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Body mass index and sex differences for mortality in hospitalized COVID-19 patients: a path analysis using a brazilian national database

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Abstract
Previous studies have shown that associations between obesity and other comorbidities favor worse outcomes in COVID-19. However, it is not clear how these factors interrelate and whether effects on men and women differ. We conducted an observational, cross-sectional study using a national COVID-19 inpatient database. We studied differences in direct and indirect effects of obesity and comorbidities according to sex and body mass index (BMI) categories in hospitalized COVID-19 patients in Brazil using path analysis models and logistic regression. For men, path analysis showed a direct association between BMI and death and a negative correlation of death and chronic cardiovascular disease (CCD). For women, the association of BMI and death was indirect, mediated by admission to the ICU and comorbidities and association with CCD was non-significant. In the logistic regression analyses, there was a positive association between death and BMI, age, diabetes mellitus, kidney and lung diseases and ICU admission. We highlight the need to consider the distinct impact of obesity and sex on COVID-19, of monitoring of BMI and of the design for specific male-targeted approaches to manage obesity.

Keywords Obesity, COVID-19, Pandemics

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Introduction

By June 2021, 6,493,773 COVID-19 deaths and 603,927,234 infected people had been reported worldwide [1]. By then, Brazil had 34,456,145 confirmed cases and 684,262 deaths, with 2.0% mortality rate [2] turning the country into one of the worst hit by the pandemic.

The severity of COVID-19 symptoms varies widely, ranging from mild or even asymptomatic to very severe, leading to death [3]. Among the main risk factors associated with the poor prognosis of COVID-19, advanced age, male sex and the presence of comorbidities stand out, with emphasis on cardiovascular diseases, lung diseases, diabetes, kidney disease, chronic liver disease and obesity [4, 5]. Body Mass Index (BMI) above 30 kg/m^2 is associated with unfavorable outcomes in patients infected with the new coronavirus [5–7].

In Brazil, 34.4% of the adult population is overweight and 25.9% has obesity [8]. Obesity is related to changes in breathing dynamics favoring complications in COVID-19, such as increased demand for ventilation and breathing effort. These changes increases chances of more severe breathing infections [6, 9]. Obesity was also found to be a strong independent factor for respiratory failure, UCI admission and death among COVID-19 patients [10].

The physiopathology of obesity involves an inflammatory state associated with chronic activation of the immune system, which negatively affects immune functions. This engenders a large release of cytokines and chemokines and the recruitment of cells that produce pro-inflammatory molecules, with increased immune responses and high rates of multisystemic complications [11]. The expression of the angiotensin-converting enzyme (ACE2) gene also seems to be increased in the subcutaneous and visceral adipose tissue, favoring the entry of the COVID-19 virus into the host cell and worsening the infection in patients with obesity [12].

Besides acting as an independent factor for unfavorable outcomes in COVID-19 infection, obesity is a risk factor for cardiovascular diseases, diabetes, high blood pressure and different kinds of cancer, which are in themselves risk factors for worse outcomes in this disease [13]. This raises initial issues on the downstream associations between obesity and obesity-related comorbidities, which can also independently impact on the course of the COVID-19 infection.

An additional question concerns differences between sexes. Even though data from the *Global Health 50/50 research initiative* identifies similar incidences (cases) of COVID-19 in men and women, men have more unfavorable outcomes and higher mortality rates in SARS-CoV-2 infection [14]. Several studies carried out in China and European countries show males are at higher risk for more severe disease outcomes and mortality [15–17].

This difference in severity and mortality between sexes has been hypothesized to be due to the higher prevalence of specific comorbidities in men, especially hypertension, cardiovascular disease (CVD), and chronic obstructive pulmonary disease (COPD) [17, 18]. Some studies highlight that male patients seem to be more vulnerable to the presence of comorbidities in COVID-19 compared to female patients [19].

A specific mention to the relevance of gender, as opposed to sex as a biological variable, should be made here. Literature has highlighted for some time the importance of considering both the biological-oriented perspective of sex and the more psychosocially centered perspective of gender in clinical studies [20]. However, there are substantial challenges involved in obtaining gender-related information in quantitative studies using administrative databases. So, in this study we are assuming differences considering sex, as opposed to gender.

It is still unclear how obesity and sex function as direct risk factors or through the mediation of comorbidities favoring worse outcomes in COVID-19. A better understanding of differences in outcomes between sexes may support the development of risk classification tools and of treatment and prevention options for men and women [21].

