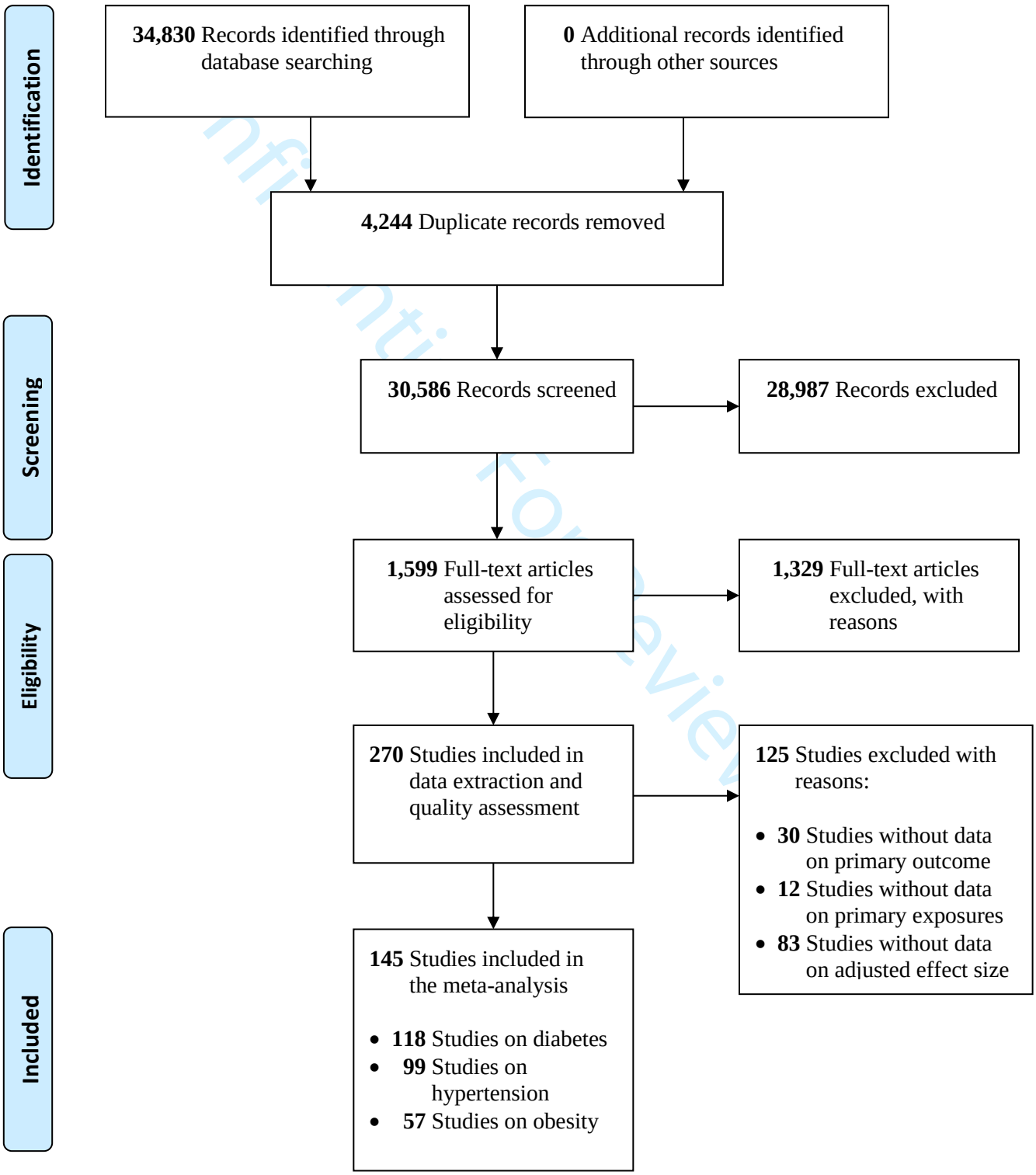
Fig. 1 – PRISMA Flow Diagram



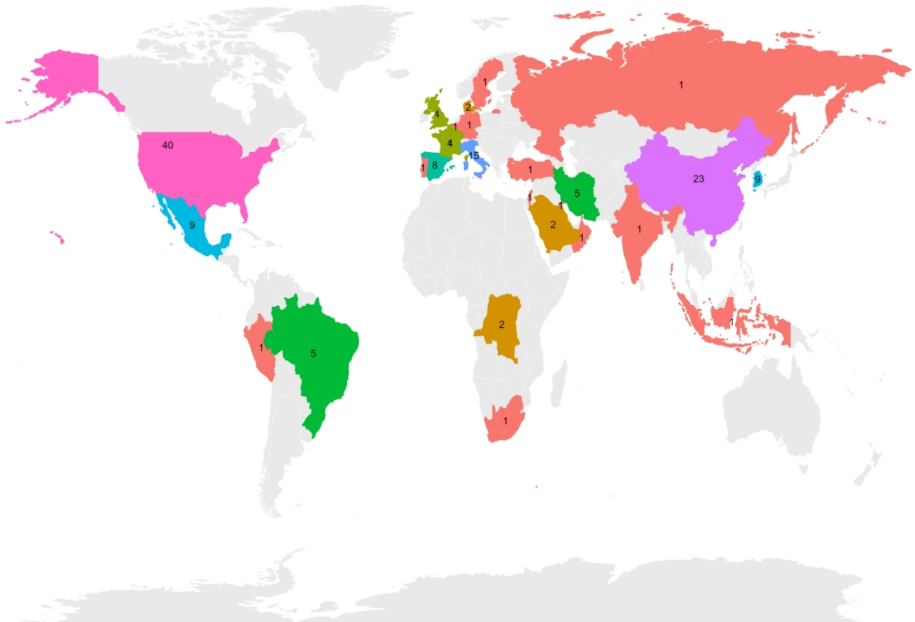


Fig. 2 – Number and Distribution of Studies Included in the Meta-Analysis by Country*
* Colors in the map represent the number of studies included in the meta-analysis by country (n=143). Studies conducted in multiple countries (n=2) were not shown in this map.

428x302mm (157 x 157 DPI)

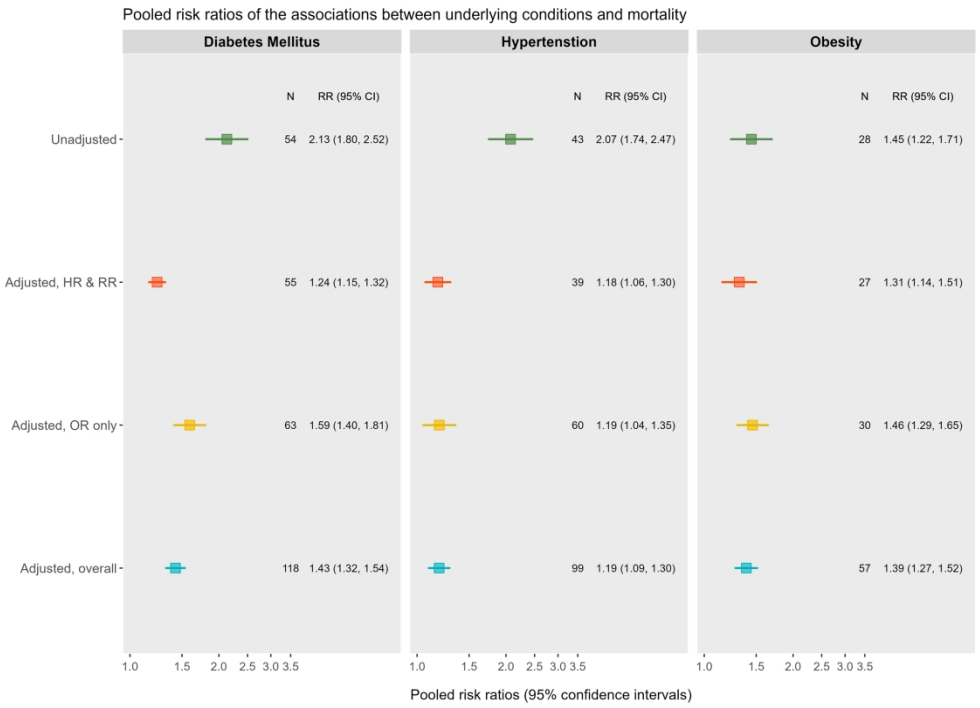


Fig. 3 – Overall Pooled Effect Estimates for the Associations of Diabetes, Hypertension, and Obesity with COVID-19 Mortality

Note: Estimates are from random-effects meta-analysis using restricted maximum likelihood method and Hartung-Knapp-Sidik-Jonkman adjusting for the standard errors.

PRR = pooled risk ratio, CI = confidence interval, HR = hazard ratio, OR = odds ratio, RR = relative risk.

420x297mm (157 x 157 DPI)

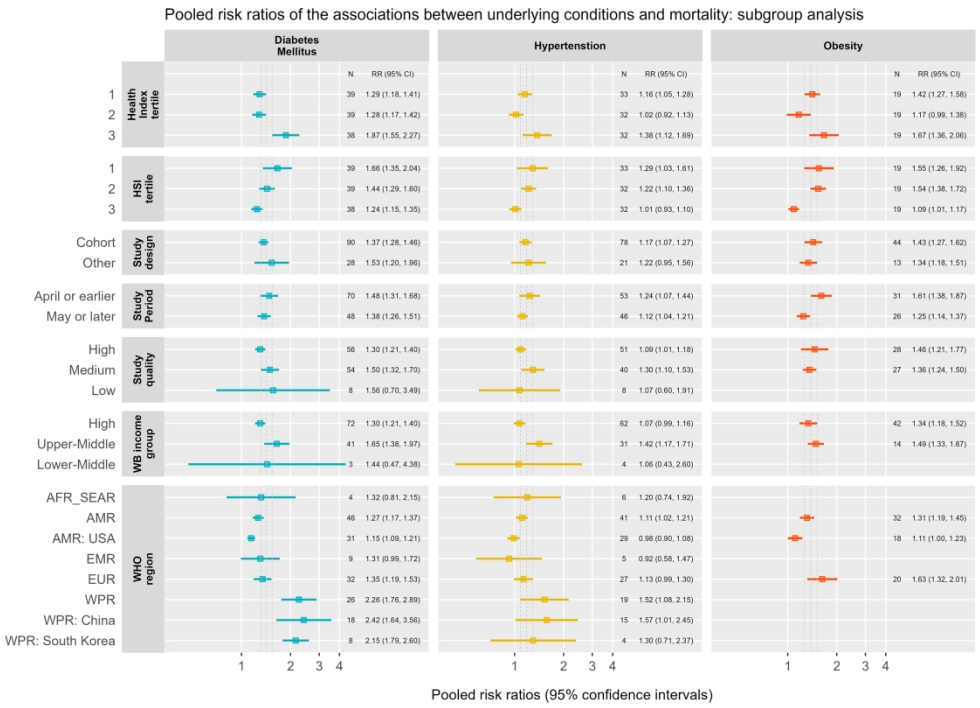


Fig. 4 – Pooled Effect Estimates for the Associations of Diabetes, Hypertension, and Obesity with COVID-19 Mortality by Subgroups

Note: Estimates are from random-effects meta-analysis using restricted maximum likelihood method and Hartung-Knapp-Sidik-Jonkman adjusting for the standard errors.

PRR = pooled risk ratio, CI = confidence interval, GHSI = Global Health Security Index, USA = United States of America, WHO = World Health Organization, WB = World Bank, AFR = African Region, SEAR = Southeast Asian Region, AMR = American Region, EMR = East Mediterranean Region, EUR = European Region, WPR = West Pacific Region.

420x297mm (157 x 157 DPI)

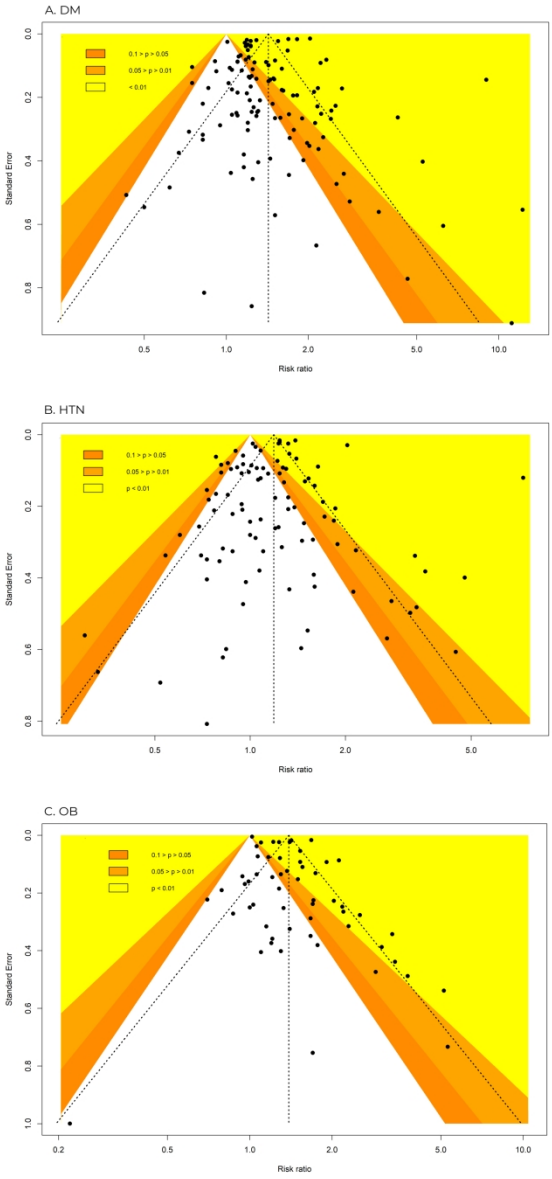


Fig. 5 – Contour-Funnel Plots of Meta-Analysis for the Association of Diabetes (A), Hypertension (B), and Obesity (C) with COVID-19 Mortality

Note: Yellow region = P<0.01, light orange region = 0.01<P<0.05, dark orange region = 0.05<P<0.10, white region = P>0.10. The vertical dashed line represents the overall pooled risk ratio estimate. The diagonal dashed lines show the expected 95% confidence intervals around the pooled risk ratio estimate, indicate the triangular region within which 95% of studies are expected to lie in the absence of both biases and heterogeneity. Each dot represents the effect estimate of a study.

