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Obesity Is Associated with Severe Disease and Mortality in Patients with Coronavirus Disease 2019 (COVID-19)

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Abstract

Background: The coronavirus disease 2019 (COVID-19) pandemic has led to global research with the aim of predicting which people are at greatest risk of developing severe disease and dying. The aim of this meta-analysis was to determine the associations between obesity and the severity of and mortality due to COVID-19.

Methods: We searched the PubMed, EMBASE, Cochrane Library and Web of Science databases for studies evaluating the associations of obesity with COVID-19. Odd risks (ORs) and 95% confidence intervals (CIs) were calculated using random- or fixed-effects models.

Results: Thirty-eight studies involving 621502 patients were included. Compared with nonobese patients, obese patients had a significantly increased risk of infection (OR 3.19, 95% CI 1.45-7.03; $I^2 = 98.3\%$), hospitalization (OR 1.77, 95% CI 1.61-1.95; $I^2 = 43.8\%$), clinically severe disease (OR 2.88, 95% CI 1.99-4.16; $I^2 = 49.9\%$), mechanical ventilation (OR 1.66, 95% CI1.42-1.94; $I^2 = 41.3\%$), intensive care unit (ICU) (OR 2.06, 95% CI1.49-2.85; $I^2 = 71.4\%$), and mortality (OR 1.48, 95% CI 1.18-1.85; $I^2 = 80.8\%$).

Conclusion: Patients with obesity may have a greater risk of developing severe COVID-19 and dying. Therefore, it is important to increase awareness of these associations with obesity in COVID-19 patients.

Keywords: Obesity, COVID-19, Predict, Severity, Mortality

Background

On Dec 31, 2019, the World Health Organization (WHO) was made aware of an outbreak involving several cases of atypical pneumonia, which were subsequently identified as being caused by a novel virus belonging to the coronavirus (CoV) family, called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) (1). On Jan 30, 2020, the WHO declared an international public health emergency due to infections by SARS-CoV-2. On Feb 20, 2020, the WHO officially named the disease caused by SARS-CoV-2 coronavirus disease 2019 (COVID-19) (2, 3). COVID-19 has posed a global health threat, causing an ongoing pandemic in many countries and territories, with a total of approximately 6287771 confirmed COVID-19 cases and 379941 deaths (4). These numbers were up to date as of June 3, 2020. The number of COVID-19 cases has been increasing around the world, and there is increasing global concern about this outbreak (5).

WHO global estimates indicate that 39% of adults are overweight and 13% are obese (6). Obesity is an increasing worldwide health concern and has been regarded as a critical risk factor for various infections, post-infection complications and mortality from severe infections (7). It has been shown to have deleterious effects on host immunity, which is the primarily cause of the increase in the risk of infections, especially severe infections (7, 8). Obesity also has been shown to affect lung function in multiple ways that are related to mechanical and inflammatory factors, making obese individuals more likely to suffer from respiratory symptoms and progress to respiratory failure (9).

In fact, accumulating evidence now suggests that the group of patients who develop severe COVID-19 may have a higher proportion with obesity than the group with non-severe COVID-19 disease; in some reports, the difference was significant (10-13). However, there is still a lack of information regarding the global prevalence of obesity in individuals with COVID-19. Investigating the influence of obesity on COVID-19 is of scientific interest. The aim of this article is to review the relationship between obesity and COVID-19. In doing so, we aim to enhance public awareness of the association between obesity and COVID-19 and provide treatment guidance for this special population. Highlighting the possible association between the aforementioned conditions could provide guidance to those working to control the COVID-19 epidemic.

Methods

Literature search

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses of Individual Participant Data (the PRISMA-IPD) statement was followed for the performance and reporting of this meta-analysis (14). Our meta-analysis focused on the relationships between obesity and the mortality due to and severity of COVID-19. PubMed, EMBASE, Cochrane Library and Web of Science were carefully searched from inception to September 2020 with the terms "COVID-19" and "novel coronavirus" in combination with terms including "obesity," and "BMI," as keywords. Two investigators (ZC and YY) independently reviewed the identified abstracts and selected the articles for full review. Disagreements were resolved by a third

investigator (JZ).

Inclusion and exclusion criteria

Inclusion criteria are as follows: (1) patients in the studies had confirmed COVID-19; (2) the BMI values were provided; (3) the comorbidities and severity of disease were provided; and (4) the studies were published in English. The exclusion criteria were as follows: (1) case reports, reviews, letters or non-human studies; (2) studies written in a language other than English; and (3) studies with insufficient information. Two investigators (ZC and YY) worked independently to decide which studies should be included, and disagreements were resolved by a third investigator (JZ).

Data extraction and quality assessment

Data extraction was independently conducted by two authors (ZC and YY) using a standardized data collection form, which included author, year, country, patients, BMI values, and outcomes (infection, hospitalization, severe disease, mechanical ventilation, intensive care unit (ICU) admission, and mortality). The characteristics of these studies are shown in Table 1.

Data synthesis and statistical analysis

All analyses and plots were performed and generated using STATA software version 13. Forest plots were used to illustrate the association between obesity and COVID-19 in the selected studies. We pooled the data and calculated the odds ratios (ORs) with 95% confidence intervals (CIs) for the dichotomous outcomes, including infection, hospitalization, severe disease, mechanical ventilation, ICU admission, and mortality. The results of the included studies were assessed with random-effect models. We used I^2 statistics to assess the magnitude of heterogeneity: 25%, 50%, and

75% represented low, moderate, and high degrees of heterogeneity, respectively (15). The choice of the appropriate model was based on the results: a fixed-effect model (inverse variance) was used to pool the data if I^2 was < 50%, and a random-effect model (DerSimonian-Laird) was used if I^2 was > 50% (15). Funnel plots were used to screen for potential publication bias. To determine the robustness of the results, a sensitivity analysis was conducted with the sequential elimination of each study from the pool. The threshold of statistical significance in this paper was set to 0.05.

