Original Article

Obesity and mortality in patients with COVID-19: A meta-analysis of prospective studies

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Background and Objectives: Previous prospective studies have reported inconsistent findings on the association between obesity and mortality in patients with COVID-19. This study aimed to investigate the association between them by using a meta-analysis of prospective studies. **Methods and Study Design:** We searched PubMed and EMBASE to retrieve studies using keywords related to this topic on January 3, 2022. Data were extracted for a random-effects meta-analysis to calculate a pooled odds ratio (OR), relative risk (RR), or hazard ratio (HR) with a 95% confidence interval (CI). **Results:** In the meta-analysis of 15 prospective cohort studies, obesity significantly increased the risk of mortality in patients with COVID-19 (OR/RR/HR, 1.52; 95% CI, 1.26 to 1.84; I^2 = 90.4%). Most of the included studies were conducted in European (n = 10) and North American (n = 4) countries. In the subgroup meta-analysis by continent, there was a significant association between them in European countries (OR/RR/HR, 1.78; 95% CI, 1.30 to 2.43; I^2 = 81.4%). Also, in the subgroup meta-analysis by data source, obesity was significantly associated with the increased mortality in patients with COVID-19 in both population- and hospital-based data. **Conclusions:** We found that obesity is associated with the increased risk of mortality in patients of COVID-19.

Key Words: obesity, COVID-19, mortality, prospective study, meta-analysis

INTRODUCTION

Coronavirus disease 2019 (COVID-19), an infectious disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), only took a few months to become a worldwide pandemic since its first emergence in Wuhan, China in late 2019.[1] According to the Johns Hopkins Coronavirus Resource Center, there were approximately 307,141,630 confirmed cases and 5,488,597 deaths in total, as of January 10th, 2022.[2] COVID-19 has significantly led to a social and economic crisis such as lower economic activity and economic growth and higher unemployment rates, altered education sectors, and environmental problems such as increased domestic and medical waste, as well as the collapse of the public health system.[3]

In the meantime, it has been reported that several factors including old age, male gender, Black and other minority races, and underlying diseases such as hypertension and diabetes are associated with the progression of COVID-19 into a critical status.[4] Also, it has been known that obesity is a major factor altering immunometabolic pathways and resulting in a poor protective immune response to infections.[5] During the short period of the COVID-19 pandemic, many prospective studies have reported the associations between obesity and the mortality of COVID-19.[6-20] Some studies showed that obesity raises COVID-19 mortality,[6-8, 11-13, 17-20] whereas others reported a negative association[9, 10, 14] or no significant association between them.[15] Also, a considerable number of meta-analyses up to about 30 articles have been published regarding the associations between obesity and the severity or mortality of COVID-19. However, most of the meta-analyses included cross-sectional studies, case-control studies, and retrospective cohort studies. Also, recent two meta-analyses[21, 22] included only one prospective study with several retrospective studies. In terms of the levels of evidence pyramid in the field of evidence-

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based medicine,[23] prospective cohort studies give us a higher level of evidence than the other remaining types of studies such as cross-sectional studies, case-control studies, and retrospective cohort studies. No meta-analysis of prospective studies has been published so far.

This study aimed to investigate the association between obesity and the mortality of COVID-19 using a meta-analysis of prospective studies. We also conducted the subgroup meta-analyses by important factors such as obesity classification, methodological quality of study, continent, and country.

METHODS

Literature search strategy

We conducted an exhaustive search for eligible studies that were published from inception till January 3, 2021 in PubMed and EMBASE. The search keywords related to the current topic are as follows: “obesity”, “body mass index”, “BMI”, “overweight”, or “bodyweight" for a risk factor, “COVID-19” for an outcome factor, and “prospective” or “longitudinal’ for a study design. The language of publication was limited to English.

Selection criteria

Studies were selected if they (i) are a prospective study, (ii) investigated the association between obesity and COVID-19-related mortality, (iii) reported the outcome measures using adjusted odds ratios (ORs), relative risks (RRs), or hazard ratios (HRs) with their 95% confidence intervals. When more than one article shared data, the most comprehensive study or the first published one was included.

