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Meta-analysis

Risk of bias and certainty of evidence on the association between obesity and mortality in patients with SARS-COV-2: An umbrella review of meta-analyses

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Introduction

The COVID-19 pandemic has impacted global morbidity and mortality without precedent in the past decades [1]. The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has cardiovascular disease as a risk factor for unfavorable outcomes [2–4]. Similarly, in other epidemics, such as H1N1 [5], elevated body mass index (BMI) is also associated with severe complications in patients with SARS-CoV-2, such as hospitalization, need for invasive mechanical ventilation, illness severity, and poor prognosis [6–8]. It is also associated with an increased risk of COVID-19 [9].

Obesity is a global epidemic with at least 2.8 million people dying each year due to being overweight or obese [10,11]. Furthermore, many chronic diseases coexist with obesity [10,12], which results in several metabolic and immune dysfunctions, such as hypoxemia, insulin resistance, chronic inflammatory diseases, and thrombosis risk [12,13]. Susceptibility to acute respiratory
distress syndrome (ARDS), the primary cause of COVID-19 mortality, is significantly greater among individuals with obesity [9,14].

Given the apparent association between SARS-CoV-2 and obesity, clustering within social groups according to patterns of inequality in the context of social and economic disparity suggests that COVID-19 is a syndemic [15]. Policymakers and health managers need reliable information to help them make accurate decisions and take timely and effective actions [16]. Pooling studies in systematic reviews (SRs) and meta-analysis (MA) are well-established medicine and health research approaches. However, poorly conducted SR-MAs can lead to inaccurate illustrations of evidence and misleading conclusions, leading to limited applicability [17]. There are concerns that in the panic to provide answers to help administer the COVID-19 pandemic, SR-MAs are being conducted without many of the keystones of robust methods [18].

A meta-analysis showed that most COVID-19 evidence syntheses described as systematic or rapid reviews were of low quality according to AMSTAR-2 [19]. The association between obesity and clinical outcomes in patients with SARS-CoV-2 has grown exponentially since the beginning of the pandemic. Thus, the current umbrella review aimed to evaluate the quality and certainty of the evidence of SR-MAs in exploring the association between obesity and mortality in patients with SARS-CoV-2 and identify the magnitude of this effect described in the available literature.

### Methods

We performed an umbrella review on the quality and certainty of evidence of SR-MAs that analyzed the association between obesity and mortality in patients with SARS-CoV-2, following the Cochrane Handbook [20]. We conducted the study according to a pre-specified protocol, its umbrella review was registered in Prospero (CRD42021253142), and it is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [21].

#### Search strategy

The current umbrella review has two main questions: 1. What is the quality and certainty of evidence on the association between obesity and mortality in patients with SARS-CoV-2? 2. What is the magnitude of the association between obesity and mortality in patients with SARS-CoV-2 demonstrated by SR-MAs?

We conducted the search question according to the acronym PECO demonstrated in Table 1.

We performed an electronic search of the following databases: PubMed, Embase, Cochrane Collaboration, and Health Virtual Library. In addition, we also considered Epistemonikos, LOVE, MedRxiv, LitCovid, and Prospero in the literature search. The searches were carried out on April 11, 2021, and updated on April 22, 2022. Mesh terms and entry terms related to obesity, SARS-CoV-2, and the study design were applied to construct the search strategy and were adjusted according to the specific database. Box 1 presents a combination of terms adopted for the search strategy performed in PubMed. The search strategies applied to the other databases are available in the Supplementary Material (Table S1).

#### Eligibility criteria

Any peer-reviewed article published since December 2019 and referred to as an SR-MA addressing a research question relating to obesity and mortality in patients with SARS-CoV-2 was eligible for inclusion. We considered reviews to be systematic if they searched at least one database, reported their selection criteria, and provided a synthesis of the included studies. Regarding eligibility, the association between obesity and mortality has been reported.

We excluded editorials, commentaries, systematic reviews without meta-analysis, protocols of systematic reviews, and preprint articles without peer reviewers until the last review, as well as SR-MAs that only reported mortality as part of a composite outcome or the difference in BMI between survivors and non-survivors.
Data management

We imported the search results into EndNote® X8 literature management software and manually excluded duplicates in the first and second stages. Two reviewers (FMS and MF) independently screened the titles and abstracts of the literature, and the third reviewer (FMS) resolved any disagreements. Two reviewers independently read the full text of selected articles to confirm their eligibility and extracted the data of each eligible meta-analysis using a standard form constructed in Google Forms® (KS and AS, PPT and GG, TC, and JL). The third review (FMS) resolved any disagreements.

Data extraction

Data extraction included information about the publication (author, year, country), systematic review methods (search strategy, inclusion and exclusion criteria, obesity diagnosis, evaluation of risk of bias in primary study, and quality of evidence), meta-analysis (statistical test applied, assessment of heterogeneity, subgroup analysis, publication bias), and results (number of studies, design of included studies, number of participants, general features of participants, frequency of obesity, BMI, frequency of death, meta-analysis results – odds ratios (OR), relative risks (RR), or hazard ratio (HR), and the respective confidence interval (CI 95%), I² for heterogeneity, potential risk of bias in primary studies, classification of the evidence quality, and the certainty of evidence)]. Two reviewers independently extracted data from each SR-MA using a standard form constructed in Google Forms. We also determined whether the authors followed some guidelines to report SR-MAs.

We investigated the potential for language or time bias; it was considered present if authors restricted the language of study selection and when the interval between the date of literature search and the SR-MA publication was higher than three months. We checked the impact factor of the journals that published SR-MAs on their respective websites.

