Obesity

Independent Role of Severe Obesity as a Risk Factor for COVID-19 Hospitalization: A Spanish Population-Based Cohort Study

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Objectives: This study analyzed the association between severe obesity and coronavirus disease 2019 (COVID-19) hospitalization and severe disease.

Methods: The incidence of hospitalization for laboratory-confirmed COVID-19 was evaluated in a prospective population-based cohort of 433,995 persons aged 25 to 79 years in Spain during March and April of 2020. Persons with and without class 3 obesity were compared using Poisson regression to estimate the adjusted relative risk (aRR) from class 3 obesity of COVID-19 hospitalization and of severe disease (intensive care unit admission or death). Differences in the effect by age, sex, and chronic conditions were evaluated.

Results: Individuals with class 3 obesity had a higher risk of hospitalization (aRR = 2.20, 95% CI: 1.66-2.93) and developing severe COVID-19 (aRR = 2.30, 95% CI: 1.20-4.40). In people younger than 50 years, these effects were more pronounced (aRR = 5.02, 95% CI: 3.19-7.90 and aRR = 13.80, 95% CI: 3.11-61.17, respectively), whereas no significant effects were observed in those aged 65 to 79 years (aRR = 1.22, 95% CI: 0.70-2.12 and aRR = 1.42, 95% CI: 0.52-3.88, respectively). Sex and chronic conditions did not modify the effect of class 3 obesity in any of the outcomes.

Conclusions: Severe obesity is a relevant risk factor for COVID-19 hospitalization and severity in young adults, having a magnitude similar to that of aging. Tackling the current obesity pandemic could alleviate the impact of chronic and infectious diseases.

Obesity (2021) **29**, 29-37.

Study Importance

What is already known?

- Several studies have pointed out older age and some comorbidities as risk factors for severe acute respiratory syndrome coronavirus 2 infection and for severe coronavirus disease 2019 (COVID-19).
- The role of obesity has yet to be determined.

What does this study add?

- Severe obesity is an independent risk factor for laboratory-confirmed COVID-19 hospitalization and for severe COVID-19.
- The excess of risk associated with severe obesity is more pronounced in younger adults.

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

- People with severe obesity should be recognized as a population at high risk of severe COVID-19 regardless of their age; thus, they should be considered in preventive protocols and clinical guidelines for groups at high risk.
- Obesity is a risk factor for both chronic and infectious diseases; therefore, it is urgent to establish further measures to tackle the obesity epidemic.

Introduction

A new coronavirus causing severe acute respiratory syndrome (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]) was first recognized at the end of 2019 in China and has spread worldwide (1). Indeed, the outbreak of coronavirus disease 2019 (COVID-19)

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 Received: 26 June 2020; **Accepted:** 2 September 2020; **Published online 6 December 2020. doi:10.1002/oby.23029**

has been declared a global pandemic by the World Health Organization (2). Although COVID-19 is not life-threatening in most people, it can be fatal for others. Several studies have pointed out older age and the presence of comorbidities as risk factors for severe disease (3-6).

Obesity is a multifactorial chronic metabolic disease that may place the population with obesity at higher risk of respiratory infections, including COVID-19, and even severe complications, independent of the presence of comorbidities. Obesity leads to an impaired immune response and induces alterations in respiratory physiology (7). Considering that the neglected health consequences of obesity worsen hand-in-hand with BMI (8), special attention should be focused on severe obesity. In accordance, obesity, and especially severe obesity, has been already described as an independent predictor of severity for other respiratory infections, such as influenza A (H1N1) (9). Although there is a growing body of studies assessing obesity as a predictor for severe COVID-19 (5,10-14), several international organizations have pointed to a lack of well-established evidence about the effect of obesity on COVID-19 (15,16).

Although the first peak of the pandemic has already passed in many countries, new cases continue being diagnosed. No vaccine is currently available, and new waves could be as devastating as the first one. Risk factors should be known in order to protect the most vulnerable populations. Because the prevalence of obesity and severe obesity is high in many countries (17), the lack of well-established evidence about obesity as a risk factor for COVID-19 makes that evaluation timely needed. In a population-based cohort, the current study aimed to evaluate severe obesity as an independent risk factor for laboratory-confirmed COVID-19 hospitalization and for severe COVID-19, defined as intensive care unit (ICU) admission or death.