P-values of Egger's test for funnel plot asymmetry are 0.29, 0.25, and 0.002 for A, B, and C, respectively.

DM = diabetes, HTN = hypertension, OB = obesity.

733x1552mm (72 x 72 DPI)

Supplementary Materials

Abbreviations used in the supplementary materials:

AFR = African Region
AMR = American Region
C-C = case-control
COSMOS-E = Conducting Systematic Reviews and Meta-Analyses of Observational Studies of Etiology
C-S = cross-sectional
DM = diabetes mellitus
EHR = electronic health (medical) record
EMR = East Mediterranean Region
ES = effect size
EUR = European Region
GHSI = Global Health Security Index
HI = high income
HR = hazard ratio
HTN = hypertension
LMI = lower middle income
MOOSE = meta-analyses Of Observational Studies in Epidemiology
NOS = Newcastle-Ottawa Scale
Ob = obesity
OR = odds ratio
PRR = pooled risk ratio
PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RR = relative risk or risk ratio
ARS = administrative/registry/surveillance or (case) reporting system
SEAR = Southeast Asian Region
UK = United Kingdom
UMI = upper middle income
USA = United States of America
WB = World Bank
WHO = World Health Organization
WPR = West Pacific Region

Supplementary Text 1

Search Strategy

Time period: December 1st, 2019, through December 31st, 2020.

Key words or terms:

1. (COVID-19 and all possible variations) AND
2. (Diabetes, obesity, hypertension, and all relevant terms) OR
3. (Comorbidity, comorbid disease or illness or condition, underlying disease or illness or condition, chronic disease or illness or condition, noncommunicable disease or NCD, predictor, risk or risk factor, determinant, cardiovascular, and metabolic).

No restrictions in language, gender, age, publication types.

Databases: all 16 databases.

Database	Strategy	Records 08/17/2020	Update 09/16/2020	Update 01/15/2021
Medline (OVID) 1946-	novel coronavir* OR novel corona virus* OR 2019 coronavirus OR coronavirus disease OR coronavirus 2019 OR betacoronavir* OR covid19 OR covid 19 OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR sars-cov OR sarscov OR 2019nCoV OR 2019-nCoV OR wuhan virus* OR ((wuhan OR hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak* AND (201912*.dt OR 2020*.dt)) OR ((coronavirus OR pandemic).mp AND (201912*.dt OR 2020*.dt)) AND Diabetes OR diabetic OR blood glucose OR glyc?emic control OR glucose control OR hyperglyc?emia OR hypoglyc?emia OR obesity OR obese OR overweight OR adipos* OR waist circumference OR BMI OR body mass index OR hypertension OR hypertensive OR high blood pressure OR comorbid* OR co-morbid* OR pre-existing OR preexisting OR underlying OR chronic disease* OR chronic illness* OR chronic condition* OR noncommunicable disease* OR cardiovascular disease* OR predictor* OR determinant* OR risk factor* OR metabolic	5856	1586	7932
Embase (OVID) 1988-	(novel coronavir* OR novel corona virus* OR 2019 coronavirus OR coronavirus disease OR coronavirus 2019 OR betacoronavir* OR covid19 OR covid 19 OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR sars-cov OR sarscov OR 2019nCoV OR 2019-nCoV OR wuhan virus*) OR ((wuhan OR hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak*) OR ((coronavirus OR pandemic).mp AND 2020*.dc) AND Diabetes OR diabetic OR blood glucose OR glyc?emic control OR glucose control OR hyperglyc?emia OR hypoglyc?emia OR obesity OR obese OR overweight OR adipos* OR waist circumference OR BMI OR body mass index OR hypertension OR hypertensive OR high blood pressure OR comorbid* OR co-morbid* OR pre-existing OR preexisting OR underlying OR chronic disease* OR chronic illness* OR chronic condition* OR noncommunicable disease* OR cardiovascular disease* OR predictor* OR determinant* OR risk factor* OR metabolic Not pubmed/medline	6461 -4050 duplicates =2411 unique items	2816 -1677 duplicates =1139 unique items	11477 -5134 duplicates =6343 unique items
Global Health (OVID)	(novel coronavir* OR novel corona virus* OR 2019 coronavirus OR coronavirus disease OR coronavirus 2019 OR betacoronavir* OR covid19 OR covid 19 OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR sars-cov OR sarscov OR 2019nCoV OR 2019-nCoV OR wuhan virus*) OR (((wuhan OR hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak*) AND 2020*.up) OR ((coronavirus OR pandemic).mp AND 2020*.up) AND Diabetes OR diabetic OR blood glucose OR glyc?emic control OR glucose control OR hyperglyc?emia OR hypoglyc?emia OR obesity OR obese OR overweight OR adipos* OR waist circumference OR BMI OR body mass index OR hypertension OR hypertensive OR high blood pressure OR comorbid* OR co-morbid* OR pre-existing OR preexisting OR underlying OR chronic disease* OR chronic illness*	1102 -744 duplicates =358 unique items	273 -107 duplicates =166 unique items	3225 -1597 duplicates =1628 unique items

	OR chronic condition* OR noncommunicable disease* OR cardiovascular disease* OR predictor* OR determinant* OR risk factor* OR metabolic			
CAB Abstracts (OVID)	(novel coronavir* OR novel corona virus* OR 2019 coronavirus OR coronavirus disease OR coronavirus 2019 OR betacoronavir* OR covid19 OR covid 19 OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR sars-cov OR sarscov OR 2019nCoV OR 2019-nCoV OR wuhan virus*) OR ((wuhan OR hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak*) OR ((coronavirus OR pandemic).mp AND 2020*.up) AND Diabetes OR diabetic OR blood glucose OR glyc?emic control OR glucose control OR hyperglyc?emia OR hypoglyc?emia OR obesity OR obese OR overweight OR adipos* OR waist circumference OR BMI OR body mass index OR hypertension OR hypertensive OR high blood pressure OR comorbid* OR co-morbid* OR pre-existing OR preexisting OR underlying OR chronic disease* OR chronic illness* OR chronic condition* OR noncommunicable disease* OR cardiovascular disease* OR predictor* OR determinant* OR risk factor* OR metabolic	501 -463 duplicates =38 unique items	125 -121 duplicates =4 unique items	685 -669 duplicates =16 unique items
PsycInfo (OVID) 1987-	(novel coronavir* OR novel corona virus* OR 2019 coronavirus OR coronavirus disease OR coronavirus 2019 OR betacoronavir* OR covid19 OR covid 19 OR nCoV OR novel CoV OR CoV 2 OR CoV2 OR sarscov2 OR sars-cov OR sarscov OR 2019nCoV OR 2019-nCoV OR wuhan virus*) OR (((wuhan OR hubei OR huanan) AND (severe acute respiratory OR pneumonia*) AND outbreak*) AND 2020*.up) OR ((coronavirus OR pandemic).mp AND 2020*.up) AND Diabetes OR diabetic OR blood glucose OR glyc?emic control OR glucose control OR hyperglyc?emia OR hypoglyc?emia OR obesity OR obese OR overweight OR adipos* OR waist circumference OR BMI OR body mass index OR hypertension OR hypertensive OR high blood pressure OR comorbid* OR co-morbid* OR pre-existing OR preexisting OR underlying OR chronic disease* OR chronic illness* OR chronic condition* OR noncommunicable disease* OR cardiovascular disease* OR predictor* OR determinant* OR risk factor* OR metabolic	159 -106 duplicates =53 unique items	74 -47 duplicates =27 unique items	609 -254 duplicates =355 unique items
CINAHL (EbscoHost)	(“novel coronavir*” OR “novel corona virus*” OR “2019 coronavirus” OR betacoronavir* OR covid19 OR “covid 19” OR nCoV OR “novel CoV” OR “CoV 2” OR CoV2 OR sarscov2 OR sars-cov OR sarscov OR 2019nCoV OR 2019-nCoV OR “wuhan virus*”) OR (((wuhan OR hubei OR huanan) AND (“severe acute respiratory” OR pneumonia*) AND outbreak*) AND PY 2020) OR ((coronavirus OR pandemic) AND PY 2020) AND Diabetes OR diabetic OR “blood glucose” OR “glyc?emic control” OR “glucose control” OR hyperglyc?emia OR hypoglyc?emia OR obesity OR obese OR overweight OR adipos* OR “waist circumference” OR BMI OR “body mass index” OR hypertension OR hypertensive OR “high blood pressure” OR comorbid* OR co-morbid* OR pre-existing OR preexisting OR underlying OR “chronic disease*” OR “chronic illness*” OR “chronic condition*” OR “noncommunicable disease*” OR “cardiovascular disease*” OR predictor* OR determinant* OR “risk factor*” OR metabolic Exclude Medline records	1668 -602 duplicates =766 unique items	264 -105 duplicates =259 unique items	1225 -569 duplicates =656 unique items
Academic Research Complete	(“novel coronavir*” OR “novel corona virus*” OR “2019 coronavirus” OR betacoronavir* OR covid19 OR “covid 19” OR nCoV OR “novel CoV” OR “CoV 2” OR CoV2 OR sarscov2 OR sars-cov OR sarscov OR 2019nCoV OR 2019-nCoV OR “wuhan virus*”) OR (((wuhan OR hubei OR huanan) AND (“severe acute respiratory” OR pneumonia*) AND outbreak*) AND PY 2020) OR ((coronavirus OR pandemic) AND PY 2020) AND Diabetes OR diabetic OR “blood glucose” OR “glyc?emic control” OR “glucose control” OR hyperglyc?emia OR hypoglyc?emia OR obesity OR obese OR overweight OR adipos* OR “waist circumference” OR BMI OR “body mass index” OR hypertension OR hypertensive OR “high blood pressure” OR comorbid* OR co-morbid* OR pre-existing OR preexisting OR underlying OR “chronic disease*” OR “chronic illness*” OR “chronic condition*” OR “noncommunicable disease*” OR “cardiovascular disease*” OR predictor* OR determinant* OR “risk factor*” OR metabolic	1644 -1096 duplicates =548 unique items	647 -448 duplicates =199 unique items	2585 -1979 duplicates =606 unique items
Africa Wide Information	(“novel coronavir*” OR “novel corona virus*” OR “2019 coronavirus” OR betacoronavir* OR covid19 OR “covid 19” OR nCoV OR “novel CoV” OR “CoV 2” OR CoV2 OR sarscov2 OR sars-cov OR sarscov OR 2019nCoV OR 2019-nCoV OR “wuhan virus*”) OR (((wuhan OR hubei OR huanan) AND (“severe acute respiratory” OR pneumonia*) AND outbreak*) AND PY 2020) OR ((coronavirus OR pandemic) AND PY 2020) AND	6 -1 duplicates =5 unique items	0	15 -3 duplicates =11 unique items

