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BRIEF REPORT

Obesity not associated with severity among hospitalized adults with seasonal influenza virus infection

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Abstract We examined seasonal influenza severity [artificial ventilation, intensive care unit (ICU) admission, and radiographic-confirmed pneumonia] by weight category among adults hospitalized with laboratory-confirmed influenza. Using multivariate logistic regression models, we found no association between obesity or severe obesity and artificial ventilation or ICU admission; however, overweight and obese patients had decreased risk of pneumonia. Underweight was associated with pneumonia (adjusted odds ratio 1.31; 95 % confidence interval 1.04, 1.64).

Keywords Influenza · Severe influenza · Influenza hospitalizations · Obesity · BMI · Body mass index

Introduction

In the wake of the 2009 influenza pandemic, several studies linked obesity or severe obesity to adverse health outcomes associated with influenza. Higher rates of hospitalization [1], longer length of stay in intensive care unit (ICU) [2], and increased risk for death [1, 3] were all reported among obese or severely obese patients with influenza A(H1N1) pdm09 virus infection. Nonetheless, data demonstrating an association between obesity/severe obesity and seasonal influenza-related adverse outcomes are limited.

Kwong and colleagues were the first to suggest a link between severe obesity and severity of seasonal influenza in a cohort study over 12 influenza seasons in Canada; severely obese adults had an increased odds of hospitalization for respiratory disease during influenza seasons compared with adults of normal weight [4]. However, this study relied on self-reported height and weight, and the outcome was not laboratory-confirmed influenza, which could lead to misclassifications. Few studies since have explored the association between obesity and seasonal influenza. Cocoros et al. [5] found a small to moderate increase in the odds of hospitalization for influenza-like illness in obese adults aged 20–59 years, while Coleman et al. [6] reported

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no association between obesity and medically attended laboratory-confirmed influenza.

In this study, we further explore the possible link between obesity and seasonal influenza severity, focusing on patients hospitalized with laboratory-confirmed influenza and accounting for several demographic and clinical characteristics of these patients.

Methods

Surveillance for influenza-associated hospitalizations

We used data gathered from October 1, 2012 to April 30, 2013, from the Centers for Disease Control and Prevention's (CDC) Influenza Hospitalization Surveillance Network (FluSurv-NET), a population-based, laboratory-based surveillance system. FluSurv-NET includes 81 counties in 15 states: California, Colorado, Connecticut, Georgia, Iowa, Maryland, Michigan, Minnesota, New Mexico, New York, Rhode Island, Ohio, Oregon, Tennessee, and Utah. Information on demographic characteristics, medical history, influenza vaccination status, clinical course during hospitalization, and treatment with influenza antiviral medications was collected through review of medical charts using a standardized abstraction form. Data were entered locally and uploaded into a CDC database. Data on influenza vaccination were verified using a vaccine registry or patients' primary care provider. FluSurv-NET has been determined to be public health practice not requiring institutional review board approval for human research protection.

Case definition

We defined a case as laboratory-confirmed influenza in a person who resided in the surveillance area and was admitted to one of the surveillance hospitals ≤14 days after or ≤3 days before the positive influenza test. Laboratory-confirmed influenza was determined by a positive test result by real time reverse transcription polymerase chain reaction, viral culture, direct or indirect fluorescent antibody staining, or a rapid influenza diagnostic test. Influenza testing was ordered at the discretion of the treating clinicians.

Body mass index

We determined body mass index (BMI) values using weight and height measurements collected from medical records (kg/m^2) as follows: underweight = BMI <18.5, normal = BMI 18.5 to <25, overweight = BMI 25 to <30, obese = BMI 30 to <35, and severely obese = BMI ≥ 35. We excluded pregnant women and individuals aged <20 due to differences in methods for categorizing BMI. If height or weight values were missing, or for cases with extreme values of study-calculated BMI (e.g., BMI ≥ 100 or BMI ≤ 10), a BMI that had been calculated and recorded in the medical chart was used.

Main outcome measures

We explored the relationship between BMI category and three influenza severity outcomes: artificial ventilation, ICU admission, and diagnosis of community-acquired, influenza-associated pneumonia. We defined artificial ventilation as either invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO). ICU admission excluded admission to a step-down unit or transitional care unit. Community-acquired, influenza-associated pneumonia was defined by new abnormal radiographic findings (including consolidation/opacity or pleural effusion) diagnosed within the first 3 days of hospital admission.

