

REVIEW ARTICLE

Obesity augments the disease burden in COVID-19: Updated data from an umbrella review

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Summary

The ongoing coronavirus disease 2019 (COVID-19) pandemic calls for identification of risk factors, which may help to identify people at enhanced risk for severe disease outcomes to improve treatment and, if possible, establish prophylactic measures. This study aimed to determine whether individuals with obesity compared to individuals with normal weight have an increased risk for severe COVID-19. We conducted a systematic literature search of PubMed, Embase and Cochrane Library and critically reviewed the secondary literature using AMSTAR-2. We explored 27 studies. Findings indicate that individuals with obesity (body mass index ≥ 30 kg/m²), as compared to individuals without obesity, experience an increased risk for hospitalization (odds ratio [OR]: 1.40–2.45), admission to the intensive care unit (OR: 1.30–2.32), invasive mechanical ventilation (OR: 1.47–2.63), and the composite outcome ‘severe outcome’ (OR or risk ratio: 1.62–4.31). We found diverging results concerning death to COVID-19, but data trended towards increased mortality. Comparing individuals with obesity to individuals without obesity, findings suggested younger individuals (<60 years) experience a higher risk of severe disease compared to older individuals (≥ 60 years). Obesity augments the severity of COVID-19 including a tendency to increased mortality and, thus, contributes to an increased disease burden, especially among younger individuals.

KEYWORDS

body mass index, COVID-19, obesity, outcomes, SARS-CoV-2, umbrella review

1 | INTRODUCTION

On 11 March 2020 the World Health Organization (WHO) classified the ongoing coronavirus disease 2019 (COVID-19) outbreak as a global pandemic.¹ The disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and reported to originate from Wuhan, China, is estimated to have infected more than 260 million individuals and resulting in more than 5.1 million deaths worldwide.²

Although people are encouraged to enter vaccination programmes the COVID-19 can still be characterized as a pandemic leading to disease and death. It is, therefore, of the utmost importance to be able to identify potential risk factors which may increase the risk of

severe illness or even death to aid these more vulnerable individuals as early as possible in the course of the disease or even, if possible, to facilitate relevant protective measures in the society.

A possible protective effect of obesity (obesity paradox) in relation to infectious diseases has previously been proposed,³ however, several studies evaluating risk factors in relation to COVID-19 severity have pointed out obesity to potentially augment the severity of the disease, including increased risk of hospitalization, of admission to intensive care units (ICU), and an increased need for invasive mechanical ventilation (IMV).⁴

After infection by SARS-CoV-2 contaminated aerosols, the average individual experience an incubation period of 5–7 days.⁵ Despite

the infection, up to 20% of infected individuals may not develop any kind of symptoms through the course of the infection.⁶ Most of the symptomatic individuals will experience a mild or moderate course of disease consisting of fever, cough, fatigue and even anosmia and ageusia.⁵ However, as many as 20% of patients may develop severe or critical disease resulting in requirement of oxygen support and hospital care or even admission to ICU to prevent and handle feared complications such as acute respiratory distress syndrome, sepsis, thromboembolism and even multiorgan failure.⁵ As the WHO estimates that nearly 2 billion individuals experience overweight or obesity (650 million with obesity)⁷ it is important to clarify whether these individuals should be considered at increased risk of developing severe COVID-19. In addition, it may be of interest to investigate if an age-dependent risk exists as a previous report has demonstrated that BMI among hospitalized individuals was negatively correlated with age ($r^2 = .051$; $p = .0002$),⁸ suggesting that the severity of COVID-19 in younger individuals with obesity might be augmented.

This ubiquitous crisis demanding a worldwide attention has resulted in the production of an enormous number of scientific publications. To explore the possible link between obesity and COVID-19 severity, it is necessary to continuously critically review and discuss the available literature. Hence, a systematic appraisal of the study quality of the available systematic reviews on the association between obesity and risk of severe a COVID-19 outcome and a discussion of their conclusions is needed.

2 | OBJECTIVES

We hypothesize that obesity is an independent risk factor for the development of severe illness following SARS-CoV-2 infection. This paper seeks to give an updated answer on the following Population, Intervention, Comparison, Outcome (PICO)⁹ question: In individuals infected with a SARS-CoV-2 (P), does obesity (I) compared to normal weight (C) affect outcomes such as hospitalization, ICU admission, need for IMV or mortality (O)?

3 | METHODS

3.1 | Search strategy and literature search

We performed a systematic literature search of PubMed, Embase and Cochrane Library using the search strings as presented in Table S1. The searches were carried out 8 February, 22 May, 25 October 2021, with no limitations regarding time period of publication. The choice of proper search terms was made in accordance with the individual database thesaurus. We performed hand searching of the lists of references of the included studies to further include studies potentially missed by the literature search.

To be included, the studies must fulfil the following criteria: (1) Publication type of systematic review with or without meta-analysis of SARS-CoV-2-positive individuals; (2) risk assessments of

the continuous variable, BMI, or the dichotomous variable, obesity (BMI ≥ 27.5 kg/m² for Asian individuals; BMI ≥ 30 kg/m² for non-Asian individuals¹⁰), regarding COVID-19 severity either as hospitalization, ICU admission, need of IMV, mortality, or any representative measurement of severe (blood oxygen saturation $< 90\%$, respiratory rate > 30 /min, signs of severe respiratory distress⁵) or critical (requirement of life sustaining treatment or acute respiratory distress⁵) disease outcome; (3) the included study must have been through a proper peer-review process.

After the removal of duplicates, studies were screened by title and abstract and excluded if found ineligible, e.g., improper publication type such as editorials, commentaries, primary studies, or secondary literature without investigations included by the aforementioned inclusion criteria. We evaluated the remaining studies for final inclusion in accordance with the inclusion criteria by full-text reading. The literature selection process is shown in Figure 1.

3.2 | Study quality assessment

To assess the quality of each included study this project used the appraisal tool 'A MeaSurement Tool to Assess systematic Reviews-2' (AMSTAR-2).¹¹ The instrument consists of 16 questions of which 7 are considered critical. By applying these questions to each study, it is possible to qualitatively rate the overall confidence in the results of the review as either 'critically low' (more than one critical flaw), 'low' (one critical flaw), 'moderate' (more than one noncritical weakness) or 'high' (no or one noncritical weakness). We excluded studies rated as 'critically low' for qualitative synthesis. Two authors (A.A. and N.K.) independently performed the quality assessment, and any differences were solved through discussion.

3.3 | Data extraction

Using the standardized data extraction tool in accordance with the guidelines for umbrella reviews by the Joanna Briggs Institute¹² One of the authors (N.K.) extracted the following data from the literature: Author, date of publication, study objectives, sources searched, search details, types and number of studies included, total number of participants, appraisal instrument used, and summary of findings, including heterogeneity.

