

Body Mass Index and Risk for Intubation or Death in SARS-CoV-2 Infection

A Retrospective Cohort Study

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Background: Obesity is a risk factor for pneumonia and acute respiratory distress syndrome.

Objective: To determine whether obesity is associated with intubation or death, inflammation, cardiac injury, or fibrinolysis in coronavirus disease 2019 (COVID-19).

Design: Retrospective cohort study.

Setting: A quaternary academic medical center and community hospital in New York City.

Participants: 2466 adults hospitalized with laboratory-confirmed severe acute respiratory syndrome coronavirus 2 infection over a 45-day period with at least 47 days of in-hospital observation.

Measurements: Body mass index (BMI), admission biomarkers of inflammation (C-reactive protein [CRP] level and erythrocyte sedimentation rate [ESR]), cardiac injury (troponin level), and fibrinolysis (D-dimer level). The primary end point was a composite of intubation or death in time-to-event analysis.

Results: Over a median hospital length of stay of 7 days (interquartile range, 3 to 14) days, 533 patients (22%) were intubated,

627 (25%) died, and 59 (2%) remained hospitalized. Compared with overweight patients, patients with obesity had higher risk for intubation or death, with the highest risk among those with class 3 obesity (hazard ratio, 1.6 [95% CI, 1.1 to 2.1]). This association was primarily observed among patients younger than 65 years and not in older patients (P for interaction by age = 0.042). Body mass index was not associated with admission levels of biomarkers of inflammation, cardiac injury, or fibrinolysis.

Limitations: Body mass index was missing for 28% of patients. The primary analyses were conducted with multiple imputation for missing BMI. Upper bounding factor analysis suggested that the results are robust to possible selection bias.

Conclusion: Obesity is associated with increased risk for intubation or death from COVID-19 in adults younger than 65 years, but not in adults aged 65 years or older.

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Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has infected more than 7 million people and resulted in more than 400 000 deaths worldwide as of June 2020. Early reports suggest that among infected individuals, 2% to 3% require mechanical ventilation for acute respiratory distress syndrome (ARDS), and overall mortality is 0.4% to 1.4% (1–3). Although preliminary data suggest efficacy of remdesivir in shortening duration of symptoms if given early in the disease course, the mainstay of therapy in SARS-CoV-2-associated respiratory failure remains avoiding ventilator-induced lung injury while awaiting lung recovery (4–7). A better understanding of risk factors for acute respiratory failure in coronavirus 2019 (COVID-19) may identify pathways for targeted prevention and treatment, a public health priority (8).

Obesity, as defined by a body mass index (BMI) greater than 30 kg/m², is a risk factor for bacterial and viral pneumonia, ARDS, and acute respiratory failure after lung transplantation (9–13). Paradoxically, multiple studies and meta-analyses suggest that obesity is associated with lower mortality from pneumonia and ARDS (12, 14, 15). For COVID-19, early reports note that obesity is more common among patients who require hospital admission or mechanical ventilation, and that it

may be associated with an increased risk for death (16–18). Subsequent large cohort studies from the United States and the United Kingdom show that obesity is a risk factor for critical illness and death from COVID-19 (19, 20). Early reports also suggest that diabetes, hypertension, and cardiovascular disease are associated with invasive mechanical ventilation and death in COVID-19 (2, 16). Whether comorbid conditions and age confound or modify the association between BMI and COVID-19 outcomes is unknown.

There are several molecular mechanisms by which obesity might potentiate acute respiratory failure in COVID-19. Increased fat mass is associated with the accumulation of immune cells, predominantly proinflammatory adipose tissue macrophages, with increased expression of inflammatory molecules, including interleukin-6 (21, 22). Elevated interleukin-6 levels are implicated in SARS-CoV-2-associated cytokine release-like syndrome; are a risk factor for death in COVID-19

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critical illness (23, 24); and are a therapeutic target for tocilizumab and sarilumab, which are being studied in clinical trials as treatments for COVID-19 (25, 26). Obesity is associated with known causes of cardiovascular disease, including hypertension, hyperlipidemia, and diabetes. Myocardial injury is prevalent among patients hospitalized with COVID-19, and even mildly elevated cardiac troponin levels are associated with an increased risk for death (27, 28). Obesity is associated with a hypercoagulable state (29–33). Autopsies reveal a high incidence of venous thromboembolism in COVID-19 (34–36). The D-dimer level, a measure of fibrinolysis, is independently associated with death in COVID-19 critical illness (24). Further investigation as to whether obesity potentiates these pathogenic mechanisms in acute respiratory failure in COVID-19 may help risk stratify patients for clinical care and clinical trials and may identify novel targets for therapy.

We hypothesized that obesity would be associated with an increased risk for intubation or death among patients hospitalized with SARS-CoV-2 infection. We also hypothesized that greater BMI would be associated with higher levels of biomarkers of inflammation (C-reactive protein [CRP] and erythrocyte sedimentation rate [ESR]), cardiac injury (high-sensitivity troponin), and fibrinolysis (D-dimer) at time of hospital admission.

METHODS

Study Design and Patients

We performed a retrospective cohort study of adults who were consecutively admitted from the emergency department (ED) to NewYork-Presbyterian/Columbia University Irving Medical Center and the affiliated Allen Hospital between 10 March 2020 and 24 April 2020 with a positive SARS-CoV-2 result on real-time reverse-transcription polymerase chain reaction (PCR) assay from nasopharyngeal swab. We excluded patients who were discharged from the ED, those who died in the ED before hospital admission, and those younger than 18 years. We followed up patients for in-hospital mortality until 10 June 2020 (that is, for at least 47 days of in-hospital observation). The study was approved by the Columbia University Institutional Review Board.