Results

Selected studies and baseline characteristics

Overall, 2567 articles of interest were found in the initial searches of the electronic databases. A total of 1800 duplicate documents were identified. Of these, 277 full-text articles were considered potentially relevant and assessed for eligibility. After the review of the titles and abstracts, 239 non-human studies, reviews and studies that were not clinical trials were excluded. The remaining 38 studies were carefully evaluated in detail. Finally, 38 studies were included (Fig. 1). Thirty-eight papers met the inclusion criteria. Of the included studies, 14 reported mortality, 11 reported ICU admission, 8 reported the development of severe disease, 7 reported mechanical ventilation, 6 reported hospitalization, and the remaining 4 reported infections. Eighteen came from the USA, 5 from China, 4 from Italy, 3 from the UK, 3 from Mexico, 3 from France, and one each from Bolivia and Spain (Table 1).

Viral infection

To test the impact of obesity on viral infection, we included 4 studies (16-19) with 621502 subjects. The data indicate that obesity significantly increased the risk of viral infection (OR = 3.19, 95% CI, 1.45, 7.03; $I^2 = 98.3\%$; Fig. 2).

Risk of hospitalization

To test the impact of obesity on the risk of hospitalization, we included 6 studies (20-25) involving 783712 subjects. The data indicate that obesity increased the risk of hospitalization (OR = 1.77, 95% CI, 1.61, 1.95; $I^2 = 43.8\%$; Fig. 3).

Risk of severe disease

To test the impact of obesity on the risk of severe disease, we included 8 studies (10, 26-32) involving 1774 subjects. The data indicate that obesity is associated with an increased risk of severe disease (OR=2.88, 95% CI, 1.99, 4.16; $I^2 = 49.9\%$; Fig. 4).

Use of mechanical ventilation

To test the impact of obesity on mechanical ventilation use, we included 7 studies (33-39) involving 2088 subjects. The data indicate that obesity is associated with the use of mechanical ventilation (OR=1.66, 95% CI, 1.42, 1.94; $I^2 = 41.3\%$; Fig. 5).

Risk of ICU admission

To test the impact of obesity on the risk of ICU admission, we included 10 studies (40-49) involving 3652 subjects. The data indicate that obesity is closely

associated with the risk of ICU admission (OR=2.06, 95% CI, 1.49, 2.85; $I^2 = 71.4\%$; Fig. 6).

Risk of mortality

To test the impact of obesity on the risk of mortality, we included 14 studies (50-63) involving 27514 subjects. The data indicate that obesity is significantly associated with the risk of mortality (OR=1.48, 95% CI, 1.18, 1.85; $I^2 = 80.8\%$; Fig. 7).

Publication bias and sensitivity analysis

We found no potential publication bias in the studies included in the meta-analysis (Fig. 8). The sensitivity analysis suggested that our results are stable and reliable (Fig. 9).

Discussion

We conducted this systematic review and meta-analysis to determine whether obesity is a predictor of the severity of and mortality due to COVID-19. In the present review, we included 38 articles involving 621502 patients. Compared with the non-obese group, obese patients had a significantly increased risk of infection, hospitalization, severe disease, mechanical ventilation, ICU admission, and mortality. **Mechanisms underlying the association of obesity with COVID-19 severity and mortality**

First, obesity, usually defined by a BMI > 30 kg/m², is characterized by visceral adipose tissue (AT) expansion and inflammation (64). AT produces a large number of adipokines that act as signalling molecules, with a wide array of effects on many organ systems, including the lungs. A potential pathophysiological mechanism underlying the effect of obesity on the severity of COVID-19 may, therefore, involve abnormalities in the production of adipokines by AT, of which leptin and adiponectin have received the most attention (65, 66). Leptin is a primarily pro-inflammatory adipokine that influences both the innate and adaptive immune responses by stimulating the production of pro-inflammatory cytokines (interleukin (IL)-2, interferon- γ and tumour necrosis factor alpha (TNF- α)) and suppressing the production of anti-inflammatory cytokines (IL-4 and IL-5) (67). In contrast, adiponectin is a predominantly anti-inflammatory adipokine that inhibits pro-inflammatory cytokines (TNF- α , IL-6, and nuclear factor- κ B) and induces anti-inflammatory cytokines (IL-10 and IL-1 receptor antagonist) (67). It is commonly thought that systemic leptin concentrations are upregulated, whereas adiponectin concentrations are paradoxically downregulated in obese individuals (68, 69). This imbalance in adiponectin/leptin production creates an unfavourable hormonal milieu that generates and maintains a chronic pro-inflammatory state, which can result in a dysregulated immune response (70).

Second, angiotensin converting enzyme-2 (ACE-2) is the putative receptor for SARS-CoV-2 entry into host cells. The ACE2 expression levels in AT exceed those expressed in the lung. Individuals with obesity have an increased volume of AT and

consequently higher ACE2 levels, which could increase their susceptibility to COVID-19 (71).

Third, impaired lung mechanics and higher concentrations of pro-inflammatory molecules may both contribute to the propensity in patients with obesity for the development of more severe complications of respiratory viral infections. Abdominal obesity restricts the movement of the diaphragm and chest wall, resulting in a reduction in functional residual capacity and making mechanical ventilation more challenging (72, 73).

