

# The Independent Risk of Obesity and Diabetes and Their Interaction in COVID-19: A Retrospective Cohort Study

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**Objective:** This study aimed to assess whether diabetes mellitus (DM) or obesity is an independent risk factor for severe coronavirus disease 2019 (COVID-19) outcomes and to explore whether the risk conferred by one condition is modified by the other.

**Methods:** This retrospective cohort study of inpatient adults with COVID-19 used multivariable Cox regression to determine the independent effects of DM and obesity on the composite outcome of intubation, intensive care unit admission, or in-hospital mortality. Effect modification between DM and obesity was assessed with a statistical interaction term and an exploration of stratum-specific effects.

**Results:** Out of 3,533 patients, a total of 1,134 (32%) had DM, 1,256 (36%) had obesity, and 430 (12%) had both. DM and obesity were independently associated with the composite outcome (hazard ratio [HR] 1.14 [95% CI: 1.01-1.30] and HR 1.22 [95% CI: 1.05-1.43], respectively). A statistical trend for potential interaction between DM and obesity was observed ( $P = 0.20$ ). Stratified analyses showed potential increased risk with obesity compared with normal weight among patients with DM (HR 1.34 [95% CI: 1.04-1.74]) and patients without DM (HR 1.18 [95% CI: 0.96-1.43]).

**Conclusions:** DM and obesity are independent risk factors associated with COVID-19 severity. Stratified analyses suggest that obesity may confer greater risk to patients with DM compared with patients without DM, and this relationship requires further exploration.

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## Introduction

Obesity and diabetes mellitus (DM) were identified early in epidemiologic studies to be risk factors associated with greater severity of coronavirus disease 2019 (COVID-19) (1-4). They were among the most common comorbidities (5,6) and predictors of critical illness in hospitalized patients (7-12). The emergence of obesity and DM as risk factors is consistent with the current understanding of their pathophysiologies, particularly in the setting of infection. Cardiovascular,

respiratory, metabolic, and immune dysfunctions that induce a proinflammatory, prothrombotic state and reduced respiratory capacity have been suggested to contribute to the development of severe COVID-19 in those with obesity or DM (13).

However, there is a paucity of data on the interaction between obesity and DM as they relate to COVID-19. In 2017 and 2018, the prevalence of obesity in adults was 42.4% (14). Crude estimates from 2013 to 2016 reported 13.0% of adults had DM, of whom 61.3%

## Study Importance

### What is already known?

- ▶ Diabetes (DM) and obesity have been consistently identified as risk factors for severe COVID-19 in multiple countries, manifesting as higher incidences of hospitalization, intensive care unit admission, invasive mechanical ventilation, or death.

### What does this study add?

- ▶ DM and obesity are independent risk factors for the severity of COVID-19 and may modify each other's effect on risk.
- ▶ Stratified analyses suggest that obesity may confer a greater risk to patients with DM compared with patients without DM.

### How might these results change the direction of research or the focus of clinical practice?

- ▶ Further exploration of this relationship may help to develop risk-stratification policies.

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had obesity (15), and among those with obesity, 20.7% had DM (16). Given this close relationship between obesity and DM, further investigation into the relative independence of these risk factors on COVID-19 outcomes may aid in risk stratification. The objective of this retrospective cohort study was to assess whether obesity or DM is an independent risk factor for severe COVID-19 outcomes and to determine whether the degree of risk conferred by one condition is affected by the presence of the other.

## Methods

### Study design and patient selection

This retrospective cohort study analyzed COVID-19-related outcomes in a population of adult patients who were admitted to New York Presbyterian (NYP) Weill Cornell Medical Center, NYP Queens Hospital, or NYP Lower Manhattan Hospital in New York, New York between March 1, 2020, and May 13, 2020. All adult patients ( $\geq 18$  years old) with COVID-19 confirmed by reverse transcriptase-polymerase chain reaction (RT-PCR) who had a documented BMI 3 months prior to or at admission were included. Multiple visits from one patient were considered as one COVID-19 episode. Patients who were discharged from the emergency department with or without admission to the observation unit were excluded. The study was approved by the Institutional Review Board, which granted a waiver of informed consent.