Data Sources

We obtained data from the NewYork-Presbyterian (NYP)/Columbia University Irving Medical Center (CUIMC) Clinical Data Warehouse. The warehouse contains electronic data for inpatient and outpatient visits at NYP/CUIMC facilities, including demographic characteristics, diagnoses, procedures, medications, laboratory tests, vital signs flowsheet data, and other clinical variables (the Appendix, available at [Annals.org](https://www.annals.org), provides details on data sources and quality control). Diagnoses were extracted from both the inpatient and outpatient records over the prior 3 years and were defined by groups of diagnosis codes in the International Classification of Diseases 10th edition, according to the Clinical Classifications Software by the Healthcare Cost and Utilization Proj-

ect (37). Positive SARS-CoV-2 test results included those from both Department of Health and CUIMC.

Exposure

Body mass index was calculated by using the first height and weight recorded during the SARS-CoV-2 hospital admission. For patients without height or weight recorded during the hospital admission, we obtained the most recent previously recorded BMI, height, or weight from the electronic medical record. Extreme values for BMI ($<10 \text{ kg/m}^2$ or $>70 \text{ kg/m}^2$), height ($<120 \text{ cm}$ or $>218 \text{ cm}$), and weight ($<17.2 \text{ kg}$ or $>220 \text{ kg}$) were excluded as being implausible (38, 39). To evaluate potential quadratic relationships between BMI and clinical outcomes, we operationalized BMI as 1) a continuous variable and 2) a categorical variable. The BMI categories were defined a priori by using the World Health Organization criteria: underweight ($<18.5 \text{ kg/m}^2$), normal weight (18.5 to 24.9 kg/m^2), overweight (25.0 to 29.9 kg/m^2), class 1 obesity (30 to 34.9 kg/m^2), class 2 obesity (35 to 39.9 kg/m^2), and class 3 obesity ($\geq 40 \text{ kg/m}^2$) (40). To be consistent with prior studies of BMI in pulmonary and critical care medicine (11, 41–44), we used overweight (BMI, 25 to 29.9 kg/m^2) as the reference group.

Biomarkers

Institutional protocols for measurement of circulating biomarkers at admission varied over the course of study. Protocols from the start of the epidemic included measurement of CRP, ESR, high-sensitivity troponin, and D-dimer at hospital admission. We log-transformed biomarker distributions that were skewed.

Outcomes

The primary outcome was measured as the time from ED presentation until intubation or in-hospital death without mechanical ventilation. For patients with multiple hospital admissions, we used the time of their first ED presentation that resulted in hospital admission until time of the intubation, death, or discharge alive during the last hospitalization. Among patients with multiple hospital admissions, intubation was observed in only the last hospital admission during the study period. The secondary outcome was measured as time from intubation until in-hospital death among mechanically ventilated patients. Patients who remain hospitalized were right-censored on the last day of follow-up (10 June 2020).

Statistical Analysis

We used Cox proportional hazards models to evaluate the association of BMI with intubation or death. We confirmed the proportional hazards assumption by regressing Schoenfeld residuals over time. We adjusted for demographic and clinical factors that have been associated with obesity, pneumonia, ARDS, or severe COVID-19: age, sex, race/ethnicity, cigarette smoking, hypertension, diabetes, cancer, asthma or chronic obstructive pulmonary disease, chronic kidney disease, and pulmonary heart disease (16, 19, 24, 45–49). We conducted analyses stratified by age, sex, diabetes, and hypertension by using Wald tests. In age-

stratified analysis, we used a cut point of 65 years, because 65 years or older often defines “older age” in health services research and splits the cohort near the median age of 67 years. We evaluated associations between BMI and peripheral blood biomarkers by using scatter plots and Pearson correlation coefficients. We used additive Cox models with penalized splines to evaluate and display nonlinear associations between BMI and our composite end point by using the pspline function in R (50, 51).

In our primary analyses, we performed multiple imputation with a Markov chain Monte Carlo method for missing BMI and race by using the mi package in Stata. We performed 2 complete-case sensitivity analyses: 1) among patients with BMI recorded during the COVID-19 hospitalization, and 2) among patients with BMI recorded during the COVID-19 hospitalization and those with BMI recorded during a prior hospitalization or clinic visit if the BMI was missing from the COVID-19 hospitalization. In the sensitivity analyses, we used a missing indicator variable to identify patients with unknown race/ethnicity. In our biomarker analyses, we used available biomarker data only.

To investigate the potential effect of selection bias due to missing BMI, we conducted a quantitative bias analysis by using an upper bounding factor approach. Upper bounding factors, conceptually similar to E-values (52), can be used to estimate the necessary strength of the association between a selecting factor and both the exposure and outcome that would be required to produce a significant finding when the true association is null (53). Larger bounding factors indicate that unmeasured selection factors would have to have stronger associations with both the exposure and outcome.

All analyses were performed by using R, version 3.3.1 (R Foundation for Statistical Computing) and STATA/IC, version 15.1 (StataCorp).

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RESULTS

There were 2673 hospital admissions from the EDs of NYP/CUIMC or the NYP/Allen Hospital with a nasopharyngeal swab that was positive for SARS-CoV-2 by PCR between 10 March 2020 and 24 April 2020 (Figure 1). We excluded 44 children (age <18 years). An additional 163 hospital admissions (6%) were repeat hospital admissions with a median of 10 days (interquartile range [IQR], 5 to 21 days) between first and last hospital admission. Sixteen percent (387 patients) did not have BMI recorded during the hospitalization, and 12% (303 patients) had an implausible BMI. Among these 28% ($n = 690$) of patients with a missing or implausible

BMI at COVID-19 hospital admission, 14% ($n = 336$) had a BMI previously recorded in their electronic medical record, leaving 14% ($n = 354$) with missing BMI. Previously recorded BMIs were measured a median of 302 days (IQR, 126 to 1171 days) before hospitalization. Patients with missing or implausible BMI ($n = 354$) were of similar age, sex, and race/ethnicity to those with available BMIs, but had fewer comorbid conditions (Appendix Table 1, available at Annals.org).