	Diabetes OR diabetic OR “blood glucose” OR “glyc?emic control” OR “glucose control” OR hyperglyc?emia OR hypoglyc?emia OR obesity OR obese OR overweight OR adipos* OR “waist circumference” OR BMI OR “body mass index” OR hypertension OR hypertensive OR “high blood pressure” OR comorbid* OR co-morbid* OR pre-existing OR preexisting OR underlying OR “chronic disease*” OR “chronic illness*” OR “chronic condition*” OR “noncommunicable disease*” OR “cardiovascular disease*” OR predictor* OR determinant* OR “risk factor*” OR metabolic			
Scopus	TITLE-ABS(“novel coronavir*” OR “novel corona virus*” OR “2019 coronavirus” OR betacoronavir* OR covid19 OR "covid 19" OR ncov OR "CoV 2" OR cov2 OR sarscov2 OR sars-cov OR sarscov OR 2019ncov OR 2019-nCoV OR "novel CoV" OR "wuhan virus") AND TITLE-ABS(Diabetes OR diabetic OR “blood glucose” OR “glyc?emic control” OR “glucose control” OR hyperglyc?emia OR hypoglyc?emia OR obesity OR obese OR overweight OR adipos* OR “waist circumference” OR BMI OR “body mass index” OR hypertension OR hypertensive OR “high blood pressure” OR comorbid* OR co-morbid* OR pre-existing OR preexisting OR underlying OR “chronic disease*” OR “chronic illness*” OR “chronic condition*” OR “noncommunicable disease*” OR “cardiovascular disease*” OR predictor* OR determinant* OR “risk factor*” OR metabolic)	4021 -3551 duplicates =470 unique items	94 -73 duplicates =21 unique items	1038 -702 duplicates =336 unique items
PMC	("novel coronavir*"[Title/Abstract] OR "novel corona virus*"[Title/Abstract] OR "2019 coronavirus"[Title/Abstract] OR "betacoronavir*"[Title/Abstract] OR "covid19"[Title/Abstract] OR "covid 19"[Title/Abstract] OR "ncov"[Title/Abstract] OR "CoV 2"[Title/Abstract] OR "cov2"[Title/Abstract] OR "sarscov2"[Title/Abstract] OR "sars-cov"[Title/Abstract] OR "sarscov"[Title/Abstract] OR "2019ncov"[Title/Abstract] OR "2019-nCoV"[Title/Abstract] OR "novel CoV"[Title/Abstract] OR "wuhan virus"[All Fields]) AND Diabetes[Title/Abstract] OR diabetic[Title/Abstract] OR “blood glucose” [Title/Abstract] OR “glyc?emic control” [Title/Abstract] OR “glucose control” [Title/Abstract] OR hyperglyc?emia[Title/Abstract] OR hypoglyc?emia[Title/Abstract] OR obesity[Title/Abstract] OR obese[Title/Abstract] OR overweight[Title/Abstract] OR adipos*[Title/Abstract] OR “waist circumference” [Title/Abstract] OR BMI[Title/Abstract] OR “body mass index”[Title/Abstract] OR hypertension[Title/Abstract] OR hypertensive[Title/Abstract] OR “high blood pressure”[Title/Abstract] OR comorbid*[Title/Abstract] OR co-morbid*[Title/Abstract] OR pre-existing[Title/Abstract] OR preexisting[Title/Abstract] OR underlying[Title/Abstract] OR “chronic disease*”[Title/Abstract] OR “chronic illness*”[Title/Abstract] OR “chronic condition*”[Title/Abstract] OR “noncommunicable disease*”[Title/Abstract] OR “cardiovascular disease*”[Title/Abstract] OR predictor*[Title/Abstract] OR determinant*[Title/Abstract] OR “risk factor*”[Title/Abstract] OR metabolic[Title/Abstract]	918 -676 duplicates =242 unique items	243 -172 duplicates =71 unique items	791 -727 duplicates =64 unique items
ProQuest Central	TI,AB(“novel coronavir*” OR “novel corona virus*” OR “2019 coronavirus” OR betacoronavir* OR covid19 OR “covid 19” OR nCoV OR “novel CoV” OR “CoV 2” OR CoV2 OR sarscov2 OR sars-cov OR sarscov OR 2019nCoV OR 2019-nCoV) AND TI,AB(Diabetes OR diabetic OR “blood glucose” OR “glyc?emic control” OR “glucose control” OR hyperglyc?emia OR hypoglyc?emia OR obesity OR obese OR overweight OR adipos* OR “waist circumference” OR BMI OR “body mass index” OR hypertension OR hypertensive OR “high blood pressure” OR comorbid* OR co-morbid* OR pre-existing OR preexisting OR underlying OR “chronic disease*” OR “chronic illness*” OR “chronic condition*” OR “noncommunicable disease*” OR “cardiovascular disease*” OR predictor* OR determinant* OR “risk factor*” OR metabolic)	1238 -844 duplicates =394 unique items	483 -339 duplicates =144 unique items	1256 -760 duplicates =496 unique items
SBT COVID-19 Library **This library covers (PrePrints - Medrxiv, BIOrxiv, Chemrxiv, SSRN, Scielo -, WHO COVID-19 database, Homeland**	Diabetes OR diabetic OR “blood glucose” OR “glyc?emic control” OR “glucose control” OR hyperglyc?emia OR hypoglyc?emia OR obesity OR obese OR overweight OR adipos* OR “waist circumference” OR BMI OR “body mass index” OR hypertension OR hypertensive OR “high blood pressure” OR comorbid* OR co-morbid* OR pre-existing OR preexisting OR underlying OR “chronic disease*” OR “chronic illness*” OR “chronic condition*” OR “noncommunicable disease*” OR “cardiovascular disease*” OR predictor* OR determinant* OR “risk factor*” OR metabolic	Preprints = 1602 WHO = 913 HLSC = 25 SciFinder = 82	Preprints = 26 WHO = 0 HLSC = 0 SciFinder =0 Clinicaltrials = 384	No longer being updated

Security COVID-19 collection, SciFinder, Clinicaltrials)		Clinicaltrials = 326		
Total		**13646**	**3467**	**18443**

Notes: Duplicates were identified using the Endnote automated "find duplicates" function with preference set to match on title, author, and year, and removed from your Endnote library. There will likely be additional duplicates found that Endnote was unable to detect.

Total records before removing duplicates = 35,556; total records after removing duplicates via Endnote 20 = 34,830; total records after further removing duplicates via Covidence = 30,586.

Supplementary Text 2

Adapted Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses

A. CASE-CONTROL STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Exposure components. A maximum of two stars can be given for the Comparability component.

Selection (Maximum 4 stars)

1) Is the case definition adequate?
   a) yes, with independent validation*
   b) yes, e.g., record linkage or based on self-reports
   c) no description
2) Representativeness of the cases
   a) consecutive or obviously representative series of cases*
   b) potential for selection biases or not stated
3) Selection of Controls
   a) community controls*
   b) hospital controls
   c) no description
4) Definition of Controls
   a) no history of disease (endpoint)*
   b) no description of source

Comparability (Maximum 2 stars)

1) Comparability of cases and controls on the basis of the design or analysis
   a) study controls for age (the most important factor)*
   b) study controls for age plus any additional factor** (This criterion could be modified to indicate specific control for a second important factor)
   c) study does not control for any confounders or no information provided

Exposure (Maximum 3 stars)

1) Ascertainment of exposure
   a) secure record (e.g., surgical records)*
   b) structured interview where blind to case/control status*
   c) interview not blinded to case/control status
   d) written self-report or medical record only
   e) no description
2) Same method of ascertainment for cases and controls
   a) Yes*
   b) no
3) Non-Response rate
   a) same rate for both groups*

b) non respondents described
c) rate different and no designation

B. COHORT STUDIES

Note: A study can be awarded a maximum of one star for each numbered item within the Selection and Outcome components. A maximum of two stars can be given for the Comparability component.

Selection (Maximum 4 stars)

1) Representativeness of the exposed cohort
   a) truly representative of the average (describe) in the community*
   b) somewhat representative of the average _____ in the community*
   c) selected group of users (e.g., nurses, volunteers)
   d) no description of the derivation of the cohort
2) Selection of the non-exposed cohort
   a) drawn from the same community as the exposed cohort*
   b) drawn from a different source
   c) no description of the derivation of the non-exposed cohort
3) Ascertainment of exposure
   a) secure record (e.g., surgical records)*
   b) structured interview*
   c) written self-report
   d) no description
4) Demonstration that outcome of interest was not present at start of study
   a) Yes*
   b) no

Comparability (Maximum 2 stars)

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor)*
   b) study controls for the most important factor plus any additional factor** (This criterion could be modified to indicate specific control for a second important factor)
   c) study does not adjust for any relevant confounders/risk factors or no information provided

Outcome (Maximum 3 stars)

1) Assessment of outcome
   a) independent blind assessment*
   b) record linkage*
   c) self-report
   d) no description
2) Was follow-up long enough for outcomes to occur
   a) yes (select an adequate follow up period for outcome of interest)*
   b) no
3) Adequacy of follow up of cohorts
   a) complete follow up - all subjects accounted for*

b) subjects lost to follow up unlikely to introduce bias - small number lost - > ____ % (select an adequate %) follow up, or description provided of those lost)*
c) follow up rate < ____% (select an adequate %) and no description of those lost
d) no statement

C. CROSS-SECTIONAL STUDIES

Note: This scale has been adapted from the Newcastle-Ottawa Quality Assessment Scale for case-control studies and cohort studies to provide quality assessment of cross-sectional studies. A study can be awarded a maximum of one star for each numbered item within the Selection component. A maximum of two stars can be given for the Comparability and Outcome components.

Selection (Maximum 4 stars)

1) Representativeness of the sample
   a) truly representative of the average in the target population* (all subjects or random sampling)
   b) somewhat representative of the average in the target group* (non-random sampling)
   c) selected group of users/convenience sample.
   d) no description of the derivation of the included subjects

2) Sample size
   a) justified and satisfactory (including sample size calculation)*
   b) not justified
   c) no information provided

3) Ascertainment of the exposure (risk factor)
   a) Secure record (e.g., surgical record)*
   b) structured interview*
   c) written self-report
   d) no description

4) Non-respondents
   a) proportion of target sample recruited attains pre-specified target or basic summary of non-respondent characteristics in sampling frame recorded*
   b) unsatisfactory recruitment rate, no summary data on non-respondents
   c) no description of the response rate or the characteristics of the responders and the non-responders

Comparability (Maximum 2 stars)

1) Comparability of cohorts on the basis of the design or analysis
   a) study controls for _____ (select the most important factor)*
   b) study controls for the most important factor plus any additional factor** (This criterion could be modified to indicate specific control for a second important factor)
   c) study does not adjust for any relevant confounders/risk factors or no information provided

Outcome (Maximum 3 stars)

1) Assessment of outcome

a) independent blind assessment**
b) record linkage*
c) self-report
d) no description

2) Statistical test
   a) statistical test used to analyse the data clearly described, appropriate and measures of association presented including confidence intervals and probability level (p-value)*
   b) statistical test is not appropriate, not described, or incomplete

Total NOS scores: 8-9 stars: high quality or low risk of bias
5-7 stars: moderate quality or moderate risk of bias
<5 stars: low quality or high risk of bias.

Supplementary Figures

Fig. S1.1 – Forest Plots for the Association of Diabetes with COVID-19 Mortality

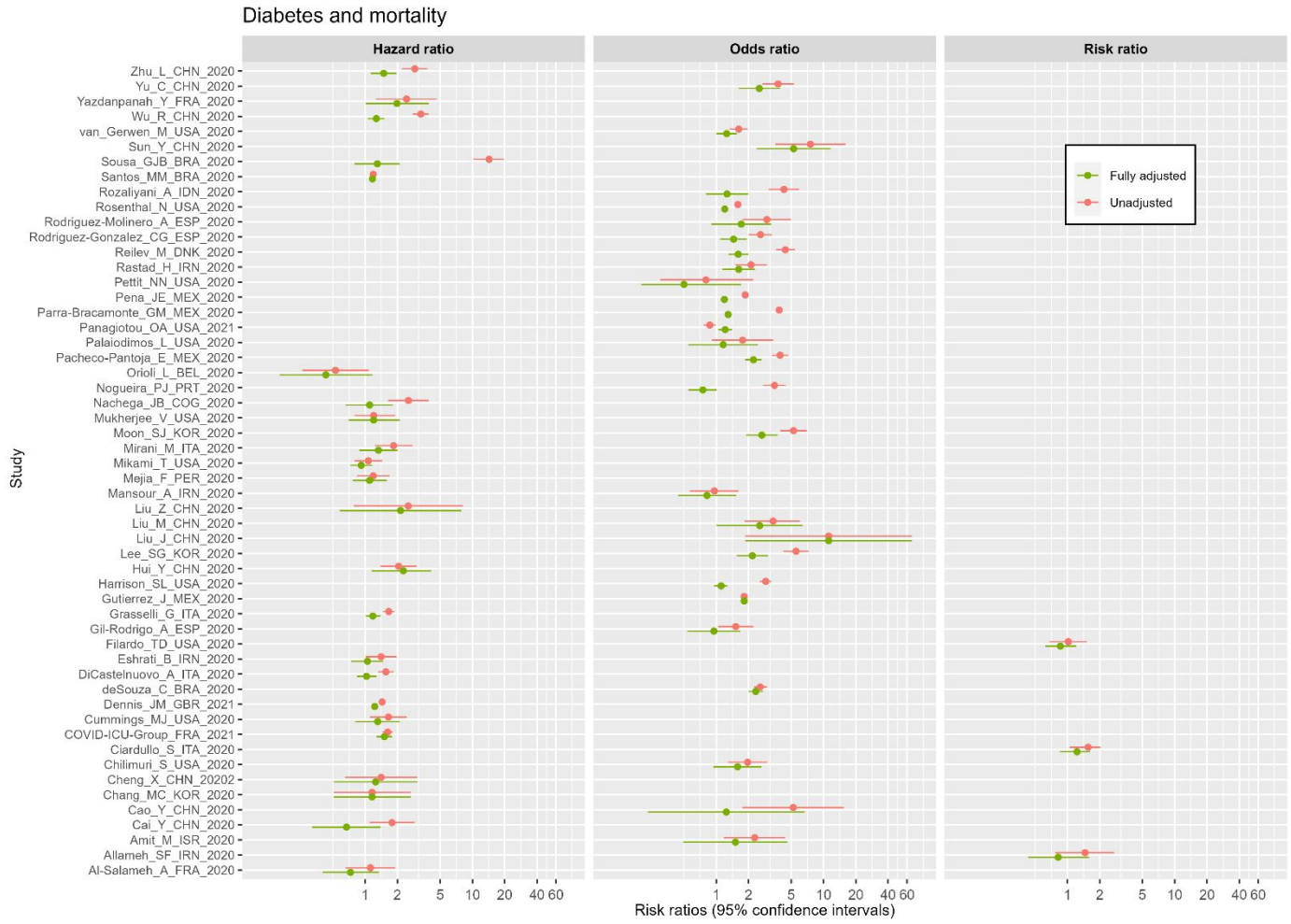


Fig. S1.2 – Forest Plots for the Association of Hypertension with COVID-19 Mortality

