Obesity Doubles Mortality in Patients Hospitalized for (SARS-CoV-2) in Paris Hospitals, France: A Cohort Study on 5,795 Patients

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Objective: Preliminary data from different cohorts of small sample size or with short follow-up indicate poorer prognosis in people with obesity compared with other patients. This study aims to precisely describe the strength of association between obesity in patients hospitalized with coronavirus disease 2019 (COVID-19) and mortality and to clarify the risk according to usual cardiometabolic risk factors in a large cohort.

Methods: This is a prospective cohort study including 5,795 patients aged 18 to 79 years hospitalized from February 1 to April 30, 2020, in the Paris area, with confirmed infection by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Adjusted regression models were used to estimate the odds ratios (ORs) and 95% CIs for the mortality rate at 30 days across BMI classes, without and with imputation for missing BMI values.

Results: Eight hundred ninety-one deaths had occurred at 30 days. Mortality was significantly raised in people with obesity, with the following ORs for BMI of 30 to 35 kg/m^2, 35 to 40 kg/m^2, and >40 kg/m^2: 1.89 (95% CI: 1.45-2.47), 2.79 (95% CI: 1.95-3.97), and 2.55 (95% CI: 1.62-3.95), respectively (18.5-25 kg/m^2 was used as the reference class). This increase holds for all age classes.

Conclusions: Obesity doubles mortality in patients hospitalized with COVID-19.

Study Importance

What is already known?

► Preliminary data from different cohorts with a small sample size (fewer than 400 patients) with short follow-up or with poorly described BMI indicate a poorer prognosis in people with obesity compared with other patients.

What does this study add?

► This cohort study of 5,795 patients aged 18 to 79 years hospitalized in Paris shows a doubling for mortality risk in patients hospitalized for severe acute respiratory syndrome coronavirus 2 infection independently of cardiometabolic risk factors.

How might these results change the focus of clinical practice?

► People with obesity in the coronavirus disease 2019 pandemic context require personalized treatment.

Introduction

Since its emergence from China at the end of 2019, the coronavirus disease 2019 (COVID-19) pandemic has become the main worldwide public health threat and it is responsible for lockdown measures affecting millions of people. COVID-19 symptoms include a wide variety of clinical presentations, from no symptoms to severe respiratory symptoms leading to death (1).

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Obesity, and especially its most extreme forms, is a source of stigma (2), high emergency care use (3), higher morbidity, and increased mortality (4). In the context of infectious disease, a high BMI has been recognized as a risk factor for nosocomial, skin, and respiratory disease infections (5). About 10 years ago, against the backdrop of the H1N1 influenza epidemic, it was clearly pointed out in a meta-analysis of more than 3,000 individuals that people with severe obesity had a twofold increased risk for intensive care unit (ICU) admission and mortality, compared with counterparts without obesity (6). In two single-center studies, the risk for need of invasive mechanical ventilation in patients with COVID-19–related severe acute respiratory syndrome was higher in patients with severe obesity than in patients with normal weight (7) but was not higher for those with class I obesity (BMI of 30 to 35 kg/m^2) (8).

Preliminary data from different small-sample-size (fewer than 400 patients) cohorts of patients with COVID-19 with short follow-up or with poorly described BMI values indicate poorer prognosis in people with obesity than in other patients. For instance, one study showed a higher mortality frequency in people with severe obesity admitted to the ICU compared with people with less-severe obesity (9). However, it is not possible to conclude from these results that obesity is an independent factor of mortality for patients with COVID-19 because of the small sample sizes of these studies, nor is it possible to have a precise estimate of the obesity effect size because of the absence of BMI categories and incomplete follow-up. These results need, therefore, to be confirmed in a large cohort, with available BMI categories and adequate follow-up. To further investigate the topic, we conducted an analysis of the association between BMI and risk for mortality at 30 days after hospitalization for COVID-19 in all Paris area–based public university hospitals.