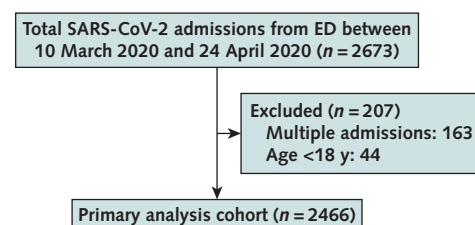
In the full cohort, the median age was 67 years (IQR, 54 to 78 years), 58% were male, and 49% were Hispanic (Appendix Table 1). The median BMI was 27.9 kg/m² (IQR, 24.3 to 32.6 kg/m²), 52% of patients had hypertension, 40% of patients had diabetes, and the median number of comorbid conditions was 2 (IQR, 0 to 3) (Appendix Table 1).

Compared with all other BMI classes, patients with class 2 or 3 obesity (BMI >35 kg/m²) were younger, less likely to be male, more likely to be black non-Hispanic, and less likely to have chronic kidney disease or a history of smoking (Table 1). Patients with BMI less than 18.5 kg/m² or greater than 35 kg/m² were more likely than those in other BMI classes to have asthma, chronic obstructive pulmonary disease, or pulmonary heart disease.

Over a median hospital length of stay of 7 days (IQR, 3 to 14 days), 533 patients (22%) were intubated, 627 (25%) died, 1247 were discharged (51%), and 59 (2%) remained hospitalized (Appendix Table 1). The 28-day in-hospital mortality was 23% (559 patients). Additive Cox models with penalized splines revealed a J-shaped association between BMI and the composite end point of death or intubation, with an inflection point of predicted risk at a BMI of 30 kg/m² (Figure 2). In fully adjusted analyses, patients who were underweight and those with BMIs above the overweight range were more likely to be intubated or die, respectively, than those who were overweight (BMI, 25 to 29.9 kg/m²). Sequential adjustment for age, demographic characteristics, and clinical variables in the models revealed that age had the largest effect on the magnitude of observed associations between BMI and the outcomes (Table 2).

We observed a similar association of BMI with in-hospital mortality among intubated patients (Appendix Table 2, available at Annals.org).

Figure 1. Study flow diagram.



ED = emergency department; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

Table 1. Patient Characteristics, by Body Mass Index Category*

Characteristic	Underweight (n = 68)	Normal Weight (n = 542)	Overweight (n = 717)	Class 1 Obesity (n = 444)	Class 2 Obesity (n = 199)	Class 3 Obesity (n = 142)
Median age (IQR), y	78 (63-85)	73 (61-83)	68 (57-78)	64 (51-73)	61 (48-71)	57 (44-69)
Men, n (%)	40 (59)	322 (59)	461 (64)	247 (56)	93 (47)	55 (39)
Race/ethnicity, n (%)						
White non-Hispanic	7 (10)	60 (11)	51 (7)	43 (10)	17 (9)	10 (7)
Black non-Hispanic	8 (12)	70 (13)	75 (10)	56 (13)	27 (14)	32 (23)
Hispanic	27 (40)	248 (46)	387 (54)	244 (55)	103 (52)	54 (38)
Other	14 (21)	78 (14)	104 (15)	51 (11)	30 (15)	19 (13)
Declined to say	12 (18)	86 (16)	100 (14)	50 (11)	22 (11)	27 (19)
Comorbid conditions						
Asthma or COPD	18 (26)	95 (18)	118 (16)	81 (18)	50 (25)	42 (30)
Hypertension	44 (65)	305 (56)	401 (56)	251 (57)	108 (54)	84 (59)
Chronic kidney disease	25 (37)	137 (25)	134 (19)	86 (19)	39 (20)	24 (17)
Diabetes	29 (43)	226 (42)	304 (42)	214 (48)	82 (41)	76 (54)
Cancer	10 (15)	100 (18)	99 (14)	52 (12)	24 (12)	14 (10)
Pulmonary heart disease	9 (13)	43 (8)	45 (6)	31 (7)	14 (7)	19 (13)
Smoking	16 (24)	90 (17)	89 (12)	55 (12)	26 (13)	11 (8)
Median comorbid conditions (IQR), n	2 (1-3)	2 (0-3)	1 (0-3)	2 (0-3)	2 (0-3)	2 (0-3)

COPD = chronic obstructive pulmonary disease; IQR = interquartile range.

* Body mass index was categorized as underweight (<18.5 kg/m²), normal (18.5 to 24.9 kg/m²), overweight (25 to 29.9 kg/m²), class 1 obesity (30 to 34.9 kg/m²), class 2 obesity (35 to 39.9 kg/m²), or class 3 obesity (≥40 kg/m²). Subgroup sizes are based on patients with known body mass index.

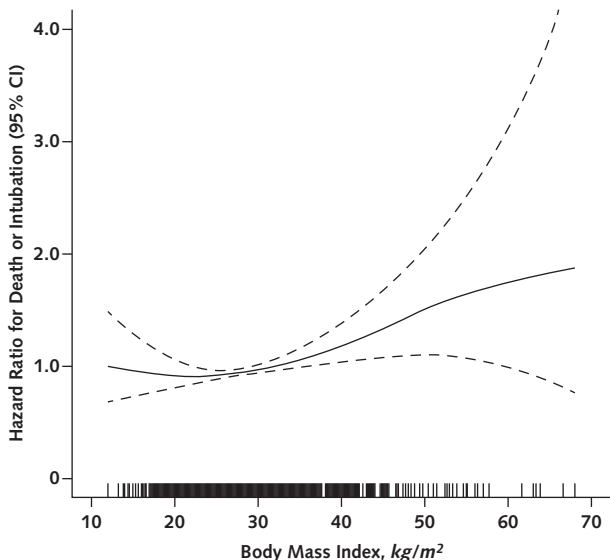
In stratified analyses, the association of BMI with intubation or death varied by age (*P* value for interaction, 0.042), but not by sex, diabetes, or hypertension (Figure 3). Obesity was consistently associated with higher risk for adverse outcome among patients younger than 65 years; this was not the case among those aged 65 years or older.