Methods

Study design and setting

A prospective population-based cohort study was performed using data from Navarra, a Spanish region of ~650,000 inhabitants. The Navarra Health Service provides health care, free at the point of service, to 97% of the population of the region. By the end of February 2020, when the first case of COVID-19 was confirmed in the region, we defined the cohort as the population aged 25 to 79 years and covered by the Health Service. Health care professionals, nursing home residents, and terminally ill patients were excluded from the current analysis, leaving a total of 433,995 individuals (Figure 1). The protocol of the study was approved by the Ethical Committee for Clinical Research of Navarra.

Data collection

Sociodemographic characteristics, health care use, major chronic conditions, risk factors, and the diagnosis of class 3 obesity of the cohort population referred at the beginning of the follow-up (March 1, 2020) were obtained from electronic medical records. These electronic clinical records have demonstrated high sensitivity and specificity to detect chronic medical conditions (18).

Sociodemographic variables included sex, age, nationality (Spanish or other), municipality size (<5,000, 5,000-100,000, and >100,000

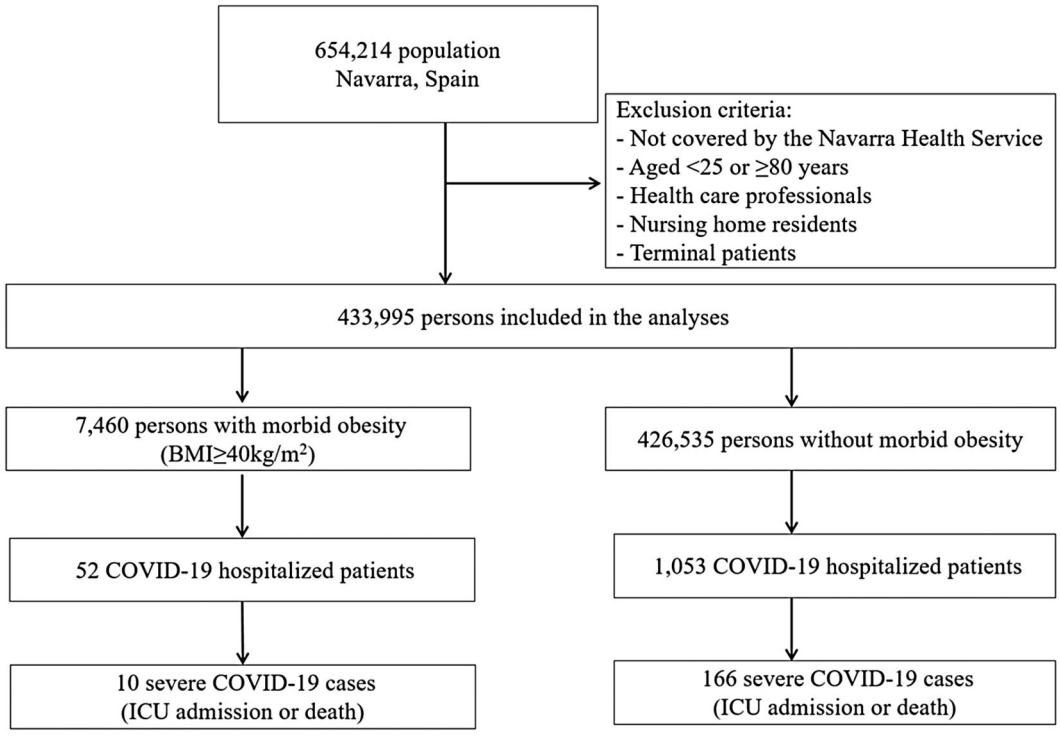

Figure 1 Flowchart of the participants included in the study.

inhabitants) and annual taxable income level (none or dependent, <18,000, 18,000-100,000, and >100,000 €). Health care use included the number of visits to primary health care centers and hospitalizations in the prior 12 months. Major chronic conditions considered were diabetes, cardiovascular disease, chronic obstructive pulmonary disease, asthma, chronic renal disease, liver cirrhosis, history of stroke, and immunodeficiency. Hypertension was considered as a separate variable. Smoking status was categorized as nonsmoker, prior smoker, current smoker, and unknown.

Class 3 obesity was defined as BMI ≥ 40 kg/m^2. People with BMI < 40 kg/m^2 or with an unknown BMI were not considered as having class 3 obesity, as the BMI is well registered in medical records of patients with severe obesity.