Selection of relevant studies and data extraction

Based on the selection criteria, two authors evaluated eligibility of the studies. Discrepancies between evaluators were solved by the third author. In each study, we extracted the data regarding the following items: study name, first author, year of publication, study design, characteristics of population, continent (Europe, North America, and Africa), country, obesity classification (BMI 25-30, 30-35, 35-40, and >40), data source (population-based and hospital-based), OR/RR/HR with its 95% CI, and adjusted variables.

Quality assessment

We assessed the methodological quality of an individual study by using the Newcastle Ottawa Scale (NOS) for observational studies.[24] The NOS is composed of three subscales including the selection of studies, comparability, and exposure. Its star system ranges 0 through 9. We considered a study given more than a mean score as a high quality study.

Main analysis and subgroup analyses

In the main analysis, we investigated the association between obesity and the mortality in patients with COVID-19 by using adjusted ORs/RRs/HRs with their 95% CIs. We used mortality data of the comparison between normal body weight and >30 of body mass index (BMI). If an individual study reported only those data of subcategories (e.g., class 1 obesity of BMI 30-34.9, class 2 obesity of BMI 35-39.9, and class 3 obesity of BMI >40), we used the highest class obesity (eg., BMI >35 or >40). We also performed subgroup meta-analyses by continent (Europe, North America, and Africa), country (France, Italy, Libya, Mexico, Spain, UK, and USA), obesity classification (BMI 25-30, 30-35, 35-40, and >40), and data source (population-based, hospital-based).

Statistical analysis

We extracted adjusted ORs, RRs, or HRs and their 95% CIs to calculate a pooled effect size with its 95% CI. Given that individual studies came from different populations, a random-effects model was used by using the DerSimonian and Laird method.[25] To explore heterogeneity in findings across studies, we used Higgins I^2, which measures the percentage of total variation among studies. If the value of I^2 is less than 0, it is set at zero; I^2 ranges from 0% (no heterogeneity) to 100% (maximal heterogeneity). If I^2 value is more than 50%, there is substantial heterogeneity.[26]

To evaluate publication bias, we used the Begg’s funnel plot and Egger’s test. If the Begg’s funnel plot is asymmetrical or the *p*-value of Egger’s test is lower than 0.05, publication bias exists. If the two tests present inconsistent results, the results from the Egger’s test were adopted because the visual inspection of a funnel plot might be misleading.[27] For statistical analyses, we used the Stata SE 15.1 software package (Stata Corp., College Station, Texas, USA).

RESULTS

Selection of relevant studies

A flow diagram for the selection process of relevant studies is shown in Figure 1. A total of 1247 articles were identified by searching PubMed and EMBASE. After removing 368 duplicate articles, we reviewed titles and abstracts of 879 articles, and then excluded 707 articles that did not meet the predetermined selection criteria. After reviewing the full texts of the remaining 172 articles, we excluded 157 articles for the following reasons: not relevant (n = 88), insufficient data (n = 51), not original study (n = 7), non-English (n = 4), not peer-reviewed (n = 2), and identical population (n = 3). Finally, a total of 15 prospective studies6-20 were included in the final analysis.

General characteristics of studies

General characteristics of the studies included in this meta-analysis are shown in Table 1. We identified a total of 1,813,472 participants from 15 prospective studies. All participants were men and women aged from 15 to 80+ years old. The continents where the individual studies had been conducted were as follows: Europe (n = 10), North America (n = 4), and Africa (n = 1). The countries where the individual studies have been conducted were as follows: UK (n = 4), USA (n = 3), France (n = 2), Spain (n = 2), Italy (n = 2), Libya (n = 1), and Mexico (n = 1). Data sources where the individual studies have been extracted from were as follows: population-based (n = 7) and hospital-based (n = 8).