We examined the overlap between SR-MAs using the corrected area (CCA) index. We calculated the CCA as proposed by Hennessy et al. First, we created a citation matrix of all primary studies (rows) included in each SR-MA (columns), and primary studies in a particular review were signalized with a checkmark. Next, we calculated the CCA using the following equation:

\[
\text{CCA} = \frac{N - r(r \times c) - r}{r}, \quad \text{where} \quad N = \text{the total number of publications (sum of total checkmarks in the citation matrix),} \quad r = \text{the number of index publications (rows), and} \quad c = \text{the number of SR-MAs (columns).}
\]

It was classified as slight overlap if CCA ranged from 0% to 5%, moderate if it varied from 6% to 10%, high if it ranged from 11% to 15%, and very high if it was higher than 15% [22].

SR-MAs’ risk of bias assessment

Two reviewers independently assessed the potential risk of bias in included SR-MA using the AMSTAR-2 tool (A Measurement Tool to Assess Systematic Reviews, version 2.0) and rated their quality as high, moderate, low, or very low. The quality of evidence was considered ‘low’ due to the observational design of the included studies by default and thereafter upgraded to ‘moderate’ or ‘high’ or down-graded to ‘very low’ depending on the following criteria: within-study risk of bias, directness of evidence, heterogeneity, precision of effect estimates and risk of publication bias, dose—response gradient, magnitude effect, and residual confounders [24].

We classified the certainty of the evidence by considering the information available in each SR-MA. Therefore, we did not assess the primary studies included in each systematic review to check the data and/or assess the potential risk of bias. We opted to downgrade the certainty of evidence to one if: 1. The authors did not mention the risk of publication bias assessment; 2. There are no details about the confounders considered in the analysis of the primary studies; 3. The authors did not assess or describe the results of the risk of bias in the primary studies; 4. The authors did not present I² statistics.

Data synthesis

We tabulated and summarized the characteristics of SR-MAs eligible for the current umbrella review. We described the OR, RR, or HR depending on the data reported by the authors. Whenever possible, the results were reported with 95% confidence intervals (95% CI). After full-text reading, we listed the excluded papers with reasons for exclusion stated.

We calculated the descriptive statistics (mean, minimum and maximum, absolute and relative frequency) when data were available to report general data of primary studies included in each SR-MA (as number of patients, body mass index, % of obesity) and to summarize the results of eligible SR-MAs (as number of studies included, number of patients).

Results

Studies selection

We identified a total of 1189 records in the electronic database searches, and after the removal of duplicates (n = 466), 723 remained for title and abstract screening. After completing this phase, we retrieved 85 records for closer examination of the full text. Of these, we included 24 SR-MAs [1,4,9,12,25–43], as illustrated in Fig. 1. Supplementary Material (Table S2) includes a list of SR-MAs excluded during full-text reading.

SR-MAs features

Table 2 details the methodological features of SR-MAs included in the current umbrella review. Nine (37.5%) SR-MAs [4,12,25,32,34,35,37,41,43] were conducted in China, two in the USA [3,30], two in the United Kingdom [1,29], and two in Singapore [28,33], while the others were conducted in different countries, as illustrated in Fig. 2. Peer-reviews journals, with impact factors ranging from 1.414 [34] and 8.483 [9], published the SR-MAs — journals with impact factors lower than 5.0 published most of them.

Seven SR-MAs (29.2%) [1,26,29,33,37,38,44] reported a protocol registered in PROSPERO, and 10 SR-MAs presented in the article or protocol at a simplified search strategy adopted to identify the primary studies [26,29–31,34,40,41,43,44]. The majority of SR-MA (n = 21; 87.5%) [1,12,25–28,31–37,39–44,49] performed a literature search in at least three databases, ranging from 2 [30,38] to 7 [42]. Eight SR-MAs (33.3%) performed a grey literature search [9,12,29,33,37,38,42]. Fourteen (58.3%) [1,4,25,28,29,31,32,35,36,38–41,44] SR-MAs restricted the search to the English language.
while one SR-MA [9] included only studies published in English or Chinese. Fourteen SR-MAs presented potential for time bias (58.3%) since the date of the literature search was longer than three months of article publication. Regarding the reviewers involved in SR-MA steps, in 14 (58.3%) [1,4,12,25,28,29,31,33e36,38,40,42] of them two reviewers performed at least the study selection or data extraction, while in eight (33.3%) [26,27,30,37,39,41,43,44] these steps were conducted by three reviewers. This information is not available for the other two SR-MAs [9,32].

Eleven (45.8%) SR-MAs [4,25,27,29,30,32,35,37,38,40,44] defined obesity according to BMI > 30 kg/m², while nine (37.5%) [9,12,26,31,33,36,39,42,43] did not describe the criteria adopted for obesity definition; one SR-MA [1] considered BMI > 25 kg/m², one [41] adopted a BMI > 24 kg/m², and the others used two different cut-off points (BMI > 30 kg/m² or BMI > 28 kg/m² for Asian) [28,34].

Regarding outcome mortality, 13 (54.2%) SR-MAs [12,26e29,31,33e37,40,42] assessed in-hospital mortality, while this information has not been clearly reported in the other 11 SR-MAs. All SR-MAs assessed outcomes other than mortality, for which data were not collected since it was not the scope of the current umbrella review.

The SR-MAs included mainly prospective and retrospective longitudinal studies and were not clearly described in the two SR-MAs [31,42]. The number of studies included in the SRs ranged from 9 [1] to 217 [43], and it was equal to or higher than 20 in most of them (n = 17; 70.8%) [4,12,25e31,33,34,36,39,40e44]. The mean number of patients included in the primary studies ranged from 325 [37] to 365,208 [25], whereas the total number of patients included in the SRs ranged from 9787 [37] to 18,260,378 [25]. The mean age of patients included in the primary studies of SR-MAs was higher than 55 years in all that described this information (n = 19; 90%); it was not reported in five SR-MAs [29,37,41,43,44]. Most SR-MAs did not report the mean BMI of patients in the primary studies (n = 20; 83.3%), and among the four studies [9,27,33,34] that described this information, it was > 25 kg/m². The risk of bias in the primary studies was assessed in the majority of SR-MAs (n = 20; 83.3%) [1,12,25,26,28e30,32e40,44] and the New-Castle Ottawa Scale was applied for this purpose in 14 of them [1,12,25,28,30,32e37,40,42] (Table 3).

