Diabetes and Overweight/Obesity Are Independent, Nonadditive Risk Factors for In-Hospital Severity of COVID-19: An International, Multicenter Retrospective Meta-analysis

Danielle K. Longmore,[1,2,3]
Jessica E. Miller,[1,4] Siroon Bekkering,[1,5]
Christoph Saner,[1,6] Edin Mifsud,[1,7]
Yanshan Zhu,[8] Richard Saffery,[1,4]
Alistair Nichol,[9,10,11] Graham Colditz,[12]
Kirsty R. Short,[8] and David P. Burgner,[1,3,4,13]
on behalf of the International BMI-COVID
consortium*

[1]Murdoch Children's Research Institute, The Royal
Children's Hospital, Parkville, Victoria, Australia
[2]Menzies School of Health Research, Charles
Darwin University, Darwin, Australia
[3]Infectious Diseases Unit, Department of General
Medicine, The Royal Children's Hospital, Parkville, Victoria, Australia
[4]Department of Paediatrics, Melbourne University, Parkville, Victoria, Australia
[5]Department of Internal Medicine and Radboud
Institute for Molecular Life Sciences, Radboud University Medical Center, Nijmegen, the Netherlands
[6]Pediatric Endocrinology, Diabetology and Metabolism, Department of Pediatrics, University
Hospital Inselspital, University of Bern, Bern,
Switzerland
[7]World Health Organization Collaborating Centre for Reference and Research on Influenza,
Doherty Institute, Melbourne, Australia
[8]School of Chemistry and Molecular Biosciences,
The University of Queensland, Brisbane, Australia
[9]Department of Intensive Care, Alfred Health,
Melbourne, Australia
[10]Australian and New Zealand Intensive Care
Research Centre, Monash University, Melbourne,
Australia
[11]University College Dublin Clinical Research Centre, St Vincent's Hospital, Dublin, Ireland
[12]Washington University, St. Louis, MO
[13]Department of Paediatrics, Monash University,
Clayton, Victoria, Australia

Corresponding authors: David P. Burgner, david.
burgner@mcri.edu.au, and Danielle K. Longmore,
danielle.longmore@mcri.edu.au

OBJECTIVE

Obesity is an established risk factor for severe coronavirus disease 2019 (COVID-19), but the contribution of overweight and/or diabetes remains unclear. In a multicenter, international study, we investigated if overweight, obesity, and diabetes were independently associated with COVID-19 severity and whether the BMI-associated risk was increased among those with diabetes.

RESEARCH DESIGN AND METHODS

We retrospectively extracted data from health care records and regional databases of hospitalized adult patients with COVID-19 from 18 sites in 11 countries. We used standardized definitions and analyses to generate site-specific estimates, modeling the odds of each outcome (supplemental oxygen/noninvasive ventilatory support, invasive mechanical ventilatory support, and in-hospital mortality) by BMI category (reference, overweight, obese), adjusting for age, sex, and prespecified comorbidities. Subgroup analysis was performed on patients with preexisting diabetes. Site-specific estimates were combined in a meta-analysis.

RESULTS

Among 7,244 patients (65.6% overweight/obese), those with overweight were more likely to require oxygen/noninvasive ventilatory support (random effects adjusted odds ratio [aOR] 1.44; 95% CI 1.15–1.80) and invasive mechanical ventilatory support (aOR 1.22; 95% CI 1.03–1.46). There was no association between overweight and in-hospital mortality (aOR 0.88; 95% CI 0.74–1.04). Similar effects were observed in patients with obesity or diabetes. In the subgroup analysis, the aOR for any outcome was not additionally increased in those with diabetes and overweight or obesity.

CONCLUSIONS

In adults hospitalized with COVID-19, overweight, obesity, and diabetes were associated with increased odds of requiring respiratory support but were not associated with death. In patients with diabetes, the odds of severe COVID-19 were not increased above the BMI-associated risk.

In the first 6 months of the coronavirus disease 2019 (COVID-19) pandemic (until 30 June 2020), >10 million people had been infected with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and >500,000 COVID-19–related deaths had been recorded (1), but striking variation in clinical severity and outcomes remains. Identifying risk factors associated with more severe COVID-19 is essential for optimizing individual treatment and resource allocation and prioritizing immunization distribution. Obesity has emerged as an important risk factor for severe COVID-19 (2), but several key questions remain unanswered (3).

First, most studies to date have focused on individuals with obesity (BMI ≥30 kg/m^2) (4), but the specific contribution of overweight (BMI between ≥25 and <30) to severe COVID-19 has only been investigated in a few studies, which have reported inconsistent results (5–10). This is a significant knowledge gap, because 40% of the global population is overweight, in addition to the 13% living with obesity (11). Second, most studies are single-center analyses and are unlikely to be globally representative, given the marked intercountry variation in overweight and obesity (12). This shortcoming has partially been addressed by meta-analyses, but these rarely include individuals who are overweight (2). Finally, both overweight and obesity frequently occur with other comorbidities, particularly type 2 diabetes (13). However, many studies have either not adjusted for these covariables or the regression models used did not allow clinical translation of findings (3). Specifically, a key clinical question is whether patients with both diabetes and higher BMI have a higher risk of severe COVID-19 compared with those with diabetes and BMI in the normal range.

In the present study, we aimed to address these unresolved questions by performing an international, retrospective, multisite analysis of 7,244 hospitalized patients with COVID-19 from 18 sites in 11 countries. We used common definitions and analyses to delineate whether overweight, obesity, and diabetes are independent risk factors for respiratory support and in-hospital mortality. In patients with diabetes, we also investigated the association between BMI category and COVID-19 severity.

RESEARCH DESIGN AND METHODS
Study Design
We conducted an international, multicenter, retrospective analysis of hospitalized patients with COVID-19 from a total of 69 hospitals in 11 countries (Supplementary Table 1) from 17 January 2020 to 2 June 2020. Data from 69 hospitals were collated to form 18 sites that each provided site-specific outcomes and estimates. We modeled the odds of in-hospital respiratory support (supplemental oxygen/noninvasive ventilatory support, invasive mechanical ventilatory support) and in-hospital mortality by BMI category, adjusting for age, sex, and prespecified comorbidities, as described later in this section. A protocol was finalized on 20 April 2020 (see Statistical Analysis Plan [SAP] in Supplementary Material) prior to commencement of the study. The study was conducted in accordance with Good Clinical Practice guidelines, local regulations, and the ethical principles described in the Declaration of Helsinki. Ethical approval was obtained at the coordinating center (Murdoch Children's Research Institute [MCRI], Royal Children's Hospital, Melbourne, Australia; approval no. HREC 63887), and local approvals were obtained at participating sites, depending on local regulations. Informed consent was not required.

Data Source
We analyzed deidentified data from existing collections of hospital data and regional databases, including the Norwegian Intensive Care and Pandemic Registry, Norway, and Washington University, St. Louis, Missouri (see Supplementary Material for participating sites and investigators). Data from smaller contributing hospitals were collected for clinical auditing processes approved by local hospitals and in accordance with local regulations. Each site followed a standardized protocol for data coding and analysis to generate site-specific estimates for each study population (see SAP in Supplementary Material). Deidentified data from hospitals in Austria, Singapore, the Netherlands, Switzerland, and Indonesia were exported to the coordinating center (MCRI) for generation of site-specific estimates. All transfer of data and site-specific estimates to the MCRI was subject to a data transfer agreement. Statisticians at the MCRI completed the meta-analyses.

Data Collection
Study participants were aged ≥18 years, admitted to hospital with COVID-19 (confirmed by PCR for SARS-CoV-2), and had height and weight recorded on admission to participating sites with local approval to participate. The period for data collection from individual sites varied (Supplementary Table 1).

Information regarding participant demographic variables (age, sex), BMI, preexisting medical conditions, clinical variables including intensive care unit admission, and treatment including oxygen and noninvasive ventilatory support and mechanical ventilatory support were identified. Supplemental oxygen was defined as the provision of oxygen via nasal canulae or face mask. Noninvasive ventilatory support was defined as the use of a device providing continuous positive airway pressure or bilevel positive airway pressure. Cardiovascular disease was defined as preexisting, physician-diagnosed coronary heart disease, ischemic stroke, heart failure, and/or peripheral vascular disease. Diabetes was defined as preexisting diabetes (including type 1 or 2). In all countries, type 2 diabetes was diagnosed according to the American Diabetes Association guidelines or local guidelines with the same diagnostic criteria as the American Diabetes Association guidelines. For three sites only (Cape Town, South Africa; Lausanne, Switzerland; and Ticino, Switzerland), a small number of patients were included who were first diagnosed with diabetes during their admission with COVID-19. Preexisting respiratory conditions and hypertension were defined as physician-diagnosed and currently on treatment. Data cleaning was performed for out-of-range values, inconsistent data, and repeated participant entries. Central source data verification was not feasible for this study, because coding was performed by the individual participating centers.