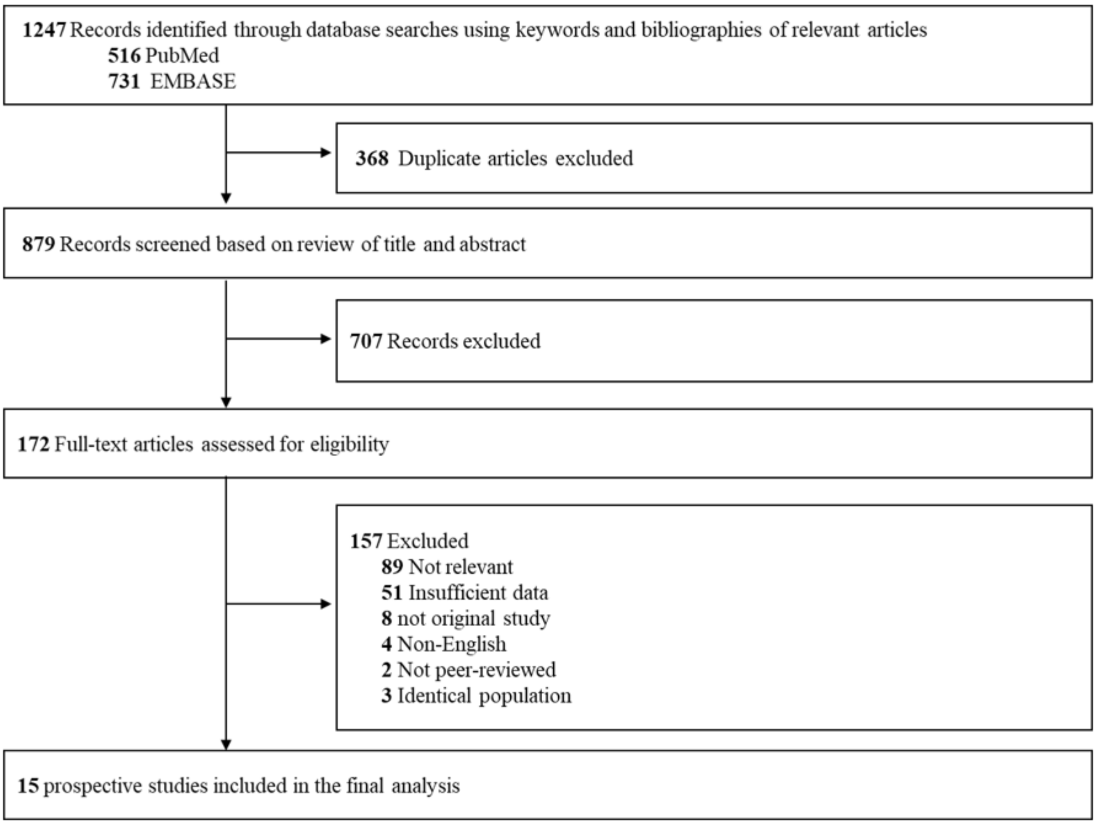

Figure 1. Flow diagram for identifying studies

Quality assessment of individual studies

As shown in Table 2, all studies were given 9 stars and thus classified as having high quality.

Main analysis

The forest plot of the main analysis is demonstrated in Figure 2. In the random-effects model meta-analysis of all 15 prospective studies, obesity statistically significantly increased the risk of mortality in patients with COVID-19 (OR/RR/HR, 1.52; 95% CI, 1.26 to 1.84; I^2 = 90.4%).

Subgroup meta-analyses

Table 3 illustrates the findings from the subgroup meta-analyses on the association between obesity and mortality in patients with COVID-19. In the subgroup meta-analysis by continent, obesity was associated with the increased risk of mortality in patients with COVID-19 in the studies conducted in Europe (RR, 1.78; 95% CI, 1.30 to 2.43; I^2 = 81.4%; n = 10). However, no significant association between them was found in both North America (RR, 1.37; 95% CI, 0.91 to 2.06; I^2 = 90.5%; n = 4) and Africa (RR/HR, 1.01; 95% CI, 0.98 to 1.04; I^2 = 100%; n = 1).

In the subgroup meta-analysis by country, an increased mortality was found in the studies conducted in UK (OR/RR/HR, 1.27; 95% CI, 0.78 to 2.07; I^2 = 77.7%; n = 4) , Italy (OR/RR/HR, 3.65; 95% CI, 1.97 to 6.74; I^2 = 0.0%; n = 2), France (OR/RR/HR, 2.76; 95% CI, 1.91 to 4.01; I^2 = 0.0%; n = 2), and Mexico (OR/RR/HR, 2.15; 95% CI, 1.46 to 3.17; I2 = 100%; n = 1). However, no significant association was observed in USA (OR/RR/HR, 1.19; 95% CI, 0.81 to 1.75; I^2 = 88.6%; n = 3), Spain (OR/RR/HR, 1.46; 95% CI, 0.60 to 3.56; I^2 = 85.2%; n = 2), and Libya (OR/RR/HR, 1.01; 95% CI, 0.98 to 1.04; I^2 = 100%; n = 1).