Finally, obesity results in physiological lung alterations, such as decreased functional residual capacity and hypoxemia (74).

All of the above mechanisms can reasonably explain how obesity increases the severity of and rate of mortality due to COVID-19.

Theoretical and practical implications

With regard to the practical implications of this information, to the best of our knowledge, this is the first systematic review and meta-analysis comprehensively assessing obesity and outcomes of COVID-19 (infection, hospitalization, severe disease, mechanical ventilation, ICU admission, and mortality). Obesity is a risk and predictive factor for severe disease and the need for advanced medical care in COVID-19 patients. Basic research is needed to identify the causal relationship between obesity and adverse outcomes of COVID-19.

Limitations of our study

First, some indicators, such as the risk of infection, ICU admission, and mortality, had greater degrees of heterogeneity, and subgroup analyses could not be performed to eliminate this heterogeneity. However, the trends were consistent across nearly all forest plots. In addition, many of the included articles did not give specific BMI values, and it is not clear how much a specific unit increase in BMI can increase the severity of and rate of mortality due to COVID-19. Last, since none of the studies were RCTs, the causal relationships between obesity and COVID-19 severity and mortality could not be determined.

Conclusion

In conclusion, patients with obesity may have a greater risk of severe COVID-19 and mortality. Our results may prompt clinicians to pay special attention to obese patients when treating COVID-19.

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Availability of data and material

The datasets used and/or analyzed during the current meta-analysis are ava ilable from the corresponding author upon reasonable request.

Ethics approval and consent to participate

Not applicable as this is a meta-analysis of previously published papers.

Competing interests

All authors declare that there is no conflict of interest.

Consent for publication

Not applicable.

Authors' contributions

JZ coordinated the study. ZC conceived of the study, along with YY and JZ, and contributed to the study design, literature search, figure generation, statistical analysis, outcome synthesis and paper drafting and editing. All authors edited and approved the final version of the manuscript to be published.

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Figure legends

Table 1-Characteristics of available studies on the relationship between obesity and COVID-19.

Fig. 1-Flow diagram.

Fig. 2-Forest plot comparing the odds of infection with SARS-CoV-2 between obese and non-obese patients.

Fig. 3-Forest plot comparing the odds of hospitalization for COVID-19 between obese and non-obese patients.

Fig. 4-Forest plot comparing the odds of severe COVID-19 between obese and non-obese patients.

Fig. 5-Forest plot comparing the odds of mechanical ventilation due to COVID-19 between obese and non-obese patients.

Fig. 6-Forest plot comparing the odds of ICU admission due to COVID-19 between obese and non-obese patients.

Fig. 7-Forest plot comparing the odds of mortality due to COVID-19 between obese and non-obese patients.

Fig. 8-Funnel plot for hospitalization (A), severe disease (B), mechanical ventilation (C), ICU admission (D), and mortality (E) between obese and non-obese patients.

Fig. 9-Sensitivity analysis for hospitalization (A), severe disease (B), mechanical ventilation (C), ICU admission (D), and mortality (E) between obese and nonobese patients.