### Data collection

Data pertaining to demographics, medical history, medications, and hospital course were queried and extracted from electronic health records and were manually verified by independent reviewers. BMI categories were defined according to the World Health Organization, including race-specific thresholds for Asian populations (overweight = 23.0-27.4 kg/m<sup>2</sup>, mild obesity = 27.5-32.4, moderate obesity = 32.5-37.4, and severe obesity =  $\geq 37.5$ ) (17,18). DM status was defined by documentation of type 1 or type 2 DM in the medical history or by hemoglobin A<sub>1c</sub>  $\geq 6.5\%$ .

### Study outcomes

The outcome of interest was a composite of intensive care unit (ICU) admission, invasive mechanical ventilation, or in-hospital mortality. Clinical courses were followed for all patients admitted during the study period until the occurrence of an event of interest, discharge, or date last observed. A patient was considered to have had an event of interest if they had at least one occurrence over the course of hospitalization(s). For patients who had more than one event of interest (e.g., intubation followed by death), the time to the earliest-occurring event was used, and for patients without events of interest, the last hospital admission was used.

### Statistical analysis

Bivariate tests (i.e., Wilcoxon rank sum,  $\chi^2$ , and Fisher exact) were used to explore associations between DM and obesity and COVID-19 outcomes, as well as other preadmission clinical variables. Multivariable Cox regression was used to assess the independent effects of DM and obesity (modeled as categorical BMI and extended obesity classes, which discerned mild, moderate, and severe obesity) on the composite COVID-19 outcome, mortality, and ICU admission/intubation separately. A competing risk analysis was used to assess ICU admission/

intubation separately from the composite outcome. A Fine and Gray proportional subdistribution hazards regression was used to model death as a competing risk for ICU admission/intubation (19). Analysis was adjusted for age, sex, race, smoking status, hypertension, pulmonary disease, chronic kidney disease, end-stage renal disease, and cardiovascular disease. Variables significantly associated with the outcome at  $P < 0.05$  were used in multivariable analysis. Effect modification between DM and BMI was assessed with a statistical interaction term and an exploration of stratum-specific effects. Analyses were also stratified by date of admission: earlier (March 1, 2020, through April 8, 2020) versus later (April 9, 2020, through May 13, 2020). These dates were selected based on clinical developments at NYP hospitals, with April 9, 2020, representing the turning point after peak patient surge. All analyses were based on nonmissing data, and missing data were not imputed.

## Results

A total of 3,732 unique adult patients were admitted to one of three tertiary care hospitals in New York from March 1, 2020, to May 13, 2020, with a confirmed COVID-19 diagnosis. Of these, 199 (5.3%) did not have BMI data, resulting in a final study cohort of 3,533.

The median age (interquartile range) was 65 (53-77) years, and 1,455 patients (41%) were female (Table 1). The median BMI was 27 (24-32); 1,256 (36%) had obesity, 1,134 (32%) had DM, and 430 (12%) had both. Of those with DM, 96% were documented as having type 2 DM. The composite outcome occurred in 63 (52%), 350 (38%), 409 (33%), and 446 (36%) patients in the underweight, normal weight, overweight, and obesity categories, respectively (Table 2).

Multivariable Cox analysis found obesity to be associated with a significantly greater risk of the composite outcome (hazard ratio [HR] 1.22 [95% CI: 1.05-1.43],  $P = 0.011$ ) compared with normal weight, with extended analysis finding moderate and severe obesity associated with the highest risk (HR 1.43 [95% CI: 1.13-1.80],  $P = 0.003$  and HR 1.49 [95% CI: 1.12-2.00],  $P = 0.007$ , respectively) (Table 3).

For mortality alone, patients with obesity did not have increased hazard relative to normal weight patients (HR 1.03 [95% CI: 0.85-1.25],  $P = 0.7$ ), but in extended BMI analysis, severe obesity showed a trend toward increased mortality (HR 1.42 [95% CI: 0.99-2.04],  $P = 0.055$ ). Notably, there was a significant effect of severe obesity on mortality earlier in the pandemic (HR 1.58 [95% CI: 1.04-2.39],  $P = 0.030$ ) that attenuated later (HR 0.75 [95% CI: 0.32-1.76],  $P = 0.5$ ).

Patients with obesity were at higher risk for ICU admission/intubation (HR 1.41 [95% CI: 1.16-1.71],  $P = 0.001$ ). In extended BMI analysis, higher risk was associated with increasing BMI values (mild = HR 1.34 [95% CI: 1.08-1.65],  $P = 0.007$ ; moderate = HR 1.55 [95% CI: 1.17-2.05],  $P = 0.002$ ; and severe = HR 1.58 [95% CI: 1.13-2.21],  $P = 0.008$ ).