In the subgroup meta-analysis by data source, obesity increased the risk of mortality in patients of COVID-19 both in studies of general population (OR/RR/HR, 1.49; 95% CI, 1.06 to 2.11; I^2 = 88.7%; n = 7) and hospitalized population (OR/RR/HR, 1.60; 95% CI, 1.19 to 2.15; I^2 = 92.3%; n = 8).

Publication bias

Figure 3 shows the Begg's funnel plot and Egger's test for identifying publication bias in the main meta-analysis of prospective studies. Publication bias was observed in the Begg's funnel plot (visually asymmetric) and Egger's test (p for bias = 0.007).

DISCUSSION

Summary of Findings

In the current meta-analysis of prospective studies, we found that obesity increased the risk of mortality in patients with COVID-19.

Possible Mechanisms on the Association between Obesity and Mortality in Patients with COVID-19

Regarding the increased risk of mortality in patients with COVID-19 by obesity, its potential biological mechanisms still remain unclear. However, previous *in vitro* and animal studies have reported that obesity is associated with low-grade chronic inflammation.[28-30] Also, inflammation can damage the immune system in both innate and adaptive responses.[31, 32] The delayed immune response,

Table 1. General characteristics of prospective cohort studies included in final analysis (n = 15)

Source (Study name)	Country	Study participants (Mean age, y; %)	Continent	Comparisons	OR/RR/HR (95% CI)	Adjusted variables
2020 Czernichow et al[6]	France	5795 patients aged 18-79 years hospitalized in Paris	Europe	BMI 18.5-24.9 vs BMI≥40	2.55 (1.62-3.95)	Age, sex, smoking history, and comorbidities
2020 Docherty et al[7]	UK	20,133 UK patients in hospital with covid-19	Europe	Clinician-defined normal weight vs. obesity	1.33 (1.19-1.49)	Age, sex, and major comorbidities
2020 Eastment et al[8]	USA	281982 VA patients, excluding VA employees, who were tested for SARS-CoV-2 nucleic acid by polymerase chain reaction (PCR) in the inpatient or outpatient setting between February 28, 2020, and June 21, 2020	North America	BMI 18.5-24.9, BMI≥40	1.42 (1.12-1.78)	Age (continuous), sex, race (Black, White, Other), ethnicity, geographic region, diabetes, cancer, hypertension, coronary artery disease, congestive heart failure, cerebrovascular disease, dialysis, chronic kidney disease, cirrhosis, asthma or chronic obstructive pulmonary disease, obstructive sleep apnea, obesity hypoventilation syndrome, alcohol dependence, substance use dependence, hyperlipidemia, and smoking
2020 Ioannou et al[9]	USA	88747 patients tested for SARS-CoV-2 nucleic acid by polymerase chain reaction between February 28 and May 14, 2020, and followed up through June 22, 2020, in the Department of Veterans Affairs (VA) national health care system, including 10 131 patients (11.4%) who tested positive	North America	BMI 18.5-24.9, BMI≥35	0.87 (0.77-0.98)	All sociodemographic characteristics, comorbid conditions, and symptoms
2020 Ken-Dror et al[10]	UK	429 adult inpatients with laboratory-confirmed COVID-19 symptoms admitted to a single Surrey centre between March and April 2020	Europe	n.a.	0.30 (0.12-0.66)	Age, CRP, respiratory rate, DBP, dementia, asthma, AIC, sensitivity/specificity, AUC
2020 Lanini et al[11]	Italy	379 COVID-19 patients	Europe	BMI<30 vs. BMI >30	5.13 (1.81-14.50)	Confounding effect of obesity, chronic renal failure, COPD, cardiovascular diseases and age >60 years.
2020 Petrilli et al[12]	USA	5279 patients with laboratory confirmed severe acute respiratory syndrome coronavirus 2 (SARS-Cov-2) infection between 1 March 2020 and 8 April 2020.	North America	Normal weight vs. BMI≥30	1.45 (0.99-2.13)	Personal characteristics and comorbidities, and one adding admission vitals and laboratory studies
2020 Thomson et al[13]	UK	156 patients with COVID-19 admitted to a large UK ICU from March to May 2020	Europe	Normal weight vs. overweight or obese	3.06 (1.16-8.74)	Age on admission, gender, ethnicity, BMI, smoking status, any comorbidity, lowest P/F ratio on first ICU day, pH at time of lowest P/F ratio, PaCO2 at time of lowest P/F ratio

BMI, body mass index; n.a., not available

Table 1. General characteristics of prospective cohort studies included in final analysis (n = 15) (cont.)