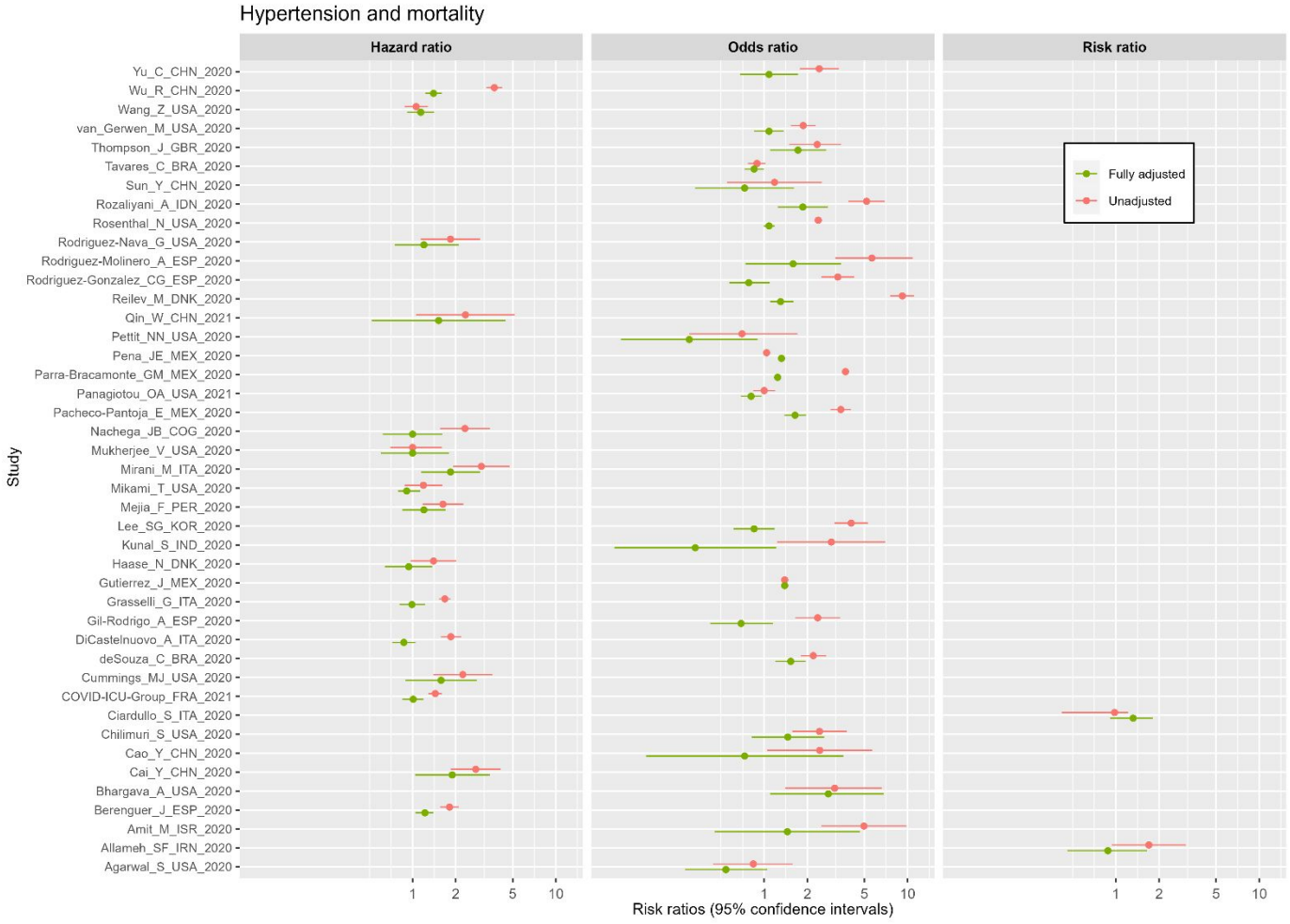


Fig. S1.3 – Forest Plots for the Association of Obesity with COVID-19 Mortality

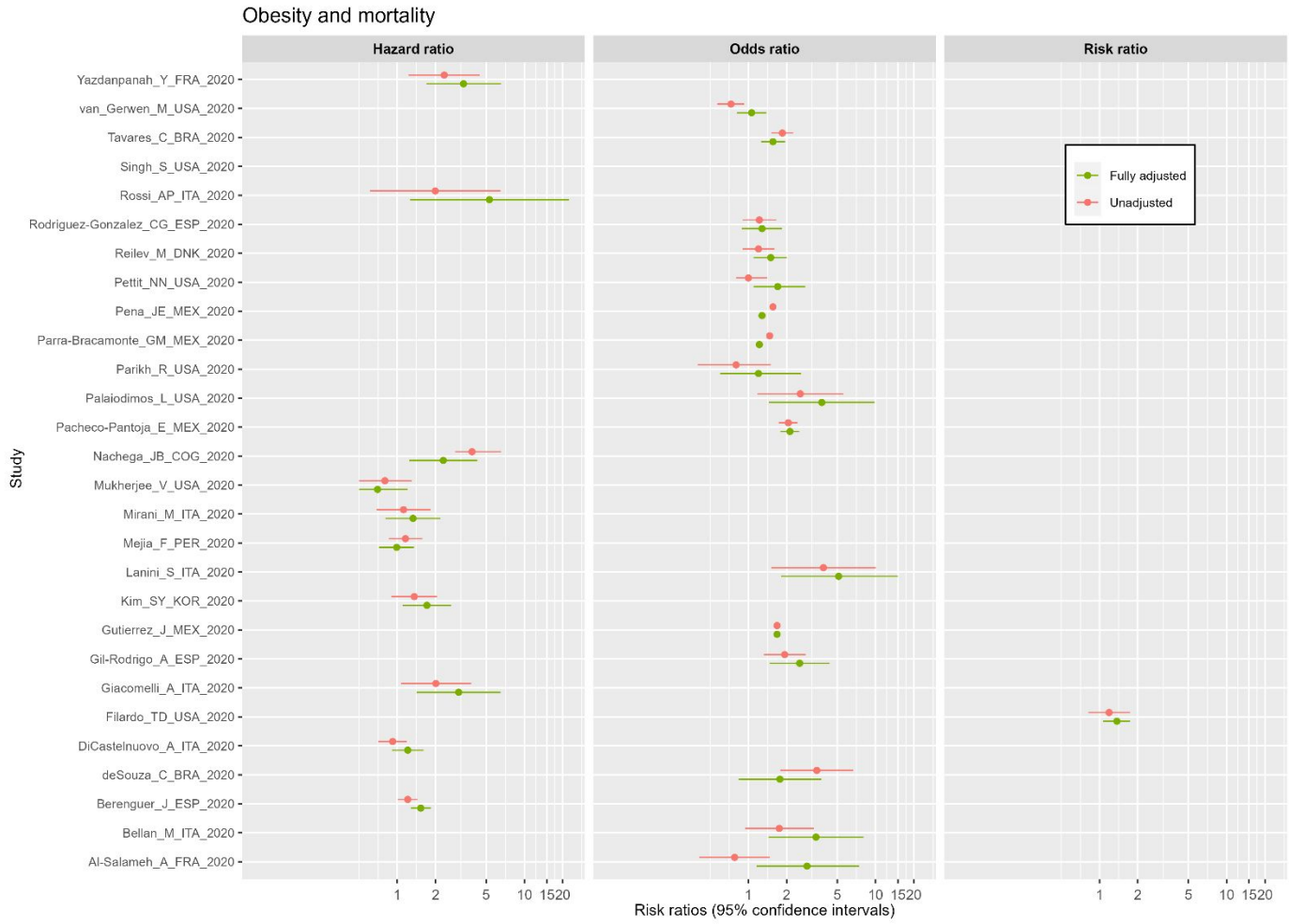


Fig. S2.1 – Influence Plot for the Association of Diabetes with COVID-19 Mortality

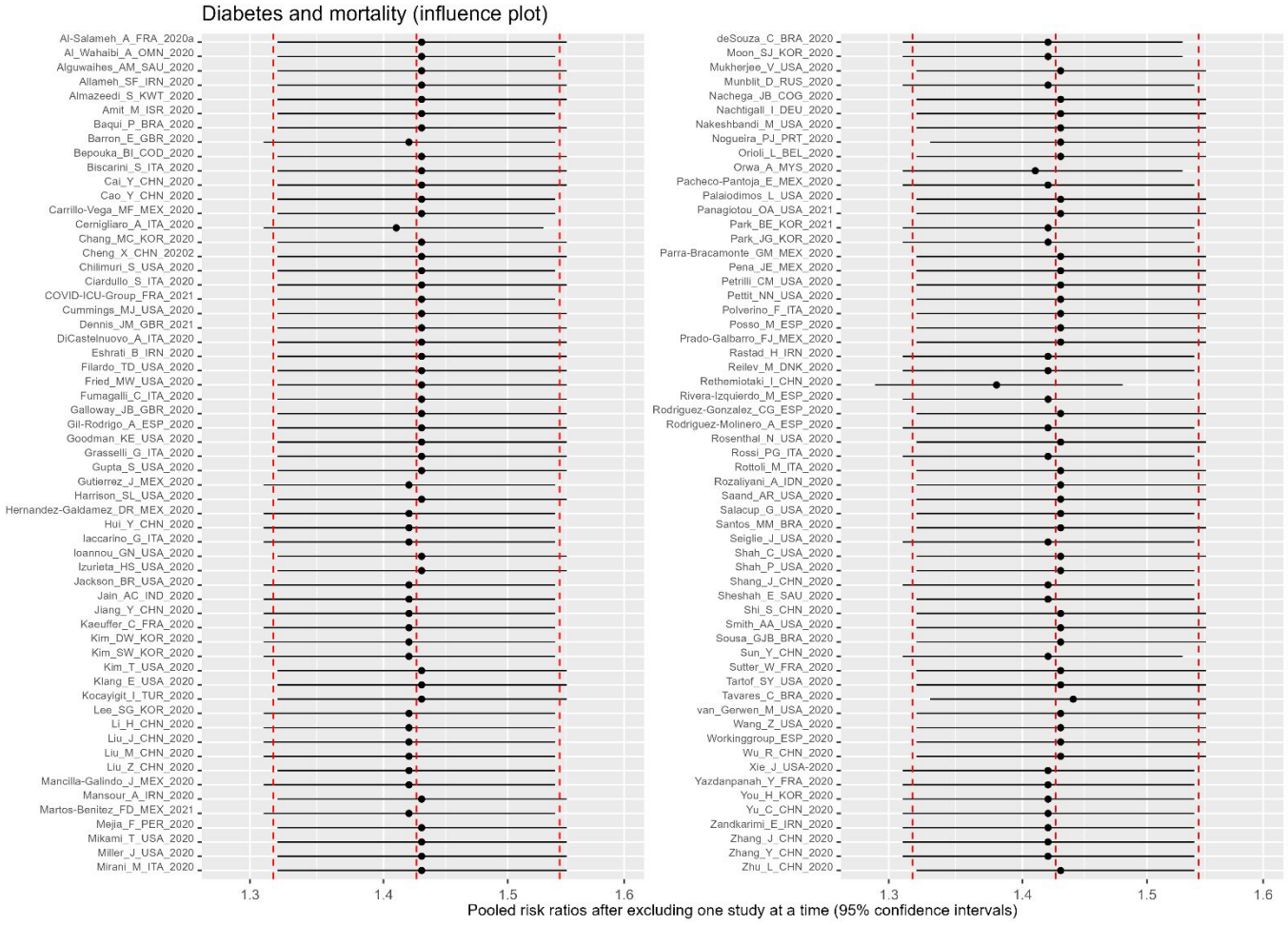


Fig. S2.2 – Influence Plot for the Association of Hypertension with COVID-19 Mortality