Outcomes

Since the beginning of March 2020, all hospitalized patients with clinical manifestation compatible with COVID-19 (19) were tested by polymerase chain reaction (PCR) in an upper-respiratory-tract sample and by rapid antibody testing of blood or serum samples. Hospitalized patients with clinical manifestations of COVID-19 and who tested positive for SARS-CoV-2 by PCR were included in this study. Those patients who tested positive for the virus by rapid antibody testing were also considered as confirmed, even without a positive PCR result. COVID-19 cases diagnosed in March and April 2020 were considered for the present study. Severe cases of COVID-19 included those with confirmed COVID-19 who were admitted to the ICU or who died of COVID-19 in the hospital or within 30 days after admission to the hospital. Hospital and ICU admissions were obtained from the Regional Health Service electronic records. Deaths were obtained from electronic medical records and administrative databases and were validated with the Daily Mortality Monitoring System. As a part of the epidemiological surveillance in the region, hospital admissions and deaths had been reviewed by public health doctors to detect those related to COVID-19, and only these hospitalizations and deaths were considered for the present study. The database was anonymized before the analysis.

Statistical analysis

Characteristics of individuals with and without class 3 obesity were assessed. Percentages were compared by χ^2 test.

The incidences of confirmed COVID-19 hospitalizations and confirmed severe COVID-19 cases per 100,000 inhabitants were compared between those with and without class 3 obesity. Poisson regression was used to assess class 3 obesity as an independent risk factor for COVID-19 hospitalization and for having a severe case. Crude relative risks (RRs) and adjusted RRs (aRRs) and their 95% CIs were calculated. In a first adjusted analysis (model 1), only sociodemographic variables were considered, and the final analysis (model 2) also included health care use, presence of any major chronic condition, presence of hypertension, and smoking status.

Analyses were stratified by age groups (25-49, 50-64, and 65-79 years old), sex, and the presence of major chronic conditions. The possible modifying effect of age, sex, and major chronic conditions on the risk associated with class 3 obesity was alternately evaluated in the fully adjusted model by the inclusion of the interaction term, and, in the case of age, by using a six-category variable that combined the three categories of age with class 3 obesity status. The population of individuals who were 25 to 49 years old without class 3 obesity was the reference category in this last analysis.

Analyses were performed using Stata Software/SE version 15 (StataCorp, College Station, Texas). P values < 0.05 were considered as statistically significant.

Results

Characteristics of the cohort population by class 3 obesity status

The study population included 433,995 persons aged 25 to 79 years, with 7,460 (1.7%) of them presenting with class 3 obesity. Compared with the rest of the cohort, among persons with class 3 obesity, there were higher proportions of women (61.4% vs. 49.9%), people aged 50 years or more (62.0% vs. 50.0%), people residing in municipalities with fewer than 5,000 inhabitants (36.8% vs. 33.4%), and people with no income or an annual income lower than 18,000€ (71.4% vs. 58.0%). In addition, a higher proportion of those with class 3 obesity had visited a primary health care center more than nine times during the previous year (30.6% vs. 17.0%) or were hospitalized (8.5% vs. 5.4%). The prevalence of major chronic conditions was nearly two times higher (46.6% vs. 24.6%), and a diagnosis of hypertension was three times more frequent (44.8% vs. 16.1%) among those with class 3 obesity compared with the rest of the cohort (Table 1).

COVID-19 hospitalization and severe cases

A total of 1,105 persons in the cohort were hospitalized for confirmed COVID-19 (255 per 100,000 inhabitants), and 176 were severe cases (41 per 100,000). Of these, 117 were admitted to the ICU and 97 died (28 died in the ICU). Although subjects with class 3 obesity made up 1.7% of the study population, they resulted in 4.7% of the COVID-19 hospitalizations and 5.7% of the severe cases (Table 2).

As compared with all others, those with class 3 obesity had crude RRs of 2.82 (95% CI: 2.14-3.73, P < 0.001) for hospitalization for COVID-19, 3.44 (95% CI: 1.82-6.52, P < 0.001) for developing a severe disease, and 3.64 (95% CI: 1.69-7.81, P < 0.001) for ICU admission (Table 2).

Severe obesity and risk of COVID-19 hospitalization

When adjusting for potential confounders, people with class 3 obesity were at double risk of hospitalization for COVID-19 compared with the rest of the population (adjusted RR [aRR]: 2.20, 95% CI: 1.66-2.93, P < 0.001). Separate effect estimates were obtained for age groups. Among people aged 25 to 49 years, class 3 obesity was associated with a five-times-higher risk of hospitalization for COVID-19 (aRR: 5.02, 95% CI: 3.19-7.90, P < 0.001); in those aged 50 to 64 years, it was associated to almost twice the risk (aRR: 1.87, 95% CI: 1.12-3.12, P = 0.017); and the association was not statistically significant in people aged 65 to 79 years (aRR: 1.22, 95% CI: 0.70-2.12, P = 0.488) (Table 3). A statistically significant interaction was observed for the effect of class 3 obesity by age group (P for interaction < 0.001).