The composite outcome occurred in 476 (42%) patients with DM versus 793 (33%) patients without DM, and in-hospital mortality occurred in 339 (30%) patients with DM versus 506 (21%) patients without DM (Table 2). DM was an independent risk factor for the composite outcome (HR 1.14 [95% CI: 1.01-1.30],  $P = 0.037$ ) as well as mortality (HR 1.19 [95% CI: 1.02-1.38],  $P = 0.024$ ) in adjusted analyses. The incidence of ICU admission/intubation was higher in

**TABLE 1** Baseline characteristics of total cohort

	<i>n</i>	
Age (y) (median [IQR])	3,533	65 (53-77)
Female	3,533	1,455 (41%)
Race	3,297	
White		1,031 (31%)
Other		1,187 (36%)
Asian		662 (20%)
Black		417 (13%)
Ethnicity	3,533	
Hispanic, Latino, or Spanish origin		1,179 (33%)
Not Hispanic, Latino, or Spanish origin		1,719 (49%)
Unknown or not specified		591 (17%)
Other		44 (1.2%)
BMI (kg/m <sup>2</sup> ) (median [IQR])	3,533	27 (24-32)
BMI categories	3,533	
Underweight		120 (3.4%)
Normal weight		926 (26%)
Overweight		1,231 (35%)
Obesity		1,256 (36%)
DM	3,533	1,134 (32%)
CAD	3,533	520 (15%)
CHF	3,533	246 (7.0%)
CVA	3,533	240 (6.8%)
Hypertension	3,533	1,962 (56%)
Pulmonary disease	3,533	587 (17%)
CKD	3,533	356 (10%)
Cirrhosis	3,533	38 (1.1%)
Hepatitis	3,533	51 (1.5%)
HIV	3,533	37 (1.0%)
Active cancer	3,533	160 (4.5%)
Transplant	3,533	73 (2.1%)
Inflammatory bowel disease	3,533	17 (0.5%)
Rheumatologic disorder	3,533	119 (3.4%)
Smoking status	3,532	743 (21%)

Data are presented as *n* (%) unless otherwise stated. Pulmonary disease included chronic obstructive pulmonary disease, asthma, interstitial lung disease, obstructive sleep apnea, pulmonary hypertension, cystic fibrosis, and pneumothorax. CKD encompassed all stages of chronic kidney disease, including end-stage renal disease. Rheumatologic disorders included scleroderma, Sjogren syndrome, seronegative spondyloarthropathies (ankylosing spondylitis, reactive arthritis, psoriatic arthritis), and vasculitis. Smoking status included both active and former use. CAD, coronary artery disease; CHF, congestive heart failure; CKD, chronic kidney disease; CVA, cerebrovascular accident; DM, diabetes mellitus; HIV, human immunodeficiency virus; IQR, interquartile range.

those with DM but did not reach statistical significance (HR 1.17 [95% CI: 0.99-1.37], *P* = 0.60).

Effect modification was explored with an interaction term between obesity and DM for the composite outcome and suggested a potential trend (*P* = 0.2), which prompted stratified analysis of the effect of obesity in individuals with and without DM. Among individuals with DM (*n* = 1,134), obesity conferred a significantly increased risk of the composite outcome (HR 1.34 [95% CI: 1.04-1.74], *P* = 0.025)

compared with normal weight in multivariable analysis (Table 3). Elevated risk was specifically noted for moderate and severe obesity (HR 1.57 [95% CI: 1.08-2.28], *P* = 0.019 and HR 2.00 [95% CI: 1.26-3.18], *P* = 0.003, respectively). Among individuals without DM (*n* = 2,399), obesity was associated with increased hazard that was not statistically significant (HR 1.18 [95% CI: 0.96-1.43], *P* = 0.11).

## Discussion

In a diverse population of hospitalized patients in New York, obesity and DM were independent risk factors of severe COVID-19 outcomes. Moderate and severe obesity were associated with greater risk of ICU admission, intubation, or in-hospital death. Obesity was associated with increased risk of ICU admission/intubation but not with in-hospital mortality in the overall cohort. However, this relationship may have been present earlier in the pandemic. DM was consistently associated with greater COVID-19 severity as well as in-hospital mortality.