Statistical Analysis
All analyses were conducted as outlined in our protocol (see SAP in Supplementary Material). Participant data are presented as frequency (percent). Each site (or the MCRI) followed a standardized protocol for data coding and analysis to generate site-specific estimates from each study population, modeling the odds of each outcome by BMI (calculated

as weight [kg] divided by height squared [m^2]) category (see SAP in Supplementary Material). BMI was categorized as underweight (≥12 to <18), normal (≥18 to <25 [reference]), overweight (≥25 to <30), and obese (≥30). In sensitivity analyses for Asian populations, respective BMI categories were based on the following ranges: ≥12 to <18.5, ≥18.5 to <24 (reference), ≥24 to <28, and ≥28 (14). Logistic regression was used to model the association between BMI category and the use of in-hospital respiratory therapies (supplemental oxygen/noninvasive ventilation, mechanical ventilation) and in-hospital mortality.

All models estimated crude (unadjusted) and adjusted odds ratios. Two levels of adjustments were made. The first level, available for all sites, included age, sex, preexisting cardiovascular disease, diabetes, preexisting respiratory conditions, and hypertension. The second level of adjustments included the first level of adjustments plus current smoking status and/or race/ethnicity, depending on data availability. The second level was available for only five sites. The crude and adjusted (first-level) models were run on data from a subgroup of patients with preexisting diabetes. No adjustment was made for multiple comparisons. Covariables had few missing data and no imputations were warranted. Site-specific adjusted estimates for BMI category, each independent covariable included in the adjusted models, and the diabetes subgroup estimates were combined in meta-analyses.

Summarized estimates included fixed and random effects models (15). Random effects estimates are presented in the text. Of note, the Los Angeles, New York, and Cape Town sites were not included in analysis of supplemental oxygen/noninvasive ventilatory support, because nearly all hospitalized patients received supplemental oxygen per local policies. Data on supplemental oxygen were not available for Austria, Norway, or Amphia (the Netherlands). Variations to the preplanned analysis were made because there were insufficient data available from the majority of sites. The outcomes not analyzed included intensive care unit length of stay, hospital length of stay, and extracorporeal membrane oxygenation use (see SAP in Supplementary Material). Site-specific analyses were performed in SAS (SAS Institute, Cary, NC), Stata (StataCorp College Station, TX), or R studio (PBC, Boston, MA) (16). Meta-analyses were performed in Stata SE, version 16.0 (17).

RESULTS

Characteristics of Patients Included in the Study

A total of 7,244 patients from 18 sites (n = 69 hospitals) in 11 countries were included in this study of hospitalized patients with COVID-19 (Supplementary Tables 1 and 3). Among these, 60.1% were male and 51.7% were older than 65 years. Overall, 34.8% were overweight and 30.8% obese; however, there was considerable variability across different individual countries and sites. Prevalence of obesity for each site country is provided in Supplementary Table 2. The rates of comorbidities and the frequency of outcomes varied across sites (Supplementary Tables 3 and 4). Prevalence of diabetes varied from 7% in Guangdong Province, China, to 46% in St. Louis, Missouri. Prevalence of diabetes among those of normal weight ranged from 6% in Milan Sacco, Italy, to 39% in Cape Town, South Africa. Prevalence of diabetes among those who were overweight or obese ranged from 7% and 5%, respectively, in Guangdong Province, China, to 47% and 53%, respectively, in St. Louis, Missouri.

Association of Overweight, Obesity With Supplemental Oxygen/ Noninvasive Ventilatory Support, Mechanical Ventilatory Support, and In-Hospital Death

Compared with normal weight, overweight and obesity were associated with increased odds of supplemental oxygen/noninvasive ventilatory support (random effects adjusted odds ratio (aOR) 1.44 [95% CI 1.15–1.80], P = 0.02; and aOR 1.75 [95% CI 1.33–2.30], P < 0.01), respectively (Fig. 1). Obesity was associated with a 73% increase in odds for invasive mechanical ventilatory support (aOR 1.73; 95% CI 1.29–2.32; P < 0.01) (Fig. 2), and a more modest association was observed for overweight (aOR 1.22; 95% CI 1.03–1.46; P = 0.02). Data on this outcome were not available from Amphia (the Netherlands).

Overweight was not associated with an increase in odds for in-hospital mortality (aOR 0.88; 95% CI 0.74–1.04; P = 0.13) (Fig. 3). Obesity was also not associated with an increase in odds of in-hospital mortality, with confidence limits including the null (aOR 1.23; 95% CI 0.92–1.64; P = 0.17). The low number of participants in the underweight group (n = 162) precluded calculation of robust odds ratios. The I^2 statistic, which describes the percentage of variation across studies that is due to heterogeneity rather than chance, was 43.6% and 53.7% among the obese groups for invasive mechanical ventilatory support and in-hospital mortality, respectively, suggesting modest heterogeneity across studies. Unadjusted site-specific odds ratios are presented in Figs. 1–3.

For the Chinese, Indonesian, and Singaporean sites, odds ratios varied slightly depending on whether the standard or Asian country–specific BMI categories were used. The variation did not meaningfully affect the summarized meta-analysis estimates (Supplementary Table 4). Additional adjustments for current smoking and race/ethnicity, where data were available, had little impact on the odds ratios (Supplementary Table 5).

Association of Diabetes With Supplemental Oxygen/Noninvasive Ventilatory Support, Mechanical Ventilatory Support, and In-Hospital Death

Compared with patients without diabetes, those with diabetes had an increased odds of needing mechanical ventilatory support in random effects models adjusted for all covariables, including BMI category and comorbidities (aOR 1.21; 95% CI 1.03–1.41; P = 0.02) (Supplementary Fig. 1). There was no increase in odds of noninvasive respiratory support or in-hospital mortality in those with diabetes (Supplementary Fig. 1). In addition to diabetes, other host factors previously associated with severe COVID-19 (i.e., increased age, male sex, preexisting cardiovascular disease, and chronic respiratory disease) (18) were each independently associated with an increased risk of one or more of the selected study outcomes (Supplementary Figs. 2–4).

Among Patients With Diabetes, Increased BMI Did Not Increase the Risk of Severe COVID-19 Outcomes