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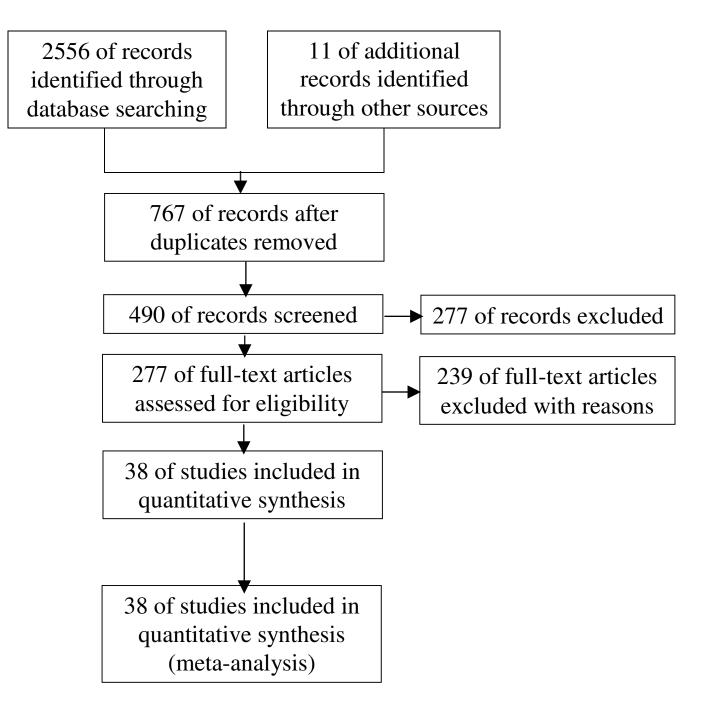
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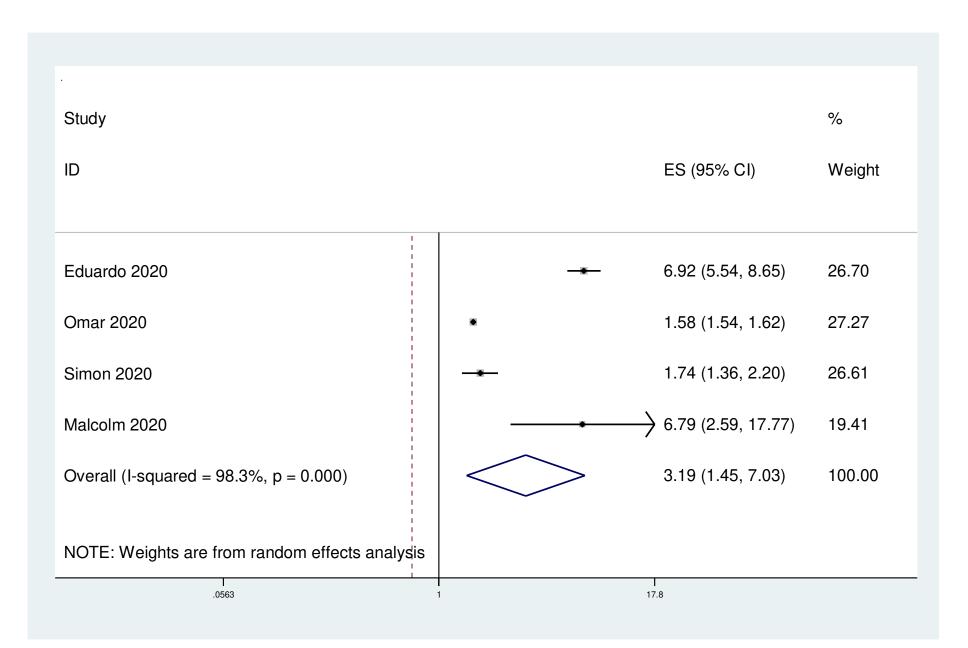
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Fisjunde	Author	Year	Country	Patients	BMI	@dicknhesre to access/download;Figure;2020-10-5 Cai meta figures.pptx ≛
1	Natasha N	2020	USA	238	30	1.7 (1.1-2.8) for mortality
2	Céline	2020	France	347	30	3.0 (1.0-8.7) for severity
3	Nikroo	2020	USA	363	NA	1.23 (0.77-1.98) for mechanical ventilation; 1.26 (0.79-1.98) for ICU; 1.03 (0.51-2.09) for mortality
4	Edgar	2020	Mexico	140	NA	2.3265 (1.0133-5.3415) for ICU
5	Во	2020	USA	58	30	1.98 (0.56 - 7.72) for hospitalisation; 2.04 (0.5 - 8.4) for mortality
6	Marie E	2020	USA	531	30	1.9 (1.1-3.3) for hospitalisation
7	Geehan	2020	USA	463	40	2.0 (1.4-3.6) for ICU
8	Eduardo	2020	Mexico	32583	NA	6.92 (5.54–8.65) for infection
9	Michael	2020	USA	1000	30	1.2911 (0.9478-1.7587) for ICU
10	Xiao	2020	USA	NA	NA	0.94 (0.86, 1.02) for mortality
11	Mark	2020	UK	387,109	30	1.97 (1.61, 2.42) for hospitalisation
12	Philip	2020	USA	50	NA	14.4 (2.7052-76.6517) for severity
13	Juan	2020	Bolivia	107	NA	12.125 (1.690-86.948) for mortality
14	Stefano	2020	Italy	132	30	1.526 (1.243-1.874) for ICU
15	J.M.	2020	Spain	172	30	4.725 (1.6143-13.8302) for ICU
16	Omar	2020	Mexico	177133	NA	1.5790(1.5358-1.6235) for infection
17	Nicole	2020	USA	928	NA	0.99 (0.58–1.71) for mortality
18	Kaveh	2020	USA	770	30	1.76 (1.24-2.48) for ICU; 1.72 (1.22-2.44) for mechanical ventilation; 1.15 (0.62-2.14) for mortality
19	Luca	2020	Italy	92	30	4.19 (1.36-12.89) for mechanical ventilation; 11.65 (3.88-34.96) for ICUs; 0.27 (0.03-2.05) for mortality
20	Eboni G	2020	USA	3626	30	1.43 (1.20–1.71) for hospitalization
21	Frederick S	2020	USA	105	30	1.2908 (0.5936-2.8071) for severity
22	Eyal	2020	USA	3,406	40	1.6 $(1.2 - 2.3)$ for the older population mortality
23	Andrea	2020	Italy	233	NA	3.04 (1.42-6.49) for mortality
24	Annemarie B1	2020	UK	20 133	NA	1.33 (1.19 to 1.49) for mortality
25	Qingxian	2020	China	383	28	3.4 (1.4–8.26) for severity
26	Jerry Y	2020	USA	67	30	0.8000 (0.1784-3.5872) for ICU
27	Markos	2020	USA	103	30	6.85 (1.05-44.82) for mechanical ventilation; 2.65 (0.64-10.95) for ICU
28	Arthur	2020	France	124	30	3.45 (0.83-14.31) for mechanical ventilation
29	Simon	2020	UK	3802	30	1.41 (1.04–1.91) for infection
30	Kenneth I	2020	China	214	25	6.32 (1.16-34.54) for severity
31	Ling	2020	China	323	30	1.2514 (0.3735-4.1935) for severity
32	Leonidas	2020	USA	200	35	3.78 (1.45 -9.83) for mortality
33	Christopher	2020	USA	5279	30	1.8 (1.47 to 2.2) for hospitalisation
34	Rui	2020	China	202	28	9.219 (2.731-31.126) for severity
35	Feng	2020	China	150	25	2.91 (1.31–6.47) for severity
36	Matteo	2020	Italy	482	30	4.96 (2.53-9.74) for ICU ; 12.1 (3.25-45.1) for mortality
37	Malcolm	2020	France	83	30	6.7879 (2.5923-17.7739) for infection
38	Mohamed	2020	USA	504	30	1.3 (1.0–1.7) for mortality; 2.4 (1.5–4.0) for mechanical ventilation