**SR-MAs results**

The mean number of studies included in the MA was 12, ranging from 2 [31] to 54 [44]. Four studies [26,27,35,39] included at least one study with more than one report, so the mean number of reports was equal to 10. The number of patients included in the MA ranged from 732 [1] to 17,636,257 [25].

The association was not statistically significant in eight (33.3%) MAs [26,30e32,34,37,38,43], while in the others, the association ranged from 1.14 to 3.52, which was higher than the 2.0 in the three SR-MAs [1,35,36]. Three SR-MAs [9,30,31] did not report I², whereas, in the remaining 21 (85.0%), it was higher than 45%. Fig. 3 and Table 3 present the results of each SR-MA.

Ten SR-MAs (41.7%) [1,9,25,27,31e33,37,38,40] did not report publication bias. Two SR-MA reported publication bias in the funnel plot graphic [36,41], while it was absent according to visual inspection or statistical test in all the others (Table 3). Only one SR-MA described in detail for each confounder. The analysis in primary studies was adjusted [9], 13 described in the meta-analysis the adjusted data of primary studies, while in 11 SR-MAs [26,30e34,36e39,41,42] this information was not clearly described.

**SR-MAs overlapping according to CCA**

We identified 128 primary studies among the 24 SR-MAs included in this umbrella review. A list of references is available in the supplementary material. Two of these were included in the forest plot figure, but the authors did not cite them in the reference
Table 2
Association between obesity and mortality in patients with SARS-CoV-2: Methodological features of SR-MAs.

| First Author, year (REF) | Local | Protocol | Search strategy (terms of PECOS) | Search databases | Search restrictions | Number of reviewers | Exposition and outcome definition | Primary studies design |
|--------------------------|-------|----------|----------------------------------|------------------|---------------------|--------------------|---------------------------------|-----------------------|
| Seidu S, 2020 [1]        | United Kingdom | CRD42020179783 | Strategy NR (E and P) | Medline, Embase, Web of Science, Cochrane Library | Language (English) | 2 | BMI ≥ 25 kg/m², outcome NR | Prospective retrospective cohort |
| Yang J, 2021 [4]         | China | NR | Strategy NR (E and P) | Medline, Embase, Cochrane Library | Language (English) | 2 | BMI ≥ 30 kg/m², outcome NR | Prospective retrospective cohort |
| Popkin BM, 2020 [9]      | USA | NR | Strategy NR (E and P) | PubMed, CNKI, ICNAC, Google Scholar, MedRxiv, BioRxiv | Language (Chinese and English) | NR | Exposition and outcome NR | All observational studies |
| Huang Y, 2020 [12]       | China | NR | Strategy NR (E and P) | PubMed, Embase, Web of Science, CNKI, Wanfang, MedRxiv | None | 2 | High BMI and WC/in-hospital death | Prospective retrospective cohort |
| Yang J, 2020 [25]        | China | NR | Strategy NR (E and O) | PubMed, Embase, Cochrane Library | Language (English) | 2 | Obesity as BMI ≥ 30 kg/m² | Prospective retrospective cohort |
| Mesas AE, 2020 [26]      | Spain | CRD42020176595 | Simplified strategy presented (O and P) | PubMed, Scopus, Web of Science | Language (English) | 3 | Outcome NR | Prospective retrospective cohort |
| Aghili SMM, 2021 [27]    | Iran | NR | Strategy NR (E and P) | Web of Science, PubMed, Scopus, Google Scholar | None | 3 | In-hospital death | Observational studies |
| Hoong CWS, 2021 [28]     | Singapore | NR | Strategy NR (E, O, and P) | Medline, Embase, Web of Science, Cochrane Library | Language (English) | 2 | BMI ≥ 30 kg/m², (≥28 kg/m² for Asian) | Prospective retrospective cohort |
| Li Y, 2021 [29]          | United Kingdom | CRD42020190031 | Full strategy described (O and P) | PubMed, WHO COVID-19, MedRxiv | Time (5 months) | 2 | In-hospital death | All observational studies |
| Zhang X, 2021 [30]       | USA | NR | Simplified strategy described (E and P) | PubMed, and Google Scholar | Time (9 months) | 3 | BMI ≥ 28 kg/m², in-hospital death | Prospective retrospective cohort |
| Ng WH, 2021 [31]         | Australia | NR | Simplified strategy described (E, O, and P) | Medline, Scopus, Web of Science, Embase | Time (10 months) | 3 | BMI ≥ 30 kg/m², outcome NR | Prospective retrospective cohort |
| Deng L, 2021 [32]        | China | NR | Strategy NR (E and P) | PubMed, Cochrane Library, Web of Science | Language (English) | 2 | Exposition NR/in-hospital death | NR |
| Ho JSY, 2020 [33]        | Singapore | CRD42020184953 | Strategy NR (E and P) | Medline, Embase, Scopus, Web of Science, CENTRAL, OpenGrey, MedRxiv, BioRxiv | Time (5 months) | 2 | BMI ≥ 30 kg/m², in-hospital death | Prospective retrospective cohort |
| Chu Y, 2020 [34]         | China | NR | Simplified strategy described (E) | PubMed, Embase, Web of Science, MedRxiv, BioRxiv | Time (5 months) | 2 | BMI ≥ 30 kg/m², and BMI ≥ 28 kg/m² for Asian/in-hospital death | Prospective retrospective cohort |
| Du Y, 2020 [35]          | China | NR | Strategy NR (E, P, and S) | Medline, Embase, Web of Science, and Cochrane Library | Language (English) | 2 | IMC ≥ 30 kg/m²/in-hospital death | Prospective retrospective cohort, and cross-sectional studies |
| Noor FM, 2020 [36]       | Bangladesh | NR | Simplified strategy described (E, O, and P) | PubMed, Science Direct, Google Scholar | Time (5 months) | 3 | Exposition NR/in-hospital death | Retrospective cohort |
| Zhao X, 2020 [37]        | China | CRD42020201461 | Strategy NR (E, P, and O) | Medline, Embase, and Web of Science, Clinical Trials | Language (English) | 2 | BMI ≥ 30 kg/m²/in-hospital death | Prospective retrospective cohort, and cross-sectional studies |
| Helvacı N, 2021 [38]     | Turkey | CRD42020199145 | Strategy NR (E and P) | Medline/PubMed, Google Scholar, Pre-prints, conference | Language (English) | 2 | BMI ≥ 30 kg/m², outcome NR | Prospective retrospective cohort studies |
| Poly TN, 2021 [39]       | Taiwan | NR | Strategy NR (E, P, and S) | PubMed, Europe PMC, ProQuest, Cochrane Library | Time (7 months) | 3 | Exposure and outcome NR | Prospective retrospective cohort |
| Pranata R, 2021 [40]     | Indonesia | NR | Simplified strategy described (E and P) | PubMed, Embase, Web of Science | Language (English) | 2 | BMI ≥ 30 kg/m²/in-hospital death | Prospective retrospective cohort Observational studies |
| Cai Z, 2021 [41]         | China | NR | Strategy NR (E and P) | PubMed, Embase, Web of Science, Cochrane Library | Language (English) | 3 | | (continued on next page) |
| First Author, year (REF) | Local Protocol Search strategy (terms) | Exposition and outcome definition | Language (English) | Time (1 year) | Time (6 months) | BMI > 24 kg/m² | BMI > 30 kg/m² | All observational studies |
|--------------------------|----------------------------------------|----------------------------------|-------------------|-------------|--------------|---------------|---------------|--------------------------|
| Dessie Z, 2021 [42]      | South Africa NR Strategy NR (P and O) | Google Scholar, Cochrane Library, Web of Science and Cumulative Index to Nursing and Allied Health (CINAHL) Complete | Full strategy described | Time (6 months) | Time (1 year) | NR | NR | NR |
| Geng J, 2021 [43]        | China NR Full strategy described       | PubMed, Embase, Web of Science and Cumulative Index to Nursing and Allied Health (CINAHL) Complete | Full strategy described | Time (9 months) | Time (11 months) | NR | NR | NR |
| Saleh Y, 2021 [44]       | France CRD4200218115 Full strategy described | PubMed, Embase, Web of Science and Cumulative Index to Nursing and Allied Health (CINAHL) Complete | Full strategy described | Time (11 months) | Time (11 months) | NR | NR | NR |