To further inform patient care, we next performed a subgroup analysis of individuals with diabetes. Specifically, we investigated if BMI category among those with diabetes was associated with the selected COVID-19 outcomes. Strikingly, there was no association between
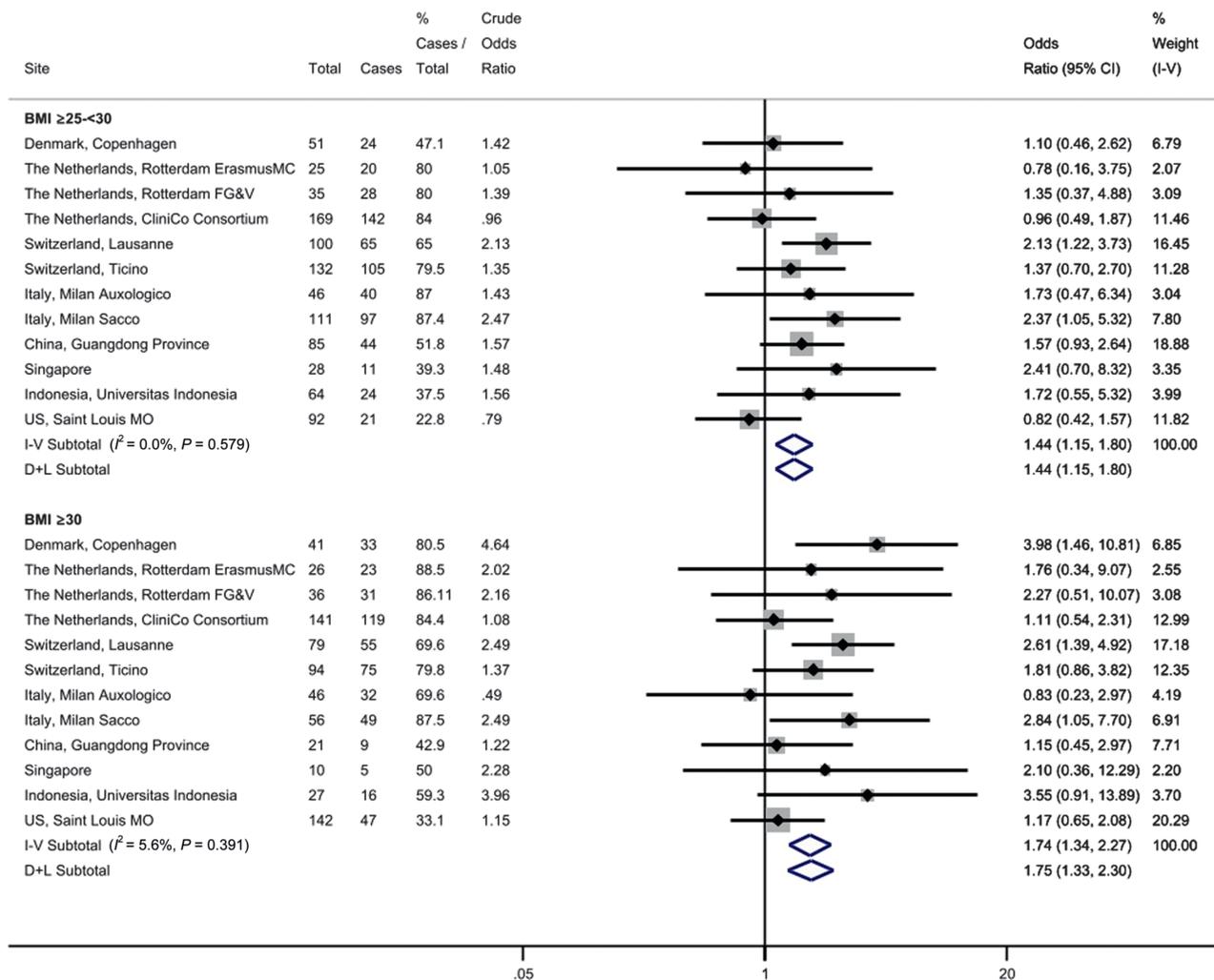
Site	Total	Cases	% Cases / Total	Crude Odds Ratio	Odds Ratio (95% CI)	% Weight (I-V)
BMI ≥25–<30						
Denmark, Copenhagen	51	24	47.1	1.42	1.10 (0.46, 2.62)	6.79
The Netherlands, Rotterdam ErasmusMC	25	20	80	1.05	0.78 (0.16, 3.75)	2.07
The Netherlands, Rotterdam FG&V	35	28	80	1.39	1.35 (0.37, 4.88)	3.09
The Netherlands, CliniCo Consortium	169	142	84	.96	0.96 (0.49, 1.87)	11.46
Switzerland, Lausanne	100	65	65	2.13	2.13 (1.22, 3.73)	16.45
Switzerland, Ticino	132	105	79.5	1.35	1.37 (0.70, 2.70)	11.28
Italy, Milan Auxologico	46	40	87	1.43	1.73 (0.47, 6.34)	3.04
Italy, Milan Sacco	111	97	87.4	2.47	2.37 (1.05, 5.32)	7.80
China, Guangdong Province	85	44	51.8	1.57	1.57 (0.93, 2.64)	18.88
Singapore	28	11	39.3	1.48	2.41 (0.70, 8.32)	3.35
Indonesia, Universitas Indonesia	64	24	37.5	1.56	1.72 (0.55, 5.32)	3.99
US, Saint Louis MO	92	21	22.8	.79	0.82 (0.42, 1.57)	11.82
I-V Subtotal ($I^2 = 0.0\%$, $P = 0.579$)					1.44 (1.15, 1.80)	100.00
D+L Subtotal					1.44 (1.15, 1.80)	
BMI ≥30						
Denmark, Copenhagen	41	33	80.5	4.64	3.98 (1.46, 10.81)	6.85
The Netherlands, Rotterdam ErasmusMC	26	23	88.5	2.02	1.76 (0.34, 9.07)	2.55
The Netherlands, Rotterdam FG&V	36	31	86.11	2.16	2.27 (0.51, 10.07)	3.08
The Netherlands, CliniCo Consortium	141	119	84.4	1.08	1.11 (0.54, 2.31)	12.99
Switzerland, Lausanne	79	55	69.6	2.49	2.61 (1.39, 4.92)	17.18
Switzerland, Ticino	94	75	79.8	1.37	1.81 (0.86, 3.82)	12.35
Italy, Milan Auxologico	46	32	69.6	.49	0.83 (0.23, 2.97)	4.19
Italy, Milan Sacco	56	49	87.5	2.49	2.84 (1.05, 7.70)	6.91
China, Guangdong Province	21	9	42.9	1.22	1.15 (0.45, 2.97)	7.71
Singapore	10	5	50	2.28	2.10 (0.36, 12.29)	2.20
Indonesia, Universitas Indonesia	27	16	59.3	3.96	3.55 (0.91, 13.89)	3.70
US, Saint Louis MO	142	47	33.1	1.15	1.17 (0.65, 2.08)	20.29
I-V Subtotal ($I^2 = 5.6\%$, $P = 0.391$)					1.74 (1.34, 2.27)	100.00
D+L Subtotal					1.75 (1.33, 2.30)	

(x-axis: .05   1   20)

Figure 1—Meta-analysis odds ratios for requirement of supplemental oxygen/noninvasive ventilatory support by BMI category. Models were adjusted for age ($<$65, ≥65 years), sex (male/female), preexisting cardiovascular disease (yes/no), diabetes (yes/no), preexisting respiratory conditions (yes/no), and hypertension (yes/no). The reference BMI is ≥18 to $<$25. The 95% CIs of the odds ratios were not adjusted for multiple testing and should not be used to infer definitive effects. Data from Norway; Amphia (in the Netherlands); Austria; South Africa; University of California, Los Angeles, California; and Cornell University, Ithaca, New York, were not included in this model because data were either not available for this outcome or all patients received the therapy. D+L, DerSimonian and Laird random effects model; FG&V, Franciscus Gasthuis & Vlietland; I-V, inverse-variance weighted fixed effects model; MC, medical center.

overweight or obesity and supplemental oxygen use/noninvasive ventilatory support (aOR 1.04 [95% CI 0.54–2.00], P = 0.91; and 1.29 [95% CI 0.68–2.46], P = 0.44, respectively), invasive mechanical ventilatory support (aOR 0.67 [95% CI 0.40–1.12], P = 0.10; and 1.25 [95% CI 0.62–2.53], P = 0.73, respectively), or in-hospital mortality (aOR 0.79 [95% CI 0.52–1.20], P = 0.28; and 1.14 [95% CI 0.61–2.13], P = 0.52, respectively) in those with preexisting diabetes (Fig. 4). In this subgroup analysis, the sample size was reduced and resulted in wide CIs.

CONCLUSIONS

In this large, international, multicenter study of patients hospitalized with COVID-19, overweight was associated overall with an increased requirement of respiratory support. The association between overweight and in-hospital mortality was not statistically significant. Similar trends were observed in patients with obesity. In addition to the associations with BMI, diabetes was independently associated with increased COVID-19 severity but not death. Importantly, among patients with diabetes, overweight/obesity were not associated with an increased risk of severe COVID-19.