Admission serum CRP, troponin, and D-dimer levels and ESR were available for 91% (1916 patients), 91% (1915 patients), 79% (1678 patients), and 86% (1815 patients) of the cohort, respectively. Body mass index was not correlated with admission CRP level or

ESR and had only weak correlation with troponin and D-dimer levels that did not appear to be of clinical significance (Appendix Figure, available at Annals.org).

In sensitivity analyses including only patients with available BMI during or before the COVID-19 hospitalization, risk estimates for being underweight or obese were similar to those observed in the primary analysis (Appendix Tables 3 and 4, available at Annals.org).

Using the upper bounds method for estimating selection bias, an unaccounted-for selection variable would have to be related to both class 3 obesity and our composite end point with a HR of 1.84 in order to produce our observed HR of 1.6 when the true HR was 1.0. As a comparison, diabetes was associated with 1.9 times the odds of class 3 obesity, and hypertension was associated with 1.4 times the odds of obesity (Appendix Table 5, available at Annals.org).

Figure 2. Association between body mass index and odds of a composite end point of intubation or death.

Additive Cox models with penalized splines adjusted for age, sex, race/ethnicity, and comorbid conditions were created. The vertical lines along the x axis represent individual study patients.

DISCUSSION

In a large multiethnic cohort study of adults hospitalized with COVID-19, we found that obesity is associated with an increased risk for death or intubation independent of age, sex, race/ethnicity, and comorbid conditions. These associations varied significantly by age. Obesity was strongly associated with intubation or death among adults younger than 65 years, but not among those aged 65 years or older. Our findings provide evidence to support recommendations from the Centers for Disease Control and Prevention in the United States and the National Health Service in the United Kingdom, which state that patients with a BMI of 40 kg/m² or greater are at high risk for poor outcomes from COVID-19 and should therefore consider prolonged social distancing (54, 55). As the United States and other countries begin to lift stay-at-home orders, these findings might inform discussions between health care providers and patients regarding advanced care planning and benefits of prolonged so-

Table 2. Association Between Body Mass Index and Composite End Point of Death or Intubation*

End Point	Underweight (n = 68)	Normal Weight (n = 542)	Overweight (n = 717)	Class 1 Obesity (n = 444)	Class 2 Obesity (n = 199)	Class 3 Obesity (n = 142)
In-hospital death at 28 days, n (%)	26 (38)	154 (28)	144 (20)	83 (19)	31 (16)	26 (18)
Deaths or intubations, n (%)	32 (47)	212 (39)	240 (33)	143 (32)	65 (33)	51 (36)
Combined death and intubation rate, n per 100 person-days	6.0 (4.2-8.4)	4.4 (3.8-5.0)	4.4 (3.9-5.0)	4.7 (3.9-5.5)	5.1 (3.9-6.4)	5.1 (3.8-6.3)
Hazard ratio (95% CI)						
Unadjusted	1.3 (0.9-1.9)	1.0 (0.9-1.2)	1 (reference)	1.0 (0.8-1.2)	1.1 (0.8-1.4)	1.1 (0.8-1.5)
Age-adjusted	1.2 (0.8-1.7)	1.0 (0.8-1.1)	1 (reference)	1.1 (0.9-1.3)	1.2 (0.9-1.6)	1.4 (1.1-2.0)
Partially adjusted†	1.2 (0.8-1.8)	1.0 (0.8-1.2)	1 (reference)	1.3 (0.97-1.7)	1.5 (1.1-2.2)	1.5 (1.1-2.1)
Fully adjusted‡	1.2 (0.9-1.8)	1.0 (0.8-1.2)	1 (reference)	1.1 (0.9-1.4)	1.3 (0.98-1.7)	1.6 (1.1-2.1)

* Body mass index was categorized as underweight (<18.5 kg/m²), normal (18.5 to 24.9 kg/m²), overweight (25 to 29.9 kg/m²), class 1 obesity (30 to 34.9 kg/m²), class 2 obesity (35 to 39.9 kg/m²), or class 3 obesity (≥40 kg/m²). Subgroup sizes are based on patients with known body mass index. Effect estimates are generated from multiple imputation models.

† Adjusted for age, sex, and race.

