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

Zixin Cai¹&, Yan Yang¹&, Jingjing Zhang¹*

¹National Clinical Research Center for Metabolic Diseases, Metabolic Syndrome
Research Center, Key Laboratory of Diabetes Immunology (Central South University),
Ministry of Education, and Department of Metabolism and Endocrinology, The
Second Xiangya Hospital of Central South University, Changsha 410011, Hunan,
China.

*Zixin Cai and Yan Yang contributed equally to this work.

*Corresponding authors: J.Z., Doctorzhangjj@csu.edu.cn.

National Clinical Research Center for Metabolic Diseases, Metabolic Syndrome
Research Center, Department of Metabolism and Endocrinology, the Second Xiangya
Hospital, Central South University, Changsha, Hunan 410011, China
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% CI 1.42-1.94; $I^2 = 41.3$%), intensive care unit (ICU) (OR 2.06, 95% CI 1.49-2.85; $I^2 = 71.4$%), 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
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-κB) 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 available 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.

**Author details**

1National Clinical Research Center for Metabolic Diseases, Metabolic Syndrome Research Center, Key Laboratory of Diabetes Immunology (Central South University), Ministry of Education, and Department of Metabolism and Endocrinology, The Second Xiangya Hospital of Central South University, Changsha 410011, Hunan, China.

**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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| Author          | Year | Country | Patients | BMI               | O       | C       | u       | l       | t       |
|----------------|------|---------|----------|-------------------|---------|---------|---------|---------|---------|
| Natasha N      | 2020 | USA     | 238      | 30                | 1.7 (1.1-2.8) for mortality | 3.0 (1.0-8.7) for severity |
| Céline         | 2020 | France  | 347      | 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 | 2.3265 (1.0133-5.3415) for ICU |
| Nikroo         | 2020 | USA     | 363      | NA                | 1.98 (0.56 - 7.72) for hospitalisation; 2.04 (0.5 - 8.4) for mortality | 1.9 (1.1–3.3) for hospitalisation |
| Edgar          | 2020 | Mexico  | 140      | NA                | 2.0 (1.4-3.6) for ICU |
| Bo             | 2020 | USA     | 58       | 30                | 6.92 (5.54-8.65) for infection |
| Marie E        | 2020 | USA     | 531      | 30                | 1.2911 (0.9478-1.7587) for ICU |
| Geehan         | 2020 | USA     | 463      | 40                | 0.94 (0.86, 1.02) for mortality |
| Eduardo        | 2020 | Mexico  | 32583    | NA                | 1.97 (1.61, 2.42) for hospitalisation |
| Michael        | 2020 | USA     | 1000     | 30                | 14.4 (2.7052-76.6517) for severity |
| Xiao           | 2020 | USA     | NA       | NA                | 12.125 (1.690-86.948) for mortality |
| Mark           | 2020 | UK      | 387,109  | 30                | 1.526 (1.243-1.874) for ICU |
| Philip         | 2020 | USA     | 50       | NA                | 4.725 (1.6143-13.8302) for ICU |
| Juan           | 2020 | Bolivia | 107      | NA                | 1.5790 (1.5358-1.6235) for infection |
| Stefano        | 2020 | Italy   | 132      | 30                | 0.99 (0.58–1.71) for mortality |
| J.M.           | 2020 | Spain   | 172      | 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 |
| Omar           | 2020 | Mexico  | 177,133  | NA                | 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 |
| Nicole         | 2020 | USA     | 928      | NA                | 1.43 (1.20–1.71) for hospitalization |
| Kaveh          | 2020 | USA     | 770      | 30                | 1.2908 (0.5936-2.8071) for severity |
| Luca           | 2020 | Italy   | 92       | 30                | 1.6 (1.2 – 2.3) for the older population mortality |
| Eboni G        | 2020 | USA     | 3626     | 30                | 3.04 (1.42-6.49) for mortality |
| Frederick S    | 2020 | USA     | 105      | 30                | 1.33 (1.19 to 1.49) for mortality |
| Eyal           | 2020 | USA     | 3,406    | 40                | 1.6 (1.4–8.26) for severity |
| Andrea         | 2020 | Italy   | 233      | NA                | 3.1 (1.91 to 1.49) for mortality |
| Annemarie B1   | 2020 | UK      | 20,133   | NA                | 3.4 (1.4–8.26) for severity |
| Qingxian       | 2020 | China   | 383      | 28                | 0.8000 (0.1784-3.5872) for ICU |
| Jerry Y        | 2020 | USA     | 67       | 30                | 6.85 (1.05-44.82) for mechanical ventilation; 2.65 (0.64-10.95) for ICU |
| Markos         | 2020 | USA     | 103      | 30                | 3.45 (0.83-14.31) for mechanical ventilation |
| Arthur         | 2020 | France  | 124      | 30                | 1.41 (1.04–1.91) for infection |
| Simon          | 2020 | UK      | 3802     | 30                | 6.32 (1.16-34.54) for severity |
| Kenneth I      | 2020 | China   | 214      | 25                | 1.2514 (0.3735-4.1935) for severity |
| Ling           | 2020 | China   | 323      | 30                | 3.78 (1.45-9.83) for mortality |
| Leonidas       | 2020 | USA     | 200      | 35                | 1.8 (1.47 to 2.2) for hospitalisation |
| Christopher    | 2020 | USA     | 5279     | 30                | 9.219 (2.731-31.126) for severity |
| Rui            | 2020 | China   | 202      | 28                | 2.01 (1.31–6.47) for severity |
| Feng           | 2020 | China   | 150      | 25                | 4.96 (2.53-9.74) for ICU; 12.1 (3.25-45.1) for mortality |
| Matteo         | 2020 | Italy   | 482      | 30                | 6.7879 (2.5923-17.7739) for infection |
| Malcolm        | 2020 | France  | 83       | 30                | 1.3 (1.0–1.7) for mortality; 2.4 (1.5–4.0) for mechanical ventilation |
| Mohamed        | 2020 | USA     | 504      | 30                | 4.1935) for severity |