The data presented here are consistent with those of previous studies that reported not only obesity but also advanced age, male sex, and preexisting cardiovascular, metabolic, and respiratory disease were associated with worse outcomes with COVID-19 (19). In the present study, neither overweight/obesity nor diabetes was associated with in-hospital mortality. Although previous analyses have suggested that obesity increases the mortality risk associated with COVID-19 (4,8,20), these studies did not necessarily make adjustments for age, sex, and other comorbidities as we did in the present study, or only found an effect on death for those with more severe obesity (BMI $>$35) (21). The data presented here are consistent with previous findings that an elevated BMI is associated with an increased requirement for respiratory support (5,22–24) and that diabetes in patients with COVID-19 is not
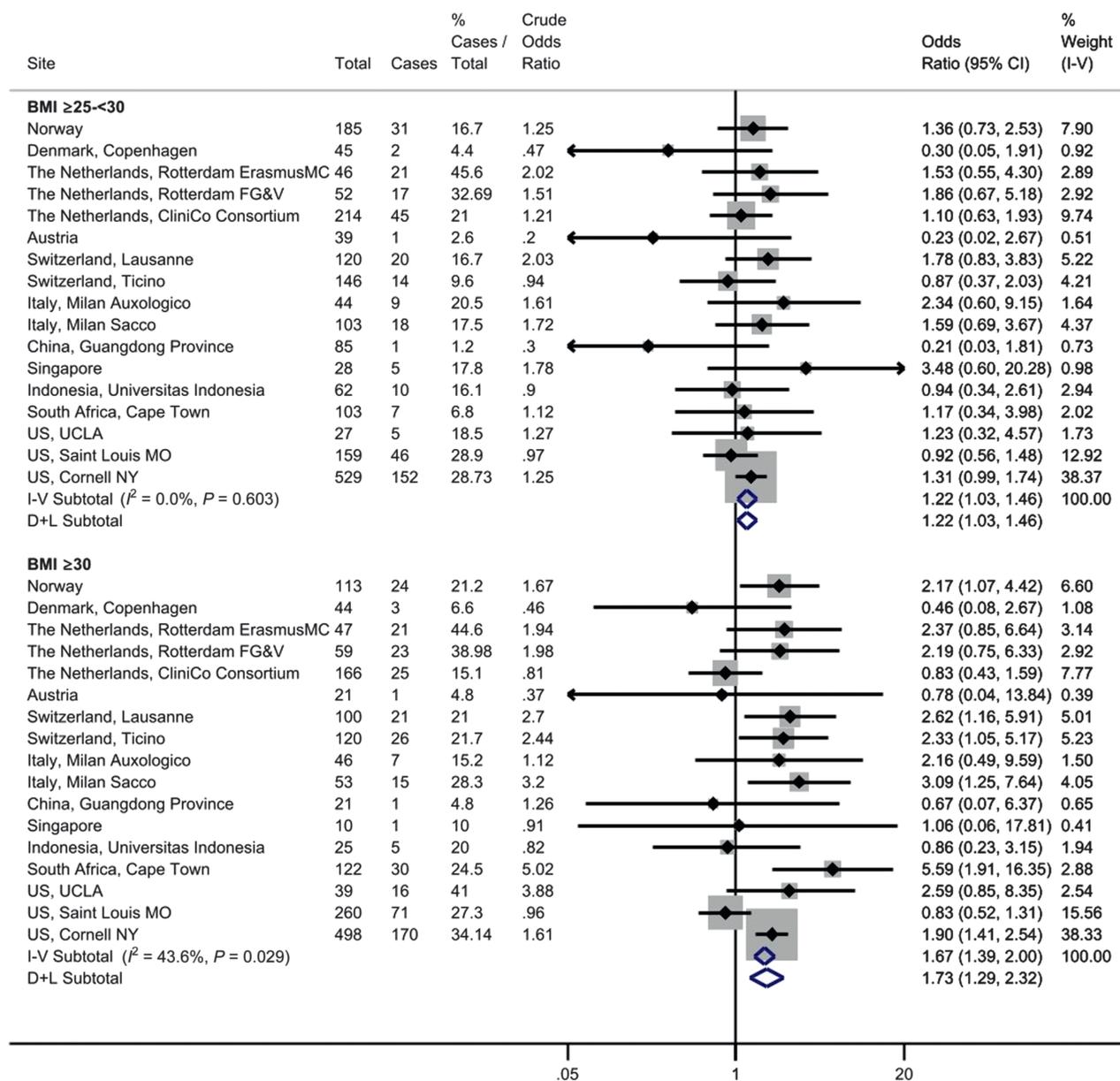
Site	Total	Cases	% Cases / Total	Crude Odds Ratio	Odds Ratio (95% CI)	% Weight (I-V)
BMI ≥25-<30						
Norway	185	31	16.7	1.25	1.36 (0.73, 2.53)	7.90
Denmark, Copenhagen	45	2	4.4	.47	0.30 (0.05, 1.91)	0.92
The Netherlands, Rotterdam ErasmusMC	46	21	45.6	2.02	1.53 (0.55, 4.30)	2.89
The Netherlands, Rotterdam FG&V	52	17	32.69	1.51	1.86 (0.67, 5.18)	2.92
The Netherlands, CliniCo Consortium	214	45	21	1.21	1.10 (0.63, 1.93)	9.74
Austria	39	1	2.6	.2	0.23 (0.02, 2.67)	0.51
Switzerland, Lausanne	120	20	16.7	2.03	1.78 (0.83, 3.83)	5.22
Switzerland, Ticino	146	14	9.6	.94	0.87 (0.37, 2.03)	4.21
Italy, Milan Auxologico	44	9	20.5	1.61	2.34 (0.60, 9.15)	1.64
Italy, Milan Sacco	103	18	17.5	1.72	1.59 (0.69, 3.67)	4.37
China, Guangdong Province	85	1	1.2	.3	0.21 (0.03, 1.81)	0.73
Singapore	28	5	17.8	1.78	3.48 (0.60, 20.28)	0.98
Indonesia, Universitas Indonesia	62	10	16.1	.9	0.94 (0.34, 2.61)	2.94
South Africa, Cape Town	103	7	6.8	1.12	1.17 (0.34, 3.98)	2.02
US, UCLA	27	5	18.5	1.27	1.23 (0.32, 4.57)	1.73
US, Saint Louis MO	159	46	28.9	.97	0.92 (0.56, 1.48)	12.92
US, Cornell NY	529	152	28.73	1.25	1.31 (0.99, 1.74)	38.37
I-V Subtotal (I^2 = 0.0%, P = 0.603)					1.22 (1.03, 1.46)	100.00
D+L Subtotal					1.22 (1.03, 1.46)	
BMI ≥30						
Norway	113	24	21.2	1.67	2.17 (1.07, 4.42)	6.60
Denmark, Copenhagen	44	3	6.6	.46	0.46 (0.08, 2.67)	1.08
The Netherlands, Rotterdam ErasmusMC	47	21	44.6	1.94	2.37 (0.85, 6.64)	3.14
The Netherlands, Rotterdam FG&V	59	23	38.98	1.98	2.19 (0.75, 6.33)	2.92
The Netherlands, CliniCo Consortium	166	25	15.1	.81	0.83 (0.43, 1.59)	7.77
Austria	21	1	4.8	.37	0.78 (0.04, 13.84)	0.39
Switzerland, Lausanne	100	21	21	2.7	2.62 (1.16, 5.91)	5.01
Switzerland, Ticino	120	26	21.7	2.44	2.33 (1.05, 5.17)	5.23
Italy, Milan Auxologico	46	7	15.2	1.12	2.16 (0.49, 9.59)	1.50
Italy, Milan Sacco	53	15	28.3	3.2	3.09 (1.25, 7.64)	4.05
China, Guangdong Province	21	1	4.8	1.26	0.67 (0.07, 6.37)	0.65
Singapore	10	1	10	.91	1.06 (0.06, 17.81)	0.41
Indonesia, Universitas Indonesia	25	5	20	.82	0.86 (0.23, 3.15)	1.94
South Africa, Cape Town	122	30	24.5	5.02	5.59 (1.91, 16.35)	2.88
US, UCLA	39	16	41	3.88	2.59 (0.85, 8.35)	2.54
US, Saint Louis MO	260	71	27.3	.96	0.83 (0.52, 1.31)	15.56
US, Cornell NY	498	170	34.14	1.61	1.90 (1.41, 2.54)	38.33
I-V Subtotal (I^2 = 43.6%, P = 0.029)					1.67 (1.39, 2.00)	100.00
D+L Subtotal					1.73 (1.29, 2.32)	

.05 1 20

Figure 2—Meta-analysis odds ratios for invasive mechanical ventilatory support by BMI category. Models were adjusted for age (<65, ≥65 years), sex (male/female), preexisting cardiovascular disease (yes/no), diabetes (yes/no), preexisting respiratory conditions (yes/no), and hypertension (yes/no). The reference BMI is ≥18 to <25. The 95% CIs of the odds ratios have not been adjusted for multiple testing and should not be used to infer definitive effects. Data from Amphia (in the Netherlands) were not available for invasive mechanical ventilatory support. D+L, DerSimonian and Laird random effects model; FG&V, Franciscus Gasthuis & Vlietland; I-V, inverse-variance weighted fixed effects model; UCLA, University of California, Los Angeles, California.

significantly associated with in-hospital mortality after appropriate adjustment (25).

The mechanisms underlying the association between BMI and COVID-19 severity likely reflect a dysregulated host response, resulting in heightened inflammation and/or a suboptimal antiviral response. There are a number of relevant immunomodulatory effects of overweight/obesity, including chronic systemic inflammation (26), reduced production of type I interferons (27), reduced antigen presentation (28), complement activation (29), and/or suboptimal T-cell responses (30). Moreover, these immunomodulatory effects may be compounded by the reduced functional respiratory capacity in individuals with overweight/obesity, which may lead to a lower threshold for noninvasive or invasive respiratory support (31).