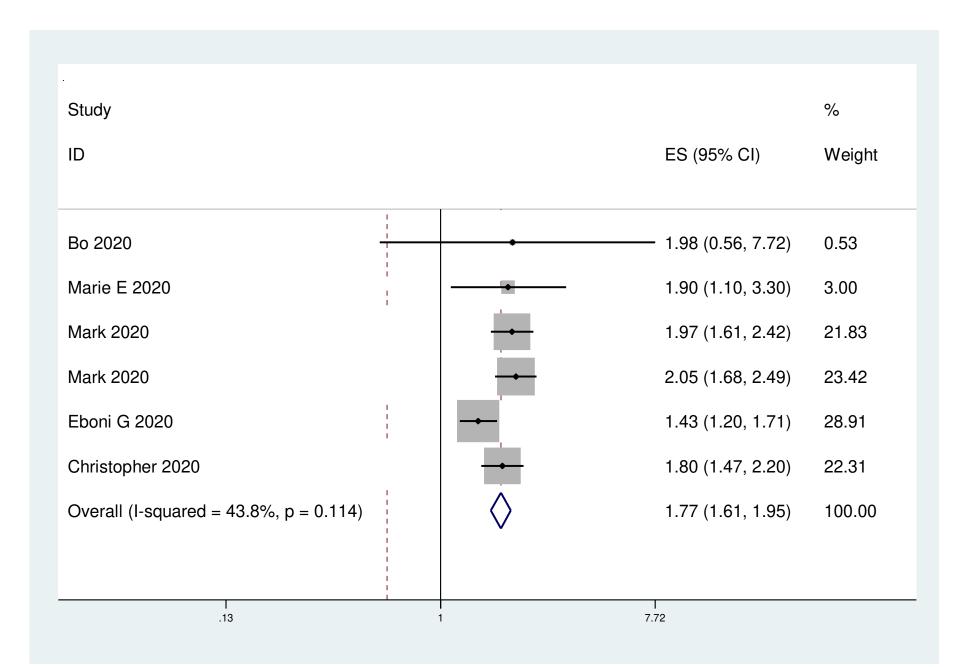


Fig. 3

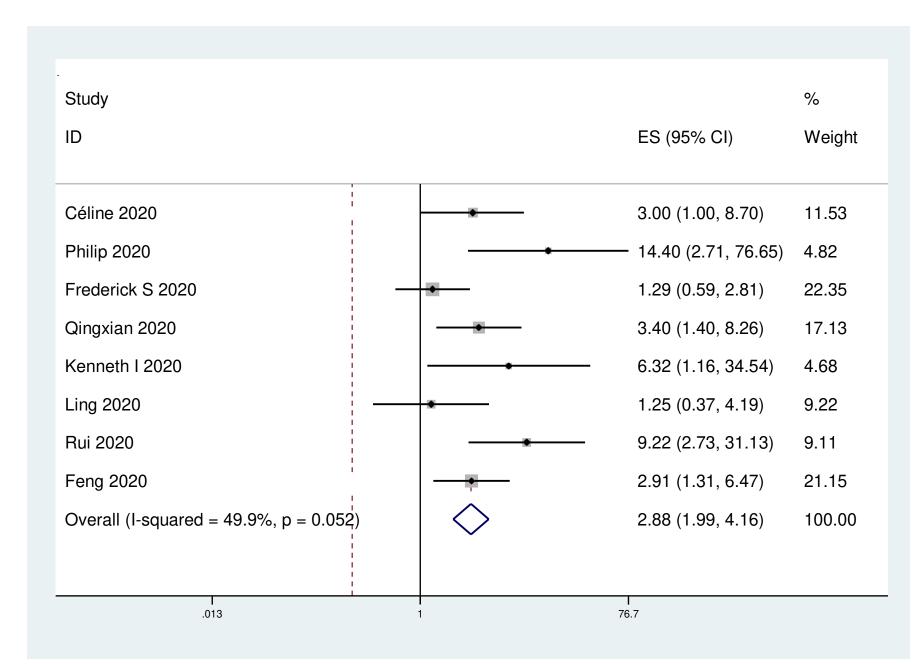
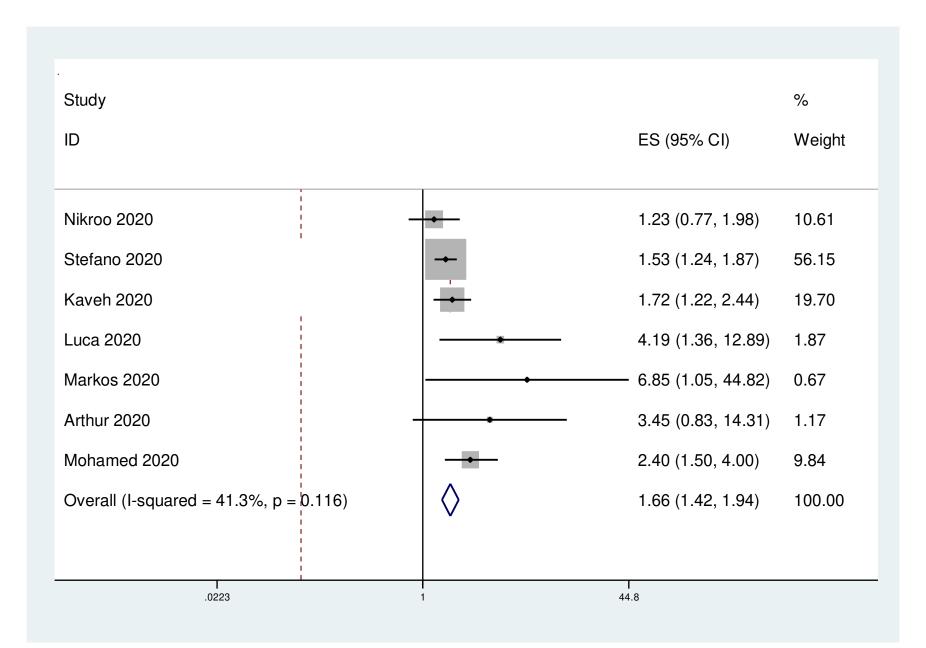