Methods

Data source

The Assistance Publique–Hôpitaux de Paris (AP-HP) is the largest hospital entity in Europe, with 39 hospitals (22,474 beds) mainly located in the Greater Paris area and 1.5 million hospitalizations per year (10% of all hospitalizations in France). Since 2014, the AP-HP has been building an analytics platform based on a clinical data repository (CDR), aggregating day-to-day clinical data from 8.8 million patients captured by clinical databases (10). The clinical data repository has received authorization from the French Data Protection Authority (Commission Nationale de l'Informatique et des Libertés, number 1980120). From the beginning of the COVID-19 epidemic, the "Entrepôt de Données de Santé COVID" (EDS-COVID) database stemmed from this initiative. The later database retrieves electronic health records from all AP-HP facilities and aggregates them into a clinical data warehouse following the Observational Medical Outcomes Partnership common data model (11). Our analysis follows recommendations provided by the Reporting of Studies Conducted Using Observational Routinely Collected Health Data Statement (12).

This study was approved by the institutional review board (authorization number IRB 00011591) of the scientific and ethical committee of the AP-HP. All subjects included in this study were informed about the reuse of their data for research, and subjects who objected to the reuse of their data were excluded from this study, in accordance with French legislation.

Patients

We retrieved all patients who tested positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by polymerase chain reaction (PCR) between February 1 and April 30 and hospitalized in one of the AP-HP hospitals from the EDS-COVID database. Patients with no bioclinical information ($n = 580$) were excluded (i.e., those with no hospitalization reports or recorded vital signs). For included patients, follow-up was recorded until May 30.

BMI values were collected from a dedicated clinical form including height, weight, and BMI, and when these values were unavailable directly from hospitalization reports, they were calculated using a dedicated natural language processing (NLP) pipeline ("COVID-19–AP-HP–NLP pipeline") that extracted height, weight, and BMI and categorized them according to the standard World Health Organization classes (<18.5 [18.5-25, 25-30, 30-35, and 35-40] kg/m^2 and >40 kg/m^2). When either height or weight was unavailable, BMI information was considered as missing.

Smoking status was defined as being a current smoker or having a history of smoking using the formerly mentioned COVID-19–AP-HP–NLP pipeline. Comorbidities were extracted from the *International Classification of Diseases, Tenth Revision (ICD-10)* codes of previous and current hospitalization: I10 for hypertension, N18 for chronic kidney disease, G473 for sleep apnea, E78 for dyslipidemia, and C00 to D48 for malignancies. Heart failure was defined as having an I50 *ICD-10* code in a previous hospitalization. Diabetes was defined as having an E11 *ICD-10* code of diabetes or having an glycated hemoglobin level greater than 6.5% in any previous hospitalization.

Indirect information concerning BMI values was also retrieved for BMI imputation in patients with missing BMI. Using four-digit E66 *ICD-10* codes, the following variables were created: E6603, E6613, E6683, and E6693 composed the *ICD-10* BMI of 25 to 30 class; E6604, E6614, E6624, E6684, and E6694 composed the *ICD-10* BMI of 30 to 35 class; E6605, E6615, E6625, E6685, and E6695 composed the *ICD-10* BMI of 35 to 40 class; E6606, E6616, E6626, E6686, and E6696 composed the *ICD-10* BMI of 40 to 50 class; and E6607, E6617, E6627, E6687, and E6697 composed the *ICD-10* BMI >50 class. Malnutrition was extracted using E43 to E46 *ICD-10* codes. Mentions of obesity in free-text reports were also retrieved using the formerly mentioned COVID-19–AP-HP–NLP pipeline.

Age at admission, sex, ICU admission, and death during hospitalization were extracted from hospital administrative data.

Outcome

The considered outcome was death during hospitalization at 30 days after a positive SARS-CoV-2 PCR test result. Outcomes were retrieved from administrative hospital data.

Statistical methods

Patients' characteristics were defined according to BMI classes and sex using medians and interquartile ranges for continuous variables and proportions for binary variables, both before and after missing BMI imputation.

We imputed missing BMI categories using predictive mean matching, considering the following as explanatory variables: comorbidities (hypertension, diabetes, sleep apnea, dyslipidemia, chronic kidney

disease, heart failure, and/or cancer), smoking status, sex, age, and indirect information regarding BMI values (obesity from free-text reports, variables extracted from four-digit E66 *ICD-10* codes, and malnutrition *ICD-10* codes). To assess the predictive ability of these variables, we performed a regression analysis on BMI using the same explanatory variables on the complete data set. To account for imputation variability, we generated five imputed samples.