It is likely that the independent role identified for diabetes in COVID-19 severity reflects the role of hyperglycemia in severe respiratory disease. Indeed, data from Denmark suggest that each 1 mmol/L increase in plasma glucose level is associated with a 6% increased risk of hospitalization for pneumonia (32). Elevated blood glucose levels are also associated with altered activity of transporters responsible for clearing the lung of interstitial edema and for maintaining the integrity of the pulmonary epithelial–endothelial barrier (33–35), both of which are likely to be important in determining the clinical outcome of SARS-CoV-2 infection. This hypothesis is
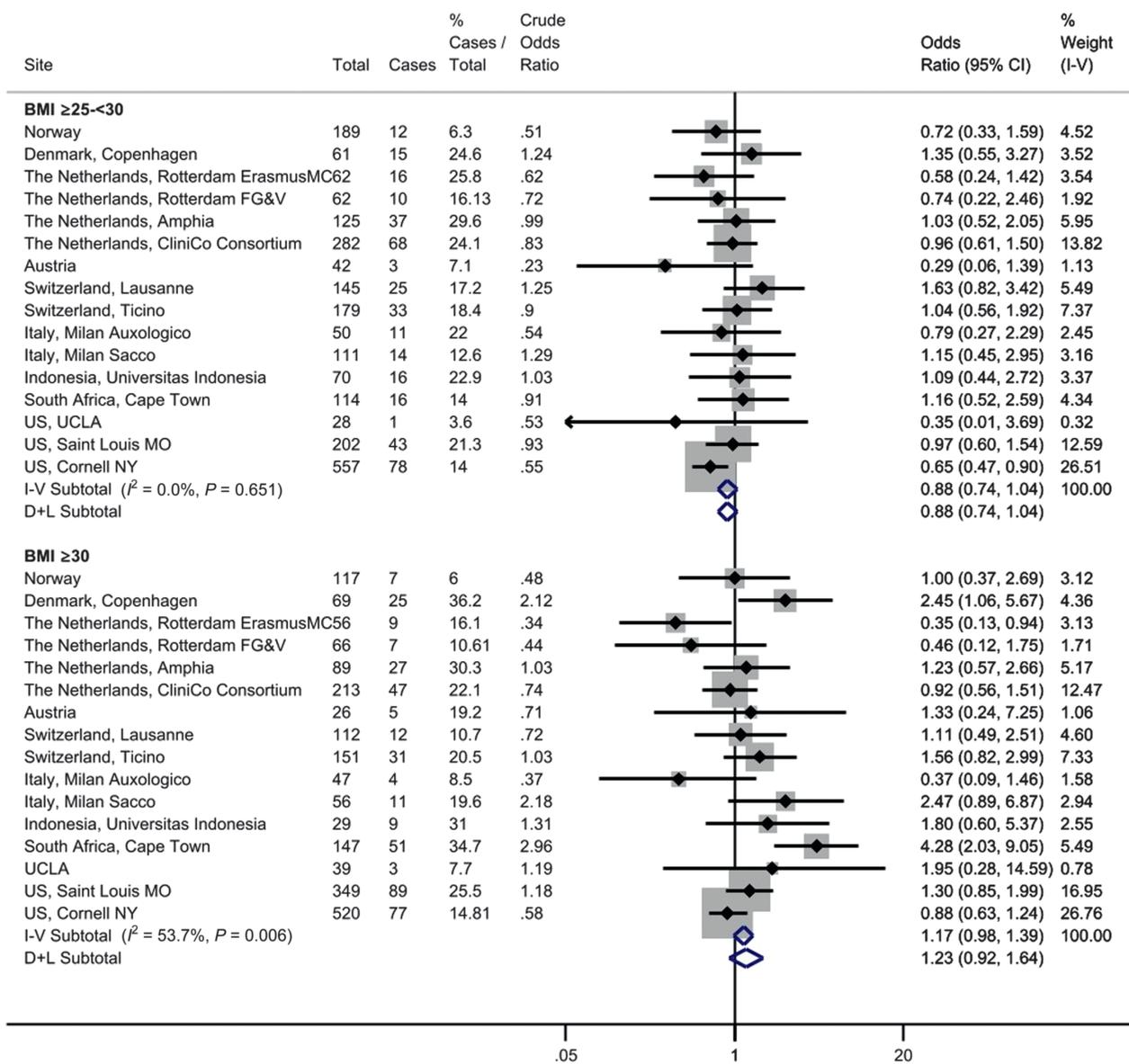
Site	Total	Cases	% Cases / Total	Crude Odds Ratio		Odds Ratio (95% CI)	% Weight (I-V)
BMI ≥25–<30							
Norway	189	12	6.3	.51		0.72 (0.33, 1.59)	4.52
Denmark, Copenhagen	61	15	24.6	1.24		1.35 (0.55, 3.27)	3.52
The Netherlands, Rotterdam ErasmusMC	62	16	25.8	.62		0.58 (0.24, 1.42)	3.54
The Netherlands, Rotterdam FG&V	62	10	16.13	.72		0.74 (0.22, 2.46)	1.92
The Netherlands, Amphia	125	37	29.6	.99		1.03 (0.52, 2.05)	5.95
The Netherlands, CliniCo Consortium	282	68	24.1	.83		0.96 (0.61, 1.50)	13.82
Austria	42	3	7.1	.23		0.29 (0.06, 1.39)	1.13
Switzerland, Lausanne	145	25	17.2	1.25		1.63 (0.82, 3.42)	5.49
Switzerland, Ticino	179	33	18.4	.9		1.04 (0.56, 1.92)	7.37
Italy, Milan Auxologico	50	11	22	.54		0.79 (0.27, 2.29)	2.45
Italy, Milan Sacco	111	14	12.6	1.29		1.15 (0.45, 2.95)	3.16
Indonesia, Universitas Indonesia	70	16	22.9	1.03		1.09 (0.44, 2.72)	3.37
South Africa, Cape Town	114	16	14	.91		1.16 (0.52, 2.59)	4.34
US, UCLA	28	1	3.6	.53		0.35 (0.01, 3.69)	0.32
US, Saint Louis MO	202	43	21.3	.93		0.97 (0.60, 1.54)	12.59
US, Cornell NY	557	78	14	.55		0.65 (0.47, 0.90)	26.51
I-V Subtotal ($I^2 = 0.0\%$, $P = 0.651$)						0.88 (0.74, 1.04)	100.00
D+L Subtotal						0.88 (0.74, 1.04)	
BMI ≥30							
Norway	117	7	6	.48		1.00 (0.37, 2.69)	3.12
Denmark, Copenhagen	69	25	36.2	2.12		2.45 (1.06, 5.67)	4.36
The Netherlands, Rotterdam ErasmusMC	56	9	16.1	.34		0.35 (0.13, 0.94)	3.13
The Netherlands, Rotterdam FG&V	66	7	10.61	.44		0.46 (0.12, 1.75)	1.71
The Netherlands, Amphia	89	27	30.3	1.03		1.23 (0.57, 2.66)	5.17
The Netherlands, CliniCo Consortium	213	47	22.1	.74		0.92 (0.56, 1.51)	12.47
Austria	26	5	19.2	.71		1.33 (0.24, 7.25)	1.06
Switzerland, Lausanne	112	12	10.7	.72		1.11 (0.49, 2.51)	4.60
Switzerland, Ticino	151	31	20.5	1.03		1.56 (0.82, 2.99)	7.33
Italy, Milan Auxologico	47	4	8.5	.37		0.37 (0.09, 1.46)	1.58
Italy, Milan Sacco	56	11	19.6	2.18		2.47 (0.89, 6.87)	2.94
Indonesia, Universitas Indonesia	29	9	31	1.31		1.80 (0.60, 5.37)	2.55
South Africa, Cape Town	147	51	34.7	2.96		4.28 (2.03, 9.05)	5.49
UCLA	39	3	7.7	1.19		1.95 (0.28, 14.59)	0.78
US, Saint Louis MO	349	89	25.5	1.18		1.30 (0.85, 1.99)	16.95
US, Cornell NY	520	77	14.81	.58		0.88 (0.63, 1.24)	26.76
I-V Subtotal ($I^2 = 53.7\%$, $P = 0.006$)						1.17 (0.98, 1.39)	100.00
D+L Subtotal						1.23 (0.92, 1.64)	

.05   1   20

Figure 3—Meta-analysis odds ratios for in-hospital mortality by BMI category. Models were adjusted for age (<65, ≥65 years), sex (male/female), preexisting cardiovascular disease (yes/no), diabetes (yes/no), preexisting respiratory conditions (yes/no), and hypertension (yes/no). The reference BMI is ≥18 to <25. The 95% CIs of the odds ratios were not adjusted for multiple testing and should not be used to infer definitive effects. Data from Guandong Province, China, and Singapore were not available for in-hospital mortality. D+L, DerSimonian and Laird random effects model; FG&V, Franciscus Gasthuis & Vlietland; I-V, inverse-variance weighted fixed effects model; UCLA, University of California, Los Angeles, California.

consistent with observations that well-controlled blood glucose levels correlated with improved clinical outcomes in patients with COVID-19 who also had diabetes (36). More severe COVID-19, however, may also be associated with elevated glucose levels (37). With respect to the relationship between longer-term glucose control and COVID-19 severity, an elevated hemoglobin A_{1c} is associated with increased risk of hospital admission due to COVID-19 in those with diabetes (38). Additional studies investigating the mechanistic roles of both BMI and diabetes in COVID-19 severity are warranted.