4 | RESULTS

4.1 | Results of literature search

The initial literature search yielded 347 potential publications. After removing duplicates, screening titles and abstracts 163 articles remained and were evaluated in detail prior to potential inclusion. This led to exclusion of further 101 articles with reasons specified in Figure 1. After full-text reading we excluded 25 articles and using the

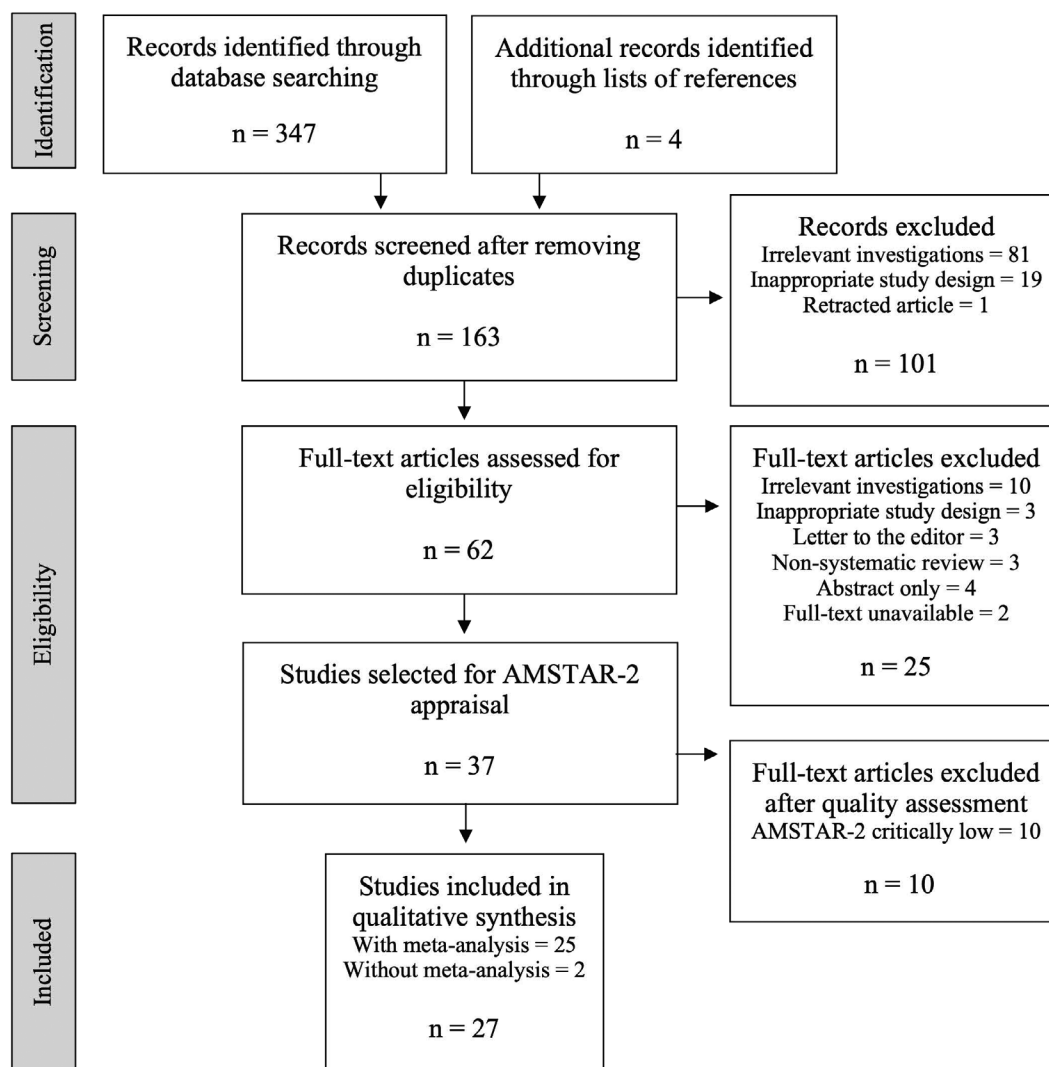


FIGURE 1 Flow diagram of study selection process

AMSTAR-2 quality assessment tool we excluded further 10 studies which led to the inclusion of 27 systematic reviews in this paper's qualitative deductions. The 27 systematic reviews included a total of 260 unique primary studies.

Table 1 shows, that the systematic reviews mainly included studies from the Regions of the Americas (USA, Mexico, Brazil, Bolivia), the European Region (Italy, France, Spain, United Kingdom, Greece, Germany, Switzerland, Israel) and Western Pacific Region (China, Singapore), whilst the Eastern Mediterranean Region (Kuwait) was represented sparsely and none of the systematic reviews included studies from the African Region or the South-East Asian Region.

4.2 | Results of study appraisal

Using the AMSTAR-2 appraisal tool to judge the methodological quality, 25^{14,17-21,24-26,28,30,32,33,35,37,41-50} of the 37 studies were evaluated as 'Low'- or 'Critically low'-quality studies; 15^{14,17-21,24-26,28,30,32,33,35,37} and 10,⁴¹⁻⁵⁰ respectively (Table S2). The

individual results of the AMSTAR-2 study quality assessment are shown in Table S3.

4.3 | Results of individual studies

The results of the included systematic reviews are presented in Table 1 and visually summarized in Table 2. Tables S4 and S5 and Figures S1 and S2 presents subgroup analyses regarding IMV and mortality, respectively. A total of five different outcomes (hospitalization, ICU, IMV, 'severe outcome' and mortality) were assessed across the 27 studies.

4.4 | Hospitalization

Eight studies examined the role of obesity in relation to hospitalization.^{14,17,19,24,27,30,35,39} Seven studies provided a meta-analysis,^{14,17,19,24,27,30,35} six of which reported significant odds ratios [ORs] ranging from 1.40³⁵ to 2.45²⁴ reflecting an increased OR for

TABLE 1 (Continued)