Multivariate odds ratios (ORs) (95% CIs) were estimated according to BMI classes, with adjustment for comorbidities, smoking status, age, and sex using logistic regressions, both including and excluding patients with missing BMI and with stratification on age class. For analysis including patients with imputed BMI, variation across imputed data sets was taken into account by incorporating sample variability in the estimated CIs. All analyses were performed using R 4.0.2 software (R Foundation for Statistical Computing, Vienna Austria), and the MICE package was used for multiple imputations process.

Results

Demographic and clinical characteristics

During the period of February 1 through April 30, 2020, a total of 8,671 patients with a PCR-confirmed SARS-CoV-2 infection were hospitalized in 1 of the 39 hospitals (Figure 1). Among them, 5,795 patients were between 18 and 80 years old and had available bioclinical data, of whom 4,056 had available BMI values (2,597 extracted from free-text reports and 1,459 extracted from clinical signs). The mean (SD) age was 58.9 (14.7) years for women ($n = 2004$) and 60.3 (13.0) years for men ($n = 3,791$) (Table 1). The mean BMI was 29.3 (7.5) kg/m^2 and 27.2 (6) kg/m^2 in women and men, respectively. Comorbidities were frequent and increased with BMI classes. People with class III obesity aggregated the most risk factors. ICU admission rates increased with BMI classes. Use of mechanical ventilation did not follow an obvious trend across BMI classes. BMI was imputed for 1,739 patients, and the main BMI predictors in the imputation model were variables derived from indirect information on BMI from hospitalization reports and *ICD-10* codes (see regression coefficients and significance in

Supporting Information Table S1). The correlation coefficient for the regression model used to assess the ability to predict BMI was 63%; therefore, the available indirect information on BMI was relevant to predict BMI.

BMI and mortality risk

Mortality was significantly higher in people with obesity when taking into account age groups, sex, smoking history, and comorbidities (Figure 2), with the following adjusted ORs for BMI of 30 to 35, 35 to 40, and >40 before missing BMI imputation: 1.89 (95% CI: 1.45-2.47), 2.79 (95% CI: 1.95-3.97), and 2.55 (95% CI: 1.62-3.95), respectively, compared with BMI of 18.5 to 25 as the reference class. This association remained similar in all age classes (Figure 3), with ORs increasing with older ages. The results were comparable after imputation with the following adjusted ORs: 1.75 (95% CI: 1.37-2.25), 2.69 (95% CI: 1.91-3.77), and 2.38 (95% CI: 1.52-3.67), respectively (Supporting Information Figure S1).

Discussion

This large study investigates the role of obesity in mortality risk at 30 days in patients hospitalized with COVID-19 in any of the 39 university public hospitals in the Paris region (France). We have shown that obesity was a major prognostic factor, independent of known chronic comorbidities.

Several hypotheses can be made to explain a worse survival rate in people with obesity compared with people without obesity. First, obesity is characterized by an increased low-grade inflammatory state that relates to a dysfunctional adipose microenvironment (13). The adipose cells are responsible for the secretion of pro-inflammatory adipokines, such as tumor necrosis factor alpha (TNF-alpha) and interleukin-6, lower adiponectin, and increased leptin. The dysregulated cytokine environment may be the early biological step that mediates multiple organ failure (14). Second, obesity is associated with several respiratory disorders, such as obstructive sleep apnea syndrome, asthma, restrictive respiratory syndrome, and obesity
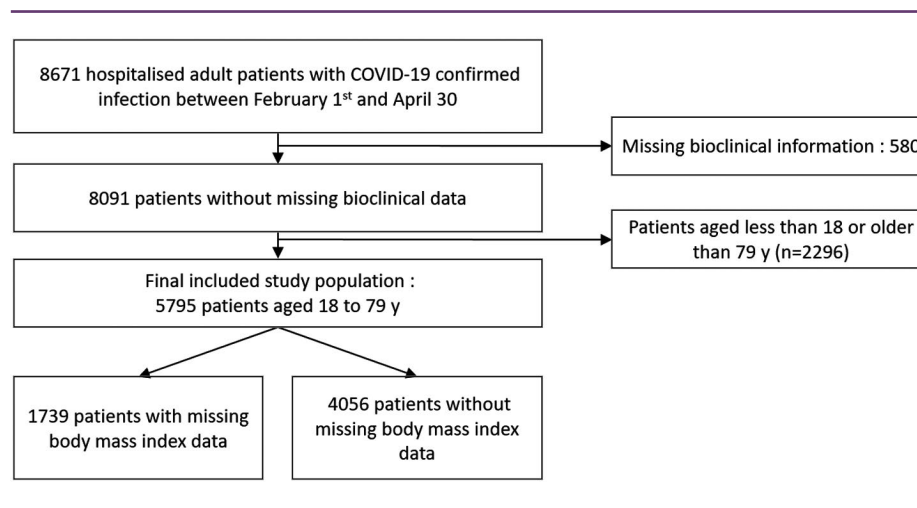