Abbreviations: BMI = body mass index; E = exposition; ICU = Intensive Care Unit; MA = meta-analysis; NR = NR; O = outcome; P = population; S = study design; SR = systematic review; WC = waist circumference; WHO = World Health Organization.

* Time restriction was considered if the interval between the date of literature search and SR-MA publication was higher than 3 months.

The majority of SR-MAs presented critically low quality (n = 16; 66.7%) [1,12,25,27,30–34,37,38,41–44], seven presented low quality [4,9,28,29,35,36,40], and one SR-MA was classified as moderate quality [26]. More than 95% of the SR-MAs did not present a list of excluded studies with justification. None of the SR-MA described funding sources for the primary studies. More than 80% of the included SR-MA did not share sufficient information about a protocol, did not investigate the impact of the risk of bias in primary studies on the meta-analysis results, and interpreted or discussed it appropriately. More than half did not describe the reason for study design selection, did not present detailed information about the studies, did not report any potential sources of conflict of interest, and did not appropriately explore or discuss the heterogeneity, as demonstrated in Fig. 4 and Supplementary Table S3. A detailed justification for the quality grading of each SR-MA according to AMSTAR-2 is provided in the Supplementary Material (Table S4).

In 15 (62.5%) SR-MAs [1,4,5,28–32,35,38,39,41–44] the authors reported that PRISMA was followed, while in 11 (45.83%) [1,4,26,28,30,34,35,39,40,41-44] MOOSE was cited as the guidance adopted in conducting the SR-MAs, while no guidance was cited in six SR-MAs. Among the 18 SR-MA that were reported following PRISMA and/or MOOSE, 12 [1,4,30–32,34,38,39,41–44] presented critically low quality according to AMSTAR-2.

### SR-MAs’ certainty of evidence according to GRADE

Considering the available information reported in SR-MAs, the certainty of evidence on the association between obesity and mortality according to GRADE for most of them (21/24) was classified as “very low,” as presented in Table 4.

All SR-MAs presented inconsistencies owing to the high statistical heterogeneity evidenced by I² (n = 21; 87.5%) or not reported I² (n = 3; 15.0%). For more than half of the SR-MAs, the risk of bias in the primary study was considered present due to the score obtained in the instrument applied for quality assessment of primary studies or due to the lack of this evaluation. Imprecision was identified in nine (37.5%) SR-MAs, while indirectness was noted for none of them since all included studies were conducted with the population of interest and the evidence is direct.

Considering the domains that should upgrade the certainty of the evidence, the majority of SR-MAs did not demonstrate a large effect (n = 21; 87.5%) and did not perform a dose–response analysis (n = 19; 79.2%), while only one described in detail the confounders adjusted in the multivariate analysis of the primary studies included [44]. Thus, the certainty of evidence could be upgraded to moderate in one SR-MA [44].