Structural equation modeling (SEM) [22] allows for the simultaneous analysis of the dependence and interrelationships between multiple variables. It estimates the direct effects and effects mediated by other factors that make up the causal network of the outcome of interest [22]. Path analysis is a special application of SEM [23] requiring large N-datasets. National health surveillance data samples obtained from countries with high incidence of COVID-19 and well-structured administrative information systems, such as Brazil, provide an opportunity for initial explorations of links or pathways between explanatory variables and outcomes using this approach.

The purpose of this study is, based on data recorded in Brazil, to assess mortality from COVID-19 in people with obesity and to describe direct and indirect effects of age, BMI, and clinical variables, according to sex.

Methods

This observational, cross-sectional study was carried out using microdata from the Influenza Epidemiological Surveillance Information System, SIVEP-Gripe (*Sistema de Informação de Vigilância Epidemiológica da Gripe-* https://sivepgripe.saude.gov.br/sivepgripe/login.html?0). The system is managed by the Brazilian Ministry of Health, in partnership with the State and Municipal Health Secretariats and is used to monitor Severe Acute Respiratory Syndrome (SARS) of any cause (influenza, COVID-19, other respiratory viruses and other or non-specified agents) [24]. Reporting of all cases is mandatory

for every public and private healthcare provider in the country.

The variables were selected from the individual record form - Case of Síndrome Respiratória Aguda Grave (inpatient SRAG) at SIVEP-Gripe [25]. The final study database included all confirmed cases of COVID-related severe acute respiratory syndrome reported between 02/21/2020 and 04/18/2021 in the SIVEP-Gripe original dataset featuring obese individuals aged 20 years and over, with recorded BMIs values for obesity (BMI≥30 kg/m^2). Confirmation and reporting of cases followed criteria of the Epidemiological Surveillance Guide of the Healthy Ministry for COVID-19: clinical, clinical-epidemiological, clinical-imaging and laboratory criteria [25]. The final dataset used in the study will be provided upon reasonable request to the authors.

As we were intending to compare differences between common variables according to sex, we excluded pregnant and postpartum women. To allow us to maintain a large N-data set, we dropped variables initially considered for the model with substantial missing information (e.g., years of school attendance as a social determinant). The goal of model specification is to identify a testable and useful model, even if it fails to account for all aspects of reality [23, 26].

We performed an initial description of the variables using frequencies, percentages, odds ratio and 95% confidence intervals stratified according to sex (male/female). Variables considered included age, race/color (regrouped as white/non-white), presence or absence of risk factors (diabetes mellitus, chronic lung disease, asthma, chronic kidney disease and chronic cardiovascular disease), presence of obesity, BMI (kg/m^2), admission to the ICU (yes/no), time from initial symptoms to final outcome (in days) based on dates informed in the database and clinical outcome (cure/death) [25]. There are no specific instructions for reporting the variable sex in SIVEP. It is probably based on assignment by the health care professional filling in the SIVEP forms and not on self-reporting [27].

To assess the direct and indirect associations of mortality from COVID-19 in people with obesity according to sex, we developed a hypothetical model, considering observed variables with valid frequencies above 5% and significance.

The model tested through trajectory analysis (*Path Analysis*) [28] included the variables age, comorbidities (chronic cardiovascular disease, diabetes, chronic renal disease and chronic respiratory disease) and admission to the ICU. Observed variables are represented by rectangles and classified as exogenous and endogenous. The endogenous variables were assigned measurement errors identified by "*e*". Specifically, for this analysis, we considered BMI as a continuous variable. We estimated the parameters using asymptomatic distribution free method. The results were presented using direct and indirect standardized regression coefficients. We obtained the indirect standardized coefficients by multiplying the coefficients of the direct tracks among the variables. The goodness of fit of the models was evaluated according to the Chi-square test (χ2) p>0.05; Root Mean Error of Approximation (RMSEA)≤0.05; Goodness of Fit Index (GFI), Comparative Fit Index (CFI) and Tucker-Lewis Index (TLI)≥0.95 [22].

To characterize the participants and analyze the data, BMI was categorized as: 30.0 to 34.9; 35.0 to 39.9; 40.0 to 49.9 and ≥50.0 kg/m^2 [29]. To determine the association of BMI with mortality according to sex, we used binary logistic regression adjusted for the variables age, comorbidities, and admission to the ICU, with estimates of *odds ratios* (ORs) with the corresponding 95% confidence intervals (CI).