Figure 1 Study population flowchart.

TABLE 1 Characteristics of the patients at baseline according to sex and BMI classes before imputation for missing values

	All BMI classes	N/A	<18.5 kg/m²	18.5-25 kg/m²	25-30 kg/m²	30-35 kg/m²	35-40 kg/m²	40+ kg/m²
Female patients								
n	2,004	617	71	329	395	318	170	104
Deceased	262 (13)	65 (11)	11 (15)	33 (10)	49 (12)	55 (17)	32 (19)	17 (16)
Intensive care	581 (29)	122 (20)	13 (18)	83 (25)	135 (34)	124 (39)	65 (38)	39 (37.5)
Mechanical ventilation	590 (29)	97 (16)	22 (31)	110 (33)	123 (31)	126 (40)	68 (40)	44 (42)
Age, mean (SD), y	59 (15)	56 (15.5)	60 (17)	61 (15)	61.3 (14)	58.9 (13)	58 (13)	58.7 (14)
Hypertension	1,042 (52)	234 (38)	30 (42)	161 (49)	216 (55)	208 (65)	118 (69)	75 (72)
Sleep apnea	99 (5)	10 (2)	4 (6)	9 (3)	12 (3)	18 (6)	24 (14)	22 (21)
Dyslipidemia	140 (7)	11 (2)	7 (10)	20 (6)	39 (10)	30 (9)	15 (9)	18 (17)
Diabetes	777 (39)	153 (25)	25 (35)	109 (33)	158 (40)	174 (55)	94 (55)	64 (62)
Heart failure	86 (4)	8 (1)	8 (11)	19 (6)	18 (5)	18 (6)	6 (4)	9 (9)
Chronic kidney disease	165 (8)	14 (2)	6 (8)	43 (13)	36 (9)	37 (12)	18 (11)	11 (11)
Cancer	244 (12)	24 (4)	18 (25)	70 (21)	72 (18)	34 (11)	17 (10)	9 (9)
Smoking	153 (8)	20 (3)	16 (23)	44 (13)	33 (8)	23 (7)	11 (6)	6 (6)
C-reactive protein, mean (SD), mg/L	87 (82)	86 (82)	62 (74)	75 (81)	87 (84)	95 (82)	100 (76)	102 (87)
Male patients								
n	3,791	1,122	105	845	1,047	474	126	72
Deceased	629 (17)	161 (14)	17 (16)	121 (14)	190 (18)	90 (19)	31 (25)	19 (26)
Intensive care	1,565 (41)	331 (30)	25 (24)	337 (40)	509 (49)	253 (53)	68 (54)	42 (58.3)
Mechanical ventilation	1,394 (37)	218 (19)	47 (45)	340 (40)	474 (45)	226 (48)	57 (45.2)	32 (44.4)
Age, mean (SD), y	60 (13)	60 (14)	61 (16)	61 (13)	61 (12)	59 (12)	56 (13)	52.3 (15)
Hypertension	2,100 (55)	497 (44)	54 (51)	479 (57)	643 (61)	301 (64)	79 (63)	47 (65)
Sleep apnea	177 (5)	18 (2)	3 (3)	16 (2)	54 (5)	51 (11)	18 (14)	17 (24)
Dyslipidemia	330 (9)	40 (4)	11 (10)	78 (9)	129 (12)	48 (10)	18 (14)	6 (8)
Diabetes	1,696 (45)	406 (36)	49 (47)	381 (45)	509 (49)	248 (52)	61 (48)	42 (58)
Heart failure	178 (5)	16 (1)	9 (9)	55 (7)	60 (6)	26 (5)	8 (6)	4 (6)
Chronic kidney disease	378 (10)	34 (3)	17 (16)	135 (16)	127 (12)	46 (10)	12 (10)	7 (10)
Cancer	412 (11)	50 (4)	33 (31)	143 (17)	138 (13)	36 (8)	9 (7)	3 (4)
Smoking	633 (17)	95 (8)	36 (34)	176 (21)	217 (21)	77 (16)	23 (18)	9 (12.5)
C-reactive protein, mean (SD), mg/L	117 (94)	117 (91)	85 (86)	113 (96)	121 (95)	121 (97)	111 (95)	117 (94)