Only two of the 24 SR-MAs applied GRADE to assess the certainty of the evidence and classified it as Low [39] and High [44]. In the first [39], the authors justified the classification attributed to the increased mortality rate among obese patients (RR was equal to 1.43). We also classified it as low, but with a different rationale: first, we downgraded the evidence because we considered that the inconsistency is present in the MA (I² = 67.94%), and it could not be explained while the authors considered it not serious, after which we upgraded it due to the dose–response demonstrated: Risk for death was higher in patients with obesity grade III (RR = 1.93; CI95% 1.50–2.48) in comparison to patients with obesity grade II.
Fig. 2. World distribution of published SR-MAs regarding association between obesity and mortality in patients with SARS-CoV-2.

(RR = 1.57; CI95% 1.12–2.20) or I (RR = 1.28; CI95% 1.05–1.55). In the other [46], we classified it as moderate while the authors considered the certainty of evidence high; they did not consider the presence of inconsistency, although the I$^2$ was equal to 91% and could not be explained in the subgroup analysis, and they considered a large effect, however, RR > 2.0, was observed only in patients with BMI >45 kg/m$^2$. Therefore, we classified the certainty of the evidence as moderate.

**Discussion**

The current umbrella review aimed to evaluate the quality and certainty of the evidence on the association between obesity and mortality in patients with SARS-CoV-2 and to recognize its magnitude range. Obesity increased the risk of death (ranging from 1.09 to 3.52) in most of the 24 SR-MAs. However, according to the AMSTAR-2 tool, most SR-MAs had critically low quality, and according to GRADE, the certainty of the evidence was very low. In addition, the CCA index indicated a slight overlap between SR-MAs.

There is no doubt that we need SR-MAs, especially during a pandemic, as several studies have explored the same question, so it is relevant to conduct a trustworthy synthesis of the best evidence available. However, the COVID-19 pandemic can threaten the integrity of SR-MAs. This is because many of the keystones of robust methods are being forgotten in rushed systematic reviews in the need to get answers to assist and manage the pandemic [19]. As stated in Hong Kong Principles [45]: “For knowledge to benefit research and society, it must be trustworthy. Trustworthy research is robust, rigorous, and transparent at all the stages of design, execution, and reporting.” This overview has shown a lack of quality in SR-MAs regarding the association between obesity and mortality because their low quality reflects the lack of a robust and rigorous method for their conduction.

AMSTAR-2 can be applied to assess the quality of SR-MAs using 16 items with simple response categories and an overall rating based on weaknesses in critical domains [23]. According to this instrument, the majority of SR-MAs reviewed had critically low quality or low quality, especially due to insufficient information about the protocol, lack of investigation and discussion about the impact of risk of bias in primary studies, and scarce examination or discussion of the heterogeneity (which was high in most MAs). SR-MAs have strict methods and should be agreed upon before the review starts, as adherence to a well-designed protocol reduces the risk of bias in the review. Biases can be introduced at several stages in the design, planning, conduct, and analysis of a primary study, and it is relevant that an SR-MA should explore the possible impact of the risk of bias in the pooled results. In addition, it is relevant that reviewers investigate possible causes of heterogeneity, including variations in the elements in the PECO framework and those resulting from design and methodological aspects, such as disparities in observational design and analysis. Furthermore, it is important to discuss the heterogeneity, including variations in the elements in the PECO framework and those resulting from design and methodological aspects, such as disparities in observational design and analysis. Furthermore, the importance of adequate literature search in systematic reviews is well established [46] - however, 14 SR-MAs included in the current review did not report the search strategy. A detailed description of primary studies is needed to determine the extent to which their results should be combined, help explain heterogeneity, and support those applying the results. It could not be observed in more than half of SR-MAS due to insufficient description of the population, the definition of obesity, and the analysis performed (adjusted or not and which confounders were included in the multivariate model when it was constructed).

A previously published meta-review also found low-quality reviews of COVID-19. The authors evaluated 280 publications (82.8%, n = 232 systematic reviews) mainly addressing research questions about disease features/symptoms (30.7%) and treatment (20.7%) of SARS-CoV-2. Only 33.0% presented a registered protocol, 19.3% searched a specific COVID-19 database, 64.6% had a reproducible search strategy, and 49.3% reported critical appraisal of the included studies. Using AMSTAR-2, less than 5% of SRs were categorized as ‘high’ or ‘moderate’ quality. The remaining patients were categorized as ‘low’ (17.0%) or ‘critically low’ (79.5%). Despite being of low quality and lacking robust and systematic methods, the reviews have received considerable attention across both academic and public platforms [19].

To ensure that a systematic review is trustworthy, the authors should prepare a transparent, complete, and accurate explanation of the review’s rationale, performance, and features. The MOOSE [46] and PRISMA [21] checklists contain specifications for reporting SR-MAs, including background, search strategy, methods, results, discussion, and conclusion. The use of these checklists should improve the clinical implementation of SR-MAs for authors, reviewers, editors, readers, and decision-makers. Among the 18 SR-MAs reported following PRISMA or MOOSE, more than 60% had critically low quality according to AMSTAR-2, suggesting that they
## Table 3
Results of SR-MA regarding the association of obesity and mortality in patients with SARS-CoV-2.