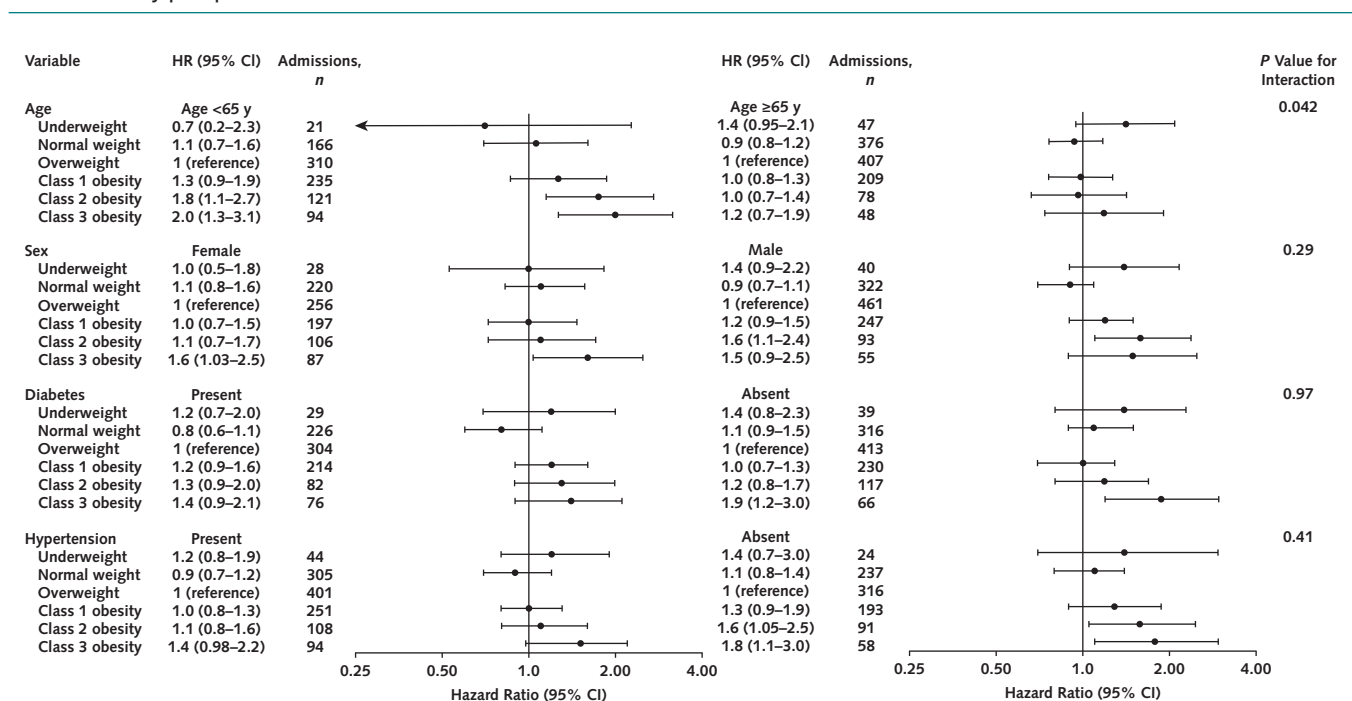
‡ Adjusted for age, sex, race/ethnicity, hypertension, asthma or chronic obstructive pulmonary disease, chronic kidney disease, pulmonary hypertension, smoking, cancer, and diabetes.

cial distancing, particularly for younger adults with class 2 or 3 obesity.

Obesity has recently been established as a risk factor for critical illness and death from COVID-19 in cohort studies from both the United States and United Kingdom (19, 20, 56, 57). Our study adds to the literature by demonstrating that the association between BMI and COVID-19 outcomes differs between younger and older adults. Our findings are consistent with prior studies that have identified obesity as a risk factor for bacterial and viral pneumonia, intensive care unit admission for H1N1 influenza, and ARDS (9-11, 41, 58). None of these prior studies conducted analyses strati-

fied by age. Therefore, we do not know whether the effect modification by age that we observe in COVID-19 is common to other types of pneumonia and ARDS. In contrast to prior studies that demonstrate an association between obesity and lower mortality in critically ill patients with pneumonia and ARDS, known as the “obesity paradox” (12, 14, 15), we found that obesity was associated with an increased risk for death among mechanically ventilated patients with COVID-19. We found that obesity is associated with intubation or death independent of several comorbid conditions, including diabetes and hypertension, which have been associated with adverse outcomes in COVID-19 (2, 24, 46). In this regard, our findings

Figure 3. Forest plots of multivariable-adjusted associations between body mass index and composite end point of death or intubation by prespecified stratification variables.



Body mass index was categorized as underweight (<18.5 kg/m²), normal (18.5 to 24.9 kg/m²), overweight (25 to 29.9 kg/m²), class 1 obesity (30 to 34.9 kg/m²), class 2 obesity (35 to 39.9 kg/m²), or class 3 obesity (≥40 kg/m²). Overweight is the reference category for the HRs. Subgroup sizes are based on patients with known body mass index. Effect estimates were generated from multiple imputation models. HR = hazard ratio.

are consistent with those of 2 recent large cohort studies (19, 20, 57). The absence of an association between obesity and intubation or death in older adults may reflect a high mortality due to comorbidity, frailty, or worse immune function with older age, which can all occur independently of BMI (59–63).

There are multiple mechanisms that may underlie the observed association of obesity with acute respiratory failure and death from SARS-CoV-2 infection. First, adipose tissue expansion in obesity leads to immune activation, resulting in increased circulating concentrations of inflammatory molecules, including interleukin-6, tumor necrosis factor- α , and monocyte chemoattractant protein-1 (21, 22, 64). It has been hypothesized that obesity may potentiate inflammation in COVID-19 (65, 66). We did not identify an association between BMI and admission ESR and CRP level; however, these are nonspecific biomarkers of inflammation that may not detect clinically meaningful differences in inflammation between obese and nonobese patients with COVID-19. We only evaluated these biomarkers at admission. Perhaps any contribution of adiposity to inflammation that drives COVID-19 disease is obscured by the time patients are symptomatic and requiring hospital admission. Future studies should examine whether specific cytokines mediate the association of obesity with worse outcomes from COVID-19.

Second, obese patients are more likely to have comorbid conditions, including diabetes and hypertension, which may predispose to greater cardiac dysfunction during an acute illness. However, we found no association between obesity and admission troponin level. Given so many reports of cardiac dysfunction in COVID-19 (28, 67), future studies are needed with more thorough and longitudinal assessments of cardiac function.

Third, adipose tissue produces multiple components of the complement pathway, which are upregulated in infection and are associated with small-vessel thrombosis (29–32). Autopsy studies of patients with COVID-19 show both small-vessel thrombosis and endothelitis with endothelial cell dysfunction (34, 36, 68, 69). We only measured fibrinolysis with D-dimer at admission. Future studies should examine whether complement activation mediates the association of obesity with worse outcomes from COVID-19. Given the limitations noted above, our biomarker analyses should be considered preliminary and hypothesis-generating.

Fourth, abdominal obesity may impair diaphragmatic excursion, leading to hypoxemia via decreased chest wall compliance with atelectasis and shunting (65). Future investigations that range from proteomic, metabolomic, and transcriptomic studies to pulmonary physiology studies might be considered to further elucidate mechanisms of more severe COVID-19 disease in obese patients. Such research has the potential to inform patient treatment decisions, and facilitate both predictive and prognostic enrichment of clinical trials aimed at preventing progression of COVID-19.