Values are n (%), except when specified otherwise.
N/A, not available.

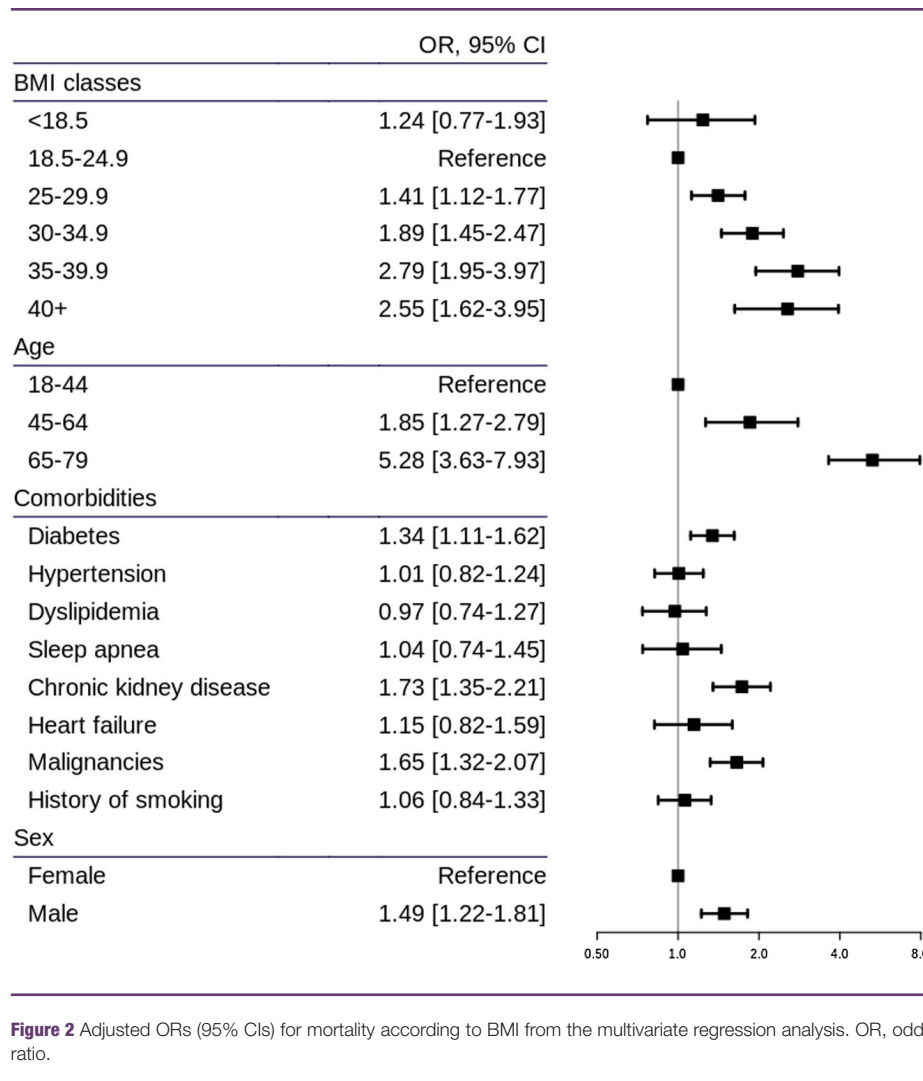|	OR, 95% CI
BMI classes	
<18.5	1.24 [0.77-1.93]
18.5-24.9	Reference
25-29.9	1.41 [1.12-1.77]
30-34.9	1.89 [1.45-2.47]
35-39.9	2.79 [1.95-3.97]
40+	2.55 [1.62-3.95]
Age	
18-44	Reference
45-64	1.85 [1.27-2.79]
65-79	5.28 [3.63-7.93]
Comorbidities	
Diabetes	1.34 [1.11-1.62]
Hypertension	1.01 [0.82-1.24]
Dyslipidemia	0.97 [0.74-1.27]
Sleep apnea	1.04 [0.74-1.45]
Chronic kidney disease	1.73 [1.35-2.21]
Heart failure	1.15 [0.82-1.59]
Malignancies	1.65 [1.32-2.07]
History of smoking	1.06 [0.84-1.33]
Sex	
Female	Reference
Male	1.49 [1.22-1.81]