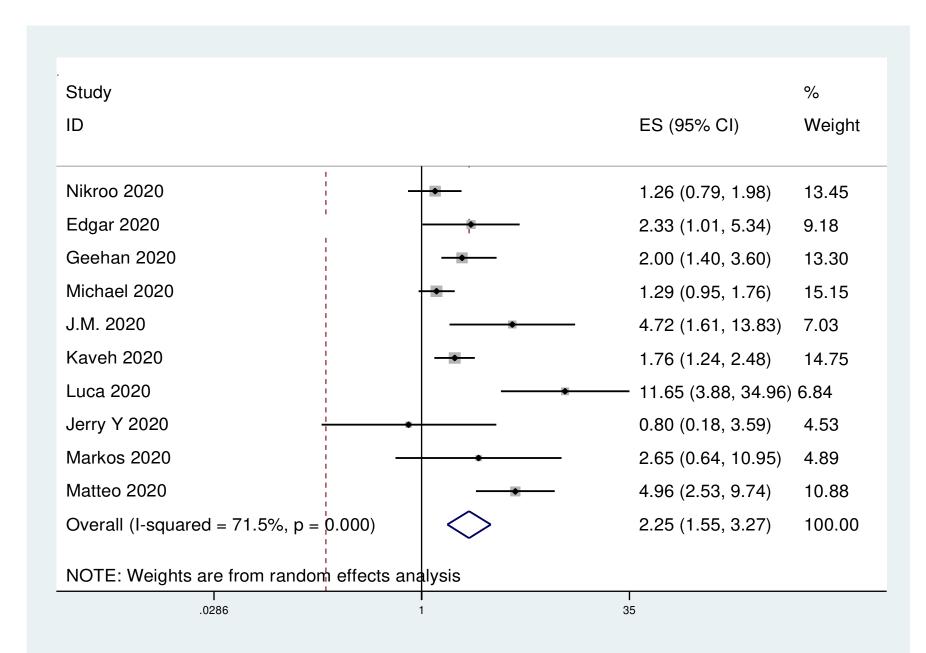
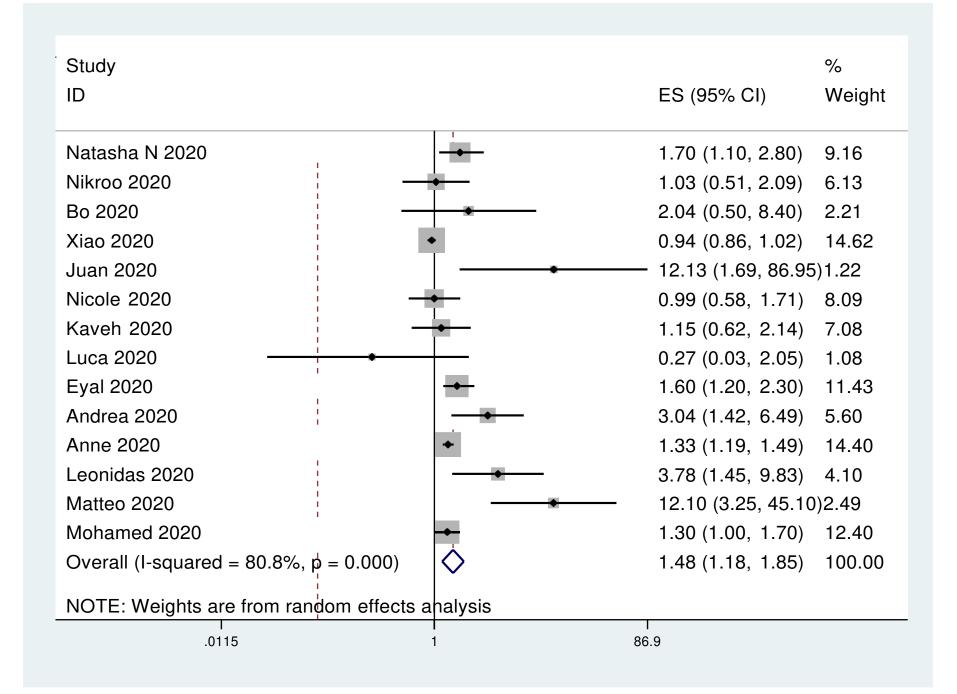
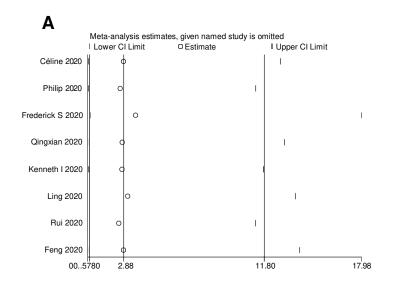