Being underweight had a borderline statistically significant association with increased risk for death or

intubation among older adults with SARS-CoV-2 infection. Being underweight is associated with an increased risk for pneumonia (70), and worse inpatient outcomes among older adults (71). Low concentrations of leptin may reduce adaptive immune responses, altering susceptibility to infection (72). Being underweight is also often associated with underlying frailty, which is associated with increased mortality in critical illness and pulmonary disease (62, 73). Additional investigations should consider measures of frailty and malnutrition to further elucidate these mechanisms.

Our study has limitations. First, admission BMI was either missing or implausible for 28% of the cohort. Reassuringly, our results were similar in sensitivity analyses performed in patients with available BMI. In our quantitative bias analysis, an upper bound of 1.84 suggests that an unmeasured selection variable that accounts for BMI not being recorded would have to be associated with a 84% increased risk for obesity as well as death or intubation after adjustment for covariables, in order to abrogate the observed association of obesity with intubation or death. It seems implausible that such a selection variable exists. The study period occurred during the outbreak of COVID-19 in New York City, and it is more likely that BMI was not recorded or inaccurately recorded with implausible values because nurses and technicians responsible for recording BMI were busy caring for a large number of patients with COVID-19.

Second, we were unable to confirm whether deceased patients developed respiratory failure or whether respiratory management differed in underweight or obese patients including the likelihood of “do not intubate” or “do not resuscitate” orders; to address this, we modeled our time-to-event as intubation or death so that we could include patients with limits of care in our study. Third, although our follow-up is longer than that in prior studies (74), this is still a short-term follow-up study. Fourth, comorbid conditions were identified from the electronic medical record, which may be incomplete because health care workers had to care for an overwhelming number of patients during the study period. However, we included diagnoses reported in prior inpatient and outpatient records in our health system. Fifth, some subgroup sizes in stratified analyses were small and may have limited our ability to detect other potentially clinically meaningful associations. Finally, we only included patients hospitalized with COVID-19. Future studies should investigate how BMI is associated with hospitalization risk and adverse outcomes among outpatients.

In conclusion, obesity is associated with increased risk for death or intubation in hospitalized adults with COVID-19 who are younger than 65 years. Additional investigations should evaluate potential mechanisms linking obesity and respiratory failure in COVID-19, including the role of specific inflammatory cytokines, complement-mediated endothelial cell dysfunction and thrombosis, and chest wall mechanics.

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Reproducible Research Statement: *Study protocol:* Available in the Appendix at Annals.org. *Statistical code:* Available from Dr. Anderson (e-mail, mdr2140@cumc.columbia.edu). *Data set:* Data sharing will be considered in the setting of appropriate institutional review board approval.

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APPENDIX: DATA EXTRACTION METHODS

The Columbia clinical data warehouse comprises over 30 years of data on over six million patients from the NewYork-Presbyterian / Columbia University Irving Medical Center, collected from electronic health records over time, currently from Epic Systems (Verona, Wisconsin) (75). The data include all outpatient and inpatient demographic characteristics, visit information, diagnoses, procedures, medications, vital signs, care provider notes, orders and prescriptions, laboratory results, radiology reports, and numerous other ancillary reports. Laboratory and ancillary data are fed directly to the warehouse from the source computing systems and serve as the gold standard for data quality reviews for clinical trials. The Observational Health Data Sciences and Informatics initiative data quality tool set called Achilles Heel includes an extensive knowledge base of data consistency checks used to verify the quality of the Columbia warehouse (76). Data are requested from the warehouse via a formal specification that is approved by an institutional committee and executed by an analyst.

Appendix Table 1. Characteristics of Patients Included in the Final Cohort and Those Excluded for Missing BMI*

Characteristic	Full Cohort (n = 2466)	Missing BMI (n = 354)	BMI Measured (n = 2112)
Median age (IQR), y	67 (54-78)	65 (53-77)	67 (55-78)
Men, n (%)	1434 (58)	894 (42)	1218 (58)
Race/ethnicity, n (%)			
White non-Hispanic	218 (9)	30 (8)	188 (9)
Black non-Hispanic	313 (13)	45 (13)	268 (13)
Hispanic	1219 (49)	156 (44)	1063 (50)
Other	365 (15)	69 (19)	296 (14)
Declined to say	351 (14)	54 (15)	297 (14)
Comorbid conditions, n (%)			
Asthma or COPD	429 (17)	25 (7)	404 (19)
Hypertension	1271 (52)	78 (22)	1193 (56)
Chronic kidney disease	456 (18)	11 (3)	445 (21)
Diabetes	996 (40)	65 (18)	931 (44)
Cancer	312 (13)	13 (4)	299 (14)
Pulmonary heart disease	168 (7)	7 (2)	161 (8)
History of smoking	292 (12)	5 (1)	287 (14)
Median comorbid conditions (IQR), n	1 (0-3)	0 (0-1)	2 (0-3)
End point, n (%)			
Death or intubation	892 (36)	149 (42)	743 (35)
Intubation	533 (22)	99 (28)	434 (21)
Death	627 (25)	106 (30)	521 (25)

COPD = chronic obstructive pulmonary disease; IQR = interquartile range.

* Body mass index was categorized as underweight (<18.5 kg/m²), normal (18.5 to 24.9 kg/m²), overweight (25 to 29.9 kg/m²), class 1 obesity (30 to 34.9 kg/m²), class 2 obesity (35 to 39.9 kg/m²), or class 3 obesity (≥40 kg/m²).