Figure 2 Adjusted ORs (95% CIs) for mortality according to BMI from the multivariate regression analysis. OR, odds ratio.

hypoventilation syndrome (15). People with obesity are at particular risk of acute respiratory distress syndrome (ARDS), whatever the etiology of the syndrome (16). One explanation for the high prevalence of ARDS in people with obesity may be the very specific pulmonary mechanics of such patients, characterized mainly by excessively high pleural pressures with generally preserved chest-wall compliance. Such a pattern leads to the frequent occurrence of negative transpulmonary pressures favoring a greater incidence of atelectasis (17). One suggested means to counteract such phenomenon is to use high positive end-expiratory pressure settings, ideally based on esophageal monitoring (18).

An important result of the study is the poorer vital prognosis observed in people with obesity and COVID-19. Such a result contrasts with the general findings of a similar or even better prognosis than in the population with ARDS without obesity (19). However, one should keep in mind the worse vital prognosis previously observed in people with obesity and H1N1 infection (6). A specific detrimental influence of the viral insult in people with obesity is, therefore, conceivable. In addition, the design of the study did not allow for precise assessment of the ventilator settings used in people with obesity and COVID-19,

compared with those without obesity. BMI data were missing in about a third of included patients and were, therefore, imputed when missing. Of note, we benefitted from a large amount of indirect information regarding missing BMI values using free-text reports and *ICD-10* codes, but this was not sufficient to accurately predict BMI values. However, ORs before and after imputation were similar.