Direct standardized coefficients and p-values were determined for all variables included in the model. A path coefficient indicates the direct effect of a variable assumed to be the cause on another variable, assumed to be the effect. Standardized coefficients allow for the comparison among the relative importance of different variables assessed by adjusting the standard deviations in such a way that, despite different units of measurement, all the variables have equal standard deviations. They are sample specific and cannot be compared across samples of studies.

For logistic regression analyses, where coefficients allow comparisons across different data samples, we determined odds Ratio (OR) and confidence interval (95%CI) for the association of age and clinical variables with mortality from COVID-19 among people with obesity, according to sex.

We conducted all analyzes using IBM SPSS and IBM SPSS AMOS 24.

In accordance with Resolution 466/2012 of the Brazilian National Health Council, approval of the study by the Research Ethics Committee was not required, as it uses public open access unidentified data.

Results

During the study period, 1,048,576 individuals were reported in the SIVEP-Gripe inpatient database. Among the 50,197 reported as obese, BMIs in the expected range of 30- 99.9 kg/m^2 were available for 13,494 (26.9%). Our study dataset, considering the exclusion criteria, included 8,772 adults with a diagnosis of COVID-19- related SRAG and an available BMI value indicating obesity (BMI>30).

Table 1 shows the descriptive analysis of the variables according to sex. In our study population, 51.7% were men and 52.1% were white. Average age was 54.4 years

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Table 1 Characteristics of individuals with obesity with confirmed COVID-19-related severe acute respiratory syndrome, according to sex, Brazil, 2020-1

Variables	Men (n = 4,535; 51.7%)	Women (n = 4,237; 48.3%)
Age in years, average, (SD)	52.3 (14.2)	56.7 (15.6)
BMI in kg/m², average (SD)	35.4 (5.9)	35.6 (6.3)
Color/race		
White	2,340 (51.6)	2,228 (57.6)
Non-white	2,195 (48.4)	2,008 (47.4)
BMI, n (%) (kg/m²)		
30,0–34,9	2,316 (51.1)	2,104 (49.7)
35,0–39,9	1,296 (28.6)	1,208 (28.5)
40,0–49,9	810 (17.9)	800 (18.9)
≥50,0	113 (2.5)	125 (3.0)
Comorbidities n (%)		
Chronic Cardiovascular Disease	2,102 (46.4)	2,259 (53.3)
Diabetes *mellitus*	1,540 (34.0)	1,737 (41.0)
Chronic Kidney Disease	212 (4.7)	277 (6.5)
Asthma	218 (5.6)	371(10.8)
Clinical course		
Symptoms to outcome (days/SD)	20.4 (15.2)	21.1(16.4)
ICU (%)	2,413 (53.2)	2,034 (48.0)
Outcome (%)		
Death	1,617 (35.7)	1,498 (35.4)

BMI: Body Mass Index; SD: Standard deviation; ICU: Intensive Care Unit

old (SD = 15.02) and average BMI 35.5 (SD = 6.09) kg/m². Reported deaths amounted to 3,115 (35.5% of patients), with similar mortality for males (35.7%) and females (35.4%). Most patients had BMI in the range of 30.0 to 34.9 kg/m² (n = 4,420; 50.4%) and were admitted to the ICU (n = 4,447; 50.7%). Regarding comorbidities, 49.7% had chronic cardiovascular disease, 37.4% diabetes mellitus, 6.7% asthma, 5.6% chronic lung disease, and 5.4% chronic kidney disease. Times from symptoms to outcomes did not differ between sexes (Table 1).

Overall frequencies for other less frequent comorbidities were neurologic disease (3.2%); blood disease (1%); Down´s syndrome (0.6%); liver disease (1.4%); and immune deficiency (2.7%) (not shown).

We performed path analyzes using models for male and female patients. Both models presented acceptable goodness-of-fit indices (Figs. 1 and 2).

Using standardized path coefficients and considering the outcome death (Table 2), the greatest direct effects in both men and women were related to admission to ICU (0.38 for men and 0.36 for women) and age (0.20 for men and 0.23 for women). BMI showed a significant correlation to death in men (0.07) but not in women. Also, chronic cardiovascular disease was only significant in men, but shows a negative correlation (-0.04). Since none of the coefficients exceeded one, we could conclude that there was no multicollinearity.

In the model tested in men with obesity, older age (β = 0.20), higher BMI values (β = 0.07), admission to the ICU (β = 0.38), presence of diabetes mellitus (β = 0.05), chronic kidney disease (β = 0.09), chronic lung disease (β = 0.05) and chronic cardiovascular disease (β= -0.04) were associated with death.