Source (Study name)	Country	Study participants (Mean age, y; %)	Continent	Comparisons	OR/RR/HR (95% CI)	Adjusted variables
2021 Castilla et al[14]	Spain	643,757 people covered by the Health Service of Navarre, Spain	Europe	Normal weight vs. BMI ≥ 40	0.88 (0.47-1.66)	Sex, age, nursing home resident, health care worker, place of birth, place of residence, income level, smoking status, hospitalization in prior year, immunodeficiency, diabetes, cardiovascular disease, COPD, asthma, chronic kidney disease, cerebrovascular disease, liver cirrhosis, dementia, hematological malignancy, non-hematological cancer, severe obesity, hypertension, and functional dependence
2021 Elhadi et al[15]	Libya	465 COVID-19 critical care patients in 11 ICUs in Libya from May 29th to December 30th 2020	Africa	BMI=<30 vs. BMI>30	1.01 (0.98–1.04)	Lower lymphocyte count, higher procalcitonin, cardiac troponin, C-reactive protein, D-dimer, total SOFA score, emergency intubation, and stress cardiomyopathy.
2021 Fresán et al[16]	Spain	433,955 hospitalized patients with COVID-19	Europe	BMI<40 vs. BMI ≥40	2.20 (1.66-2.93)	Age, sex, and chronic conditions
2021 Giacomelli et al[17]	Italy	520 COVID-19 patients admitted to two COVID-19 hospitals in Milan	Europe	Normal weight vs. BMI≥30	2.17 (1.10-4.31)	Age, critical disease at hospital admission, obesity, anemia, D-dimer, estimated glomerular filtration rate, lactate dehydrogenase, and creatine kinase
2021 Hamrouni et al[18]	UK	259,397 general population from UK Biobank	Europe	BMI 18.5-25 vs. BMI≥30	1.79 (1.32-2.43)	Baseline age, sex, ethnicity, physical activity level, Townsend Deprivation Index, smoking status, alcohol intake, educational attainment, number of illnesses and number of treatments/medications taken
2021 Torres-torres et al[19]	Mexico	13,062 consecutive SARS-CoV-2 positive pregnant individuals	North America	Normal weight vs. BMI≥30	2.15 (1.46-3.17)	Age, diabetes, obesity, hypertension, renal chronic disease-asthma, and ethnicity
2021 Yazdanpanah et al[20]	France	246 patients with reverse-transcriptase polymerase chain reactions virologically confirmed COVID-19 between January 24 and March 15, 2020	Europe	n.a.	3.32 (1.70-6.52)	Age, sex, ethnic group, smoking history, comorbidities

BMI, body mass index; n.a., not available

Table 2. Methodological quality of studies based on the Newcastle-Ottawa scale

Study	Selection				Comparability	Outcome			Total
	Representativeness of exposed cohort	Selection of non-exposed cohort	Ascertainment of exposure	No present of outcomes of interest at start of the study	Comparability of cohorts	Assessment of outcome	Long follow-up enough for outcomes	Adequacy of follow-up of cohorts	
Czernichow et al, 2020	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Docherty et al, 2020	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Eastment et al, 2020	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Ioannou et al, 2020	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Ken-Dror et al, 2020	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Lanini et al, 2020	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Petrilli et al, 2020	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Thomson et al, 2020	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Castilla et al, 2021	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Elhadi et al, 2021	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Fresán et al, 2021	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Giacomelli et al, 2021	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Hamrouni et al, 2021	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Torres-torres et al, 2021	☆	☆	☆	☆	☆☆	☆	☆	☆	9
Yazdanpanah et al, 2021	☆	☆	☆	☆	☆☆	☆	☆	☆	9