This study was considerably facilitated by the EDS-COVID database, which retrieves electronic health records from all AP-HP facilities and aggregates them into a clinical data warehouse. This clinical data warehouse allowed real-time retrieval of a large set of data to deeply characterize our study population. This approach was secured by a data-quality program, ensuring a high standard of quality for this database (10). Furthermore, even if we had been able to collect a large sample size, BMI does not capture body composition or even variations in weight. Indeed, our data indicate poorer prognosis with aging, both for undernutrition and severe obesity, which strongly relates to muscle-mass loss and sarcopenia in the context of an hypercatabolic state related to COVID-19 infection (20). It has been previously shown that sarcopenic obesity is associated with a longer hospital stay and a less successful recovery after an ICU stay (21). Our results might be limited
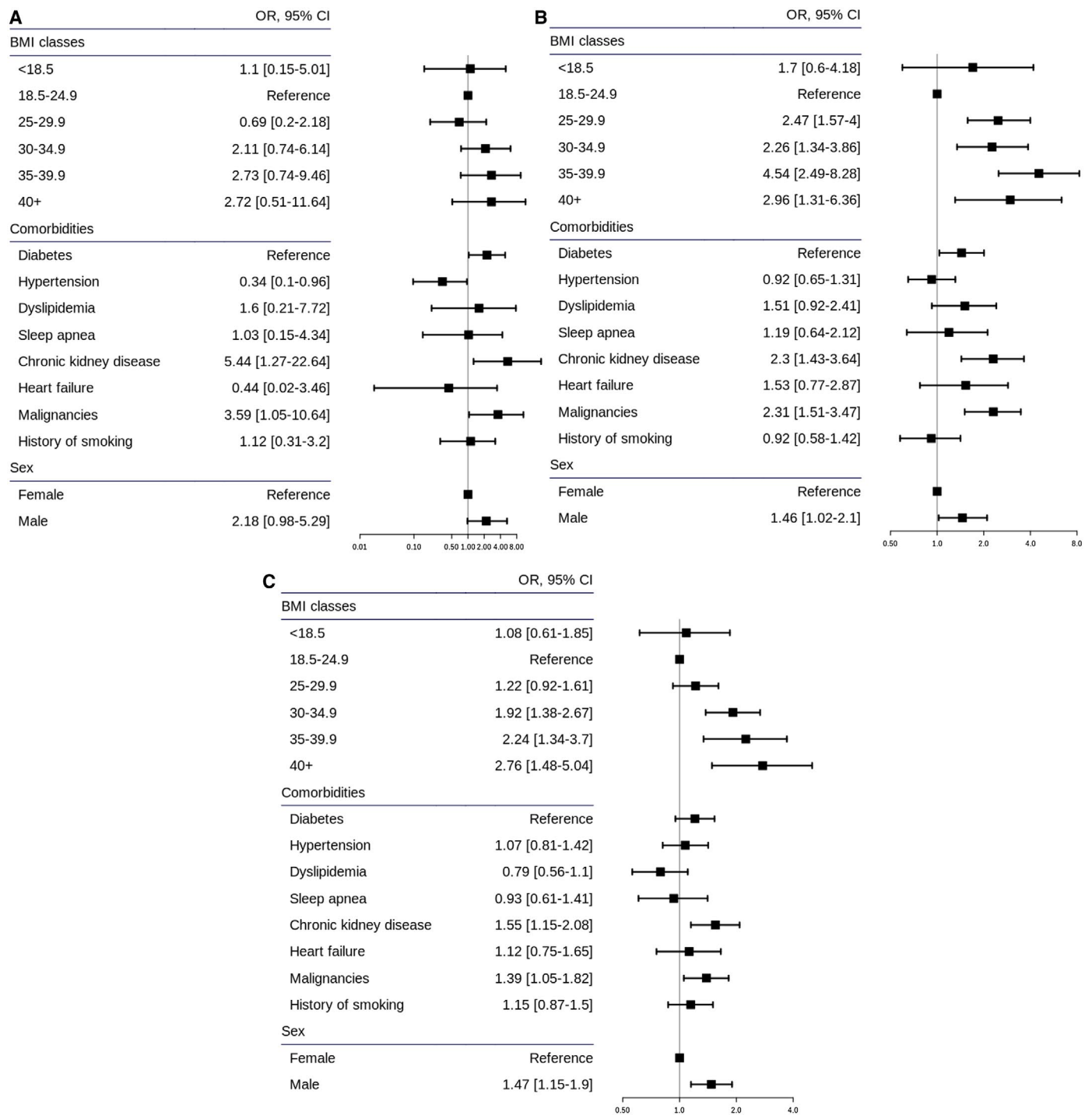
A

	OR, 95% CI
BMI classes	
<18.5	1.1 [0.15-5.01]
18.5-24.9	Reference
25-29.9	0.69 [0.2-2.18]
30-34.9	2.11 [0.74-6.14]
35-39.9	2.73 [0.74-9.46]
40+	2.72 [0.51-11.64]
Comorbidities	
Diabetes	Reference
Hypertension	0.34 [0.1-0.96]
Dyslipidemia	1.6 [0.21-7.72]
Sleep apnea	1.03 [0.15-4.34]
Chronic kidney disease	5.44 [1.27-22.64]
Heart failure	0.44 [0.02-3.46]
Malignancies	3.59 [1.05-10.64]
History of smoking	1.12 [0.31-3.2]
Sex	
Female	Reference
Male	2.18 [0.98-5.29]