Table 1
2556 of records identified through database searching

11 of additional records identified through other sources

767 of records after duplicates removed

490 of records screened

277 of records excluded

277 of full-text articles assessed for eligibility

239 of full-text articles excluded with reasons

38 of studies included in quantitative synthesis

38 of studies included in quantitative synthesis (meta-analysis)
Study ID | ES (95% CI) | Weight |
--- | --- | --- |
Eduardo 2020 | 6.92 (5.54, 8.65) | 26.70 |
Omar 2020 | 1.58 (1.54, 1.62) | 27.27 |
Simon 2020 | 1.74 (1.36, 2.20) | 26.61 |
Malcolm 2020 | 6.79 (2.59, 17.77) | 19.41 |
Overall (I-squared = 98.3%, p = 0.000) | 3.19 (1.45, 7.03) | 100.00 |

NOTE: Weights are from random effects analysis
| Study ID     | ES (95% CI)       | Weight |
|-------------|-------------------|--------|
| Bo 2020     | 1.98 (0.56, 7.72) | 0.53   |
| Marie E 2020| 1.90 (1.10, 3.30) | 3.00   |
| Mark 2020   | 1.97 (1.61, 2.42) | 21.83  |
| Mark 2020   | 2.05 (1.68, 2.49) | 23.42  |
| Eboni G 2020| 1.43 (1.20, 1.71) | 28.91  |
| Christopher 2020 | 1.80 (1.47, 2.20) | 22.31  |
| Overall (I-squared = 43.8%, p = 0.114) | 1.77 (1.61, 1.95) | 100.00 |
| Study          | ID | ES (95% CI)          | Weight |
|---------------|----|----------------------|--------|
| Céline 2020   |    | 3.00 (1.00, 8.70)    | 11.53  |
| Philip 2020   |    | 14.40 (2.71, 76.65)  | 4.82   |
| Frederick S 2020 | | 1.29 (0.59, 2.81)    | 22.35  |
| Qingxian 2020 |    | 3.40 (1.40, 8.26)    | 17.13  |
| Kenneth I 2020|    | 6.32 (1.16, 34.54)   | 4.68   |
| Ling 2020     |    | 1.25 (0.37, 4.19)    | 9.22   |
| Rui 2020      |    | 9.22 (2.73, 31.13)   | 9.11   |
| Feng 2020     |    | 2.91 (1.31, 6.47)    | 21.15  |
| Overall       |    | 2.88 (1.99, 4.16)    | 100.00 |