| First Author, year (Ref) | Records identified/ Eligible studies (Country) | Risk of bias in primary studies | Participants Type | Total number (mean by study) | Mean age | Mean BMI, % of obesity | Meta-Analysis results regarding mortality |
|--------------------------|-----------------------------------------------|---------------------------------|-------------------|-------------------------------|----------|------------------------|----------------------------------------|
|                         |                                               |                                 |                   |                               |          |                        | N° studies (reports) patients OR/HR/RR (95% CI) Publication bias Subgroup analysis |
| Seidou S, 2020 [1]      | 20/9 (33% from China)                         | NR                              | Inpatients/critically ill patients 47/1853/302 (35.6% from USA) | 5420 (547) | 56.8                    | NR 4 (4) RR = 3.52 (1.32 66% NR NR |
| Yang J, 2021 [4]        | 917/41 (58% from USA)                        | NOS mean – 6.9                  | Outpatients/inpatients/ critically ill patients 219543 (5354) | 4920 (547) | 56.8                    | NR 4 (4) RR = 0.89 (0.32 81% NR NR |
| Popkin BM, 2020 [5]     | 1733/75 (26.6% from USA)                     | NOS mean – 8.0                  | Inpatients/critically ill patients 399461 (5326) | 219543 (5354) | 56.8                    | NR 4 (4) RR = 0.89 (0.32 81% NR NR |
| Huang Y, 2020 [12]      | 7163/33 (34% from China)                     | NOS mean – 9.0                  | Outpatients/inpatients/ critically ill patients 45650 (1383) | 4920 (547) | 56.8                    | NR 4 (4) RR = 0.89 (0.32 81% NR NR |
| Yang J, 2020 [25]       | 977/50 (50% from USA)                        | NOS mean – 7.3                  | Inpatients/critically ill patients 18260378 (305208) | 18260378 (305208) | 57.31                   | NR 4 (4) RR = 0.89 (0.32 81% NR NR |
| Mesas AE, 2020 [26]     | 12,254/60 (51% from USA)                    | QUIPS                           | Inpatients/critically ill patients 51225 (854) | 51225 (854) | 63.04                   | NR 4 (4) RR = 0.89 (0.32 81% NR NR |
| Aghili SMM, 2021 [27]   | NR/55 (32% from USA)                         | Result NR                       | Inpatients/critically ill patients 25508 (4739) | 18540 (325) | 59.61                   | NR 4 (4) RR = 0.89 (0.32 81% NR NR |
| Hoong CWS, 2021 [28]    | 997/20 (55% from USA)                       | NOS mean – 6.3                  | Inpatients/critically ill patients 28355 (1417) | 28355 (1417) | 66.4                    | NR 4 (4) RR = 0.89 (0.32 81% NR NR |
| Li Y, 2021 [29]         | 2643/40 (45% from China)                    | JBICA 73% as “good quality”    | Inpatients/critically ill patients 30141 (1370) | 30141 (1370) | 60.1                    | NR 4 (4) RR = 0.89 (0.32 81% NR NR |
| Zhang X, 2021 [30]      | 584/22 (40.9% from USA)                     | NOS mean – 6.5                  | Inpatients/critically ill patients 6081 (533) | 30141 (1370) | 60.1                    | NR 4 (4) RR = 0.89 (0.32 81% NR NR |
| Ng WH, 2021 [31]        | 1123/53 (28.3% from USA)                    | NOS mean – 8.0                  | Inpatients/critically ill patients 375859 (7091) | 375859 (7091) | 55.3                    | NR 4 (4) RR = 0.89 (0.32 81% NR NR |
| Deng L, 2021 [32]       | 251/11 (55% from USA)                       | NOS mean – 9.0                  | Inpatients/critically ill patients 6081 (533) | 375859 (7091) | 55.3                    | NR 4 (4) RR = 0.89 (0.32 81% NR NR |
| All studies with high quality NOS | All studies with high quality NOS | All studies with high quality NOS | All studies with high quality NOS | All studies with high quality NOS | All studies with high quality NOS | All studies with high quality NOS |
| Ho J, 2020 [33]         | 1493/61 (41% from USA)                      | Moderate to good quality        | Inpatients/critically ill patients 270241 (4430) | 270241 (4430) | 57.6                    | NR 4 (4) RR = 0.89 (0.32 81% NR NR |
| Chu Y, 2020 [34]        | 552/22 (54% from China)                     | NOS mean – 6.6                  | Inpatients/critically ill patients 12591 (572) | 12591 (572) | 60.5                    | NR 4 (4) RR = 0.89 (0.32 81% NR NR |
| Du Y, 2020 [35]         | 2174/16 (56.25% from USA)                   | NOS mean – 10.0                  | Inpatients/critically ill patients 109881 (6868) | 109881 (6868) | 68.6                    | NR 4 (4) RR = 0.89 (0.32 81% NR NR |
| Noor FM, 2020 [36]      | 2147/58 (45% from China)                    | NOS mean – 7.2                  | Inpatients/critically ill patients 122101 (2105) | 122101 (2105) | 60.6                    | NR 4 (4) RR = 0.89 (0.32 81% NR NR |
| Zhao X, 2020 [37]       | 842/11 with Covid-19 (36.6% from USA)       | NOS mean – 6.0                  | Inpatients/critically ill patients 9787 (325) | 9787 (325) | 57.6                    | NR 4 (4) RR = 0.89 (0.32 81% NR NR |
| Study | Year | Country | Data Type | Study Design | Total | Sample Size | BMI | CI | Risk of Bias | Adjusted OR | 95% CI | Sex, Comorbidity, Smoking | Findings |
|-------|------|---------|-----------|--------------|-------|-------------|-----|----|-------------|-------------|--------|--------------------------|----------|
| Helvaci N, 2021 | [38] | USA | Outpatients, inpatients, critically ill patients | NHLBI | 68,214 (3590) | 56.58 | NR | 6 (6) | 4.0%–61.3% | 10,511 | OR – 1.28 (0.76 – 2.16) | Continent |
| Puly TN, 2021 | [39] | USA | Outpatients/inpatients, critically ill patients | QUIPS | 543,399 (31,965) | 62.70 | NR | 17 (17) | RR – 1.42 (1.24 – 1.63) | Absent | Sex, comorbidity, smoking |
| Pranata R, 2021 | [40] | USA | Inpatients | NOS mean – 8.3 | 34,390 (2866) | 62.93 | NR | 543,399 (31,965) | OR – 1.55 (1.16 – 2.06) | NR | NR |
| Cai Z, 2021 | [41] | USA | Inpatients | NOS mean – 8.3 | 625,153 (13,590) | 62.93 | NR | 29,051 (18) | OR – 1.61 (1.29 – 2.01) | Absent | Present (funnel plot) |
| Dessie Z, 2021 | [42] | China | Inpatients | NOS from 7 to 9 points | 423,117 (10,079) | 48.9 to 77 | NR | 29,305 (9) | OR – 1.34 (1.17 – 1.52) | Absent | (Egger test and Funnel plot) |
| Geng J, 2021 | [43] | China | Inpatients | JBI | 624,986 (2880) | NR | NR | 27 (NR) | OR – 1.19 (0.94 – 1.51) | 155,450 | Morbid obesity |
| Saleh Y, 2021 | [44] | Asia | Inpatients | ROBINS-I | 1,304,587 (7014) | NR | NR | 54 (54) | RR – 1.45 (1.30 – 1.61) | Absent | (Egger test and Funnel plot) |