BMI, body mass index; n.a., not available

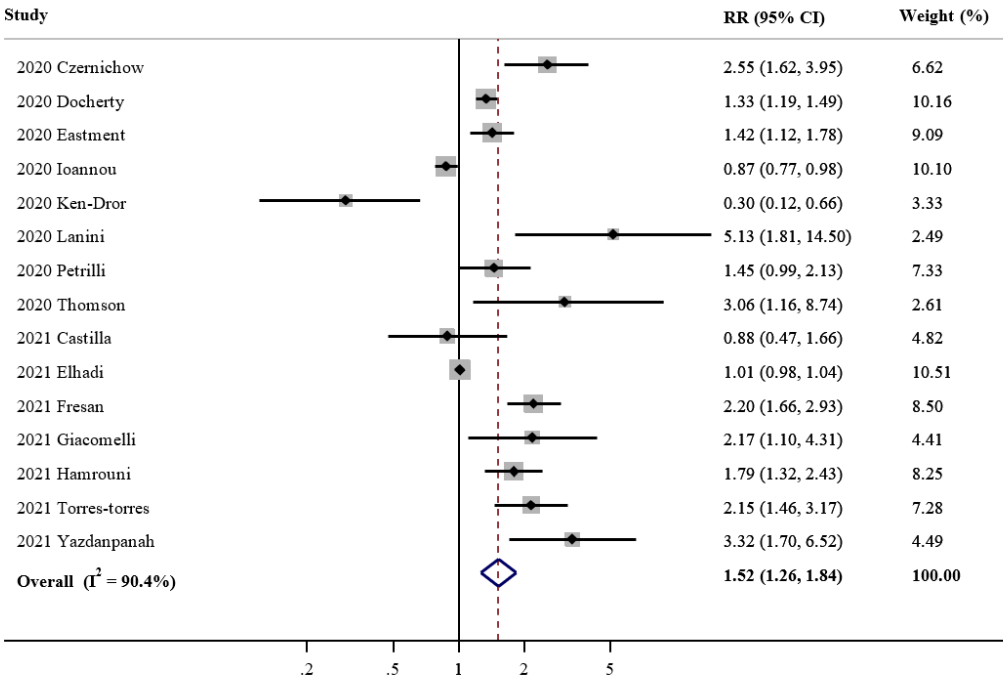

Figure 2. Obesity and COVID-19 mortality in a meta-analysis of prospective studies (n = 15). RR, relative risk; CI, confidence interval

Table 3. Obesity and COVID-19 in the subgroup meta-analysis of prospective cohort studies

Factors	No. of Studies	Summary OR/RR/HR (95% CI)	Heterogeneity, I^2 (%)
All	15	1.52 (1.26, 1.84)	90.4
Continent			
Europe	10	1.78 (1.30, 2.43)	81.4
North America	4	1.37 (0.91, 2.06)	90.5
Africa	1	1.01 (0.98, 1.04)	
Country			
UK	4	1.27 (0.78, 2.07)	83.2
USA	3	1.19 (0.81, 1.75)	88.6
France	2	2.76 (1.91, 4.01)	0.0
Italy	2	3.65 (1.97, 6.74)	0.0
Spain	2	1.46 (0.60, 3.56)	85.2
Libya	1	1.01 (0.98, 1.04)	
Mexico	1	2.15 (1.46, 3.17)	
Data source			
Population-based	7	1.49 (1.06, 2.11)	88.7
Hospital-based	8	1.60 (1.19, 2.15)	92.3

OR, odds ratio; RR, relative risk; HR, hazard ratio; CI, confidence interval; BMI, body mass index

which enables the viral spread of infections in human bodies, could be one of the factors responsible for the higher risk of mortality.[31] Additionally, decreased antiviral pressure leads to an increased susceptibility of the host to secondary bacterial infections and significantly impairs the healing process of the lung epithelium, raising mortality rate in obese patients.[31]

Also, there is a correlation between higher BMI and lung damage.[16, 32] Obesity is well recognized for adversely influencing lung function, specifically asthma control.[33] The effect of obesity on lung volumes can be detrimental; obesity could impair the lung parenchyma and bronchi, leaving patients more vulnerable to severe COVID-19 outcomes.[16, 33]

Besides, lower pre-pandemic physical activity is associated with a greater risk of COVID-19 mortality.[18] A study of COVID-19 patients reports that physical inactivity is an important indicator of the severity of the infection.[34] Fit adults tend to be more protected from common health risks that are elevated due to obesity, and this effect is even greater in the obese population compared with the overweight and normal weight population.[35]