To expand on the combined effect of severe obesity and age, we compared six categories that were a combination of the three categories of age with class 3 obesity status, using the youngest group without class

TABLE 1 Characteristics of persons with and without class 3 obesity[a] in the population-based cohort

	Persons with class 3 obesity		Persons without class 3 obesity		
Sociodemographic and clinical variables	*N*	%	*N*	%	*P* value
Sex					<0.001
Female	4,578	61.4	212,768	49.9	
Male	2,882	38.6	213,767	50.1	
Age (y)					<0.001
25-49	2,834	38.0	213,220	50.0	
50-64	2,661	35.7	129,465	30.4	
65-79	1,965	26.3	83,850	19.7	
Country of origin					0.047
Spain	6,165	82.6	348,672	81.7	
Other	1,295	17.4	77,863	18.3	
Municipality size, inhabitants					<0.001
>100,000	2,159	28.9	137,284	32.2	
5,000-100,000	2,557	34.3	146,967	34.5	
<5,000	2,744	36.8	142,284	33.4	
Annual taxable income level (€)					<0.001
None/dependent	709	9.5	15,357	3.6	
<18,000	4,619	61.9	232,026	54.4	
18,000-100,000	2,108	28.3	176,300	41.3	
>100,000	24	0.3	2,852	0.7	
Primary health care visits in prior 12 months					<0.001
0	721	9.7	86,068	20.2	
1-4	2,564	34.4	178,219	41.8	
5-9	1,889	25.3	89,630	21.0	
>9	2,286	30.6	72,618	17.0	
Hospitalization in prior 12 months	634	8.5	23,158	5.4	<0.001
Smoking status					
Unknown	3,322	44.5	268,514	63.0	
Never smoker	1,969	26.4	60,797	14.3	
Current smoker	1,552	20.8	76,336	17.9	
Prior smoker	617	8.3	20,888	4.9	
Major chronic condition	3,575	46.6	104,800	24.6	<0.001
Hypertension	3,345	44.8	68,543	16.1	<0.001
Total	7,460	100	426,535	100	

[a]Class 3 obesity: BMI ≥ 40kg/m^2.

3 obesity as the reference category. We observed that although the risk of hospitalization for COVID-19 among the population without class 3 obesity increased with age, among those with class 3 obesity, the risk was high from young ages and remained similarly high regardless of age (Figure 2).

Because no evidence of association between severe obesity and COVID-19 hospitalization in older ages was observed, we explored differences in the effect of class 3 obesity by sex and major chronic conditions only among people from 25 to 64 years old. Class 3 obesity increased the risk of COVID-19 hospitalization both in women (aRR: 3.22, 95% CI: 2.06-5.02, $P<0.001$) and men (aRR: 2.82, 95% CI: 1.69-4.71, $P<0.001$). No statistically significant interaction between class 3 obesity and sex was observed (P for interaction = 0.201) (Table 4). Similarly, class 3 obesity was associated with increased risk of COVID-19 hospitalization in people with and without major chronic conditions (aRR: 3.53, 95% CI: 2.30-5.42, $P<0.001$ and aRR: 2.29, 95% CI: 1.31-4.01, $P=0.004$, respectively). No interaction between class 3 obesity and the presence of major chronic conditions was detected (P for interaction = 0.620) (Table 4).

Class 3 obesity and risk of severe COVID-19

Severe COVID-19 (admission to the ICU or death) was twice as frequent in persons with class 3 obesity as compared with the rest of the population (aRR: 2.30, 95% CI: 1.20-4.40, $P=0.012$). Separate estimates were obtained by age group. Among people aged 25 to 49 years, class 3 obesity showed an aRR of 13.80 (95% CI: 3.11-61.17, $P<0.001$) for severe COVID-19, and this association was not statistically significant in persons aged 50 to 64 (aRR: 2.07, 95% CI: 0.62-6.85, $P=0.234$) or 65 to 79 years (aRR: 1.42, 95% CI: 0.52=3.88, $P=0.496$) (Table 5).