Quantitative studies											Qualitative appraisal (AMSTAR-2)
Author (year/month)	Studied countries	Outcome	Comparisons	Studies (n)	Sample size (n)	OR or RR (95% CI)	I ²	Adjustments			
Deng et al. ²⁰ (2021/Jan)	USA: 6	ICU	Without obesity	7	1812	OR: 1.86 (1.45–2.39)	NA	Random-effects model with adjustments for age, gender Fixed-effect and generalized least square method for dose-response analyses		Low	
	Italy: 2	IMV	Without obesity	7	2167	OR: 1.74 (1.39–2.17)	NA				
	Singapore	SO	Without obesity	9	2442	OR: 1.79 (1.52–2.11)	NA				
	China	Mortality	Without obesity	7	5175	OR: 1.05 (0.65–1.71)	NA				
Hoong et al. ²¹ (2021/Jan)	USA: 2	SO	Without obesity	6	17 861	OR: 2.02 (1.41–2.89)	73.5	Random-effects model meta-regression adjusting for age, gender, CVD, CKD, chronic respiratory disease, diabetes, hypertension		Low	
	China: 2	Mortality	Without obesity	4	17 322	OR: 1.51 (1.13–2.21)	46.2				
	UK Italy										
Ho et al. ²² (2020/Dec)	USA: 10	ICU	Without obesity	8	9869	OR: 1.25 (0.99–1.58)	31.0	Random-effects univariate meta-regression		Moderate	
	China: 7	SO	Without obesity	6	1111	OR: 3.13 (1.41–6.92)	82.6				
	Italy: 2	Mortality	Without obesity	12	45 768	OR: 1.33 (1.07–1.66)	88.5				
	UK										
	Mexico Spain										
Mesas et al. ²³ (2020/Nov)	USA: 7	Mortality	Without obesity	17	20 289	OR: 1.09 (0.84–1.42)	82.9	Random-effects model adjusting for age, gender, comorbidities (unspecified)		High	
	Italy: 3										
	Brazil: 2										
	Spain: 2										
	Israel										
Yang et al. ²⁴ (2020/Oct)	USA: 15	Hosp.	BMI ≥ 30 vs. BMI < 25	9	259 842	OR: 2.45 (1.78–3.39)	92.0	NA		Low	
	Mexico: 4	ICU	BMI ≥ 30 vs. BMI < 30	9	182 758	OR: 1.30 (1.21–1.40)	14.0				
	Italy: 2	IMV	BMI ≥ 30 vs. BMI < 25	7	183 101	OR: 1.59 (1.35–1.88)	46.0				
	Brazil	Mortality	BMI ≥ 30 vs. BMI < 30	8	345 273	OR: 1.65 (1.21–2.25)	95.0				
	UK										
	Bolivia										
Chu et al. ²⁵ (2020/Oct)	USA: 5	ICU	Without obesity	2	1233	OR: 1.57 (1.18–2.09)	0.0	Random-effects meta-regression adjusting for age, hypertension, diabetes, CVD, COPD		Low	
	China: 4	IMV	Without obesity	2	718	OR: 2.13 (1.10–4.14)	54.0				
	France	SO	Without obesity	4	519	OR: 4.31 (2.42–7.65)	0.0				
	Italy	Mortality	Without obesity	3	5102	OR: 0.89 (0.32–2.51)	81.0				
	Italy: 2	Mortality	Without obesity	7	13 477	RR: 2.18 (1.09–4.34)	98.6				
Noor et al. ²⁶ (2020/Sept)	USA	Mortality	Without obesity	7	13 477	RR: 2.18 (1.09–4.34)	98.6	Random-effects method, however, no statement regarding adjustments		Low	
	Brazil										
	Spain										
	Greece										
	Switzerland										

(Continues)

TABLE 1 (Continued)

Quantitative studies										
Author (year/month)	Studied countries	Outcome	Comparisons	Studies (n)	Sample size (n)	OR or RR (95% CI)	I ²	Adjustments	Qualitative appraisal (AMSTAR-2)	
Seidu et al. ³⁴ (2020/June)	USA: 2	SO 1	BMI > 35 vs. BMI < 25	3	3945	RR: 3.76 (1.97–7.16)	29.0	Random-effects model on multivariate adjusted risk estimates (if available). No statement specifying the adjusted parameters	Moderate	
	China: 2	SO 2	BMI > 25 vs. BMI < 25	6	4169	RR: 2.35 (1.43–3.86)	71.0			
	Italy: 2	Mortality	BMI > 25 vs. BMI < 25	4	565	RR: 3.52 (1.32–9.42)	66.0			
	Singapore France									
Chang et al. ³⁵ (2020/May)	USA: 5	Hosp.	Without obesity	2	8655	OR: 1.40 (1.30–1.60)	0.0	Unadjusted ORs	Low	
	France	IMV	Without obesity	4	644	OR: 2.00 (1.40–2.90)	0.0			
Figliozzi et al. ³⁶ (2020/May)	NA	SO	Without obesity	NA	5184	OR: 2.28 (0.76–6.90)	81.0	Random-effects meta-regression, 10 out of 35 studies provided adjusted ORs adjusted for age, smoking, diabetes, CVD, malignancy, acute cardiac, kidney and liver injury, D-dimer, steroids	Moderate	
Zhou et al. ³⁷ (2020/April)	China	SO	Without obesity	3	560	OR: 2.29 (1.22–4.29)	38.5	Random-effects model, however, no statement concerning potential adjustments	Low	
	UK	Mortality	Without obesity	1	2936	OR: 1.15 (0.98–1.34)	NA			
	USA									
	France									
Qualitative studies										
Author (year/month)	Studied countries	Outcome	Comparisons	Studies (n)	Sample size (n)	Findings	Qualitative appraisal (AMSTAR-2)			
Tamara et al. ³⁸ (2020/May)	China	Hosp.	Obesity vs.	3	806	Obesity is proclaimed as an independent risk factor for the requirement of advanced medical treatment due to COVID-19 This declaration is synthesized as the rate of hospitalization in individuals with obesity is increased – especially those younger than 60 years old. Comparing patients experiencing obesity Grade I and II to normo- or overweight patients, the risk of receiving critical care (including IMV [only Grade II obesity]) is increased	Moderate			
	USA	IMV	normo- and overweight							
	France	SO								
Peres et al. ³⁹ (2020/Aug)	USA: 4	Hosp.	Without obesity	9	17 568	Obesity is proposed as a likely risk factor for experiencing poor outcome in patients with COVID-19 This is synthesized as the prevalence of chronic diseases including obesity is higher in individuals requiring hospitalization especially those younger than 60 years old with obesity; of these hospitalized patients the ones admitted to the ICU significantly presents a higher BMI Finally, patients with obesity and other concurrent chronic diseases (e.g., NALFD, diabetes, cardiovascular diseases, asthma, hypertension) seem to experience higher rates of hospitalization, IMV as well as mortality	Moderate			
	China: 3	ICU								
	France	SO								
	Mexico	Mortality								

Note: Studies by Poly et al., Noor et al., Sales-Peres et al., and Seidu et al. reported effect estimates as risk ratios (RR). All other quantitative studies reported odds ratios (OR). Qualitative appraisal: Critically low: More than one critical flaw; Low: One critical flaw; Moderate: More than one noncritical weakness; High: No or one noncritical weakness.

Abbreviations: CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; Hosp., hospitalization; NA, not available; SO, 'Severe outcome' ([composite outcome consisting of WHO-defined severity⁴⁰ incl. ICU, IMV and mortality]).

^aCOPD, asthma, interstitial lung disease and pulmonary hypertension.

^bHeart failure, coronary artery disease and cardiomyopathy.