Fig. 4
| Study          | ID     | ES (95% CI)       | Weight |
|---------------|--------|-------------------|--------|
| Nikroo 2020   |        | 1.23 (0.77, 1.98) | 10.61  |
| Stefano 2020  |        | 1.53 (1.24, 1.87) | 56.15  |
| Kaveh 2020    |        | 1.72 (1.22, 2.44) | 19.70  |
| Luca 2020     |        | 4.19 (1.36, 12.89)| 1.87   |
| Markos 2020   |        | 6.85 (1.05, 44.82)| 0.67   |
| Arthur 2020   |        | 3.45 (0.83, 14.31)| 1.17   |
| Mohamed 2020  |        | 2.40 (1.50, 4.00) | 9.84   |
| Overall (I-squared = 41.3%, p = 0.116) |        | 1.66 (1.42, 1.94) | 100.00 |

Fig. 5
### Study Weights

| Study ID       | ES (95% CI)            | Weight | %     |
|----------------|------------------------|--------|-------|
| Nikroo 2020    | 1.26 (0.79, 1.98)      | 13.45  |       |
| Edgar 2020     | 2.33 (1.01, 5.34)      | 9.18   |       |
| Geehan 2020    | 2.00 (1.40, 3.60)      | 13.30  |       |
| Michael 2020   | 1.29 (0.95, 1.76)      | 15.15  |       |
| J.M. 2020      | 4.72 (1.61, 13.83)     | 7.03   |       |
| Kaveh 2020     | 1.76 (1.24, 2.48)      | 14.75  |       |
| Luca 2020      | 11.65 (3.88, 34.96)    | 6.84   |       |
| Jerry Y 2020   | 0.80 (0.18, 3.59)      | 4.53   |       |
| Markos 2020    | 2.65 (0.64, 10.95)     | 4.89   |       |
| Matteo 2020    | 4.96 (2.53, 9.74)      | 10.88  |       |
| Overall (I-squared = 71.5%, p = 0.000) | 2.25 (1.55, 3.27) | 100.00 |

**NOTE:** Weights are from random effects analysis
Study ID | ES (95% CI) | Weight
--- | --- | ---
Natasha N 2020 | 1.70 (1.10, 2.80) | 9.16
Nikroo 2020 | 1.03 (0.51, 2.09) | 6.13
Bo 2020 | 2.04 (0.50, 8.40) | 2.21
Xiao 2020 | 0.94 (0.86, 1.02) | 14.62
Juan 2020 | 12.13 (1.69, 86.95) | 1.22
Nicole 2020 | 0.99 (0.58, 1.71) | 8.09
Kaveh 2020 | 1.15 (0.62, 2.14) | 7.08
Luca 2020 | 0.27 (0.03, 2.05) | 1.08
Eyal 2020 | 1.60 (1.20, 2.30) | 11.43
Andrea 2020 | 3.04 (1.42, 6.49) | 5.60
Anne 2020 | 1.33 (1.19, 1.49) | 14.40
Leonidas 2020 | 3.78 (1.45, 9.83) | 4.10
Matteo 2020 | 12.10 (3.25, 45.10) | 2.49
Mohamed 2020 | 1.30 (1.00, 1.70) | 12.40
Overall (I-squared = 80.8%, p = 0.000) | 1.48 (1.18, 1.85) | 100.00

NOTE: Weights are from random effects analysis
Funnel plot with pseudo 95% confidence limits

A

B

C

D

E

Fig. 9