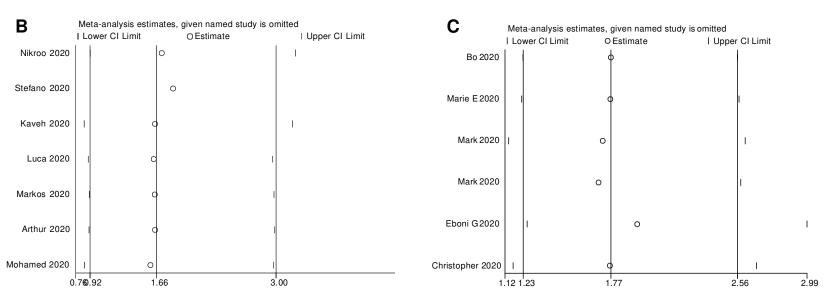
Fig. 4





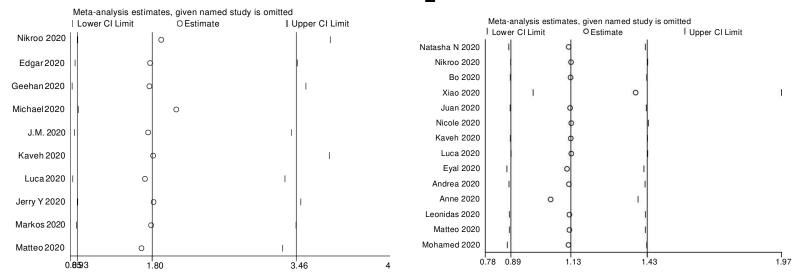




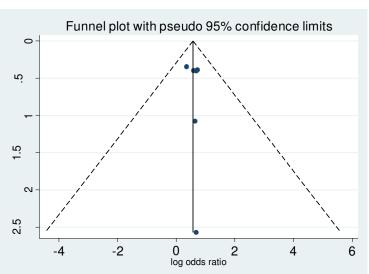


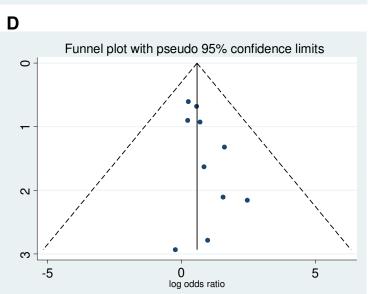
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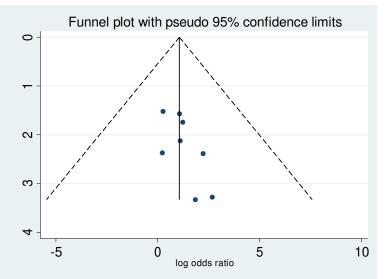


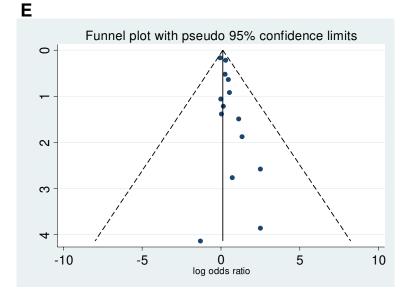
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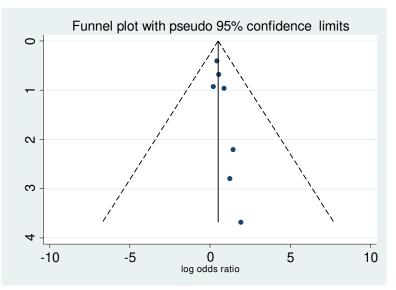








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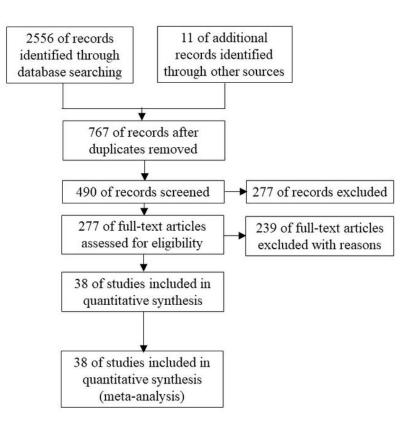
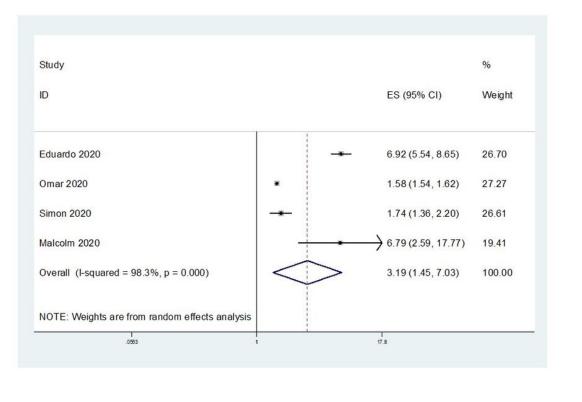


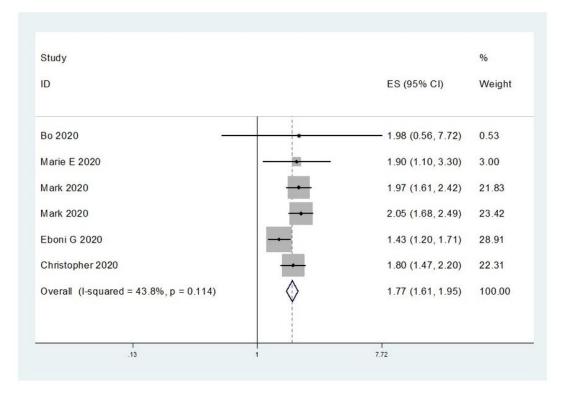
Fig. 1

Figure 1

Flow diagram.



Forest plot comparing the odds of infection with SARS-CoV-2 between obese and non-obese patients.



Forest plot comparing the odds of hospitalization for COVID-19 between obese and non-obese patients.