TABLE 2 Visual summarization of evidence from quantitative and qualitative research syntheses

Intervention	Author	Year	Month	Hosp.	ICU	IMV	SO	Mortality	Qualitative appraisal
QUANTITATIVE STUDIES									
Obesity vs. without obesity	Hoong et al ²¹	2021	Jan.						Low
	Yang Jiao et al ²⁴	2020	Oct.						Low
	Ho et al ²²	2020	Dec.						Moderate
	Pranata et al ³²	2020	June						Low
	Yang Jun et al ²⁷	2020	Sept.						High
	Chu et al ²⁵	2020	Oct.						Low
	Földi et al ³³	2020	June						Low
	Zhang et al ¹⁷	2021	March						Low
	Helvacı et al ¹⁹	2021	Feb.						Low
	Noor et al ²⁶	2020	Sept.						Low
	Chang et al ³⁵	2020	May						Low
	Huang et al ³⁰	2020	Aug.						Low
	Zhao et al ²⁹	2020	Aug.						High
	Sales-Peres et al ³¹	2020	July						High
	Poly et al ¹⁸	2021	Feb.						Low
	Zhou et al ³⁷	2020	April						Low
	Figliozzi et al ³⁶	2020	May						Moderate
	Mesas et al ²³	2020	Nov.						High
	Deng et al ²⁰	2021	Jan.						Low
	Raeisi et al ¹⁴	2021	July						Low
Dessie et al ¹³	2021	Aug.						High	
Severe obesity vs. without severe obesity	Booth et al ¹⁶	2021	March						High
BMI ≥ 30 kg/m ² vs. BMI < 30 kg/m ²	Du et al ²⁸	2020	Sept.						Low
	Li et al ¹⁵	2021	March						High
BMI ≥ 25kg/m ² vs. BMI < 25kg/m ²	Seidu et al ³⁴	2020	June						Moderate
QUALITATIVE STUDIES									
Obesity and/or overweight vs. normoweight	Peres et al ³⁹	2020	Aug.						Moderate
Obesity vs. without obesity	Tamara et al ³⁸	2020	May						Moderate
	No association between intervention and outcome is assessed, $p > 0.05$, if quantitative synthesis is provided								
	The intervention increases risk for outcome: $1 < OR \text{ or } RR < 2$, $p < 0.05$, if quantitative synthesis is provided								
	The intervention increases risk for outcome: $2 \leq OR \text{ or } RR$, $p < 0.05$, if quantitative synthesis is provided								

hospitalization in individuals with obesity compared to individuals without obesity following SARS-CoV-2 infection (Figure 2A). Only the study by Helvacı et al.¹⁹ reported a nonsignificant OR of 1.30, however, the confidence interval showed a near significant finding (95% confidence interval [CI]: 1.00–1.69). The two studies without meta-analysis^{38,39} provided concordant qualitative conclusions.

Yang et al.²⁷ compared different BMI intervals to BMI < 25 kg/m² suggesting the OR for hospitalization increased gradually with increasing BMI: 25 kg/m² ≤ BMI < 30 kg/m², OR: 1.30 (95% CI: 1.09–1.57); 30 kg/m² ≤ BMI < 40 kg/m², OR: 2.09 (95% CI: 1.34–3.26); BMI ≥ 40 kg/m², OR: 2.76 (95% CI: 1.76–4.32).

This, however, was in contrast to the study of Yang et al.²⁴ who found no association between hospitalization and the BMI interval of 30–34.9 kg/m² compared to BMI < 25 kg/m², OR: 1.10 (95% CI: 0.88–1.37).

4.5 | ICU

Eleven studies investigated the association between obesity and ICU admission^{14,17,19,20,22,24,25,27,30,33,39} among SARS-CoV-2 positive individuals and 10 studies provided a meta-analysis.^{14,17,19,20,22,24,25,27,30,33} Peres et al.³⁹ concluded that individuals with obesity experienced an increased risk of ICU admission compared to individuals without obesity, however, they did not provide a meta-analysis to support their findings.

Eight of the 10 meta-analyses reported significant ORs of ICU admission when comparing individuals with obesity to individuals

without obesity^{14,17,19,20,24,25,27,30} ranging from 1.30²⁴ to 2.32³⁰ (Figure 2B).

Although Ho et al.²² and Földi et al.³³ reported an OR > 1, their findings were considered nonsignificant (95% CI: 0.99–1.58; 1.00–1.46, respectively). Despite this, Ho et al.²² did report a significant mean difference in BMI of 2.32 kg/m² (95% CI: 1.04–3.60, $p < .001$) comparing the ICU to the non-ICU group.

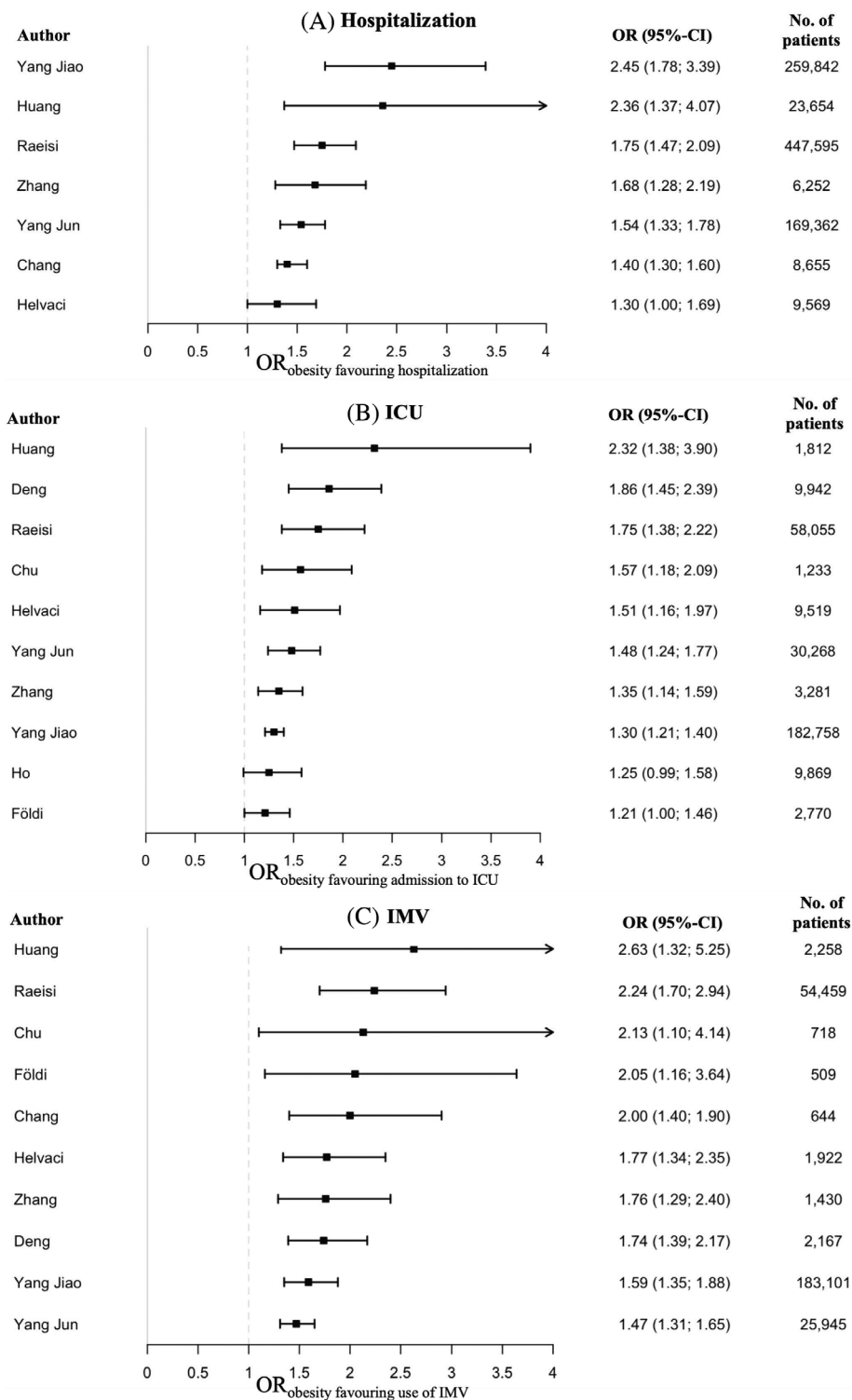
Deng et al.²⁰ used the generalized least square method to determine that the OR for ICU admission increased in a dose-response manner meaning for each rise in BMI of 5 kg/m², the OR for ICU admission increased by 20%, OR: 1.20 (95% CI: 1.11–1.30), when comparing individuals with obesity to individuals without obesity.