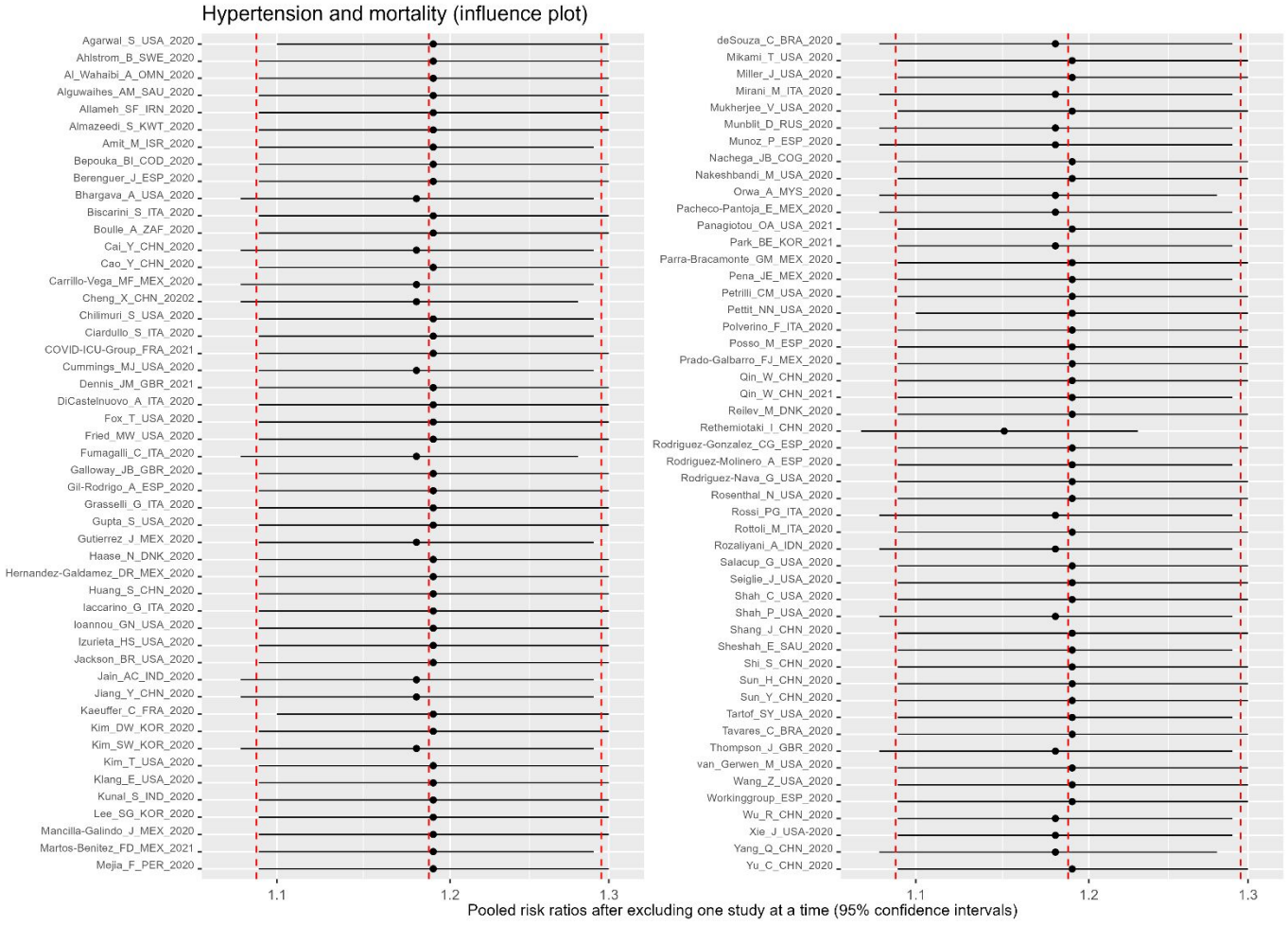
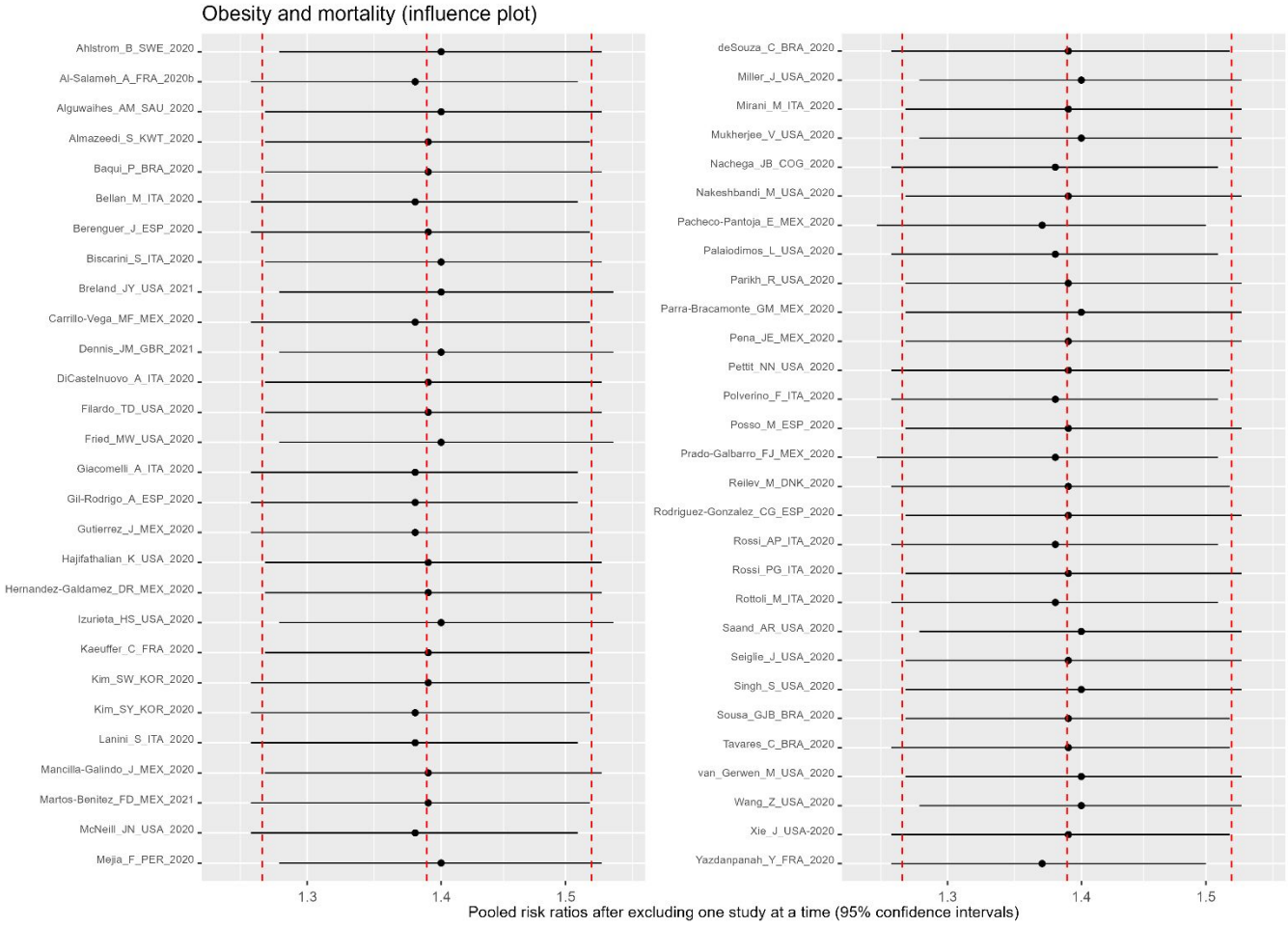


Fig. S2.3 – Influence Plot for the Association of Obesity with COVID-19 Mortality



Supplementary Tables

Table S1 – Overall Pooled Effect Estimates for the Association of Diabetes, Hypertension, and Obesity with COVID-19 Mortality

Exposure	Effect Estimate	N	PRR* (95% CI)	τ^2 (95% CI)	I^2 (95% CI)
Diabetes	Unadjusted	54	2.13 (1.80, 2.52)	0.31 (0.21, 0.53)	0.99 (0.99, 0.99)
Diabetes	Adjusted (overall)	118	1.43 (1.32, 1.54)	0.12 (0.10, 0.21)	0.94 (0.93, 0.95)
Diabetes	Adjusted (OR)	63	1.59 (1.40, 1.81)	0.17 (0.12, 0.34)	0.96 (0.95, 0.96)
Diabetes	Adjusted (HR/RR)	55	1.24 (1.15, 1.32)	0.02 (0.01, 0.11)	0.79 (0.73, 0.84)
Hypertension	Unadjusted	43	2.07 (1.74, 2.47)	0.28 (0.18, 0.47)	0.99 (0.99, 0.99)
Hypertension	Adjusted (overall)	99	1.19 (1.09, 1.30)	0.12 (0.09, 0.21)	0.91 (0.89, 0.92)
Hypertension	Adjusted (OR)	60	1.19 (1.04, 1.35)	0.17 (0.11, 0.33)	0.91 (0.89, 0.92)
Hypertension	Adjusted (HR/RR)	39	1.18 (1.06, 1.30)	0.06 (0.03, 0.16)	0.91 (0.89, 0.93)
Obesity	Unadjusted	28	1.45 (1.22, 1.71)	0.12 (0.07, 0.32)	0.85 (0.80, 0.89)
Obesity	Adjusted (overall)	57	1.39 (1.27, 1.52)	0.06 (0.04, 0.18)	0.96 (0.96, 0.97)
Obesity	Adjusted (OR)	30	1.46 (1.29, 1.65)	0.06 (0.03, 0.24)	0.98 (0.97, 0.98)
Obesity	Adjusted (HR/RR)	27	1.31 (1.14, 1.51)	0.06 0.03, 0.24)	0.77 (0.66, 0.84)

Note: * PRR = pooled risk ratio. τ^2 = a measure of between-study variance; I^2 = a statistic of the proportion of total variability explained by between-study variance. Estimates are from random-effects meta-analysis using restricted maximum likelihood method and Hartung-Knapp-Sidik-Jonkman adjusting for the standard errors.

HR = hazard ratio; OR = odds ratio; RR = relative risk.

Table S2.1 – Pooled Effect Estimates for the Association between Diabetes and COVID-19 Mortality by Subgroups

Study- or Country-Level Variable	Subgroups	N	PRR* (95% CI)	τ^2 (95% CI)	I^2 (95% CI)
Type of risk ratio	OR	63	1.59 (1.40, 1.81)	0.17 (0.12, 0.34)	0.96 (0.95, 0.96)
	HR	48	1.26 (1.17, 1.36)	0.02 (0.01, 0.13)	0.73 (0.64, 0.79)
	RR	7	1.08 (0.94, 1.24)	0.01 (0.00, 0.15)	0.36 (0.00, 0.73)
Study period	May 2020 - November 2020	48	1.38 (1.26, 1.51)	0.07 (0.05, 0.15)	0.97 (0.96, 0.97)
	December 2019 - April 2020	70	1.48 (1.31, 1.68)	0.17 (0.12, 0.35)	0.82 (0.78, 0.86)
Study design	Cohort	90	1.37 (1.28, 1.46)	0.05 (0.04, 0.13)	0.79 (0.75, 0.83)
	Other	28	1.53 (1.20, 1.96)	0.31 (0.20, 0.76)	0.98 (0.97, 0.98)
Study quality	Low	8	1.56 (0.70, 3.49)	0.71 (0.26, 4.23)	0.87 (0.76, 0.93)
	Medium	54	1.50 (1.32, 1.70)	0.16 (0.11, 0.31)	0.96 (0.96, 0.97)
	High	56	1.30 (1.21, 1.40)	0.02 (0.01, 0.11)	0.79 (0.73, 0.84)
WHO region	EMR	9	1.31 (0.99, 1.72)	0.05 (0.00, 0.35)	0.38 (0.00, 0.72)
	EUR	32	1.35 (1.19, 1.53)	0.07 (0.04, 0.21)	0.93 (0.91, 0.94)
	AMR	46	1.27 (1.17, 1.37)	0.05 (0.03, 0.08)	0.95 (0.95, 0.96)
	AFR/SEAR	4	1.32 (0.81, 2.15)	0.00 (0.00, 2.11)	0.06 (0.00, 0.86)
	WPR	26	2.26 (1.76, 2.89)	0.24 (0.10, 0.57)	0.85 (0.80, 0.89)
WPR	-China	18	2.42 (1.64, 3.56)	0.41 (0.15, 1.05)	0.90 (0.85, 0.93)
	-South Korea	8	2.15 (1.79, 2.60)	0.00 (0.00, 0.15)	0.00 (0.00, 0.68)
WB income level	High	72	1.30 (1.21, 1.40)	0.05 (0.03, 0.11)	0.93 (0.92, 0.94)
	Upper middle	41	1.65 (1.38, 1.97)	0.22 (0.14, 0.49)	0.95 (0.94, 0.96)
	Lower middle	3	1.44 (0.47, 4.38)	0.07 (0.00, 8.80)	0.36 (0.00, 0.79)
Health index score tertile	1st	39	1.29 (1.18, 1.41)	0.06 (0.03, 0.11)	0.96 (0.95, 0.97)
	2nd	39	1.28 (1.17, 1.42)	0.04 (0.02, 0.12)	0.93 (0.91, 0.94)
	3rd	38	1.87 (1.55, 2.27)	0.24 (0.13, 0.47)	0.86 (0.82, 0.89)
GHSI score tertile	1st	39	1.66 (1.35, 2.04)	0.27 (0.15, 0.54)	0.89 (0.86, 0.92)
	2nd	39	1.44 (1.29, 1.60)	0.07 (0.04, 0.18)	0.93 (0.91, 0.94)
	3rd	38	1.24 (1.15, 1.35)	0.03 (0.02, 0.08)	0.96 (0.95, 0.97)

Note: * PRR = pooled risk ratio. τ^2 = a measure of between-study variance; I^2 = a statistic of the proportion of total variability explained by between-study variance. Estimates are from random-effects meta-analysis using restricted maximum likelihood method and Hartung-Knapp-Sidik-Jonkman adjusting for the standard errors.

HR = hazard ratio; OR = odds ratio; RR = relative risk; GHSI = Global Health Security Index.