**Abbreviations:** BMI – body mass index; CI – confidence interval; ICU – intensive unit care; JBICA – Joanna Briggs Institute Critical Appraisal tool; JBI – Joanna Briggs Institute; HR – hazard ratio; OR – odds ratio; QUIPS – Quality In Prognosis Studies; RR – relative risk; ROBINS-I – Risk Of Bias In Non-Randomized Studies of Interventions; WHO – World Health Organization; USA – United States of America.
did not correctly fulfill checklists, because a high score in AMSTAR-2 is in concordance with a complete reporting of SR-MAs. Full reporting allows readers to assess the appropriateness of the methods and, therefore, the integrity of the findings. Presenting and summarizing the features of primary studies can help healthcare providers and policymakers evaluate the applicability of the results [47]. It also facilitates replication and review updates as well as their inclusion in overviews and guidelines [48,49].

Describing certainty in the body of evidence for an outcome and the implications of findings should help construct appropriate recommendations for practice or policy [50]. Only two SR-MA applied the GRADE approach to evaluate the certainty of the
| First Author, year (Ref) | Risk of bias | Inconsistency | Imprecision | Indirectness | Publication bias | Large effect | Dose response | Confounders | Evidence grading |
|--------------------------|--------------|---------------|-------------|--------------|----------------|--------------|---------------|-------------|------------------|
| Seidu S, 2020 [1]        | Present      | Present (I² = 66%) | Identified (95%CI 1.32–9.42) | NI            | Result NR      | Identified (RR = 3.52) | NR          | Considered, but not detailed | Very low ○○○○ |
| Yang J, 2021 [4]         | Present      | Present (I² = 74.4%) | NI (95% CI 1.04–1.26) | NI            | Absent         | NI (OR = 1.14) | Demonstrated by subgroup analysis (significant RR in BMI ≥40 kg/m²) | Very low ○○○○ |
| Popkin BM, 2020 [9]      | Present      | NR             | NI (IC95% 1.22–1.80) | NI            | NR             | NI (OR = 1.49) | NR          | Considered and detailed | Very low ○○○○ |
| Huang Y, 2020 [12]       | Present      | Present (I² = 69.2%) | NI (95% CI 1.20–1.85) | NI            | Absent         | NI (OR = 1.65) | NR          | Considered, but not detailed | Very low ○○○○ |
| Yang J, 2020 [25]        | Present      | Present (I² = 85%) | NI (IC95% 1.21–2.25) | NI            | Absent         | NI (OR = 1.65) | NR          | Considered, but not detailed | Very low ○○○○ |
| Mesas AE, 2020 [26]      | Present      | Present (I² = 82.9%) | Identified (IC95% 0.84–1.41) | NI            | Absent         | NI (OR = 1.65) | NR          | Considered, but not detailed | Very low ○○○○ |
| Aghili SMM, 2021 [27]    | Present      | Present (I² = 76.6%) | NI (IC95% 1.24–1.45) | NI            | NR             | NI (OR = 1.75) | NR          | Considered, but not detailed | Very low ○○○○ |
| Hoong CWs, 2021 [28]     | Present      | Present (I² = 46.2%) | NI (95% CI 1.13–2.21) | NI            | Absent         | NI (OR = 1.75) | NR          | Considered, but not detailed | Very low ○○○○ |
| Li Y, 2021 [29]          | Absent       | Present (I² = 87.5%) | NI (95%CI 1.02–2.48) | NI            | Absent         | NI (OR = 1.75) | NR          | Considered, but not detailed | Very low ○○○○ |
| Zhang X, 2021 [30]       | Present      | NR             | Identified (95%CI 0.74–1.25) | NI            | Absent         | NI (OR = 0.75) | NR          | Considered, but not detailed | Very low ○○○○ |
| Ng WH, 2021 [31]         | Present      | Absent (Low heterogeneity) | Identified (95%CI0.96–2.57) | NI            | NR             | NI (HR = 1.58) | NR          | Considered, but not detailed | Very low ○○○○ |
| Deng L, 2021 [32]        | Absent       | Present (I² = 66.6%) | Identified (95%CI 0.65–1.71) | NI            | Absent         | NI (OR = 1.50) | NI          | Considered, but not detailed | Very low ○○○○ |
| Ho JSY, 2020 [33]        | Absent       | Present (I² = 88.5%) | NI (95% CI 1.07–1.66) | NI            | NR             | NI (OR = 1.63) | NR          | Considered, but not detailed | Very low ○○○○ |
| Chu Y, 2021 [34]         | Present      | Present (I² = 81%) | Identified (95%CI 0.32–2.51) | NI            | Absent         | NI (OR = 0.86) | NR          | Considered, but not detailed | Very low ○○○○ |
| Du Y, 2020 [35]          | Present      | Present (I² = 79.3%) | NI (95% CI 1.64–4.37) | NI            | Absent         | Identified (OR = 2.68) | ↑ 9% risk of death for each ↑ 1 kg/m² of BMI | Low ○○○○ |
| Noor FM, 2020 [36]       | Present      | Present (I² = 98.6%) | NI (95% CI 1.10–4.34) | NI            | Present        | Identified (RR = 2.18) | NR          | Considered, but not detailed | Very low ○○○○ |
| Zhao X, 2020 [37]        | Present      | Present (I² = 57%) | Identified (95%CI 0.85–2.90) | NI            | Absent         | NI (OR = 1.57) | NR          | Considered, but not detailed | Very low ○○○○ |
| Helvacı N, 2021 [38]     | Present      | Present (I² = 80%) | Identified (95% CI 0.76–2.16) | NI            | NR due to the studies number ≥10. | NI (OR = 1.57) | NR          | Considered, but not detailed | Very low ○○○○ |