Yang et al.²⁴ reported similar results for ICU admission, demonstrating increasing ORs with increasing BMIs compared to BMI < 30 kg/m²: ≥30 kg/m², OR: 1.30 (95% CI: 1.21–1.40); ≥35 kg/m², OR: 1.86 (95% CI: 1.31–2.63); ≥40 kg/m², OR: 1.96 (95% CI: 1.27–3.02).

4.6 | IMV

Eleven studies focused on the need for IMV in relation to SARS-CoV-2 infected individuals with obesity.^{14,17,19,20,24,25,27,30,33,35,38} All studies except one provided a meta-analysis³⁸ but all reported a positive association between individuals with obesity and COVID-19 and the need for IMV. Five of the ORs even identified at least a twofold increase of the OR.^{14,25,30,33,35} Overall, the ORs ranged from 1.47²⁷

FIGURE 2 Forest plot summarizing the association between obesity and the risk of hospitalization (A), risk of admission to intensive care unit (B) and risk of receiving invasive mechanical ventilation (C). Yang Jiao compared BMI ≥ 30 kg/m² to BMI < 25 kg/m²; all others compared obesity to without obesity



to 2.63³⁰ considering the unfavourable outcome of the need for IMV (Figure 2C).

Only two studies presented heterogeneity of high value^{25,30} ($50\% \leq I^2 < 75\%$ ⁵¹) whilst the rest were characterized as either moderate^{14,24,33} ($25\% \leq I^2 < 50\%$ ⁵¹) or low²⁷ ($0\% < I^2 < 25\%$ ⁵¹) if heterogeneity was described at all.^{20,35} Zhang et al.¹⁷ did not provide any estimate of heterogeneity. These levels of heterogeneity for the IMV-meta-analysis represent the lowest for all the five outcomes

(hospitalization, ICU, IMV, 'severe outcome' and mortality) describing COVID-19 severity (Table 1).

Four studies further quantified the relationship between an elevated BMI and the increased OR for IMV.^{20,24,27,33} Yang et al.,²⁴ Yang et al.,²⁷ and Földi et al.³³ all compared different BMI ranges of BMIs ≥ 25 kg/m² to individuals with BMI < 25 kg/m². They all found similar trends that increasing levels of BMI increased the OR for the need for IMV. The data is shown in Table S4 and visually illustrated in

Figure S1. It should be noted that 11 of 21 primary studies used in the subgroup analyses in the four secondary studies^{20,24,27,33} were used ≥ 2 times.

Deng et al.²⁰ even further elaborated this association by using the generalized least square method to develop a model showing that for every 5 kg/m² increment in BMI the OR for the need for IMV increased by 16%, OR: 1.16 (95% CI: 1.10–1.23), when comparing individuals with obesity to individuals without obesity.

4.7 | 'Severe outcome'

'Severe outcome' is a composite outcome as the definition of severe COVID-19 varied among the studies depending on the reports by the primary studies.

Some studies used the definition of severe disease as presented in the Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19)⁵² but did not differentiate between severe or critical disease.^{22,25,32,39} Others extended the definition to include admission to ICU and/or IMV^{16,17,20,28,30,34,37,38} and/or mortality.^{14,21,29} Only two studies^{31,36} did not elaborate their definition of severe COVID-19.

In total, 17 studies evaluated the possible link between obesity and severe outcome of COVID-19.^{14,16,17,20–22,25,28–32,34,36–39} Tamara et al.³⁸ and Peres et al.³⁹ did not provide a meta-analysis, however, both studies reported an increased risk for a 'severe outcome' for individuals with obesity compared to individuals without obesity. Both studies referred to the study by Lighter et al.⁵³ that examined the association between age (< or ≥ 60 years) and obesity grade I (30 kg/m² \leq BMI < 35 kg/m²) and obesity grade II (35 kg/m² \leq BMI < 40 kg/m²) compared to individuals with BMI < 30 kg/m², respectively, and the risk of being admitted to an ICU as a measure of 'severe outcome'. In this study only the individuals aged <60 years with obesity grade I and II experienced a significant increased risk of being admitted to an ICU compared to individuals <60 years with BMI <30 kg/m².

Of the other 14 studies providing a meta-analysis, only Figliozzi et al.³⁶ and Sales-Peres et al.³¹ disagreed with this conclusion as they did not find individuals with obesity compared to individuals without obesity of being at increased risk of a severe outcome of COVID-19: OR: 2.28 (95% CI: 0.76–6.90) and risk ratio (RR): 1.40 (95% CI: 0.91–2.17), respectively.

Overall, the significant ORs or RRs for 'severe outcome' of COVID-19 in individuals with obesity compared to individuals without obesity ranged between 1.62¹⁴ and 4.31²⁵ with nine studies reporting ORs >2.0,^{16,17,21,22,25,29,30,34,37} but only Chu et al.²⁵ described the association to be significantly greater than 2.0, OR: 4.31 (95% CI: 2.42–7.65) (Figure 3).

Pranata et al.³² found that the severity of COVID-19 acted in a dose-dependent manner in parallel to an augmented outcome. Using BMI 20 kg/m² as reference, Pranata et al.³² found the increasing ORs as follows: BMI 25 kg/m², OR: 1.02 (95% CI: 0.99–1.05); BMI 30 kg/m², OR: 1.09 (95% CI: 1.04–1.15); BMI 35 kg/m², OR: 1.28 (95% CI: 1.17–

1.41); BMI 40 kg/m², OR: 1.61 (95% CI: 1.31–1.97). The association was described as linear with an increasing OR of 1.05 (95% CI: 1.03–1.08) for each BMI increment of 5 kg/m². The linearity only persisted until BMIs of 30–35 kg/m² after which, the curve (association) steepened.

Seidu et al.³⁴ confirmed this association as they compared BMIs ≥ 25 and >35 kg/m² to BMI <25 kg/m² and reported RRs of 2.35 (95% CI: 1.43–3.86) and 3.76 (95% CI: 1.97–7.16), respectively.

Four studies stratified individuals with obesity by age.^{25,34,38,39} Among younger individuals (mean age < 60 years) Chu et al.²⁵ estimated an OR for a severe outcome for individuals with obesity compared to individuals without obesity to be OR: 3.30 (95% CI: 2.13–5.10). In contrast, the same association for individuals with a mean age ≥ 60 years displayed a statistically significant lower OR: 1.72 (95% CI: 1.40–2.11).