Table S2.2 – Pooled Effect Estimates for the Association between Hypertension and COVID-19 Mortality by Subgroups

Study- or Country-Level Variable	Subgroups	N	PRR* (95% CI)	τ^2 (95% CI)	I^2 (95% CI)
Type of risk ratio	OR	60	1.19 (1.04, 1.35)	0.17 (0.11, 0.33)	0.91 (0.89, 0.92)
	HR	35	1.19 (1.06, 1.33)	0.06 (0.03, 0.18)	0.92 (0.89, 0.93)
	RR	4	1.06 (0.65, 1.73)	0.06 (0.00, 1.00)	0.67 (0.03, 0.89)
Study period	May 2020 - November 2020	46	1.12 (1.04, 1.21)	0.03 (0.02, 0.13)	0.86 (0.82, 0.89)
	December 2019 - April 2020	53	1.24 (1.07, 1.44)	0.21 (0.13, 0.36)	0.93 (0.91, 0.94)
Study design	Cohort	78	1.17 (1.07, 1.27)	0.07 (0.05, 0.18)	0.87 (0.84, 0.89)
	Other	21	1.22 (0.95, 1.56)	0.25 (0.13, 0.58)	0.96 (0.95, 0.97)
Study quality	Low	8	1.07 (0.60, 1.91)	0.29 (0.07, 2.25)	0.71 (0.40, 0.86)
	Medium	40	1.30 (1.10, 1.53)	0.20 (0.13, 0.40)	0.95 (0.94, 0.96)
	High	51	1.09 (1.01, 1.18)	0.02 (0.01, 0.10)	0.62 (0.49, 0.72)
WHO region	AMR	41	1.11 (1.02, 1.21)	0.04 (0.02, 0.13)	0.89 (0.85, 0.91)
	EUR	27	1.13 (0.99, 1.30)	0.07 (0.04, 0.21)	0.94 (0.92, 0.95)
	EMR	5	0.92 (0.58, 1.47)	0.00 (0.00, 0.54)	0.00 (0.00, 0.79)
	AFR/SEAR	6	1.20 (0.74, 1.92)	0.07 (0.00, 2.28)	0.59 (0.00, 0.83)
	WPR	19	1.52 (1.08, 2.15)	0.39 (0.17, 0.90)	0.92 (0.88, 0.94)
WPR	-China	15	1.57 (1.01, 2.45)	0.49 (0.20, 1.27)	0.93 (0.89, 0.95)
	-South Korea	4	1.30 (0.71, 2.37)	0.09 (0.00, 1.99)	0.64 (0.00, 0.88)
WB income level	High	62	1.07 (0.99, 1.16)	0.05 (0.03, 0.14)	0.90 (0.88, 0.92)
	Upper middle	31	1.42 (1.17, 1.71)	0.20 (0.11, 0.42)	0.91 (0.88, 0.93)
	Lower middle	4	1.06 (0.43, 2.60)	0.05 (0.00, 7.90)	0.47 (0.00, 0.82)
Health index score tertile	1st	33	1.16 (1.05, 1.28)	0.04 (0.03, 0.15)	0.89 (0.86, 0.92)
	2nd	32	1.02 (0.92, 1.13)	0.02 (0.01, 0.22)	0.60 (0.40, 0.73)
	3rd	32	1.38 (1.12, 1.69)	0.24 (0.13, 0.46)	0.92 (0.89, 0.94)
GHSI score tertile	1st	33	1.29 (1.03, 1.61)	0.28 (0.14, 0.52)	0.90 (0.87, 0.92)
	2nd	32	1.22 (1.10, 1.36)	0.05 (0.03, 0.16)	0.92 (0.90, 0.94)
	3rd	32	1.01 (0.93, 1.10)	0.02 (0.01, 0.19)	0.62 (0.44, 0.74)

Note: * PRR = pooled risk ratio. τ^2 = a measure of between-study variance; I^2 = a statistic of the proportion of total variability explained by between-study variance. Estimates are from random-effects meta-analysis using restricted maximum likelihood method and Hartung-Knapp-Sidik-Jonkman adjusting for the standard errors.

HR = hazard ratio; OR = odds ratio; RR = relative risk; GHSI = Global Health Security Index.

Table S2.3 – Pooled Effect Estimates for the Association between Obesity and COVID-19 Mortality by Subgroups

Study- or Country-Level Variable	Subgroups	N	PRR* (95% CI)	τ^2 (95% CI)	I^2 (95% CI)
Type of risk ratio	HR	23	1.34 (1.13, 1.59)	0.09 (0.04, 0.33)	0.80 (0.71, 0.86)
	OR	30	1.46 (1.29, 1.65)	0.06 (0.03, 0.24)	0.98 (0.97, 0.98)
	RR	4	1.23 (1.03, 1.48)	0.00 (0.00, 0.07)	0.00 (0.00, 0.85)
Study period	May 2020 - November 2020	26	1.25 (1.14, 1.37)	0.03 (0.01, 0.11)	0.98 (0.98, 0.98)
	December 2019 - April 2020	31	1.61 (1.38, 1.87)	0.08 (0.04, 0.31)	0.72 (0.60, 0.80)
Study design	Cohort	44	1.43 (1.27, 1.62)	0.08 (0.05, 0.26)	0.91 (0.89, 0.93)
	Other	13	1.34 (1.18, 1.51)	0.03 (0.01, 0.12)	0.95 (0.93, 0.97)
Study quality	High	28	1.46 (1.21, 1.77)	0.12 (0.07, 0.51)	0.78 (0.69, 0.85)
	Medium	27	1.36 (1.24, 1.50)	0.04 (0.02, 0.08)	0.98 (0.98, 0.98)
	Low	2	-	-	-
WHO region	EUR	20	1.63 (1.32, 2.01)	0.10 (0.04, 0.44)	0.75 (0.61, 0.84)
	EMR	2	-	-	-
	AMR	32	1.31 (1.19, 1.45)	0.05 (0.03, 0.12)	0.98 (0.97, 0.98)
	WPR	2	-	-	-
	AFR/SEAR	1	-	-	-
WPR	China	0	-	-	-
	South Korea	2	-	-	-
WB income group	High	42	1.34 (1.18, 1.52)	0.07 (0.05, 0.28)	0.75 (0.66, 0.81)
	Upper middle	14	1.49 (1.33, 1.67)	0.03 (0.01, 0.09)	0.94 (0.91, 0.96)
	Lower middle	1	-	-	-
Health index score tertile	1st	19	1.42 (1.27, 1.58)	0.04 (0.02, 0.09)	0.99 (0.98, 0.99)
	2nd	19	1.17 (0.99, 1.38)	0.04 (0.02, 0.41)	0.64 (0.41, 0.78)
	3rd	19	1.67 (1.36, 2.06)	0.07 (0.02, 0.41)	0.53 (0.20, 0.72)
GHSI score tertile	1st	19	1.55 (1.26, 1.92)	0.06 (0.02, 0.60)	0.58 (0.31, 0.75)
	2nd	19	1.54 (1.38, 1.72)	0.03 (0.01, 0.14)	0.91 (0.88, 0.94)
	3rd	19	1.09 (1.01, 1.17)	0.00 (0.00, 0.19)	0.63 (0.40, 0.78)

Note: * PRR = pooled risk ratio. τ^2 = a measure of between-study variance; I^2 = a statistic of the proportion of total variability explained by between-study variance. Estimates are from random-effects meta-analysis using restricted maximum likelihood method and Hartung-Knapp-Sidik-Jonkman adjusting for the standard errors.

HR = hazard ratio; OR = odds ratio; RR = relative risk; GHSI = Global Health Security Index.

Table S3 – Characteristics of Studies Included in the Meta-Analysis on the Associations of Diabetes, Hypertension, and Obesity with COVID-19 Mortality, December 2019 – December, 2020 (n=145)

Study ID	Country	WHO region	WB income level	Health index score	GHSI score	Start date	End date	Data source	Study design	Exposure			Sample size	Mean age, y	Men, %	Effect estimate type	Funding source	NOS score
										DM	HTN	OB						
Agarwal_S_USA_2020[1]	USA	AMR	HI	73.9	76.2	3/11/2020	5/7/2020	EHR	Cohort	No	Yes	No	1,279	67.9	49.3	OR	Not reported	9
Ahlstrom_B_SWE_2020[2]	Sweden	EUR	HI	82.1	66.4	1/31/2020	5/27/2020	ARS	Cohort	No	Yes	Yes	9,905	61.0	74.0	HR	Independent	9
Al_Wahaibi_A_OMN_2020[3]	Oman	EMR	HI	75.2	40.9	2/24/2020	7/19/2020	ARS	C-S	Yes	Yes	No	68,967	40.0	74.9	OR	None or NA	4
Alguwaihes_AM_SAU_2020[4]	Saudi Arabia	EMR	HI	74.5	45.0	5/15/2020	7/15/2020	EHR	C-S	Yes	Yes	Yes	439	55.0	68.3	HR	Independent	7
Allameh_SF_IRN_2020[5]	Iran	EMR	UMI	74.8	39.5	2/20/2020	3/19/2020	EHR	Cohort	Yes	Yes	No	396	56.9	61.8	RR	Not reported	8
Almazeedi_S_KWT_2020[6]	Kuwait	EMR	HI	76.9	40.1	2/24/2020	4/20/2020	EHR	Cohort	Yes	Yes	Yes	1,096	41.0	81.0	OR	Independent	9
Al-Salameh_A_FRA_2020a[7]	France	EUR	HI	80.5	62.6	10/1/2020	4/21/2020	EHR	Cohort	Yes	No	No	432	73.0	55.1	HR	None or NA	9
Al-Salameh_A_FRA_2020b[8]	France	EUR	HI	80.5	62.6	1/24/2020	5/1/2020	EHR	Cohort	No	No	Yes	329	81.0	59.6	OR	Not reported	9
Amit_M_ISR_2020[9]	Israel	EUR	HI	82.8	50.7	3/5/2020	4/27/2020	EHR	Cohort	Yes	Yes	No	156	72.0	69.0	OR	None or NA	9
Baqui_P_BRA_2020[10]	Brazil	AMR	UMI	72.0	51.0	2/27/2020	5/4/2020	ARS	C-S	Yes	No	Yes	7,371	55.2	45.5	HR	None or NA	8
Barron_E_GBR_2020[11]	UK	EUR	HI	78.8	68.3	3/1/2020	5/11/2020	ARS	C-S	Yes	No	No	61,414,470†	40.9	49.9	OR	None or NA	8
Bellan_M_ITA_2020[12]	Italy	EUR	HI	81.1	51.9	3/1/2020	4/28/2020	EHR	Cohort	No	No	Yes	407	71.0	59.0	OR	None or NA	9
Bepouka_BI_COD_2020[13]	D.R. Congo	AFR	LMI	48.6	26.0	3/23/2020	6/15/2020	EHR	Cohort	Yes	Yes	No	141	49.6	67.4	HR	Not reported	9
Berenguer_J_ESP_2020[14]	Spain	EUR	HI	80.5	60.4	1/31/2020	3/17/2020	EHR	Cohort	No	Yes	Yes	4,035	70.0	61.0	HR	Independent	9
Bhargava_A_USA_2020[15]	USA	AMR	HI	73.9	76.2	3/8/2020	6/14/2020	EHR	Cohort	No	Yes	No	265	50.4	52.8	OR	None or NA	4
Biscarini_S_ITA_2020[16]	Italy	EUR	HI	81.1	51.9	2/21/2020	3/31/2020	ARS	Cohort	Yes	Yes	Yes	427	67.0	68.1	HR	Independent	9
Boulle_A_ZAF_2020[17]	South Africa	AFR	UMI	56.6	47.5	3/1/2020	6/9/2020	ARS	Cohort	No	Yes	No	2,978	53.4	37.9	HR	Independent	9
Breland_JY_USA_2021[18]	USA	AMR	HI	73.9	76.2	3/2/2020	5/20/2020	EHR	Cohort	No	No	Yes	9,347	65.0	91.0	OR	Independent	8
Cai_Y_CHN_2020[19]	China	WPR	UMI	82.8	49.0	1/20/2020	3/3/2020	EHR	Cohort	Yes	Yes	No	941	57.0	48.0	HR	Independent	9
Cao_Y_CHN_2020[20]	China	WPR	UMI	82.8	49.0	1/5/2020	2/22/2020	EHR	C-S	Yes	Yes	No	101	56.6	66.3	OR	Independent	8
Carrillo-Vega_MF_MEX_2020[21]	Mexico	AMR	UMI	72.1	55.1	2/28/2020	4/23/2020	ARS	C-S	Yes	Yes	Yes	9,946	48.2	57.8	OR	Independent	7
Cernigliaro_A_ITA_2020[22]	Italy	EUR	HI	81.1	51.9	1/3/2020	6/26/2020	ARS	C-S	Yes	No	No	2,847	50.0	49.5	OR	Not reported	5
Chang_MC_KOR_2020[23]	South Korea	WPR	HI	84.1	65.9	2/1/2020	4/10/2020	EHR	Cohort	Yes	No	No	106	67.6	50.1	HR	Independent	9
Cheng_X_CHN_2020[24]	China	WPR	UMI	82.8	49.0	1/11/2020	2/20/2020	ARS	Cohort	Yes	Yes	No	220	59.5	48.2	HR	Independent	8
Chilimuri_S_USA_2020[25]	USA	AMR	HI	73.9	76.2	3/9/2020	4/9/2020	EHR	Cohort	Yes	Yes	No	375	63.0	63.0	OR	None or NA	9
Ciardullo_S_ITA_2020[26]	Italy	EUR	HI	81.1	51.9	2/22/2020	5/15/2020	EHR	Cohort	Yes	Yes	No	373	72.0	65.4	RR	None or NA	9
COVID-ICU-Group_FRA_2021[27]	France, Switzerland, and Belgium	EUR				2/25/2020	5/4/2020	EHR	Cohort	Yes	Yes	No	4,244	63.0	74.0	HR	Independent	9
Cummings_MJ_USA_2020[28]	USA	AMR	HI	73.9	76.2	3/2/2020	4/1/2020	EHR	Cohort	Yes	Yes	No	257	62.0	67.0	HR	Independent	9