For women with obesity, we identified a direct association between older age (β = 0.23). admission to the ICU (β = 0.36), presence of diabetes mellitus (β = 0.06), chronic kidney disease (β = 0.07), chronic lung disease (β = 0.03) and death. BMI was indirectly associated and was mediated by admission to the ICU (β = 0.012).

Logistic regression analysis after adjustment showed that age, diabetes, chronic kidney disease, chronic lung disease and admission to ICU were associated with death in patients of both sexes (Table 3). Chronic cardiovascular disease was only associated with death in male patients, with an OR of 0.81 (95%CI = 0.70–0.94). After adjustment for age, chronic cardiovascular disease, diabetes mellitus, chronic lung disease, chronic kidney disease and admission to ICU, elevated BMI was associated with death in both men and women (Table 2). Male patients with a BMI between 40 and 49.9 kg/m² and ≥50.0 kg/m² had greater chance of death when compared with those with a BMI between 30 kg/m² and 34.9 kg/m², with ORs of 1.50 (95%CI = 1.32–1.94) and 3.0 (95%CI = 1.94–4.64), respectively. In women, an association was found only for BMI ≥50.0 kg/m², with 1.81 (95%CI = 1.19–2.77) more chance of death compared to those with a BMI between 30 kg/m² and 34.9 kg/m².

ICU: Intensive Care Unit; BMI: Body Mass Index. *Adjusted by all variables included in regression models.

In the logistic regression analysis, where coefficients allow comparisons across different data samples, differences between sexes in increased chances of dying were very similar in diabetes mellitus (32% for men and 29% for women) but differed for chronic lung disease (men 87% and women 49%) and chronic kidney disease (132% for men and 75% for women).

Worsening of the disease and admission to the ICU remained the biggest risk factor for mortality for people with obesity. Upon admission to ICU, the chance of dying increased 7.4 times in men and 5.88 times in women when compared to no admission to the ICU.

Discussion

Initial descriptions of frequencies for COVID-19 mortality, disease duration and UCI use in our study did not hint at substantial differences between sexes. However, pathway analysis shows that obesity in men has a direct effect on COVID-19 deaths, not mediated by comorbidities. Obesity is, thus, a key factor in unfavorable COVID outcomes in men. On the other hand, we did not find this direct relationship of BMI and death in women. In
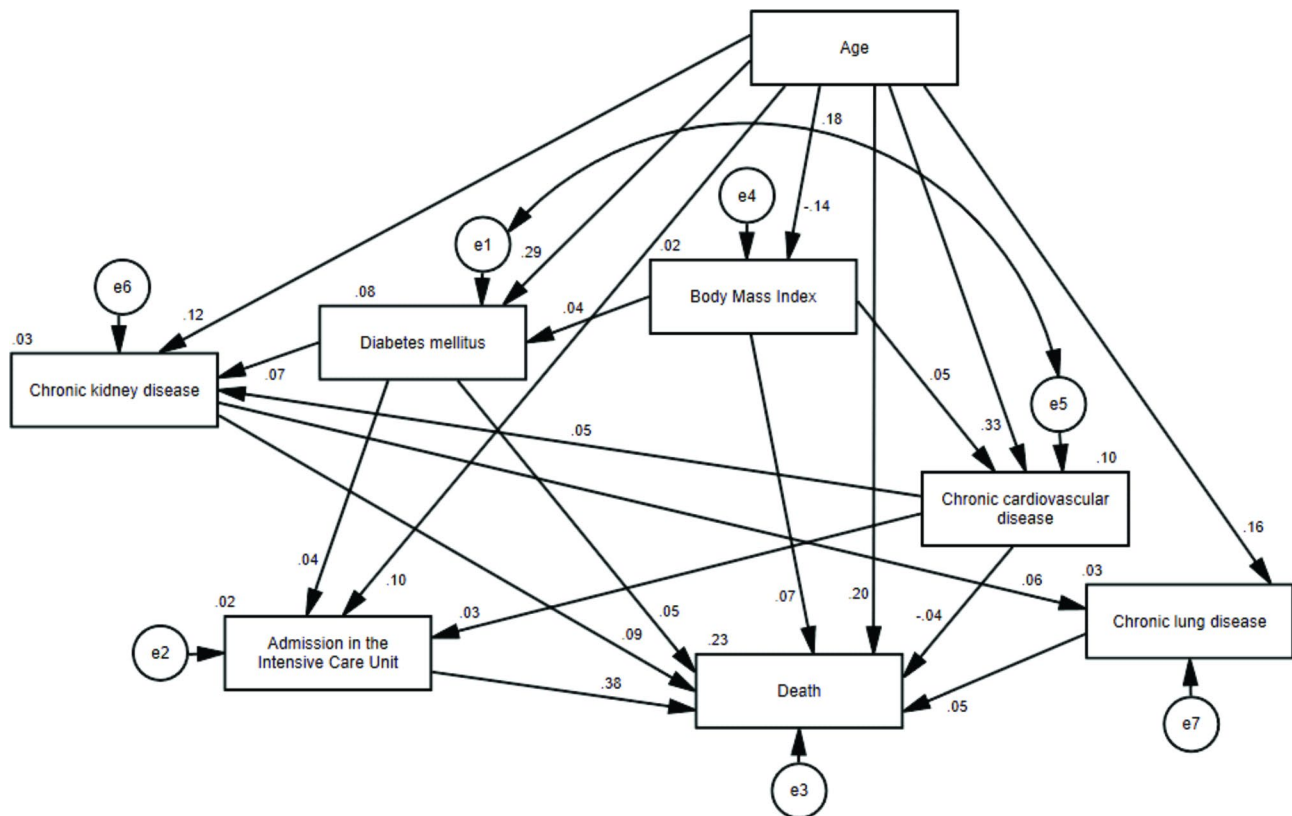
Fig. 1 Model of the association between body mass index and death for male patients with obesity diagnosed with Covid-19 (χ2 = 8.245; p = 0.311; RMSEA = 0.006; CFI = 0.999; GFI = 1.000; TLI = 0.998)