Seidu et al.³⁴ provided a similar analysis as they also divided their individuals by the mean age <60 and ≥ 60 years. However, their findings contrasted the ones by Chu et al.,²⁵ as Seidu et al.³⁴ estimated the strongest association between 'severe outcome' and BMI ≥ 25 kg/m² versus BMI < 25 kg/m² to be among the older group, RR: 3.41 (95% CI: 2.28–5.09), whilst no such link was found for the younger group, RR: 1.47 (95% CI: 0.90–2.40).

4.8 | Mortality

The most detrimental outcome of COVID-19 is death. Twenty-one studies reported on the association between death in relation to SARS-CoV-2 infection and obesity and/or overweight.^{13–15,17–30,32,34,37,39}

Fourteen studies found an association between mortality in relation to COVID-19^{13–15,18,21,22,24,26–28,30,32,34,39} and overweight and/or obesity versus BMI < 25 kg/m² without obesity, and seven studies found no such association.^{17,19,20,23,25,29,37}

Twelve of the 13 studies provided a meta-analysis with ORs or RRs ranging between 1.14²⁷ to 3.34²⁸ when comparing individuals with obesity to individuals without obesity (Figure 4).

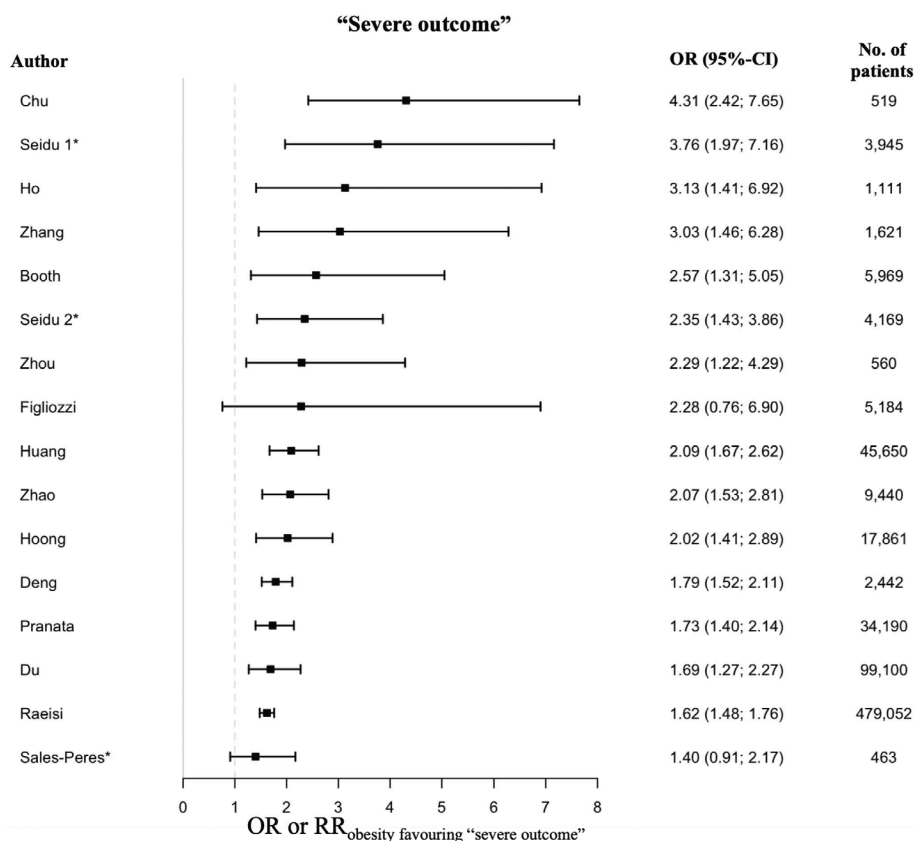
Comparing individuals with a BMI ≥ 25 kg/m² to individuals with a BMI <25 kg/m², Seidu et al.³⁴ found an RR of 3.52 (95% CI: 1.32–9.42).

Despite nonsignificant ORs reported by seven studies^{17,19,20,23,25,29,37} it should be noted that only two studies^{17,25} reported an OR < 1.0 and the study by Zhou et al.³⁷ provided a near significant positive association (OR: 1.15 [95% CI: 0.98–1.34]).

A subgroup analysis, comparing mortality of different BMI intervals to BMI <25 kg/m² were conducted by both Yang et al.²⁴ and Yang et al.²⁷ These results are presented in Table S5 suggesting that only individuals with BMI ≥ 40 kg/m² experienced a significant increased mortality after a SARS-CoV-2 infection. However, when using BMI <30 kg/m² as reference, Yang et al.²⁴ found a dose-response relationship: BMI ≥ 30 kg/m², OR: 1.65 (95% CI: 1.21–2.25); 35 kg/m² \leq BMI <40 kg/m², OR: 1.91 (95% CI: 1.04–3.49); BMI ≥ 40 kg/m², OR: 1.71 (95% CI: 1.32–2.22).

Du et al.²⁸ performed a dose-response meta-analysis regarding the association between mortality and obesity and reported a linear

FIGURE 3 Forest plot summarizing the association between obesity and the risk of the composite outcome ‘severe outcome’. Booth compared severe obesity to without severe obesity; Du compared BMI ≥ 30 kg/m² to BMI < 30 kg/m²; Seidu 1 compared BMI > 35 kg/m² to BMI < 25 kg/m²; Seidu 2 compared BMI ≥ 25 kg/m² to BMI < 25 kg/m²; all others compared obesity to without obesity. Seidu 1, Seidu 2, and Sales-Peres reported effect estimates as risk ratios (RR); all others reported odds ratios (OR)



association ($p_{\text{nonlinearity}} = .12$) with a risk of 6% for each 1 kg/m² increase in BMI (OR: 1.06 [95% CI: 1.02–1.10]). This is in contrast to the study by Deng et al.²⁰ as they reported a possible nonlinear association ($p_{\text{nonlinearity}} < .05$), however, a possible association was not reported (OR: 0.96 [95% CI: 0.83–1.11]).

Mesas et al.²³ stratified SARS-CoV-2 positive individuals by age >60 or ≤ 60 years and investigated the risk of dying by comparing individuals with obesity to individuals without obesity. However, they only reported nonsignificant findings (age > 60 years: OR: 0.90 [95% CI: 0.67–1.20]; age ≤ 60 years: OR: 1.62 [95% CI: 0.92–2.83]). Despite the nonsignificant finding the effect estimates seem to trend towards individuals with obesity younger than 60 years are at increased risk of dying following SARS-CoV-2 infection.

5 | DISCUSSION

By comparing individuals with overweight and obesity to individuals without overweight and obesity, we found in this updated umbrella review that overweight, and obesity augmented disease progression of COVID-19 with increased hospitalization, ICU admission, need for IMV and the composite outcome of ‘severe outcome’. Fourteen of 21 studies reported an association between obesity and increased mortality, with some studies^{24,27,28} reporting a dose–response relationship between the two. However, since seven of the included studies found no relationship, further investigations are required to clarify if a possible association exists between obesity and death due to COVID-19.