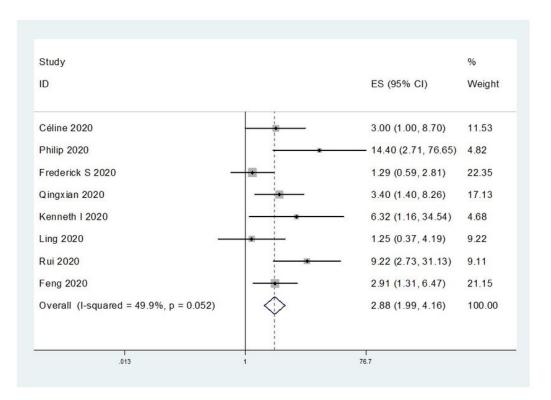


Fig. 4

Figure 4

Forest plot comparing the odds of severe COVID-19 between obese and non-obese patients.

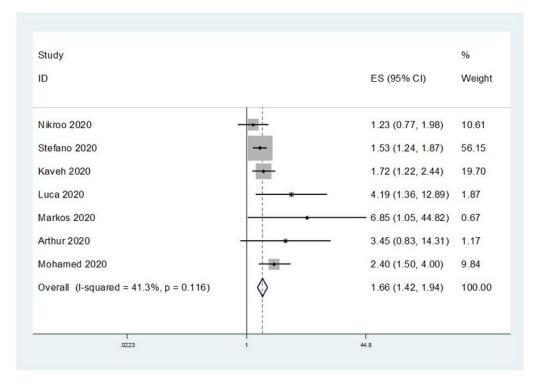
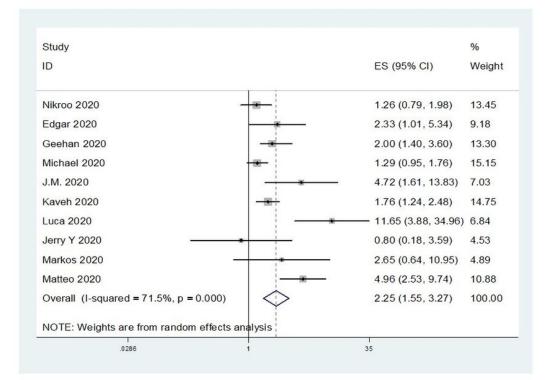


Fig. 5

Figure 5

Forest plot comparing the odds of mechanical ventilation due to COVID-19 between obese and non-obese patients.



Forest plot comparing the odds of ICU admission due to COVID-19 between obese and non-obese patients.

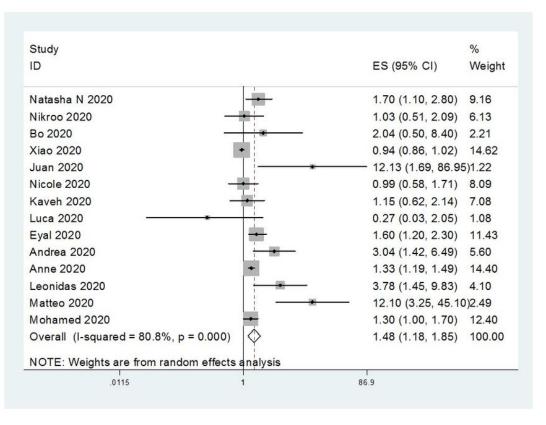


Fig. 7

Figure 7

Forest plot comparing the odds of mortality due to COVID-19 between obese and non-obese patients.

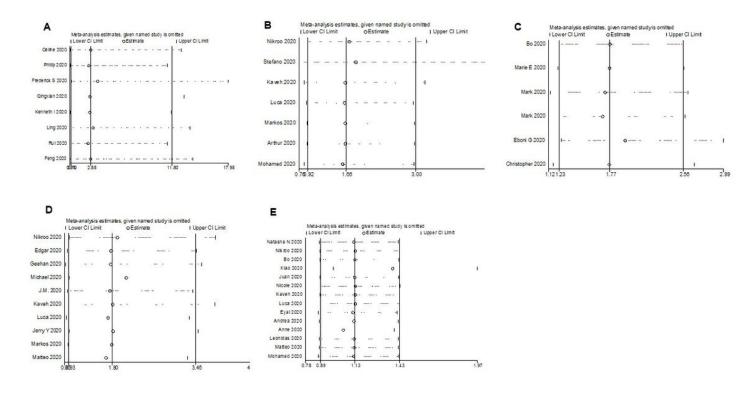
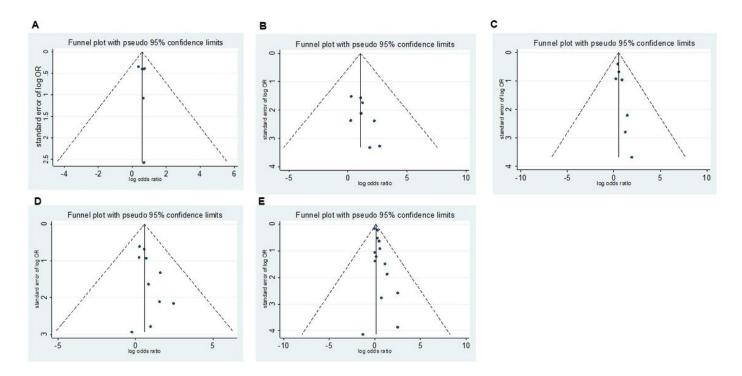


Fig. 8

Funnel plot for hospitalization (A), severe disease (B), mechanical ventilation (C), ICU admission (D), and mortality (E) between obese and non-obese patients.



Sensitivity analysis for hospitalization (A), severe disease (B), mechanical ventilation (C), ICU admission (D), and mortality (E) between obese and nonobese patients.