their case, death was indirectly related to co-morbidities and by the need for admission to the ICU. Comorbidities and admission to ICU seemed, thus, to be more "decisive" than obesity for the outcome death in COVID-19 infected women.

As shown in the logistic regression analyses, for women with BMIs in the extreme obesity range (>50 Kg/m^2) obesity increased the risk of COVID-19 death by 69%. Men in the same BMI range showed a three times higher magnitude of association (200%). Men also evidenced an increased risk for COVID-19 mortality at lower levels of obesity (>40 kg/m^2) compared to women. As the reference for comparison in our study was the 30–35 kg/m^2 BMI range, the actual magnitude of the effect tends to be even greater. Previous studies using < 30 kg/m^2 BMI as reference showed increases in mortality of 27% relative to mild obesity (30–35 kg/m^2 BMI) [30].

Obesity alone is a more significant risk factor than cardiovascular disease and diabetes for in-hospital COVID-19 mortality [31] and should be treated as a crucial biological factor [32]. This creates a very worrisome context in countries with high prevalence of obesity and where the pandemic remains out of control for long spells. Approximately 34 million Brazilians ≥ 50 years of age have at least one risk condition for severe COVID-19,

obesity being among three most prevalent [33]. Current evidence already suggests the need to prioritize obese young individuals for vaccination should COVID-19 persist as a recurrent seasonal infection [31]. Our study suggests the need for special emphasis on men.

Male sex was also found to be an independent risk factor for COVID-19 disease in previous studies using Brazilian data [32]. The greater vulnerability of men with obesity to death from coronaviruses independently of other comorbidities calls for strengthening gender-oriented public-health recommendations concerning the risks of obesity [34]. In many countries, traditional gender perspectives on aesthetics undervalue and even discourage concerns over body weight in men. The quest for beauty, heavily linked to slimness, addresses mainly women. Public health strategies for obesity in men may, thus, pose greater challenges than in the case of women.