Currently, it is estimated that ~90% of patients with type 2 diabetes are overweight or obese (39). Previous studies have suggested that among patients with COVID-19 who have diabetes, nonsurvivors had a greater prevalence of comorbidities compared with survivors (25). Given the clear independent role of BMI in COVID-19 severity, we reasoned that patients with both diabetes and an elevated BMI may be at increased risk of severe disease outcomes compared with patients with diabetes and a BMI in the normal range. Surprisingly, BMI was not associated with the risk of in-hospital

respiratory support or death among patients with both COVID-19 and diabetes. Larger studies will be needed to confirm these findings; however, this finding may reflect a "threshold effect" of susceptibility to severe COVID-19 in these conditions. This hypothesis will require clinical and experimental evaluation.

Our data will inform public policy, particularly for risk-stratification of severe COVID-19 disease. The U.S. Centers for Disease Control and Prevention identifies individuals with obesity (BMI ≥30) as being at increased risk for severe disease, as well as those with cardiovascular
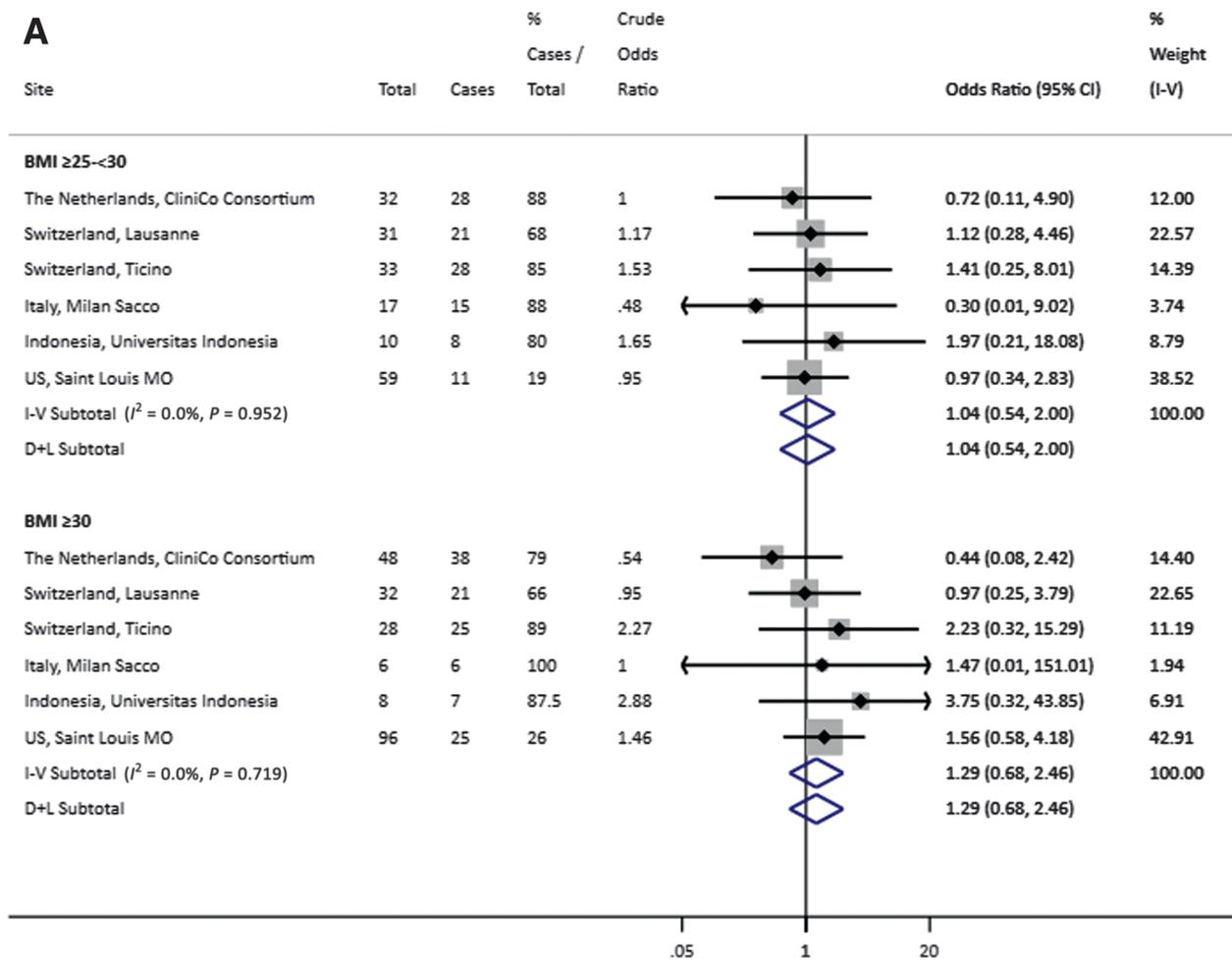
Figure 4—Meta-analysis odds ratios for supplemental oxygen/noninvasive ventilatory support (*A*), invasive mechanical ventilatory support (*B*), and in-hospital mortality by BMI category in patients with preexisting diabetes (*C*). Models were adjusted for age (<65, ≥65 years), sex (male/female), preexisting cardiovascular disease (yes/no), preexisting respiratory conditions (yes/no), and hypertension (yes/no). The reference BMI is ≥18 to <25. The 95% CI of the odds ratios have not been adjusted for multiple testing and should not be used to infer definitive effects. Data from New York were not available for this subgroup analysis. D+L, DerSimonian and Laird random effects model; FG&V, Franciscus Gasthuis & Vlietland; I-V, inverse-variance weighted fixed effects model.

disease, and has recently outlined that individuals who are overweight may be at increased risk (40). Similarly, the most recent guidelines from Public Health England consider overweight and obesity as risk factors for severe COVID-19 (41), in contrast to more conservative guidelines from the U.K. National Health Service that suggested an increased risk only for a BMI ≥40 (42). The World Health Organization now considers obesity a risk factor for severe COVID-19 disease (43). Inconsistent recommendations may impede optimal patient care and compromise clear public health messaging. To our knowledge, there is currently no clinical guidance on the role of BMI in COVID-19 risk stratification of patients with diabetes.

We acknowledge limitations of our study. Data on socioeconomic status were not available, limiting the interpretation of these findings, particularly because there may be important relationships among BMI, race/ethnicity, and socioeconomic status (44). Adjustment for confounders including smoking and race/ethnicity was only possible for five sites, with no difference in odds ratio observed. Supplemental oxygen use varied; oxygen was administered to all hospitalized patients at a limited number of sites, affecting our ability to determine the influence of host comorbidities on this outcome. There may also be varying and unmeasurable differences in thresholds for escalating care in those with overweight and obesity.