Comparisons with previous systematic reviews and meta-analyses

Findings of our study are consistent with those from the previous systematic reviews and meta-analyses.[21, 22] Seidu et al reported obesity as a significant risk factor for severe COVID-19 outcomes such as mortality in the systematic review and meta-analysis of cohort studies.[21] However, they included only one prospective cohort study with eight retrospective cohort studies,[21] whereas our study included 17 prospective studies. The reason for the big difference in the numbers of the included studies is that

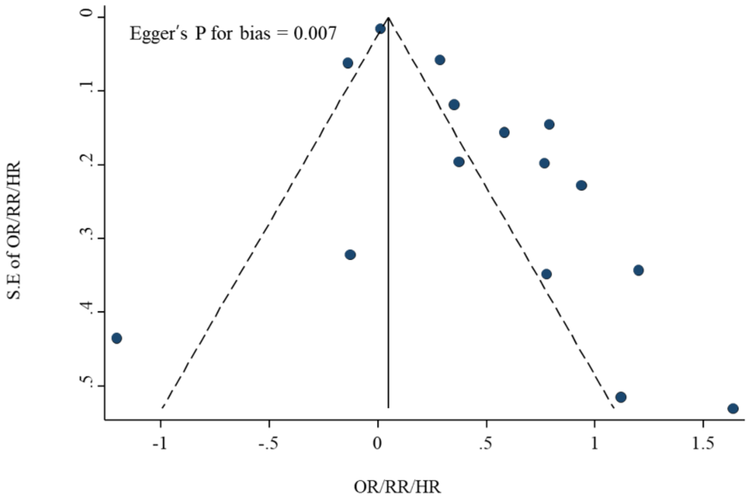

Figure 3. Begg's funnel plot and Egger's test for identifying publication bias in a meta-analysis of prospective studies (n = 15). OR, odds ratio; RR, relative risk; HR, hazard ratio; S.E, standard error

they searched databases in May, 2020. Since then, a lot of prospective studies on this topic have been published. Another meta-analysis of Rico-Martin et al showed that metabolic syndrome and its individual components such as obesity, with an exception of hypertension, also contribute to higher risk of mortality in COVID-19 patients. However, they also included only one prospective cohort study and four retrospective cohort studies.[22] The reason for the big difference in the numbers of the included studies is that they only involved the associations between metabolic syndrome regarding obesity and the mortality of COVID-19.

Strengths and Limitations

Although many previous systematic reviews and meta-analyses have reported the findings on the similar topics to ours, they mostly included studies with lower levels of evidence such as cross-sectional studies and case-control studies than cohort studies. Moreover, there was no meta-analysis of prospective studies on this topic. Thus, as far as we know, this study is the most comprehensive meta-analysis ever on the association between obesity and mortality in patients with COVID-19.

However, there are several limitations in our study. First, there was substantial heterogeneity in the subgroup meta-analyses, as well as in the main analysis. We tried to perform subgroup meta-analyses by some factors (data not shown). However, no specific findings were found. Second, we found that there was publication bias in the main analysis, which means that the studies showing negative or no significant results were not published. Thus, our findings might be exaggerated in the impact of obesity on COVID-19 mortality. Third, most of the published and included studies in the current study on this topic came from the Western countries, such as European and American countries. Thus, our findings should not be generalized to the whole populations in the world. Further studies are warranted to confirm our findings in Eastern countries. Fourth, we tried to compare mortality between normal body weight vs. BMI >30. However, five studies of 15 studies reported only data of subcategories (e.g., class 1 obesity of BMI 30-34.9, class 2 obesity of BMI 35-39.9, and class 3 obesity of BMI >40), and we used the highest class obesity (eg., BMI >35 or >40). This might lead to overestimation of the effect of obesity on COVID-19 mortality. Last, we did not consider studies such as preprint articles that are posted on a public server before formal peer-review and therefore may have missed some studies that include important information related to this topic. However, we think that limiting sources to findings from published peer-reviewed articles would produce more reliable results. Also, in this COVID-19 pandemic era, many studies on this topic have been being published in the short term period. Thus, further updated meta-analyses are warranted to confirm our findings.

In conclusion, this systematic review and meta-analysis of prospective studies found that obesity is associated with the increased risk of mortality in patients with COVID-19. Our findings give the clinicians and the public the importance of maintaining ideal body weight regarding the outcomes of COVID-19.

AUTHOR DISCLOSURES

No competing interests are reported.

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