Results from our total cohort analysis support previous observations that have found that obesity and DM are associated with greater COVID-19 severity (2-4,7-12). Our study also expands upon an early report on the association between obesity and COVID-19 severity in this population (11), with a longer observation period and a larger cohort. As with other studies (7,12), severe obesity was consistently identified as a risk factor for COVID-19 severity. Uniquely, we found the increased mortality associated with severe obesity attenuated over time, potentially due to the accrual of clinical experience and more effective management protocols.

We observed a trend indicating potential statistical interaction between obesity and DM, which prompted an exploratory analysis on whether obesity conferred additional risk to DM relative to one condition alone. The stratified analysis revealed adjusted HRs of 1.34 and 1.18 for patients with DM and without DM, respectively. The relative sizes of these effects suggest that DM may modify the risk of COVID-19 severity conferred by obesity. Others have estimated obesity to mediate 49.5% of the total effect of DM on 30-day lethality due to COVID-19 (20).

The strengths of this study include a large racially diverse population, the use of race-specific BMI cutoffs for accurate categorization, and an extended BMI risk stratification. The timing of symptom onset to admission was also examined as a potential downstream effect of COVID-19 severity and was not found to be a confounder, as it demonstrated the expected relationship (that a shorter interval would correlate with greater severity). Weaknesses include lack of information regarding chronic disease duration, DM-related complications, and glycemic management outcomes. Our findings pertain only to hospitalized patients and do not include outpatient factors (e.g., weight-management interventions, anti-obesity medications, or bariatric surgery) that may affect other measures of COVID-19 severity, such as hospitalization admission. The scope of our observations is derived from an approximately 2-month time period during which COVID-19 treatment modalities were rapidly changing, and a longer duration (i.e., March 2020, through December 2020) would be useful to explore how the risk conferred by obesity or DM evolves over time as treatment strategies continue to be refined and formalized. Further investigation is warranted to better understand the risk discrepancy between patients with obesity and DM versus those with obesity without DM.

**TABLE 2** Distribution of outcomes in study population

	ICU admission or intubation	Death	Composite outcome
Underweight ( <i>n</i> = 120)	22 (18)	55 (46)	63 (52)
Normal weight ( <i>n</i> = 926)	185 (20)	269 (29)	350 (38)
Overweight ( <i>n</i> = 1,231)	299 (24)	261 (21)	409 (33)
Obesity ( <i>n</i> = 1,256)	350 (28)	260 (21)	447 (36)
Mild ( <i>n</i> = 777)	207 (27)	161 (21)	271 (35)
Moderate ( <i>n</i> = 290)	87 (30)	59 (20)	110 (38)
Severe ( <i>n</i> = 189)	56 (30)	40 (21)	66 (35)
DM			
Yes ( <i>n</i> = 1,134)	301 (27)	339 (30)	476 (42)
No ( <i>n</i> = 2,399)	555 (23)	506 (21)	793 (33)

Data presented as *n* (%) of each category with outcome. DM, diabetes mellitus; ICU, intensive care unit.

**TABLE 3** Multivariable analysis of the effect of obesity or DM on the composite outcome

	Total cohort ( <i>N</i> = 3,353)			DM ( <i>N</i> = 1,134)			No DM ( <i>N</i> = 2399)		
	HR	95% CI	<i>P</i>	HR	95% CI	<i>P</i>	HR	95% CI	<i>P</i>
<b>BMI categories</b>									
Normal weight	Ref	-	-	Ref	-	-	Ref	-	-
Underweight	1.21	0.92-1.60	0.2	1.68	1.07-2.65	0.024	1.01	0.71-1.44	>0.9
Overweight	0.96	0.83-1.12	0.6	1.12	0.87-1.44	0.4	0.88	0.73-1.07	0.2
Obesity	1.22	1.05-1.43	0.011	1.34	1.04-1.74	0.025	1.18	0.96-1.43	0.11
<b>Obesity classes</b>									
Mild	1.13	0.95-1.34	0.2	1.21	0.91-1.60	0.2	1.11	0.89-1.38	0.4
Moderate	1.43	1.13-1.80	0.003	1.57	1.08-2.28	0.019	1.36	1.00-1.85	0.048
Severe	1.49	1.12-2.00	0.007	2.00	1.26-3.18	0.003	1.29	0.88-1.88	0.2
<b>DM</b>	1.15	1.01-1.30	0.035						

CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; Ref, reference.

## Conclusion

DM and obesity are independent risk factors associated with COVID-19 severity. Stratified analyses suggest obesity may confer greater risk to patients with DM compared with patients without DM. This relationship may aid the development of risk-stratification protocols and requires further exploration. **O**

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