Dennis_JM_GBR_2021[29]	UK	EUR	HI	78.8	68.3	3/1/2020	7/27/2020	ARS	Cohort	Yes	Yes	Yes	19,256	67.0	60.1	HR	Independent	9
deSouza_C_BRA_2020[30]	Brazil	AMR	UMI	72.0	51.0	7/26/2020	8/1/2020	ARS	Cohort	Yes	Yes	Yes	9,807	70.2	47.5	OR	Not reported	8
DiCastelnuovo_A_ITA_2020[31]	Italy	EUR	HI	81.1	51.9	2/19/2020	5/23/2020	EHR	Cohort	Yes	Yes	Yes	3,894	67.0	61.7	HR	None or NA	9
Eshrati_B_IRN_2020[32]	Iran	EMR	UM	74.8	39.5	2/22/2020	3/25/2020	ARS	Cohort	Yes	No	No	3,188	55.1	60.4	HR	Independent	9
Filardo_TD_USA_2020[33]	USA	AMR	HI	73.9	76.2	3/9/2020	4/8/2020	EHR	Cohort	Yes	No	Yes	270	58.0	67.4	RR	None or NA	8
Fox_T_USA_2020[34]	USA	AMR	HI	73.9	76.2	3/1/2020	4/24/2020	EHR	C-S	No	Yes	No	355	66.2	51.0	OR	None or NA	8
Fried_MW_USA_2020[35]	USA	AMR	HI	73.9	76.2	2/15/2020	4/20/2020	ARS	C-S	Yes	Yes	Yes	11,721	65.0	53.4	OR	Industry	7
Fumagalli_C_ITA_2020[36]	Italy	EUR	HI	81.1	51.9	2/22/2020	4/10/2020	EHR	Cohort	Yes	Yes	No	516	67.0	66.9	HR	None or NA	8
Galloway_JB_GBR_2020[37]	UK	EUR	HI	78.8	68.3	3/1/2020	4/17/2020	EHR	Cohort	Yes	Yes	No	1,157	71.0	57.6	HR	None or NA	9
Giacomelli_A_ITA_2020[38]	Italy	EUR	HI	81.1	51.9	2/21/2020	4/20/2020	EHR	Cohort	No	No	Yes	233	61.0	69.1	HR	None or NA	9
Gil-Rodrigo_A_ESP_2020[39]	Spain	EUR	HI	80.5	60.4	3/1/2020	4/30/2020	EHR	Cohort	Yes	Yes	Yes	1,000	62.3	56.2	OR	None or NA	6
Goodman_KE_USA_2020[40]	USA	AMR	HI	73.9	76.2	4/15/2020	6/15/2020	ARS	Cohort	Yes	No	No	66,646	62.8	52.9	RR	Independent	9
Grasselli_G_ITA_2020[41]	Italy	EUR	HI	81.1	51.9	2/20/2020	5/30/2020	EHR	Cohort	Yes	Yes	No	3,988	63.0	80.0	HR	Independent	9
Gupta_S_USA_2020[42]	USA	AMR	HI	73.9	76.2	3/4/2020	4/4/2020	EHR	Cohort	Yes	Yes	No	2,215	60.5	64.8	OR	Independent	8
Gutierrez_J_MEX_2020[43]	Mexico	AMR	UMI	72.1	55.1	2/28/2020	9/16/2020	ARS	C-S	Yes	Yes	Yes	654,858	46.1	52.2	OR	None or NA	8
Haase_N_DNK_2020[44]	Denmark	EUR	HI	80.6	67.3	3/10/2020	6/16/2020	EHR	Cohort	No	Yes	No	323	68.0	74.0	HR	Industry	9
Hajifathalian_K_USA_2020[45]	USA	AMR	HI	73.9	76.2	3/4/2020	4/9/2020	EHR	Cohort	No	No	Yes	770	63.5	60.8	RR	Not reported	9
Harrison_SL_USA_2020[46]	USA	AMR	HI	73.9	76.2	1/20/2020	5/26/2020	EHR	Cohort	Yes	No	No	31,461	50.0	45.5	OR	Independent	8
Hernandez-Galdamez_DR_MEX_2020[47]	Mexico	AMR	UMI	72.1	55.1	2/15/2020	6/27/2020	ARS	C-S	Yes	Yes	Yes	211,003	45.7	54.7	OR	Not reported	8
Huang_S_CHN_2020[48]	China	WPR	UMI	82.8	49.0	12/30/2019	4/19/2020	EHR	Cohort	No	Yes	No	310	62.0	56.0	OR	Not reported	9
Hui_Y_CHN_2020[49]	China	WPR	UMI	82.8	49.0	1/28/2020	3/10/2020	EHR	Cohort	Yes	No	No	167	65.0	65.3	HR	Independent	9
Iaccarino_G_ITA_2020[50]	Italy	EUR	HI	81.1	51.9	3/9/2020	4/9/2020	ARS	C-S	Yes	Yes	No	1,591	66.5	64.0	OR	Independent	7
Ioannou_GN_USA_2020[51]	USA	AMR	HI	73.9	76.2	2/28/2020	5/14/2020	EHR	Cohort	Yes	Yes	No	10,131	63.6	91.0	HR	Independent	9
Izurieta_HS_USA_2020[52]	USA	AMR	HI	73.9	76.2	4/1/2020	5/8/2020	ARS	C-S	Yes	Yes	Yes	25,333,329†	73.0	44.0	OR	Independent	8
Jackson_BR_USA_2020[53]	USA	AMR	HI	73.9	76.2	3/1/2020	3/31/2020	EHR	Cohort	Yes	Yes	No	297	60.0	50.0	OR	Independent	9
Jain_AC_IND_2020[54]	INDIA	SEAR	LMI	67.1	43.6	4/15/2020	6/15/2020	EHR	Cohort	Yes	Yes	No	425	49.0	73.4	OR	None or NA	7
Jiang_Y_CHN_2020[55]	China	WPR	UMI	82.8	49.0	1/30/2020	4/10/2020	EHR	Cohort	Yes	Yes	No	281	70.0	50.9	OR	Independent	9
Kaeuffer_C_FRA_2020[56]	France	EUR	HI	80.5	62.6	3/20/2020	3/20/2020	EHR	Cohort	Yes	Yes	Yes	1,045	66.0	59.0	OR	Independent	7
Kim_DW_KOR_2020[57]	South Korea	WPR	HI	84.1	65.9	1/20/2020	3/26/2020	ARS	C-S	Yes	Yes	No	9,148	46.0	39.0	OR	Independent	7
Kim_SW_KOR_2020[58]	South Korea	WPR	HI	84.1	65.9	2/18/2020	7/10/2020	EHR	Cohort	Yes	Yes	Yes	2,254	57.0	35.8	HR	Independent	8
Kim_SY_KOR_2020[59]	South Korea	WPR	HI	84.1	65.9	1/20/2020	4/30/2020	ARS	Cohort	No	No	Yes	4,057	50.0	42.5	HR	Independent	8
Kim_T_USA_2020[60]	USA	AMR	HI	73.9	76.2	3/1/2020	5/12/2020	EHR	Cohort	Yes	Yes	No	10,861	65.0	59.6	OR	Independent	9
Klang_E_USA_2020[61]	USA	AMR	HI	73.9	76.2	3/1/2020	5/17/2020	EHR	Cohort	Yes	Yes	No	572	60.0	69.4	OR	Not reported	9
Kocayigit_I_TUR_2020[62]	Turkey	EUR	UMI	75.1	49.8	3/20/2020	4/10/2020	EHR	Cohort	Yes	No	No	169	65.8	46.7	OR	Not reported	7

Kunal_S_IND_2020[63]	India	SEAR	LMI	67.1	43.6	1/30/2020	5/7/2020	EHR	Cohort	No	Yes	No	108	51.2	64.8	OR	None or NA	5
Lanini_S_ITA_2020[64]	Italy	EUR	HI	81.1	51.9	1/29/2020	3/28/2020	EHR	Cohort	No	No	Yes	379	61.7	72.0	OR	Independent	9
Lee_SG_KOR_2020[65]	South Korea	WPR	HI	84.1	65.9	3/26/2020	5/15/2020	ARS	C-S	Yes	Yes	No	7,339	47.1	40.1	OR	None or NA	7
Li_H_CHN_2020[66]	China	WPR	UMI	82.8	49.0	1/22/2020	3/17/2020	EHR	Cohort	Yes	No	No	453	61.0	52.0	HR	Independent	8
Liu_J_CHN_2020[67]	China	WPR	UMI	82.8	49.0	12/29/2019	2/28/2020	EHR	Cohort	Yes	No	No	1,190	57.0	53.4	OR	None or NA	7
Liu_M_CHN_2020[68]	China	WPR	UMI	82.8	49.0	1/1/2020	3/4/2020	EHR	Cohort	Yes	No	No	665	58.0	47.8	OR	Independent	9
Liu_Z_CHN_2020[69]	China	WPR	UMI	82.8	49.0	2/8/2020	4/15/2020	EHR	Cohort	Yes	No	No	934	62.0	48.6	HR	None or NA	9
Mancilla-Galindo_J_MEX_2020[70]	Mexico	AMR	UMI	72.1	55.1	2/28/2020	5/30/2020	ARS	Cohort	Yes	Yes	Yes	83,779	46.3	56.6	HR	None or NA	9
Mansour_A_IRN_2020[71]	Iran	EMR	UMI	74.8	39.5	2/25/2020	4/21/2020	EHR	C-S	Yes	No	No	353	61.7	57.5	OR	None or NA	7
Martos-Benitez_FD_MEX_2021[72]	Mexico	AMR	UMI	72.1	55.1	1/1/2020	5/13/2020	ARS	C-S	Yes	Yes	Yes	38,324	46.9	58.3	OR	None or NA	7
McNeill_JN_USA_2020[73]	USA	AMR	HI	73.9	76.2	2/28/2020	4/27/2020	EHR	Cohort	No	No	Yes	781	61.0	58.0	OR	Independent	7
Mejia_F_PER_2020[74]	Peru	AMR	UMI	76.4	53.8	3/29/2020	6/11/2020	OTH	Cohort	Yes	Yes	Yes	369	59.0	65.3	HR	None or NA	6
Mikami_T_USA_2020[75]	USA	AMR	HI	73.9	76.2	3/12/2020	4/17/2020	EHR	Cohort	Yes	Yes	No	3,708	66.0	57.0	HR	Not reported	6
Miller_J_USA_2020[76]	USA	AMR	HI	73.9	76.2	3/7/2020	4/30/2020	EHR	Cohort	Yes	Yes	Yes	2,316	64.5	51.8	OR	Independent	7
Mirani_M_ITA_2020[77]	Italy	EUR	HI	81.1	51.9	2/20/2020	4/9/2020	EHR	Cohort	Yes	Yes	Yes	387	66.0	66.7	HR	Not reported	8
Moon_SJ_KOR_2020[78]	South Korea	WPR	HI	84.1	65.9	1/20/2020	5/15/2020	ARS	C-S	Yes	No	No	5,307	56.0	39.0	OR	Independent	7
Munoz_P_ESP_2020[79]	Spain	EUR	HI	80.5	60.4	3/1/2020	5/10/2020	OTH	Cohort	No	Yes	No	100	61.5	52.0	OR	Independent	9
Mukherjee_V_USA_2020[80]	USA	AMR	HI	73.9	76.2	3/10/2020	5/18/2020	EHR	Cohort	Yes	Yes	Yes	137	59.0	72.3	HR	Not reported	9
Munblit_D_RUS_2020[81]	Russia	EUR	UMI	71.6	47.1	4/8/2020	5/28/2020	EHR	Cohort	Yes	Yes	No	3,480	56.0	50.5	OR	Independent	7
Nachega_JB_COG_2020[82]	D.R. Congo	AFR	LMI	48.6	26.0	3/10/2020	7/31/2020	ARS	Cohort	Yes	Yes	Yes	766	46.0	65.3	HR	Independent	9
Nachtigall_I_DEU_2020[83]	Germany	EUR	HI	81.1	65.7	2/12/2020	6/12/2020	OTH	Cohort	Yes	No	No	1,904	73.0	51.5	HR	Independent	9
Nakeshbandi_M_USA_2020[84]	USA	AMR	HI	73.9	76.2	3/10/2020	4/13/2020	EHR	Cohort	Yes	Yes	Yes	504	68.0	53.0	RR	Not reported	9
Nogueira_PJ_PRT_2020[85]	Portugal	EUR	HI	77.6	58.7	1/1/2020	4/21/2020	ARS	C-S	Yes	No	No	20,293	52.1	41.3	OR	None or NA	7
Orioli_L_BEL_2020[86]	Belgium	EUR	HI	80.6	61.9	3/1/2020	5/6/2020	ARS	C-S	Yes	No	No	192	67.0	50.0	HR	None or NA	4
Orwa_A_MYS_2020[87]	Worldwide	World				12/30/2019	4/21/2020	ARS	C-S	Yes	Yes	No	828	49.4	59.1	OR	None or NA	6
Pacheco-Pantoja_E_MEX_2020[88]	Mexico	AMR	UMI	72.1	55.1	2/28/2020	4/30/2020	ARS	Cohort	Yes	Yes	Yes	19,224	46.6	58.2	OR	Not reported	7
Palaiodimos_L_USA_2020[89]	USA	AMR	HI	73.9	76.2	3/9/2020	4/12/2020	EHR	Cohort	Yes	No	Yes	200	64.0	49.0	OR	None or NA	9
Panagiotou_OA_USA_2021[90]	USA	AMR	HI	73.9	76.2	3/16/2020	9/15/2020	EHR	Cohort	Yes	Yes	No	5,256	79.0	39.0	OR	Independent	9
Parikh_R_USA_2020[91]	USA	AMR	HI	73.9	76.2	3/1/2020	5/1/2020	EHR	Cohort	No	No	Yes	160	60.4	65.6	OR	None or NA	9
Park_BE_KOR_2021[92]	South Korea	WPR	HI	84.1	65.9	2/15/2020	4/24/2020	ARS	Cohort	Yes	Yes	No	2,269	55.5	36.0	OR	Independent	9
Park_JG_KOR_2020[93]	South Korea	WPR	HI	84.1	65.9	2/20/2020	4/14/2020	EHR	Cohort	Yes	No	No	289	72.0	46.0	HR	Independent	8
Parra-Bracamonte_GM_MEX_2020[94]	Mexico	AMR	UMI	72.1	55.1	1/13/2020	7/17/2020	ARS	Cohort	Yes	Yes	Yes	331,298	44.0	53.8	OR	Not reported	8
Pena_JE_MEX_2020[95]	Mexico	AMR	UMI	72.1	55.1	2/28/2020	11/13/2020	ARS	C-S	Yes	Yes	Yes	121,225	50.0	59.8	OR	Not reported	7
Petrilli_CM_USA_2020[96]	USA	AMR	HI	73.9	76.2	3/1/2020	4/8/2020	EHR	Cohort	Yes	Yes	No	5,279	54.0	49.5	HR	Independent	9