Given that this analysis involves patients admitted to hospital with COVID-19 only, we also were unable to assess whether patients with diabetes and obesity were more likely to experience out-of-hospital death due to COVID-19 infection. These patients were not captured in the data, and this may have resulted in an underestimation of overall mortality. At some sites, BMI was not consistently recorded during the study period, which may have introduced site-specific bias. Because of the relatively small numbers of patients at some sites, we were unable to stratify BMI categories to include underweight (BMI <18.5) or BMI >40, so we were unable to report specific odds ratios for these groups. We were unable to
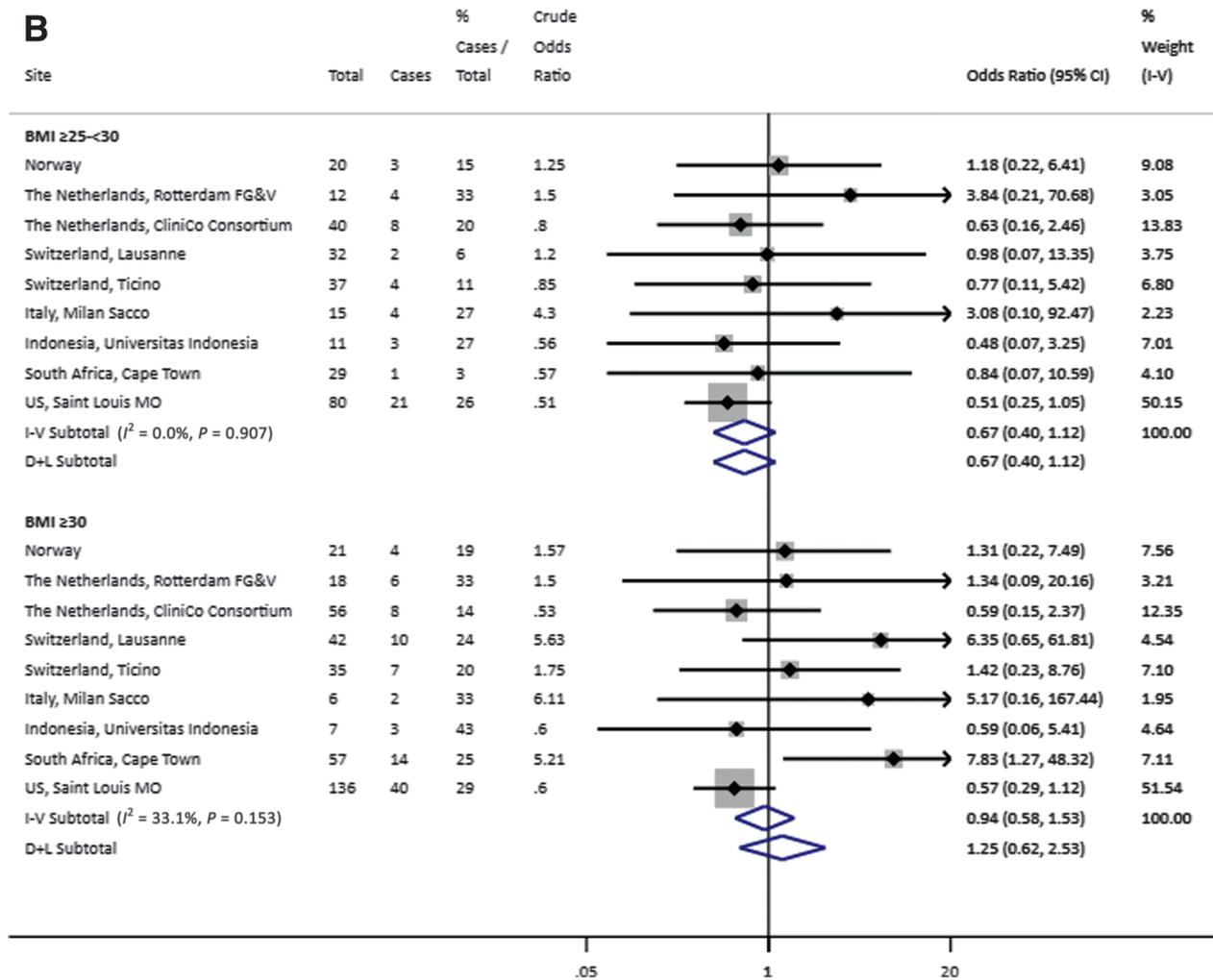
Figure 4—*Continued.*

differentiate between type 1 and type 2 diabetes from the data available. Notwithstanding, the majority of patients with diabetes included would be expected to have type 2 diabetes, given the expected prepandemic relative prevalence (25). Moreover, type 1 diabetes has not been associated with increased severity of COVID-19 (45); therefore, we believe the findings for patients with diabetes predominantly represent those with type 2 diabetes. It is important to note that the modest sample size of this study precludes precise estimates of risk, particularly with respect to the associations among the subgroup of patients with diabetes. We acknowledge that the number of deaths likely decreased over the period of the study, which may have altered results dependent on dates of data collection and the timing of COVID-

19 surges in different countries. Given that improvements in clinical care did not occur uniformly in all countries, however, we were unable to adjust for this in our analysis. Finally, although we enrolled multiple sites, our findings should not be considered regionally or globally representative and the study population was underrepresented for low- and middle-income countries, which may limit generalizability.

Notwithstanding, to our knowledge, this study remains one of the largest multinational studies to date on the risk factors associated with severe COVID-19. Inclusion of individuals from low- and middle-income countries and disadvantaged or higher-risk populations in such analyses is essential, and it is hoped that as the pandemic progresses and more data become available, data

from these populations can be added to our ongoing analysis; potential collaborators are encouraged to contact the corresponding authors.

In conclusion, our findings highlight the importance of maintaining a healthy BMI, because patients with either overweight or obesity are at risk for severe COVID-19. Although reducing the current levels of overweight and obesity is unlikely in the short term to have an impact on the COVID-19 pandemic, doing so may contribute to reducing disease burden in future viral pandemics (41,46). Furthermore, the absence of an association between overweight/obesity and COVID-19 severity among those with diabetes should guide additional exploration of mechanistic pathways and may inform risk stratification and appropriate patient treatment. Finally, our findings

C

Site	Total	Cases	% Cases / Total	Crude Odds Ratio		Odds Ratio (95% CI)	% Weight (I-V)
BMI ≥25–<30							
Norway	22	2	9	.9		0.81 (0.08, 7.94)	3.35
The Netherlands, Rotterdam ErasmusMC	15	4	27	.36		0.66 (0.07, 6.28)	3.50
The Netherlands, Rotterdam FG&V	16	4	25	.89		0.32 (0.01, 7.61)	1.61
The Netherlands, Amphia	25	8	32	1.18		0.94 (0.11, 7.50)	3.97
The Netherlands, CliniCo Consortium	57	17	30	.64		0.65 (0.25, 1.70)	19.26
Switzerland, Lausanne	41	9	22	1.34		1.83 (0.44, 7.83)	8.53
Switzerland, Ticino	47	10	21	.62		0.69 (0.21, 2.29)	12.40
Italy, Milan Sacco	17	3	18	.89		0.64 (0.05, 8.76)	2.59
Indonesia, Universitas Indonesia	13	5	38	.44		0.44 (0.08, 2.29)	6.50
South Africa, Cape Town	35	6	17	1.66		2.10 (0.51, 8.69)	8.80
US, Saint Louis MO	95	15	16	.67		0.67 (0.31, 1.46)	29.48
I-V Subtotal (I^2 = 0.0%, P = 0.930)						0.79 (0.52, 1.20)	100.00
D+L Subtotal						0.79 (0.52, 1.20)	
BMI ≥30							
Norway	24	3	12	1.29		1.71 (0.20, 14.49)	3.56
The Netherlands, Rotterdam ErasmusMC	11	2	18	.22		0.28 (0.03, 2.44)	3.38
The Netherlands, Rotterdam FG&V	20	2	10	.3		0.06 (0.00, 2.45)	1.07
The Netherlands, Amphia	25	9	36	1.41		2.13 (0.23, 20.13)	3.27
The Netherlands, CliniCo Consortium	73	17	23	.46		0.51 (0.20, 1.35)	17.91
Switzerland, Lausanne	46	4	9	.45		1.09 (0.21, 5.72)	6.00
Switzerland, Ticino	48	13	27	.85		1.16 (0.36, 3.77)	11.84
Italy, Milan Sacco	6	1	17	1		1.67 (0.09, 31.86)	1.90
Indonesia, Universitas Indonesia	8	3	37.5	.42		0.47 (0.08, 2.94)	4.92
South Africa, Cape Town	76	31	41	5.51		9.41 (2.61, 33.96)	9.92
US, Saint Louis MO	184	48	26	1.27		1.25 (0.64, 2.45)	36.24
I-V Subtotal (I^2 = 45.5%, P = 0.050)						1.16 (0.77, 1.74)	100.00
D+L Subtotal						1.14 (0.61, 2.13)	

Axis markers: .05   1   20

Figure 4—*Continued.*

may inform immunization prioritization for higher-risk groups.