Appendix Table 2. Association Between Body Mass Index and Survival Among Patients Requiring Intubation*

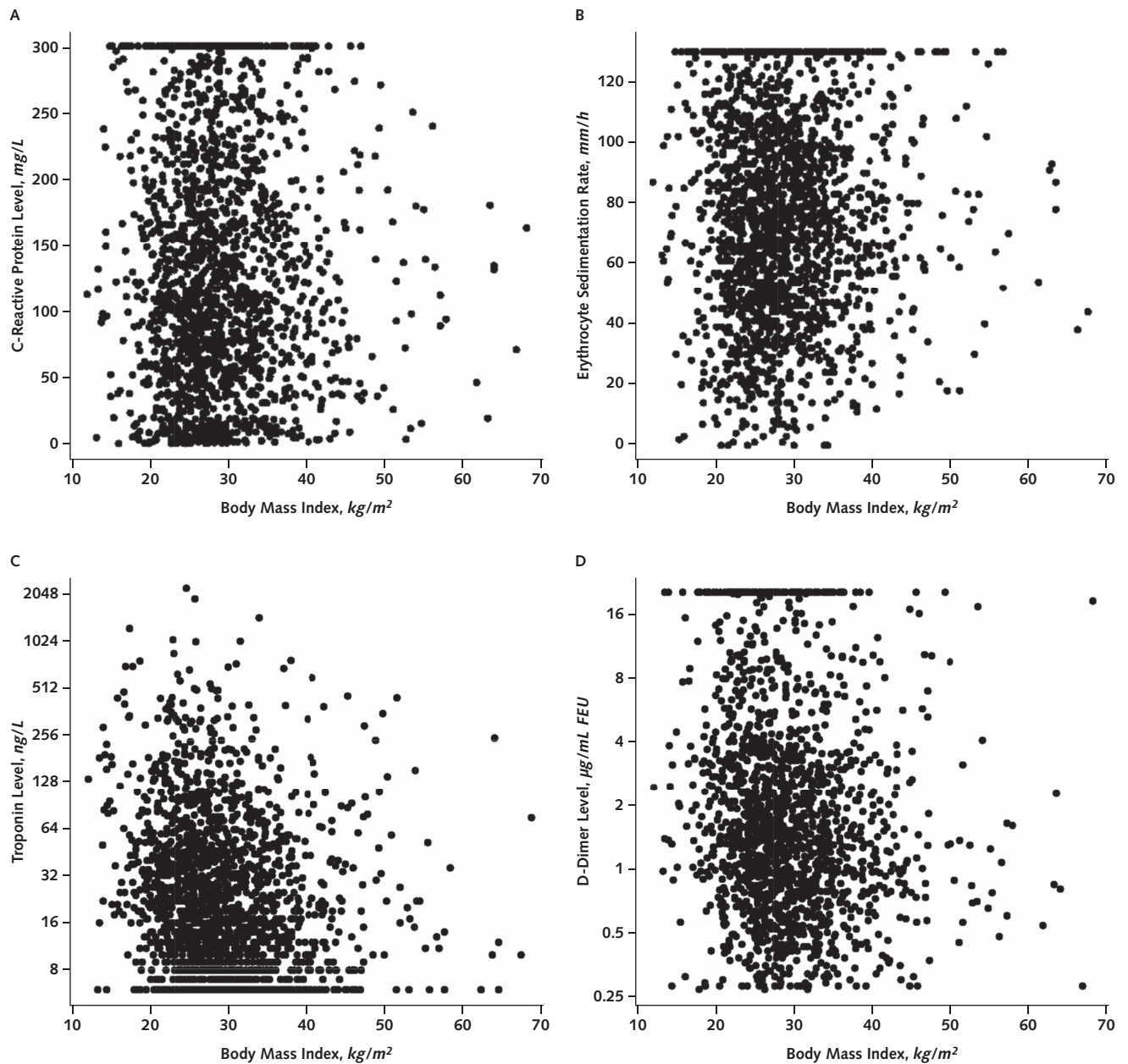
End Point	Underweight (n = 10)	Normal Weight (n = 93)	Overweight (n = 142)	Class 1 Obesity (n = 99)	Class 2 Obesity (n = 48)	Class 3 Obesity (n = 42)
Deaths, n (%)	7 (70)	51 (55)	66 (46)	52 (52)	18 (38)	18 (43)
Death rate, n per 100 person-days	7.7 (3.3-15.1)	2.8 (2.1-3.7)	1.8 (1.4-2.3)	2.3 (1.7-3.0)	1.2 (0.7-1.8)	1.7 (1.0-2.6)
Hazard ratio (95% CI)						
Unadjusted	2.9 (1.3-6.4)	1.4 (0.95-2.0)	1 (reference)	1.2 (0.8-1.7)	0.7 (0.4-1.1)	0.9 (0.5-1.5)
Age-adjusted	2.4 (1.1-5.3)	1.4 (0.96-2.0)	1 (reference)	1.3 (0.9-1.9)	0.9 (0.6-1.6)	1.4 (0.8-2.3)
Partially adjusted†	2.5 (1.1-5.4)	1.4 (0.99-2.1)	1 (reference)	1.3 (0.9-1.9)	1.0 (0.6-1.6)	1.4 (0.8-2.3)
Fully adjusted‡	2.4 (1.1-5.3)	1.5 (1.02-2.2)	1 (reference)	1.4 (0.97-2.0)	1.0 (0.6-1.7)	1.6 (0.9-2.7)

* Body mass index was categorized as underweight (<18.5 kg/m²), normal (18.5 to 24.9 kg/m²), overweight (25 to 29.9 kg/m²), class 1 obesity (30 to 34.9 kg/m²), class 2 obesity (35 to 39.9 kg/m²), or class 3 obesity (≥40 kg/m²). Subgroup sizes are based on patients with known body mass index. Effect estimates are generated from multiple imputation models.

† Adjusted for age, sex, and race.

‡ Adjusted for age, sex, race/ethnicity, hypertension, asthma or chronic obstructive pulmonary disease, chronic kidney disease, pulmonary hypertension, smoking, cancer, and diabetes.

Appendix Figure. Scatter plots evaluating the association between body mass index and biomarkers of inflammation, cardiac injury, and fibrinolysis.