TABLE 2 Cases and incidence rates of confirmed COVID-19 who was admitted to the hospital, to intensive care unit or who died, according to the prior diagnosis of class 3 obesity[a]

	Population, *N* = 433,995		Class 3 obesity, *N* = 7,460		No class 3 obesity, *N* = 426,535		Persons with class 3 obesity vs. all others	
Events related to COVID-19	***N***	**Rate[b]**	***N***	**Rate[b]**	***N***	**Rate[b]**	**RR (95% CI)**	***P* value**
Hospitalization	1,105	255	52	697	1,053	247	2.82 (2.14-3.73)	<0.001
Severe cases[c]	176	41	10	134	166	39	3.44 (1.82-6.52)	<0.001
Intensive care unit admission	117	27	7	94	110	26	3.64 (1.69-7.81)	<0.001
Deaths	97	22	4	54	93	22	2.46 (0.90-6.69)	0.078

[a]Class 3 obesity: BMI ≥ 40kg/m^2.
[b]Rates are expressed as cases per 100,000 persons.
[c]Severe cases include patients who were admitted to the intensive care unit or died.
RR, relative risk.

TABLE 3 Association of class 3 obesity[a] and COVID-19 hospitalization in a cohort of population aged 25-79 years

	All study population	25-49 years	50-64 years	65-79 years
Class 3 obesity, *n*/*N*	52/7,460	23/2,834	16/2,661	13/1,965
No class 3 obesity, *n*/*N*	1,053/426,535	247/213,220	362/129,465	444/83,850
Crude, RR (95% CI); *P* value	2.82 (2.14-3.73);<0.001	7.01 (4.57-10.74); <0.001	2.15 (1.30-3.55); 0.003	1.25 (0.72-2.17);0.429
Model 1[b], RR (95% CI); *P* value	2.62 (1.98-3.47);<0.001	6.59 (4.27-10.16);<0.001	2.34 (1.41-3.87);<0.001	1.36 (0.78-2.37);0.274
Model 2[c], RR (95% CI); *P* value	2.20 (1.66-2.93);<0.001	5.02 (3.19-7.90);<0.001	1.87 (1.12-3.12);0.017	1.22 (0.70-2.12); 0.488

[a]Class 3 obesity: BMI ≥ 40kg/m^2.
[b]Adjusted for sociodemographic characteristics: sex, age, country of origin, municipality size, and annual taxable income level.
[c]Additionally adjusted for health-related characteristics: primary health care visits in prior 12 months, hospitalization in prior 12 months, smoking status, hypertension, and major chronic conditions.
RR, relative risk.

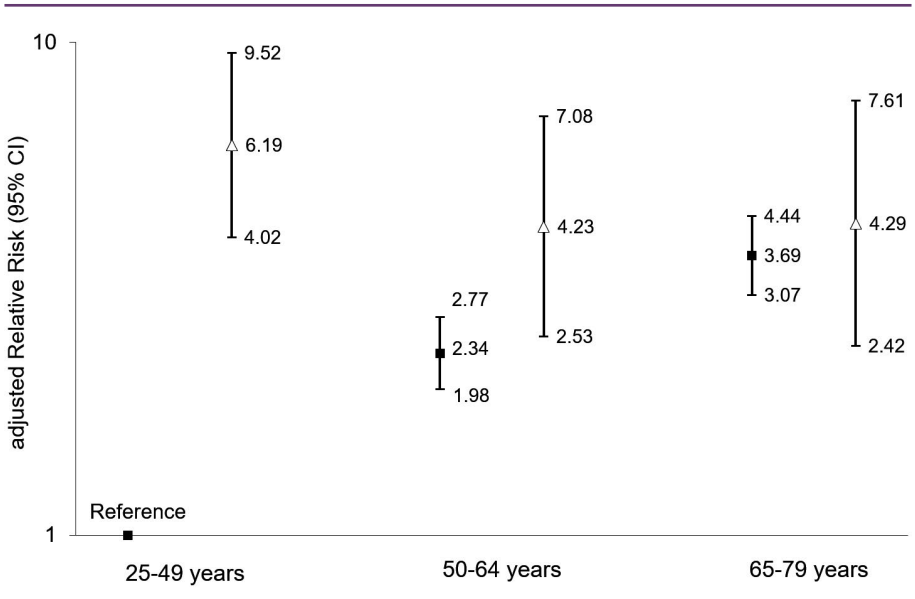

Figure 2 Combined effect of age and class 3 obesity status on the risk of COVID-19 hospitalization. Black squares denote individuals without class 3 obesity, and white triangles denote individuals with class 3 obesity (logarithmic scale). Class 3 obesity: BMI ≥ 40kg/m^2. Relative risks were adjusted for sex, age, country of origin, municipality size, annual taxable income level, primary health care visits in prior 12 months, hospitalization in prior 12 months, smoking status, hypertension, and major chronic conditions.