Abbreviations: CI = confidence interval; HR = hazard ratio; NI = not identified; NR = not reported; NS = not significant; OR = odds ratio; RR = relative risk.

GRADE Working Group grades of evidence: High quality: Further research is very unlikely to change our confidence in the estimate of effect. Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate. Low quality: We are very uncertain about the estimate. Very low quality: We are very uncertain about the estimate. Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Comorbidities, physical inactivity, and unhealthy diet is involved in the interaction, immune impairments, and adipose inflammation added to the comorbidities, physical inactivity, and unhealthy diet is involved in the inconsistency, risk of bias in primary studies, and imprecision.

The overlap in meta-reviews results from the use of multiple identical primary studies in similar reviews [22]. In the current umbrella review, the CCA was 4.8%, which is classified as slight. Although most SR-MAs showed a significant association between obesity and mortality, the number of studies included ranged significantly. Partially, this could be explained by the interval between the date of publication of SR-MA and their search literature since this interval was higher than three months in more than 50% of SR-MAs. This may have contributed to a possible time bias since primary studies on COVID-19 are being published quickly.

The proliferation of SR and the growing demand from policymakers have driven newer methods of evidence synthesis—a meta-review of SR. The current umbrella review has some strength: (a) it was conducted according to the Cochrane Handbook and followed the PRISMA checklist; and (b) a protocol was registered in PROSPERO, and we conducted a literature search in different databases. However, some limitations need to be pointed out: (a) we did not contact the authors for more detailed information and evaluated the quality of SR-MA and the certainty of evidence considering the information presented by authors in the published material. (b) We did not have access to the full text of one potentially eligible SR. (c) We did not include preprints within our synthesis (n = 4) because they were not eligible, as they had not been peer-reviewed. Consequently, there is a possibility that the available evidence on the association between obesity and mortality in patients with SARS-CoV-2 is even less robust than the current meta-review suggests.

This umbrella review has shown significant room for improvement in SR-MAs’ reporting quality and consistency. Greenhalgh et al. [50] pointed out that balancing gold-standard systematic reviews with faster pragmatic ones is necessary. Considering the pandemic, the challenge is to offer indications of trustworthiness in available evidence in real-time. Therefore, the results regarding the association between obesity and mortality in patients with SARS-CoV-2 should be interpreted with caution, given the substantial methodological drawbacks that were detected. Although there are mechanisms to support this association [9], its true magnitude is unknown due to the lack of high-quality and well-graded evidence. In addition, a dose-response effect could not be demonstrated in the majority of SR-MAs. All stakeholders—journal editors, peer reviewers, and users of SR-MAs—should be encouraged to pay particular attention to the methods of SR-MAs. Regardless of the pandemic, we should always aspire to trustworthy scientific evidence.

Besides the poor quality of SR-MAs included in this umbrella review, the majority of these studies point to an association between obesity and mortality in patients with SARS-CoV-2. Thus, one would assume that these types of findings increase motivation for individuals with obesity to start the treatment of this condition with lifestyle changes and other therapies, and for governments to prioritize their protection by putting them at the front of the line to receive vaccines, and to stimulate prevention and treatment of overweight/obesity. The interaction between metabolic dysfunction, immune impairments, and adipose inflammation added to the comorbidities, physical inactivity, and unhealthy diet is involved in the mechanisms responsible for the clinical manifestations, including a higher risk of death in patients with SARS-CoV-2 infection and obesity [9]. Regardless of this, it is necessary to highlight that the decisions for the management of these patients would be more directed and precise if the real magnitude of association between mortality and obesity would be known, and if we would have clarity if there exists a dose—response effect in this association (for each increase of 1 kg/m² in BMI is a linear increase in risk of death is observed?).

Conclusions

Obesity was associated with mortality in patients with SARS-CoV-2 infection in most SR-MAs included in this umbrella review. However, for the majority of SR-MAs, the quality was critically low, and the certainty of evidence was graded as very low. Although there is a physiological basis supporting this association between obesity and mortality in patients with SARS-CoV-2, we should always aspire to trustworthy scientific evidence.

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Author contributions

FMS and ATS contributed to the conception and development of the overall study; FMS and JL screened references identified by the search and assessed studies for inclusion; FMS, ATS, JL, PPT, GBC, KS, and TC extracted data; FMS, PPT, and JL assessed the quality of included reviews, graded the certainty of evidence, produced figures and tables. MF performed the literature search, screened references identified by the search, assessed studies for inclusion; ATS, FMS, JL, and PPT drafted the manuscript. All authors read and approved the final review version.

Availability of data, code and other materials

Part of them are available as supplementary material. Other materials can be provided by authors if required.

Conflict of interest

The authors declare that they have no conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2022.08.014.

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