FEU = fibrinogen equivalent units. A. C-reactive protein level (1916 patients; $r = -0.02$; $P = 0.38$). To convert values to nmol/L, multiply by 9.524. B. Erythrocyte sedimentation rate (1815 patients; $r = 0.03$; $P = 0.25$). C. Troponin level (1915 patients; $r = -0.15$; $P < 0.001$). D. D-dimer level (1678 patients; $r = -0.12$; $P < 0.001$). To convert values to nmol/L, multiply by 5.476.

Appendix Table 3. Association Between Body Mass Index and Composite End Point of Death or Intubation in Patients With Body Mass Index Measured Before or During Admission*

End Point	Underweight (n = 68)	Normal Weight (n = 542)	Overweight (n = 717)	Class 1 Obesity (n = 444)	Class 2 Obesity (n = 199)	Class 3 Obesity (n = 142)
Death or intubation, n (%)	32 (47)	212 (39)	240 (33)	143 (32)	65 (33)	51 (36)
Rate of death or intubation, n per 100 person-days	6.0 (4.3-8.5)	4.4 (3.8-5.0)	4.4 (3.9-5.0)	4.7 (4.0-5.5)	5.1 (4.0-6.5)	5.1 (3.9-6.7)
Hazard ratio (95% CI)						
Unadjusted	1.3 (0.9-1.9)	1.0 (0.9-1.2)	1 (reference)	1.0 (0.8-1.2)	1.1 (0.8-1.4)	1.1 (0.8-1.5)
Age-adjusted	1.2 (0.8-1.7)	1.0 (0.8-1.1)	1 (reference)	1.1 (0.9-1.3)	1.2 (0.9-1.6)	1.4 (1.06-2.0)
Partially adjusted†	1.2 (0.8-1.8)	1.0 (0.8-1.2)	1 (reference)	1.1 (0.9-1.3)	1.3 (0.96-1.7)	1.5 (1.1-2.1)
Fully adjusted‡	1.2 (0.9-1.8)	1.0 (0.8-1.2)	1 (reference)	1.1 (0.9-1.4)	1.3 (0.98-1.8)	1.6 (1.1-2.1)

* Body mass index was categorized as underweight (<18.5 kg/m²), normal (18.5 to 24.9 kg/m²), overweight (25 to 29.9 kg/m²), class 1 obesity (30 to 34.9 kg/m²), class 2 obesity (35 to 39.9 kg/m²), or class 3 obesity (≥40 kg/m²).

† Adjusted for age, sex, and race.

‡ Adjusted for age, sex, race/ethnicity, hypertension, asthma or chronic obstructive pulmonary disease, chronic kidney disease, pulmonary hypertension, smoking, cancer, and diabetes.

Appendix Table 4. Association Between Body Mass Index and Composite End Point of Death or Intubation in Patients With Body Mass Index Measured During Admission*

End Point	Underweight (n = 54)	Normal Weight (n = 454)	Overweight (n = 603)	Class 1 Obesity (n = 383)	Class 2 Obesity (n = 166)	Class 3 Obesity (n = 116)
Deaths or intubation, n (%)	22 (41)	168 (37)	187 (31)	109 (28)	50 (30)	38 (33)
Rate of death or intubation, n per 100 person-days	4.9 (3.2-7.4)	3.9 (3.4-4.6)	3.9 (3.4-4.5)	4.0 (3.4-4.9)	4.3 (3.3-5.7)	4.5 (3.3-6.2)
Hazard ratio (95% CI)						
Unadjusted	1.3 (0.8-1.9)	1.1 (0.9-1.3)	1 (reference)	1.0 (0.8-1.2)	1.1 (0.8-1.5)	1.1 (0.8-1.6)
Age-adjusted	1.1 (0.7-1.7)	1.0 (0.8-1.2)	1 (reference)	1.0 (0.8-1.3)	1.2 (0.9-1.7)	1.4 (1.0-2.0)
Partially adjusted†	1.1 (0.7-1.8)	1.0 (0.8-1.2)	1 (reference)	1.1 (0.8-1.4)	1.3 (0.9-1.7)	1.5 (1.1-2.2)
Fully adjusted‡	1.2 (0.7-1.8)	1.0 (0.8-1.2)	1 (reference)	1.1 (0.9-1.4)	1.3 (0.95-1.8)	1.6 (1.1-2.3)

* Body mass index was categorized as underweight (<18.5 kg/m²), normal (18.5 to 24.9 kg/m²), overweight (25 to 29.9 kg/m²), class 1 obesity (30 to 34.9 kg/m²), class 2 obesity (35 to 39.9 kg/m²), or class 3 obesity (≥40 kg/m²).

† Adjusted for age, sex, and race.

‡ Adjusted for age, sex, race/ethnicity, hypertension, asthma or chronic obstructive pulmonary disease, chronic kidney disease, pulmonary hypertension, smoking, cancer, and diabetes.

Appendix Table 5. Multivariable Associations Between Baseline Characteristics and Class 3 Obesity*

Characteristic	Prevalence Ratio (95% CI)	P Value
Age	0.4 (0.3-0.5)	<0.001
Male sex	0.4 (0.3-0.5)	<0.001
Race/ethnicity		
White non-Hispanic	1 (reference)	
Black non-Hispanic	1.3 (0.8-2.3)	0.29
Hispanic	0.6 (0.4-1.1)	0.113
Other	1.0 (0.5-1.8)	0.97
Declined to say	1.4 (0.8-2.4)	0.23
Comorbid conditions		
Cancer	0.4 (0.2-0.7)	0.001
Hypertension	1.4 (1.04-1.8)	0.025
Chronic kidney disease	0.5 (0.4-0.8)	0.001
Smoking	0.8 (0.5-1.2)	0.23
Pulmonary heart disease	2.4 (1.7-3.2)	<0.001
Diabetes	1.9 (1.4-2.4)	<0.001

* Class 3 obesity was defined as a body mass index of 40 kg/m² or greater.

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