TABLE 4 Association of class 3 obesity[a] and COVID-19 hospitalization in the study population aged 25-64 years by sex and major chronic conditions

	Total	Female	Male	No major chronic conditions	Major chronic conditions
Class 3 obesity, *n*/*N*	39/5,495	23/3,249	16/2,246	13/3,285	26/2,197
No class 3 obesity, *n*/*N*	609/342,685	276/168,827	333/173,559	421/276,840	188/62,858
Crude, RR (95% CI); *P* value	3.99 (2.89-5.52); <0.001	4.34 (2.83-6.64); <0.001	3.71 (2.25-6.13); <0.001	2.59 (1.49-4.50); <0.001	4.15 (2.75-6.25); <0.001
Model 1[b], RR (95% CI); *P* value	3.75 (2.70-5.20); <0.001	4.00 (2.60-6.16); <0.001	3.49 (2.11-5.77); <0.001	2.54 (1.46-4.42); 0.001	3.96 (2.61-6.00); <0.001
Model 2[c], RR (95% CI); *P* value	2.97 (2.13-4.16); <0.001	3.22 (2.06-5.02); <0.001	2.82 (1.69-4.71); <0.001	2.29 (1.31-4.01); 0.004	3.53 (2.30-5.42); <0.001

[a]Class 3 obesity: BMI ≥ 40kg/m^2.
[b]Adjusted for sociodemographic characteristics: sex (when not stratified for), age, country of origin, municipality size, and annual taxable income level.
[c]Additionally adjusted for health-related characteristics: primary health care visits in prior 12 months, hospitalization in prior 12 months, smoking status, hypertension, and major chronic conditions (when not stratified for).
RR, relative risk.

TABLE 5 Association of class 3 obesity[a] and development of severe COVID-19[b] in a cohort of population aged 25-79 years

	All study population	25-49 years	50-64 years	65-79 years
Class 3 obesity, *n*/*N*	10/7,460	3/2,834	3/2,661	4/1,965
No class 3 obesity, *n*/*N*	166/426,535	7/213,220	48/129,465	111/83,850
Crude, RR (95% CI); *P* value	3.44 (1.82-6.52); <0.001	32.24 (8.34-124.69); <0.001	3.04 (0.95-9.76); 0.062	1.54 (0.57-4.17); 0.398
Model 1[c], RR (95% CI); *P* value	3.02 (1.59-5.74); <0.001	22.75 (5.49-94.44); <0.001	3.20 (0.99-10.35); 0.052	1.77 (0.65-4.80); 0.267
Model 2,[d], RR (95% CI); *P* value	2.30 (1.20-4.40); 0.012	13.80 (3.11-61.17); <0.001	2.07 (0.62-6.85); 0.234	1.42 (0.52-3.88); 0.496

[a]Class 3 obesity: BMI ≥ 40kg/m^2.
[b]Severe disease was considered admission to the intensive care unit or death.
[c]Adjusted for sociodemographic characteristics: sex, age, country of origin, municipality size, and annual taxable income level.
[d]Additionally adjusted for health-related characteristics: primary health care visits in prior 12 mo, hospitalization in prior 12 mo, smoking status, hypertension, and major chronic conditions.
RR, relative risk.

A statistically significant interaction was observed in the effect of class 3 obesity by age group (P for interaction < 0.001).

Taking people under 50 years old without severe obesity as reference category, age increased the risk of severe COVID-19 among people without class 3 obesity, but for those with class 3 obesity, the risk was higher from young ages and did not change significantly with age (Figure 3).

No significant interaction was observed between class 3 obesity and either sex or major chronic conditions for the risk of severe COVID-19 (P for interaction = 0.961 and 0.586, respectively).

Discussion

The results show that severe obesity is an independent risk factor for hospitalization for COVID-19 in adults younger than 65 years old. In adults aged 25 to 49 years, class 3 obesity was associated with a 5-fold–higher risk of hospitalization for COVID-19 and with a 14-fold–higher risk of severe COVID-19. The risks remained high regardless of age, but the excesses of risk observed in the youngest tended to attenuate and disappear with older age. These findings are particularly relevant because of the high and increasing prevalence of severe obesity from young ages in many countries worldwide, including Spain (17,20). No significant differences were observed for the effect of severe obesity by sex or presence of a major chronic condition.