References

1. World Health Organization. *Coronovirus Disease (COVID-19) Situation Report -162*. Geneva, World Health Organization, 2020, p. 17
2. Popkin BM, Du S, Green WD, et al. Individuals with obesity and COVID-19: a global perspective

on the epidemiology and biological relationships. Obes Rev 2020;21:e13128

3. Selvin E, Juraschek SP. Diabetes epidemiology in the COVID-19 pandemic. Diabetes Care 2020; 43:1690–1694

4. Rottoli M, Bernante P, Belvedere A, et al. How important is obesity as a risk factor for respiratory failure, intensive care admission and death in hospitalised COVID-19 patients? Results from a single Italian centre. Eur J Endocrinol 2020;183: 389–397

5. Simonnet A, Chetboun M, Poissy J, et al.; LICORN and the Lille COVID-19 and Obesity study group. High prevalence of obesity in severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) requiring invasive mechanical ventilation. Obesity (Silver Spring) 2020;28:1195–1199

6. Halasz G, Leoni ML, Villani GQ, Nolli M, Villani M. Obesity, overweight and survival in critically ill patients with SARS-CoV-2 pneumonia: is there an obesity paradox? Preliminary results from Italy. Eur J Prev Cardiol. 7 July 2020 [Epub ahead of print]. DOI: 10.1177/2047487320939675

7. Hamer M, Gale CR, Kivimäki M, Batty GD. Overweight, obesity, and risk of hospitalization for COVID-19: a community-based cohort study of adults in the United Kingdom. Proc Natl Acad Sci U S A 2020;117:21011–21013

8. Tartof SY, Qian L, Hong V, et al. Obesity and mortality among patients diagnosed with COVID-19: results from an integrated health care organization. Ann Intern Med 2020;173:773–781

9. Nakeshbandi M, Maini R, Daniel P, et al. The impact of obesity on COVID-19 complications: a retrospective cohort study. Int J Obes 2020;44: 1832–1837

10. Petrilli CM, Jones SA, Yang J, et al. Factors associated with hospital admission and critical illness among 5279 people with coronavirus disease 2019 in New York City: prospective cohort study. BMJ 2020;369:m1966

11. World Health Organization. Obesity and overweight, 2020. Accessed 17 October 2020. Available from https://www.who.int/news-room/fact-sheets/detail/obesity-and-overweight

12. World Health Organization. Prevalence of obesity among adults, BMI >= 30 (crude estimate) (%). 2017. Accessed 19 October 2020. Available from https://www.who.int/data/gho/data/indicators/indicator-details/GHO/prevalence-of-obesity-among-adults-bmi-=-30-(crude-estimate)-(-)

13. Smith KB, Smith MS. Obesity statistics. Prim Care 2016;43:121–135, ix

14. World Health Organization Expert Consultation. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. Lancet 2004;363:157–163

15. Harris R, Bradburn M, Deeks J, Harbord R, Altman D, Sterne J. metan: Fixed- and random-effects meta-analysis. Stata J 2008;8:3–28

16. RStudio. Integrated Development for R. RStudio, 2020. Accessed 3 September 2020. Available from https://www.rstudio.com/

17. Statacorp. Stata Statistical Software: release 16. College Station, TX, StataCorp LLC, 2019

18. Zaki N, Alashwal H, Ibrahim S. Association of hypertension, diabetes, stroke, cancer, kidney disease, and high-cholesterol with COVID-19 disease severity and fatality: a systematic review. Diabetes Metab Syndr 2020;14:1133–1142

19. Williamson EJ, Walker AJ, Bhaskaran K, et al. Factors associated with COVID-19-related death using OpenSAFELY. Nature 2020;584:430–436

20. Anderson MR, Geleris J, Anderson DR, et al. Body mass index and risk for intubation or death in SARS-CoV-2 infection: a retrospective cohort study. Ann Intern Med 2020;173:782–790

21. Klang E, Kassim G, Soffer S, Freeman R, Levin MA, Reich DL. Severe obesity as an independent risk factor for COVID-19 mortality in hospitalized patients younger than 50. Obesity (Silver Spring) 2020;28:1595–1599

22. Watanabe M, Caruso D, Tuccinardi D, et al. Visceral fat shows the strongest association with the need of intensive care in patients with COVID-19. Metabolism 2020;111:154319

23. Monteiro AC, Suri R, Emeruwa IO, et al. Obesity and smoking as risk factors for invasive mechanical ventilation in COVID-19: a retrospective, observational cohort study. PLoS One 2020; 15:e0238552

24. Cariou B, Hadjadj S, Wargny M, et al.; CORONADO Investigators. Phenotypic characteristics and prognosis of inpatients with COVID-19 and diabetes: the CORONADO study. Diabetologia 2020;63:1500–1515

25. Shi Q, Zhang X, Jiang F, et al. Clinical characteristics and risk factors for mortality of COVID-19 patients with diabetes in Wuhan, China: a two-center, retrospective study. Diabetes Care 2020;43:1382–1391

26. Suganami T, Tanaka M, Ogawa Y. Molecular mechanisms underlying obesity-induced chronic inflammation. In *Chronic Inflammation: Mechanisms and Regulation*. Miyasaka M, Takatsu K, Eds. Tokyo, Springer Japan, 2016, pp. 291–298

27. Siegers JY, Novakovic B, Hulme KD, et al. A high-fat diet increases influenza A virus-associated cardiovascular damage. J Infect Dis 2020; 222:820–831

28. Smith AG, Sheridan PA, Tseng RJ, Sheridan JF, Beck MA. Selective impairment in dendritic cell function and altered antigen-specific CD8+ T-cell responses in diet-induced obese mice infected with influenza virus. Immunology 2009;126:268–279

29. Lockhart SM, O'Rahilly S. When two pandemics meet: why is obesity associated with increased COVID-19 mortality? Med (N Y) 2020;1: 33–42

30. Paich HA, Sheridan PA, Handy J, et al. Overweight and obese adult humans have a defective cellular immune response to pandemic H1N1 influenza A virus. Obesity (Silver Spring) 2013;21: 2377–2386

31. Kassir R. Risk of COVID-19 for patients with obesity. Obes Rev 2020;21:e13034

32. Benfield T, Jensen JS, Nordestgaard BG. Influence of diabetes and hyperglycaemia on infectious disease hospitalisation and outcome. Diabetologia 2007;50:549–554

33. Yamashita T, Umeda F, Hashimoto T, et al. Effect of glucose on Na, K-ATPase activity in cultured bovine aortic endothelial cells. Endocrinol Jpn 1992;39:1–7

34. Rivelli JF, Amaiden MR, Monesterolo NE, et al. High glucose levels induce inhibition of Na,K-ATPase via stimulation of aldose reductase, formation of microtubules and formation of an acetylated tubulin/Na,K-ATPase complex. Int J Biochem Cell Biol 2012;44:1203–1213

35. Hulme KD, Yan L, Marshall RJ, et al. High glucose levels increase influenza-associated damage to the pulmonary epithelial-endothelial barrier. eLife 2020;9:e56907

36. Zhu L, She Z-G, Cheng X, et al. Association of blood glucose control and outcomes in patients with COVID-19 and pre-existing type 2 diabetes. Cell Metab 2020;31:1068–1077.e3

37. Coppelli A, Giannarelli R, Aragona M, et al.; Pisa COVID-19 Study Group. Hyperglycemia at hospital admission is associated with severity of the prognosis in patients hospitalized for COVID-19: the Pisa COVID-19 Study. Diabetes Care 2020; 43:2345–2348

38. Merzon E, Green I, Shpigelman M, et al. Haemoglobin A1c is a predictor of COVID-19 severity in patients with diabetes. Diabetes Metab Res Rev. 27 August 2020 [Epub ahead of print]. DOI: 10.1002/dmrr.3398

39. Public Health England. *Adult Obesity and Type 2 Diabetes*. London, Public Health England, 2014, pp. 39

40. Centers for Disease Control and Prevention. People with certain medical conditions, 2020. Accessed 26 October 2020. Available from https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-with-medical-conditions.html

41. Blackshaw J, Feeley A, Mabbs L, et al. *Excess Weight and COVID-19: Insights from New Evidence*. London, Public Health England, 2020

42. National Health Service. Coronavirus (COVID-19): Shielded patients list, 2020. Accessed 13 July 2020. Available from https://digital.nhs.uk/coronavirus/shielded-patient-list#risk-criteria

43. World Health Organization. COVID-19: vulnerable and high risk groups, 2020. Accessed 12 July 2020. Available from https://www.who.int/westernpacific/emergencies/covid-19/information/high-risk-groups

44. McLaren L. Socioeconomic status and obesity. Epidemiol Rev 2007;29:29–48

45. Vangoitsenhoven R, Martens PJ, van Nes F, et al. No evidence of increased hospitalization rate for COVID-19 in community-dwelling patients with type 1 diabetes. Diabetes Care 2020; 43:e118–e119

46. Short KR, Kedzierska K, van de Sandt CE. Back to the future: lessons learned from the 1918 influenza pandemic. Front Cell Infect Microbiol 2018;8:343