The ongoing COVID-19 pandemic pose a challenge to the limited medical resources⁵⁴ in the healthcare system and may force clinicians to prioritize the access to medical services for the most vulnerable patient groups. Possibly, COVID-19 patients with overweight and obesity admitted to the hospital should be prioritized compared to COVID-19 patients with normal body weight. However, it is important to note that only the most affected individuals will be admitted to the hospital and all the effect estimates presented throughout this paper should be reserved for these patients. In general, only 0.2% of all SARS-CoV-2 positive individuals are hospitalized.⁵⁵ Nevertheless, as stated earlier individuals with overweight and/or obesity are more prone to hospitalization as compared to individuals without overweight and/or obesity.

Concerning the mortality, an insufficient power among some of the primary studies may distort the reported association resulting in an underestimation of the reported effect. Multiple of greatly used primary studies included a small number of individuals and an even smaller number of individuals with obesity.^{56–58} For instance, the study by Ong et al.⁵⁶ was a minor study with just 91 patients, in which only four individuals died (three with BMI <25 kg/m²; one with BMI ≥ 25 kg/m²). Halvatsiotis et al.⁵⁸ reported 26 deaths (14 without obesity; 12 with obesity) among only 90 ICU-hospitalized individuals with COVID-19, however, possibly due to the lack of power, the association between obesity and death due to COVID-19 was found nonsignificant ($p = .08$). In comparison, the primary study by Gao et al.⁵⁵ utilizing data from more than 6.9 million patients reported a 4% increase in mortality for each increment in BMI above 23 kg/m².

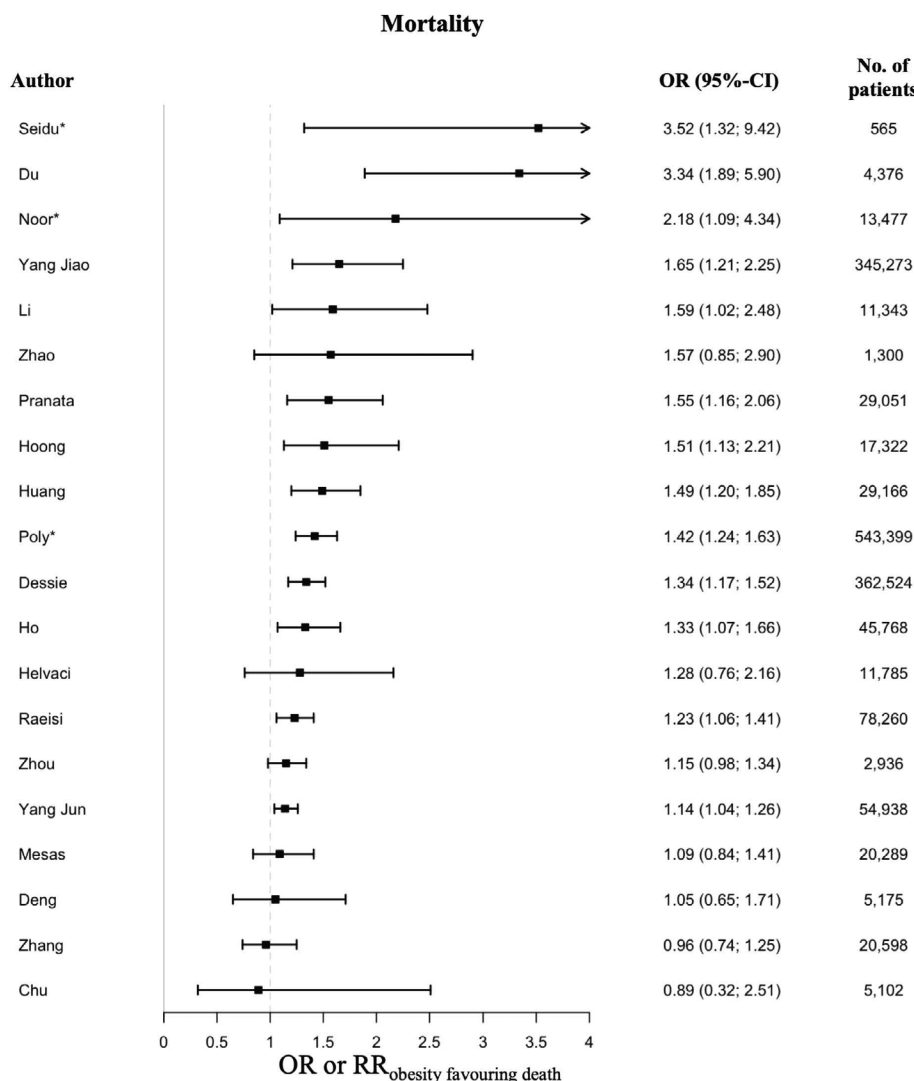


FIGURE 4 Forest plot summarizing the association between obesity and mortality. Du, Li, and Yang compared BMI ≥ 30 kg/m² to BMI < 30 kg/m²; Seidu compared BMI ≥ 25 kg/m² to BMI < 25 kg/m². All others compared obesity to without obesity. Seidu, Noor, and Poly reported effect estimates as risk ratios (RR); all others reported odds ratios (OR)

Few studies provided a stratified analysis on the association between disease progression and age.^{23,25,34,38,39} Of these, three found disease progression to be greatest among the younger (<60 years) individuals^{25,38,39} when comparing individuals with obesity to individuals without obesity, whilst another study reported the strongest association among the older (≥ 60 years) individuals,³⁴ and a fifth study did not find any significant associations when stratifying individuals by age.²³

Despite the secondary literature reporting diverging results concerning the role of obesity in relation to disease severity and age, primary studies with great *n* numbers (i.e., >100,000) may provide evidence for an increased risk associated with overweight or obesity. The primary study by Kompaniyets et al.⁵⁹ found that in 148 494 SARS-CoV-2 infected adults from 238 U.S. hospitals that younger individuals (<65 years) with obesity were at a relatively higher risk of severe disease than their older counterparts (≥ 65 years) when comparing to individuals with normal weight. Concerning the risk of hospitalization and death, the younger individuals needed a BMI of 25–29.9 and 35–39.9 kg/m² to reach significant ORs, OR: 1.07 (95% CI: 1.03–1.10) and OR: 1.31 (95% CI: 1.08–1.59), whilst the older

group needed a BMI of 40–44.9 kg/m² on both occasions, OR: 1.04 (95% CI: 1.01–1.07) and OR: 1.19 (95% CI: 1.06–1.33). Gao et al.⁵⁵ provided similar findings as they reported significantly higher hazard ratios (HRs) for SARS-CoV-2 positive individuals aged 20–39 years versus aged >60 years concerning hospitalization, ICU admission and death after adjustments for various comorbidities, HR_{Hosp. 20–39}: 1.09 (95% CI: 1.08–1.10) versus HR_{Hosp. 60–79}: 1.04 (95% CI: 1.03–1.05), HR_{ICU 20–39}: 1.13 (95% CI: 1.11–1.16) versus HR_{ICU 60–79}: 1.05 (95% CI: 1.04–1.07), HR_{Death 20–39}: 1.17 (95% CI: 1.11–1.23) versus HR_{Death 60–79}: 1.03 (95% CI: 1.02–1.04), meaning that at any given time after exposure to SARS-CoV-2, an event (hospital admission, admission to ICU or death) is more likely occur in the younger group comparing individuals with obesity to individuals without obesity as compared to the older group. Such findings were somewhat in line with Chu et al.²⁵ and contrasting Seidu et al.³⁴ Both Gao et al.⁵⁵ and Chu et al.²⁵ adjusted their findings for various comorbidities whilst Seidu et al.³⁴ did not follow the same stringent methodology, as they only reported an increased risk of ‘severe outcome’ concerning BMI ≥ 25 kg/m² versus BMI <25 kg/m² among individuals >60 years exploiting both nonspecified adjusted estimates as well as unadjusted

estimates in their meta-analysis. Maybe this discrepancy in relation to age and disease severity can be explained merely by differences in the adjustments in the meta-analyses.