Our study population was highly affected by COVID-19 in the first wave of the pandemic; 255 persons per 100,000 inhabitants were hospitalized for COVID-19, and 41 per 100,000 presented severe COVID-19. The prevalence of class 3 obesity in the cohort was quite high (1.7%), but it was much higher among patients hospitalized for COVID-19 (4.7%) and among those with severe COVID-19 cases (5.7%). Initially, BMI was hardly included among the potential risk factors for COVID-19 (21-23). Later on, several studies found that patients with obesity, and particularly severe obesity, were highly represented among patients with severe COVID-19 and among those with unfavorable outcomes (5,13,24-26). However, the lack of a control population in those studies was a limitation for assessing the role of obesity in COVID-19.

Some other studies have aimed to assess the independent role of obesity as a risk factor. Several studies with differences in design, threshold established for obesity, and definition of severe disease have suggested that obesity may be an independent risk factor for severe COVID-19 among diagnosed or hospitalized patients. These investigations have

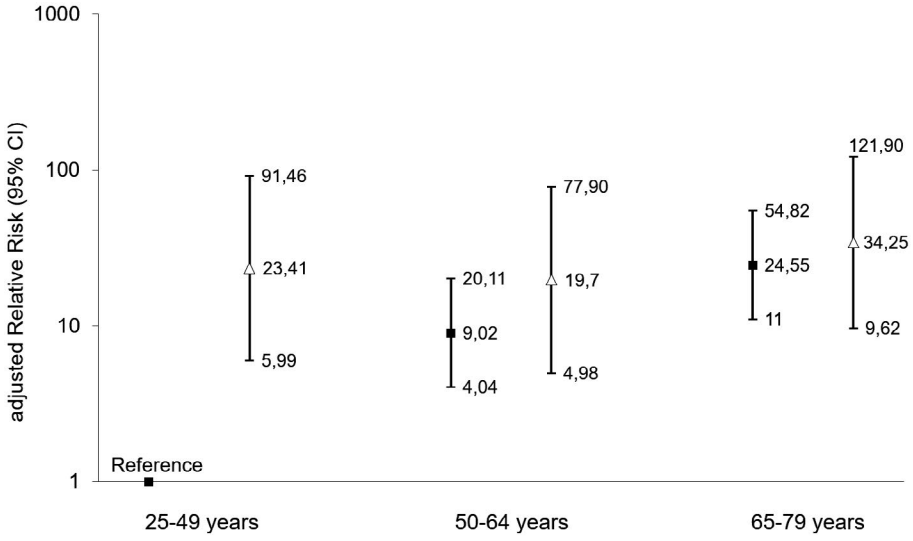

Figure 3 Combined effect of age and class 3 obesity status on the risk of severe COVID-19 (intensive care unit admission for or death from COVID-19). Black squares denote individuals without class 3 obesity, and white triangles denote individuals with class 3 obesity (logarithmic scale). Class 3 obesity: BMI ≥ 40kg/m^2. Relative risks were adjusted for sex, age, country of origin, municipality size, annual taxable income level, primary health care visits in prior 12 months, hospitalization in prior 12 months, smoking status, hypertension, and major chronic conditions.

shown that a higher BMI incremented the risk of severe COVID-19, defined as pneumonia (27,28), the necessity of invasive mechanical ventilation (10,11,14), being admitted to the ICU (11,14), or mortality (29), independently of other potential risk factors. All of these studies provided evidence about the role of obesity among infected patients. However, our cohort study explored the risk of severe disease, in addition to the risk of hospitalization for COVID-19, in the overall population. We observed that severe obesity was an independent risk factor for both outcomes. Similar findings were observed in two population-based studies, which found that people with obesity, and especially those with severe obesity, were at higher risk for being hospitalized (30) and for in-hospital death (31) in relation to those with a BMI < 30 kg/m^2, independently of age, sex, smoking status, or the presence of comorbidities.

Some studies have suggested that the role of obesity as a risk factor could differ depending on age. A descriptive investigation found a significant negative correlation between BMI and age, in which younger individuals admitted to the ICU for COVID-19 were more likely to have obesity (32). A retrospective study of patients with SARS-CoV-2 infection suggested that the effect of obesity would be substantial for COVID-19 hospitalization and severe disease, but only in those patients younger than 60 years old (12). Nevertheless, that study did not consider the potential effects of the sociodemographic and other health-related characteristics of the patients. Another study of similar characteristics found that the independent association of obesity and ICU admission holds true across all age groups, including patients older than 60 years (14). Our findings suggested that the risk for COVID-19 hospitalization and severe disease among those with class 3 obesity was high from young ages, and these risks remained similar, regardless of age. Nevertheless, the excess of risk associated with severe obesity was high in people younger than 50 years and tended to attenuate with age, disappearing at older ages. The excess of risk usually observed in the older population was moved to younger ages in persons with severe obesity. This would indicate that severe obesity implies a risk in young people as important as age for the general population. The effect of class 3 obesity was not additive to that of age in producing COVID-19 hospitalization and severe COVID-19. Hence, it could be speculated that there is a common physiopathological mechanism shared by severe obesity and age in increasing the risk of severe COVID-19; although that pathway would be activated over the years in persons without severe obesity, the presence of severe obesity would stimulate that route from younger ages. Indeed, previous studies have suggested that obesity may accelerate the rate of aging (33).