The availability of consistent BMI information for little over one quarter of patients reported as obese in SIVEP-Gripe signals the need to emphasize the importance of this measurement. This would include training healh care professionals on how to measure BMI or on how to get quick information from online apps. As previously shown in a study on hypertension, in addition to minding gender differences in risk awareness, emphasis on measurement
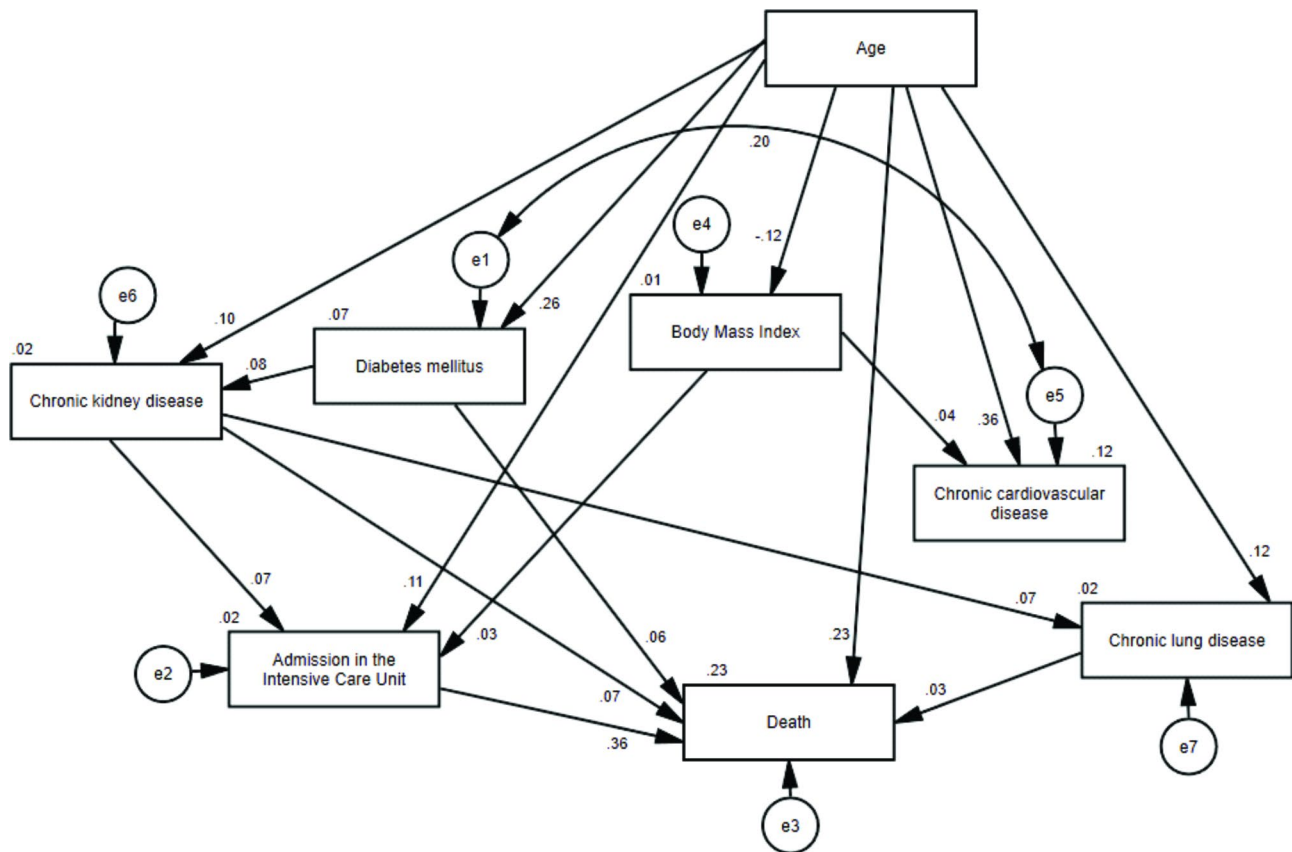
Fig. 2 Model of the association between body mass index and death for female patients with obesity diagnosed with Covid-19 (χ2 = 8.245; p = 0.311; RMSEA = 0.006; CFI = 0.999; GFI = 1.000; TLI = 0.998)

tends to favour a more adequate monitoring of risk factors [35].

An unexpected finding in our study was the counter-intuitive result for risk of death from COVID-19 found for obese men reporting chronic cardiovascular disease (CCD). A recent study came to suggest a possible key role of cardiovascular disease in COVID-19 by showing that the age pattern of the male-to-female ratio in mortality closely mirrors that of overall mortality from cardiovascular disease [36]. Several other studies also cite CCD as a risk factor in both men and women [37].

Previous Brazilian studies using the SIVEP-Gripe have nevertheless detected non-significant, negative, or dubious impacts of CCD on COVID-19 deaths. Souza et al. (2020). used an adjusted Cox regression model to establish associations of CCD with fatal outcomes in COVID-19 and found a HR of 0.95 (0.93–0.98) [38, 39]. Hallak et al. (2022), using microdata for São Paulo found negative and statistically significant coefficients for heart disease in logistic regression models for death from COVID-19 [32]. Another study in a São Paulo hospital analyzed a very stratified set of cardiovascular conditions in 2,675 patients to better understand associations between CCD and COVID-19 deaths (including hypertension,

arrhythmias, coronary artery disease, previous myocardial infarction, cardiac surgery and valve and congenital heart diseases). It confirmed that none of them acted as independent risk factors for death [40].