Regarding the risk of IMV, Kompaniyets et al.⁵⁹ found no differences between the different age groups suggesting that the primary contributor to the risk of IMV might be the mechanical compression of lungs forced by a high bodyweight.^{60,61} It should be noted that once exposed to IMV, BMI might not be associated to death due to COVID-19.⁶² This was demonstrated in a prospective multicentre study,⁶³ reporting BMI >40 kg/m² to be associated with increased mortality following SARS-CoV-2 infection and ICU admission (OR: 1.51 [95% CI: 1.01–2.25]). However, when exposed to IMV on Day 1 of ICU admission the association attenuated (OR: 1.13 [95% CI: 0.69–1.82]). Such result may indicate a relative protective effect of IMV in individuals with obesity, but selection bias is highly likely to influence the result. In this observational study clinicians used IMV based on their clinical experience rather than randomization. Maybe clinicians are more likely to use IMV in individuals with overweight and obesity earlier than in other patients.

Schwarzbach et al.⁶⁴ recently published a study looking at numerous pre-existing health conditions, including overweight and obesity, and severe COVID-19 outcomes. Like our study, they used the umbrella review approach summarizing the available evidence as of 11 December 2020. In total, Schwarzbach et al.⁶⁴ identified 13 systematic reviews exploiting 52 unique primary studies evaluating the possible association of severe COVID-19 and excess bodyweight. Schwarzbach et al.⁶⁴ re-evaluated the primary studies and reported pooled effect estimates stratified for studied geographical region. In support of our findings, they also reported an increased risk of severe COVID-19 outcomes when exposed to obesity compared to normal weight, however, methodological differences among the primary studies hindered the comparability resulting in some of the effect estimates to be based on only few primary studies.

In total, we identified 27 systematic reviews which included 260 unique primary studies. This suggests that a considerable amount of literature was published after the study by Schwarzbach et al,⁶⁴ hence the need for an update on the association between overweight and obesity and a severe COVID-19 outcome. Despite not presenting pooled effect estimates, we believe our paper provides an updated summarization on the evidence solely dedicated to the association between excess bodyweight and a severe COVID-19 outcome as presented by Schwarzbach et al.⁶⁴

Various mechanisms may explain the possible increased risk of severe disease in individuals with obesity following SARS-CoV-2-infection. First, the combination of obesity-induced chronic low-grade inflammation^{65,66} and the subsequent dysfunctional immune system⁶⁷ may represent optimal conditions for a 'cytokine storm'. Second, the abundance of the ACE-2-receptor, facilitating SARS-CoV-2 cell entry, in the alveolar epithelial tissue may cause respiratory failure to COVID-19, however, ACE-2 is also well represented in visceral adipose tissue (VAT). Following the increasing levels of VAT paralleling the increasing levels of BMI,⁶⁸ individuals with obesity maybe represent a better reservoir for the SARS-CoV-2 during secondary

viremia than lean individuals. Third, individuals with obesity may be more vulnerable than individuals with normal weight to respiratory diseases as obesity itself results in mechanical alterations in the motion of breathing: Decreased compliance of the chest wall,⁶⁰ increased airway resistance⁶¹ and decreasing various lung volumes.⁴⁰ The obesity-induced extraordinary load to the respiratory system on top of a possible exposition to enhanced viral load during secondary viremia and impaired immune response may contribute to individuals with obesity experiencing a more severe course of disease than individuals without obesity.

5.1 | Limitations

This paper has several limitations. First, by exploiting previously published systematic reviews this umbrella review was influenced by a considerable amount of overlapping data resulting in somewhat concordant findings among the systematic reviews. Hereby, we could not generate a pooled effect estimate for any of the five outcomes. On average each primary study was used 2.33 times. The abundant overlapping data should be kept in mind when comparing systematic reviews on the topic of obesity and COVID-19. Hence, future secondary studies should include enough 'newer' primary studies for the possibility of reaching new conclusions.

Second, is the lack of comparability among primary studies, hence secondary studies as well, observed as levels of I^2 (Table 1). The high levels of heterogeneity were listed as the reason for the two qualitative studies to refrain from quantitative deductions.^{38,39}

Third, no study restricted the group of reference to individuals with normal weight only. The most commonly used comparator group was individuals without obesity (BMI <30 kg/m² for non-Asian individuals and BMI <28 kg/m² for Asian individuals¹⁰). This group of reference also included individuals with underweight (i.e., BMI < 18.5 kg/m²) which diminished the reported associations as individuals with underweight previously has been reported to experience a worse prognosis following SARS-CoV-2 infection compared to individuals with normal weight.^{55,59,69} Therefore, we could not use individuals with normal weight as comparator as stated in the PICO question. Future studies should exclude underweight individuals when assessing the role of obesity in relation to COVID-19 outcomes.

Lastly, the study quality among the systematic reviews varied greatly according to AMSTAR-2. The key limitation was the lack of a prespecified protocol before conducting the study^{17,18,20,21,24–26,28,30,32,35,41–45,47,48,50} (Item no. 2). This, however, might be considered as a downside but was probably and understandably due to the urgent need to understand and manoeuvre the COVID-19 pandemic. Table S3 shows the full results of the AMSTAR-2 appraisal.

6 | CONCLUSION

In conclusion, this updated umbrella review provides an overview of the available secondary literature summarizing that individuals with

obesity compared to individuals without obesity experience an increased risk of COVID-19 severity measured as hospitalization, ICU admission, need for IMV, as well as the composite outcome 'severe outcome'. Overall, the data also seem to trend towards obesity acting as an individual risk factor for death due to COVID-19. In addition, obesity might affect the COVID-19 disease course in a dose-response manner with an incremental effect particularly seen among individuals younger than 60 years compared to individuals ≥ 60 years.

CONFLICT OF INTERESTS

The authors declare no conflict of interests.

AUTHOR CONTRIBUTIONS

Nickolai M. Kristensen: Literature search and selection, study appraisal, interpretation of studies, manuscript drafting. **Sigrid B. Gribsholt:** Study concept and design, critical revision of manuscript, general support and manuscript guidance. **Anton L. Andersen:** Study appraisal and interpretation of studies, creation of figures and revision of manuscript. **Bjørn Richelsen:** Study concept and design, critical revision of manuscript, general support and manuscript guidance. **Jens M. Bruun:** Study concept and design, critical revision of manuscript, general support and manuscript guidance. All authors have approved final version of the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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