Pettit_NN_USA_2020[97]	USA	AMR	HI	73.9	76.2	3/1/2020	4/18/2020	EHR	Cohort	Yes	Yes	Yes	238	58.5	47.5	OR	Not reported	9
Polverino_F_ITA_2020[98]	Italy	EUR	HI	81.1	51.9	3/25/2020	4/22/2020	OTH	C-S	Yes	Yes	Yes	3,179	69.0	68.3	OR	Independent	8
Posso_M_ESP_2020[99]	Spain	EUR	HI	80.5	60.4	2/23/2020	5/12/2020	EHR	Cohort	Yes	Yes	Yes	834	78.2	46.5	OR	None or NA	8
Prado-Galbarro_FJ_MEX_2020[100]	Mexico	AMR	UMI	72.1	55.1	2/27/2020	4/27/2020	ARS	Cohort	Yes	Yes	Yes	15,529	55.0	57.8	HR	None or NA	9
Qin_W_CHN_2020[101]	China	WPR	UMI	82.8	49.0	12/19/2019	2/20/2020	EHR	Cohort	No	Yes	No	582	64.0	50.3	OR	Independent	6
Qin_W_CHN_2021[102]	China	WPR	UMI	82.8	49.0	1/31/2020	3/6/2020	EHR	Cohort	No	Yes	No	262	63.5	46.9	HR	Independent	9
Rastad_H_IRN_2020[103]	Iran	EMR	UMI	74.8	39.5	2/20/2020	3/25/2020	EHR	Cohort	Yes	No	No	2,957	54.8	53.7	OR	Independent	8
Reilev_M_DNK_2020[104]	Denmark	EUR	HI	80.6	67.3	2/27/2020	5/19/2020	ARS	Cohort	Yes	Yes	Yes	11,122	48.0	42.0	OR	Independent	7
Rethemiotaki_I_CHN_2020[105]	China	WPR	UMI	82.8	49.0	12/19/2019	2/20/2020	ARS	C-S	Yes	Yes	No	44,672	55.0	64.0	OR	Not reported	7
Rivera-Izquierdo_M_ESP_2020[106]	Spain	EUR	HI	80.5	60.4	3/16/2020	4/10/2020	OTH	Cohort	Yes	No	No	238	64.7	55.0	HR	Independent	9
Rodriguez-Gonzalez_CG_ESP_2020[107]	Spain	EUR	HI	80.5	60.4	3/1/2020	3/24/2020	OTH	Cohort	Yes	Yes	Yes	1,208	65.0	58.0	OR	Independent	9
Rodriguez-Molinero_A_ESP_2020[108]	Spain	EUR	HI	80.5	60.4	3/12/2020	5/2/2020	EHR	Cohort	Yes	Yes	No	418	65.4	57.0	OR	None or NA	9
Rodriguez-Nava_G_USA_2020[109]	USA	AMR	HI	73.9	76.2	3/1/2020	5/25/2020	OTH	Cohort	No	Yes	No	313	68.0	58.0	HR	Not reported	9
Rosenthal_N_USA_2020[110]	USA	AMR	HI	73.9	76.2	4/1/2020	5/31/2020	ARS	C-S	Yes	Yes	No	64,781	57.0	49.0	OR	Independent	7
Rossi_AP_ITA_2020[111]	Italy	EUR	HI	81.1	51.9	3/8/2020	3/30/2020	ARS	Cohort	No	No	Yes	95	62.5	82.1	HR	Not reported	9
Rossi_PG_ITA_2020[112]	Italy	EUR	HI	81.1	51.9	2/27/2020	4/2/2020	ARS	Cohort	Yes	Yes	Yes	2,653	63.2	50.1	HR	Independent	9
Rottoli_M_ITA_2020[113]	Italy	EUR	HI	81.1	51.9	3/1/2020	4/27/2020	ARS	Cohort	Yes	Yes	Yes	482	66.2	63.0	HR	None or NA	9
Rozaliyani_A_IDN_2020[114]	Indonesia	SEAR	UMI	72.7	49.2	3/2/2020	4/29/2020	ARS	Cohort	Yes	Yes	No	4,052	45.8	54.0	OR	Not reported	9
Saand_AR_USA_2020[115]	USA	AMR	HI	73.9	76.2	3/15/2020	5/30/2020	ARS	Cohort	Yes	No	Yes	495	68.0	58.4	HR	None or NA	9
Salacup_G_USA_2020[116]	USA	AMR	HI	73.9	76.2	3/1/2020	4/24/2020	EHR	Cohort	Yes	Yes	No	242	66.0	51.0	OR	Not reported	9
Santos_MM_BRA_2020[117]	Brazil	AMR	UMI	72.0	51.0	2/20/2020	6/2/2020	ARS	Cohort	Yes	No	No	80,123	51.0	57.0	HR	Not reported	9
Seiglie_J_USA_2020[118]	USA	AMR	HI	73.9	76.2	3/11/2020	4/30/2020	ARS	Cohort	Yes	Yes	Yes	450	63.3	57.6	OR	Independent	9
Shah_C_USA_2020[119]	USA	AMR	HI	73.9	76.2	1/1/2020	5/31/2020	EHR	Cohort	Yes	Yes	No	487	68.4	56.1	OR	None or NA	9
Shah_P_USA_2020[120]	USA	AMR	HI	73.9	76.2	3/2/2020	5/6/2020	EHR	Cohort	Yes	Yes	No	522	63.0	41.8	OR	Not reported	8
Shang_J_CHN_2020[121]	China	WPR	UMI	82.8	49.0	12/25/2019	3/20/2020	EHR	Cohort	Yes	Yes	No	584	59.0	47.4	HR	Independent	9
Sheshah_E_SAU_2020[122]	Saudi Arabia	EMR	HI	74.5	45.0	5/1/2020	7/31/2020	OTH	Cohort	Yes	Yes	No	300	49.7	86.3	OR	Independent	8
Shi_S_CHN_2020[123]	China	WPR	UMI	82.8	49.0	1/1/2020	2/23/2020	EHR	Cohort	Yes	Yes	No	671	63.0	48.0	HR	Independent	8
Singh_S_USA_2020[124]	USA	AMR	HI	73.9	76.2	1/20/2020	5/31/2020	EHR	C-C	No	No	Yes	16,224	50.0	39.0	RR	Independent	8
Smith_AA_USA_2020[125]	USA	AMR	HI	73.9	76.2	3/1/2020	4/22/2020	EHR	Cohort	Yes	No	No	346	66.9	56.0	RR	None or NA	8
Sousa_GJB_BRA_2020[126]	Brazil	AMR	UMI	72.0	51.0	2/20/2020	4/14/2020	ARS	Cohort	Yes	No	Yes	2,070	44.0	49.0	HR	None or NA	7
Sun_H_CHN_2020[127]	China	WPR	UMI	82.8	49.0	1/29/2020	3/5/2020	EHR	Cohort	No	Yes	No	244	69.0	54.5	OR	Not reported	9
Sun_Y_CHN_2020[128]	China	WPR	UMI	82.8	49.0	1/15/2020	4/15/2020	EHR	Cohort	Yes	Yes	No	3,400	61.0	49.0	OR	Not reported	8
Sutter_W_FRA_2020[129]	France	EUR	HI	80.5	62.6	2/26/2020	4/20/2020	EHR	C-C	Yes	No	No	1,206	71.2	61.8	HR	None or NA	8

Tartof_SY_USA_2020[130]	USA	AMR	HI	73.9	76.2	2/13/2020	5/2/2020	EHR	Cohort	Yes	Yes	No	6,916	49.1	45.0	RR	Independent	9
Tavares_C_BRA_2020[131]	Brazil	AMR	UMI	72.0	51.0	2/26/2020	6/30/2020	ARS	C-S	Yes	Yes	Yes	89,405	58.9	56.5	OR	None or NA	7
Thompson_J_GBR_2020[132]	UK	EUR	HI	78.8	68.3	3/12/2020	5/19/2020	EHR	Cohort	No	Yes	No	470	68.7	54.0	OR	None or NA	9
van_Gerwen_M_USA_2020[133]	USA	AMR	HI	73.9	76.2	3/20/2020	5/13/2020	EHR	Cohort	Yes	Yes	Yes	2,015	56.8	55.3	OR	None or NA	9
Wang_Z_USA_2020[134]	USA	AMR	HI	73.9	76.2	3/1/2020	4/15/2020	EHR	C-S	Yes	Yes	Yes	3,273	65.0	57.0	HR	None or NA	7
Workinggroup_ESP_2020[135]	Spain	EUR	HI	80.5	60.4	1/31/2020	4/27/2020	ARS	C-S	Yes	Yes	No	218,652	61.0	43.8	OR	Not reported	7
Wu_R_CHN_2020[136]	China	WPR	UMI	82.8	49.0	12/10/2019	3/18/2020	ARS	Cohort	Yes	Yes	No	21,392	50.0	52.0	HR	Independent	7
Xie_J_USA-2020[137]	USA	AMR	HI	73.9	76.2	3/30/2020	4/5/2020	OTH	Cohort	Yes	Yes	Yes	287	61.5	43.0	OR	Independent	9
Yang_Q_CHN_2020[138]	China	WPR	UMI	82.8	49.0	1/1/2020	2/29/2020	EHR	Cohort	No	Yes	No	226	53.9	51.8	HR	None or NA	8
Yazdanpanah_Y_FRA_2020[139]	France	EUR	HI	80.5	62.6	1/24/2020	3/15/2020	ARS	Cohort	Yes	No	Yes	246	65.0	57.0	HR	Independent	9
You_H_KOR_2020[140]	South Korea	WPR	HI	84.1	65.9	1/20/2020	3/31/2020	ARS	Cohort	Yes	No	No	5,473	45.0	44.6	OR	Not reported	9
Yu_C_CHN_2020[141]	China	WPR	UMI	82.8	49.0	1/14/2020	3/26/2020	OTH	Cohort	Yes	Yes	No	1,464	64.0	50.3	OR	Independent	9
Zandkarimi_E_IRN_2020[142]	Iran	EMR	UMI	74.8	39.5	2/22/2020	5/18/2020	EHR	Cohort	Yes	No	No	1,831	57.7	55.7	HR	Independent	9
Zhang_J_CHN_2020[143]	China	WPR	UMI	82.8	49.0	1/1/2020	3/17/2020	EHR	Cohort	Yes	No	No	312	57.0	44.9	HR	Independent	9
Zhang_Y_CHN_2020[144]	China	WPR	UMI	82.8	49.0	1/29/2020	3/12/2020	OTH	Cohort	Yes	No	No	258	64.2	54.0	HR	Independent	8
Zhu_L_CHN_2020[145]	China	WPR	UMI	82.8	49.0	12/30/2019	3/20/2020	OTH	Cohort	Yes	No	No	7,337	54.0	47.4	HR	Independent	4

Note: UK = United Kingdom, USA = United States of America, HI = high income, UMI = upper middle income, LMI = lower middle income, GHSI = global health security index, WHO = World Health Organization, WB = World Bank, AFR = African Region, SEAR = Southeast Asian Region, AMR = American Region, EMR = East Mediterranean Region, EUR = European Region, WPR = West Pacific Region, EHR = electronic health (medical) record, ARS = administrative/registry/surveillance or (case) reporting system, C-C = case-control, C-S = cross-sectional, DM = diabetes mellitus, HTN = hypertension, OB = obesity, ES = effect size, OR = Odds ratio, HR = hazard ratio, RR = relative risk, NOS = Newcastle-Ottawa Scale.

† Population size.

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