Outside Brazil, a survey using a large UK National Health Service (NHS) dataset also showed that neither diagnosed hypertension nor high blood pressure impacted patient´s outcomes in COVID. with marginal or small effects for other preexisting CCD [41]. All these findings suggest that the relevance of cardiovascular disease in unfavorable COVID-19 outcomes may occur in the context of acute cardiovascular events developed in the course of the disease and not necessarily of preexisting chronic heart conditions [40]. However, the contradictions between results in studies examining the relevance of cardiovascular disease in COVID-19 severity emphasize the need to revisit these relationships in future research to better understand the trends.

Hypertension, atherosclerosis-related and other causes of chronic cardiovascular disease are grouped under the single variable CCD in the SIVEP-Gripe. Several studies have shown possible differences in the contributions of hypertension [42] and other cardiovascular diseases to COVID-19 severity [43]. Given the large N-data set

Table 2 Direct standardized coefficients for variables* analyzed in the model of the association between body mass index and death, according to sex, Brazil, 2020-1

Direct effects	Estimate	p-value
Men		
Age to:		
Chronic Kidney Disease	0.12	<0.001
Diabetes mellitus	0.29	<0.001
Body Mass Index	-0.14	<0.001
Chronic Cardiovascular Disease	0.33	<0.001
Chronic Lung Disease	0.16	<0.001
Admission to the Intensive Care Unit	0.10	<0.001
Death	0.20	<0.001
Chronic Kidney Disease to:		
Chronic Lung Disease	0.06	0.008
Death	0.09	<0.001
Diabetes mellitus to:		
Chronic Kidney Disease	0.07	<0.001
Admission to the Intensive Care Unit	0.04	0.012
Death	0.05	<0.001
Body Mass Index to:		
Diabetes mellitus	0.04	0.002
Chronic Cardiovascular Disease	0.05	0.003
Death	0.07	<0.001
Chronic Cardiovascular Disease to:		
Chronic Kidney Disease	0.05	0.002
Admission to the Intensive Care Unit	0.03	0.030
Death	-0.04	0.005
Admission to the Intensive Care Unit to:		
Death	0.38	<0.001
Chronic Lung Disease to:		
Death	0.05	<0.001
Women		
Age to:		
Chronic Kidney Disease	0.10	<0.001
Diabetes mellitus	0.24	<0.001
Body Mass Index	-0.12	<0.001
Chronic Cardiovascular Disease	0.36	<0.001
Chronic Lung Disease	0.12	<0.001
Admission to the Intensive Care Unit	0.11	<0.001
Death	0.23	<0.001
Chronic Kidney Disease to:		
Admission to the Intensive Care Unit	0.07	<0.001
Chronic Lung Disease	0.07	<0.001
Death	0.07	<0.001
Diabetes mellitus to:		
Chronic Kidney Disease	0.08	<0.001
Death	0.06	<0.001
Body Mass Index to:		
Admission to the Intensive Care Unit	0.03	<0.001
Chronic Cardiovascular Disease	0.04	0.018
Chronic Lung Disease to:		
Death	0.03	0.028
Admission to the Intensive Care Unit to:		
Death	0.36	<0.001

*Only significant relationships between variables are shown

Table 3 Odds Ratio (OR) and confidence interval (95%CI) for the association of age and clinical variables with mortality from COVID-19 among people with obesity, according to sex. Brazil. 2020-1

Variables	Death			
	Men OR (IC95%)*	p-value	Women OR (IC95%)*	p-value
Age in Years	1.04 (1.03–1.04)	< 0.001	1.04 (1.03–1.05)	< 0.001
Color				
White	1		1	
Non White	1.48 (1.26–1.74)	< 0.001	1.66 (1.41–1.96)	< 0.001
Symptoms to outcome (days)	0.98 (0.98–0.99)	0.79	0.98 (0.98–0.99)	< 0.001
Chronic Cardiovascular Disease		0.01		0.07
No	1		1	
Yes	0.81 (0.69–0.96)		1.17 (0.99–1.39)	
Diabetes*mellitus*		< 0.001		< 0.001
No	1		1	
Yes	1.32 (1.15–1.55)		1.29 (1.15–1.52)	
Chronic Kidney Disease		< 0.001		< 0.001
No	1		1	
Yes	2.32 (1.64–3.29)		1.75 (1.25–2.45)	
Chronic Lung Disease		0.001		0.021
No	1		1	
Yes	1.87 (1.29–2.69)		1.49 (1.10–2.04)	
Asthma		0.88		0.84
No	1		1	
Yes	1.22 (0.84–1.76)		1.05 (0.79–1.40)	
Admission to ICU		< 0.001		< 0.001
No	1		1	
Yes	7.40 (6.25–8.88)		6.88 (5.79–8.12)	
BMI (kg/m^2)		< 0.001		0.017
30.0 a 34.9	1		1	
35.0 a 39.9	1.10 (0.92–1.31)		0.92 (0.77–1.39)	
40.0 a 49.9	1.50 (1.22–1.85)		1.03 (0.82–1.27)	
≥50.0	3.00 (1.91–4.94)		1.69 (1.06–2.71)	