Some physiopathological mechanisms underlying the relation between obesity and COVID-19 have been hypothesized (7,34,35). Individuals with obesity present low-grade chronic inflammation (36). This could impair the immune system, in terms of both innate and adaptive responses (37), and affect the lung parenchyma and bronchi (38). Additionally, persons with obesity could present a restrictive pattern and reduced lung volumes, leading to detrimental effects on pulmonary function (39). It is feasible that thromboembolism, which currently seems to be one of the mechanisms potentially involved in worsening lung damage and in death due to COVID-19, could be mediated by angiotensin-converting enzyme 2 (ACE2) (40). ACE2 is expressed in lungs, a major target tissue affected by COVID-19, but the level of ACE2 expression in adipose tissue is higher than that in the lungs (41), making people with obesity especially susceptible. The active form of vitamin D has been found to be involved in various inflammatory, infectious, and pulmonary diseases by modulating the expression of ACE2 (42). Indeed, it has been hypothesized that vitamin D deficiency could potentially increase the susceptibility to complications and mortality due to COVID-19 (42). A high prevalence of deficiency in vitamin D has been found in people with obesity (43). All the proposed

mechanisms could also be facilitated by senescence: a proinflammatory environment, reduction of the functionality of the immune system, natural deterioration of the lung physiology, dysregulation of ACE2, or deficiency of vitamin D (44,45).

The main strengths of our study are its prospective cohort design, the population representativeness, the relatively large size of the studied population, and that only laboratory-confirmed cases were considered. Additionally, cases only included patients for whom COVID-19 was the main reason for hospitalization or who were experiencing a severe outcome; nevertheless, it is possible that some deaths due to COVID-19 could have been missed if they occurred before hospital admission. Analyses were adjusted for most potentially confounding variables. Severe obesity and comorbidities were obtained from clinical records before the hospital admission to prevent information bias.

The current study also has some limitations. This study compared those with diagnosed class 3 obesity (BMI ≥ 40kg/m^2) with people without this diagnosis, including those whose BMI was lower than 40kg/m^2 and those without information; as class 3 obesity is a very relevant health condition, it is likely to be usually reflected in the clinical records. Among people without the diagnosis of class 3 obesity, we were not able to distinguish among those with normal weight, overweight, and class I or class II obesity. A higher risk could be expected if comparing people with class 3 obesity with those with normal weight; in that case, our results could be considered an underestimation. In addition, several studies have highlighted that different levels of obesity, not exclusively class 3 obesity, place people at higher risk of severe COVID-19 and that disease severity increases with BMI (10,11,30,31). Using a BMI ≥ 40kg/m^2 as the threshold might give a false sense of security to people with obesity with a lower BMI. In addition, a high proportion of individuals were classified as having an unknown smoking status. Analyses were rerun removing that variable from the models, and the main results did not substantially change (data not shown).

Conclusion

Our findings highlight that class 3 obesity is an independent and relevant risk factor for COVID-19 hospitalization and severe disease in the population. Class 3 obesity is associated with an increased risk for hospitalization and severe COVID-19 in young adults. Although the risk of severe obesity remains similar in older adults, the excess risk diminishes and disappears with aging, suggesting that the role of severe obesity in young people could have a magnitude similar to that of aging in the general population. Therefore, young people with class 3 obesity should be recognized as a population at risk of severe COVID-19, and they should be considered in preventive protocols and clinical guidelines for groups at high risk. In addition, further policies should be carried out to tackle the obesity pandemic in our society, which could have benefits for fighting both noncommunicable and infectious diseases.

Funding agencies: This study was supported by the Horizon 2020 program of the European Commission (I-MOVE-COVID-19, grant 101003673) and by the Carlos III Institute of Health (COV20/00542, CM19/00154, and INT19/00028).

Disclosure: The authors declared no conflict of interest.

Author contributions: UF, MG, and JC conceived the study. All authors were involved in collecting information. MG and JC analyzed data. UF, MG, and JC participated in data interpretation. UF revised the literature and wrote the first version of the manuscript. All authors have revised and approved the final version of the paper.

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