B

	OR, 95% CI
BMI classes	
<18.5	1.7 [0.6-4.18]
18.5-24.9	Reference
25-29.9	2.47 [1.57-4]
30-34.9	2.26 [1.34-3.86]
35-39.9	4.54 [2.49-8.28]
40+	2.96 [1.31-6.36]
Comorbidities	
Diabetes	Reference
Hypertension	0.92 [0.65-1.31]
Dyslipidemia	1.51 [0.92-2.41]
Sleep apnea	1.19 [0.64-2.12]
Chronic kidney disease	2.3 [1.43-3.64]
Heart failure	1.53 [0.77-2.87]
Malignancies	2.31 [1.51-3.47]
History of smoking	0.92 [0.58-1.42]
Sex	
Female	Reference
Male	1.46 [1.02-2.1]

C

	OR, 95% CI
BMI classes	
<18.5	1.08 [0.61-1.85]
18.5-24.9	Reference
25-29.9	1.22 [0.92-1.61]
30-34.9	1.92 [1.38-2.67]
35-39.9	2.24 [1.34-3.7]
40+	2.76 [1.48-5.04]
Comorbidities	
Diabetes	Reference
Hypertension	1.07 [0.81-1.42]
Dyslipidemia	0.79 [0.56-1.1]
Sleep apnea	0.93 [0.61-1.41]
Chronic kidney disease	1.55 [1.15-2.08]
Heart failure	1.12 [0.75-1.65]
Malignancies	1.39 [1.05-1.82]
History of smoking	1.15 [0.87-1.5]
Sex	
Female	Reference
Male	1.47 [1.15-1.9]

Figure 3 Adjusted ORs (95% CIs) for mortality according to BMI for age class: **(A)** 18-44, **(B)** 45-64, and **(C)** 65-79 years. OR, odds ratio.

by the fact that only mortality during hospitalization was considered. However, it is unlikely that patients hospitalized for COVID-19 died of their infection after being discharged from hospital. Therefore, the subsequent underestimation of mortality due to this potential bias is likely to be limited.

Conclusion

In summary, our data show for the first time in a large multicenter setting that obesity is related to mortality in patients hospitalized with COVID-19. The presence or absence of cardiometabolic risk factors

did not modify the increased mortality risk. In the context of a global COVID-19 pandemic lockdown, the detrimental effect of an increasingly sedentary lifestyle and increased food intake will worsen quality of life, depression risk (22), and global mortality in fragile patients with severe obesity. Thus, people with obesity in the COVID-19 pandemic context require a personalized treatment.**O**

Acknowledgments

The authors thank the EDS AP-HP COVID-19 consortium integrating the AP-HP Health Data Warehouse team as well as all the AP-HP staff and volunteers who contributed to the implementation of the EDS-COVID database and to the operating solutions for this database (list in the Appendix Table A1).

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APPENDIX

Table A1. List of collaborators

Name	Name	Affiliation	Contribution
Ancel	Pierre-Yves	AP-HP Paris University Center	Local CDW coordinator
Bauchet	Alain	AP-HP Saclay University	
Benoit	Vincent	WIND Department AP-HP Greater Paris University Hospital	Data engineer
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Bellamine	Ali	WIND Department AP-HP Greater Paris University Hospital	Data engineer, data scientist
Bey	Romain	WIND Department AP-HP Greater Paris University Hospital	Data engineer, data scientist, regulatory assessment
Bourmaud	Aurélie	AP-HP Paris University North	Local CDW coordinator
Bréant	Stéphane	WIND Department AP-HP Greater Paris University Hospital	Coordination of clinical research informatics
Burgun	Anita	Department of Biomedical Informatics, HEGP, AP-HP Greater Paris University Hospital	Medical and scientific coordination
Carrat	Fabrice	AP-HP Sorbonne University	
Caucheteux	Charlotte	Université Paris-Saclay, Inria, CEA	Data integration and analysis
Champ	Julien	INRIA Sophia-Antipolis – ZENITH team, LIRMM, Montpellier, France	Data integration and analysis
Cormont	Sylvie	WIND Department AP-HP Greater Paris University Hospital	Data standardization

Name	Name	Affiliation	Contribution
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Collégiales of AP-HP: anesthésie-réanimation, médecine intensive réanimation, infectiologie, virologie, nutrition