in SIVEP-Gripe and its evident usefulness in clinical and epidemiological studies, being able to distinguish arterial hypertension from other CCDs would contribute to better illuminate the relationships between CCD and death in COVID-19 [43]. The Mexican Epidemiologic Surveillance Database for Respiratory Viral diseases (Sistema de Vigilancia Epidemiológica de Enfermedades Respiratorias Virales), for instance, distinguishes hypertension from cardiopathy. In a study using this specific database hypertension was associated with increased risk of death from COVID-19, whereas cardiopathy was not [44].

Literature confirms our regression analysis findings that age [45, 46], diabetes mellitus [47–49], chronic kidney disease [50, 51], chronic lung disease [4, 52, 53] and admission to ICU [50, 51] are all associated with COVID-19 mortality in people with obesity of both sexes. For chronic lung disease the effect was modest but statistically significant, with slight difference between sexes (odds ratio varying from 1.5 for men to 1.6 in women). The greatest risk for adverse health outcomes was

admission to the ICU [54–56]. Chronic kidney disease (CKD) was the second most important independent risk factor for COVID-19 mortality. It increased women´s risk by 39% and by 149% in men. This result supports the adoption in Brazil of special measures for COVID-19 protection in dialysis environments during outbreaks [56], wider use of screening to detect early-stage kidney disease and campaigns to inform the public and health professionals of increased vulnerability to severe Covid-19 and other infections in CKD [57].

Differences in male vulnerability to COVID-19 [32] and the many hypotheses concerning distinct demands, behaviors and ways of life incident upon men highlight the importance of considering the gender approach in future studies [20, 58]. On the other hand, links between testosterone, obesity and responses to COVID-19 emphasize biological aspects of the differences between sexes. The relationship between testosterone and COVID-19 seems to be dependent upon the specific disease stage, but there is a well-stablished association

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between low levels of testosterone, SARS-COV2-induced oxidative stress and greater disease severity [59]. The obesity-associated hypotestosteronemia seen in moderate and severe male obesity [60] may thus predispose to worse outcomes in COVID-19.

Obesity-associated hypotestosteronemia by itself leads to a vicious cycle of increasing adiposity. It remains a functional and reversible status but requires substantial weight loss to be reversed [60]. In moderate and severe obesity this may only be achievable by bariatric surgery or modern anti-obesity drugs. Therefore, one cannot overstate the importance of starting to manage overweight and mild obesity in primary care settings. Since 2009 there is a national program for men´s health improvement delivered at primary health care facilities in Brazil [61]. The inclusion of obesity control targets [62] in this program could contribute to developing gender-sensitive approaches to obesity.

This study has limitations and strengths. The considerable number of missing data stands out as a limitation. Since filling instructions in administrative records are often not sufficiently precise by academic research standards, there are no guarantees regarding the control of filling in the data and associated biases. Despite the adequate fit, our model is not unique and there may be other valid ways to explain the relationships under study. Additionally, since the interaction of COVID-19 with other variables is still under study, erroneous causal relationships may have been established in the process of designing the hypothetical model. As strengths, we highlight the use of the large-N free access national database of hospitalized patients with COVID-19 and the specific perspective of comparison between sexes adopted in our study.

In conclusion, as short-term approaches in COVID outbreaks, our study supports strict protective measures to avoid infection and priority vaccination in men with BMI>40 kg/m^2, especially in those with CKD and chronic lung disease. Longer-term public health recommendations would include systematic monitoring of BMI and fostering adequate gender sensitive approaches to the management of obesity in primary care.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12889-023-16218-1.

Supplementary Material 1

Declarations

Ethics approval and consent to participate
Not required (Open-access administrative database with deidentified variables was used in this study).

Consent for publication
Not applicable.

Competing interests
The authors declare no conflict of interest.

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