Covariates

Potential confounders were defined a priori based on biological plausibility and previous findings in the literature. We included in the multivariate analysis medical comorbidities recognized by the Advisory Committee on Immunization Practices (ACIP) as risk factors for influenza associated complications as well as lifestyle, demographic characteristics, and patient care factors that could be associated with BMI or selected influenza outcomes.

Demographic characteristics

The selected demographic characteristics we controlled for were age, sex, and race/ethnicity. Age was classified into five categories: 20 to <50, 50 to <65, 65 to <75, 75 to <85, and ≥85 years. Race/ethnicity was abstracted from medical records and classified as White non-Hispanic, Black non-Hispanic, Hispanic, and other/unknown to ensure a sufficient number of subjects in each category to perform statistical analyses.

Comorbidities

We controlled for the following comorbidities: cardiovascular disease (CVD), chronic lung disease (CLD), chronic metabolic disease (CMD), neuromuscular disorder, neurologic disorder, immunocompromised condition, renal disease, and asthma. CVD included conditions such as coronary heart disease, cardiac valve disorders, and congestive heart failure (excluding isolated hypertension). CLD included conditions such as chronic obstructive pulmonary disease and interstitial lung disease. CMD included conditions such as diabetes mellitus and thyroid dysfunction. Neuromuscular disorder included conditions such as multiple sclerosis and muscular dystrophy. Neurologic disorder included conditions such as seizures, cerebral palsy, and cognitive dysfunction. Immunocompromised condition included immunoglobulin deficiency, leukemia, HIV/AIDS, organ transplantation, and individuals taking immunosuppressive medications. Renal diseases included acute or chronic renal failure and nephrotic syndrome.

Lifestyle factors

The selected lifestyle factors we controlled for were alcohol abuse and smoking status. Alcohol abuse was defined as follows: "current" if the patient had indication of current (past 12 months) alcohol abuse or if no time frame was specified, "former" if the patient quit abusing alcohol more than 12 months ago, or "non-abuser" if there was no indication of alcohol abuse, dependency, or alcoholism on the patient's medical record. Smoking was defined as follows: "current" if the patient indicated that s/he was currently (past 12 months) smoking or if no time frame was specified, "former" if the patient quit smoking more than 12 months ago, or "non-smoker" if there was no indication of smoking on the patient's medical record.

Patient care factors

We classified influenza vaccination into the following: (1) patients who received influenza vaccine at least 14 days prior to hospitalization, or (2) patients who did not receive influenza vaccine for the 2012–2013 season or patients who received influenza vaccine during hospitalization.

Antiviral administration was classified into three categories: "prompt" for patients who received antivirals on day of hospital admission, "late" for patients who received antivirals from day 2 to day 5 (inclusive) in the hospital, "none" for patients who received antivirals after day five in hospital or no antivirals at all.

Statistical analyses

We performed a bivariate analysis using the Chi square test of homogeneity to determine whether, for a given covariate, the frequency of cases was distributed equally across the five BMI categories. To evaluate the association between obesity or severe obesity and severe influenza-related outcomes, we used logistic regression models with logit link function to calculate the odds of having a severe outcome for each of the five BMI categories. For each outcome—artificial ventilation, ICU admission, and community-acquired pneumonia—we ran unadjusted, sex- and age-adjusted, and fully-adjusted (for all covariates of interest) models. The normal weight BMI category was the reference group for all models. We produced odds ratio (OR) point estimates, 95 % Wald confidence limits, and associated p values for each BMI categories for our 3 outcome variables. SAS Version 9.3 was used for all statistical analyses.

Results

There were a total of 9048 hospitalized adults aged 20 years or older with laboratory-confirmed influenza identified during the 2012–2013 influenza season (Table 1). The majority of subjects (7552) were aged 50 or above, with only 16.5 % (1496) under 50 years old. There were 413 (4.6 %) patients who were underweight, 2847 (31.5 %) were normal weight, 2701 (29.9 %) were overweight, 1526 (16.9 %) were obese, and 1561 (17.3 %) were severely obese Age distribution varied by BMI category; 31 % of cases in the underweight category and 31.8 % in the normal weight category were $\geq$85 years, while this age group was less represented among obese (15.8 %) and severely obese (6.3 %) categories. Females were the majority in the underweight (65.6 %) and severely obese (63.4 %) BMI categories.

The percentage of cases with CMD or asthma increased as BMI category increased, while the percentages of cases with neurologic disorder, neuromuscular disorder, and immunosuppressive condition decreased as BMI category increased. The timing of antiviral administration was similarly distributed across BMI categories, with the majority of cases receiving antiviral treatment on day of admission. A significantly higher percentage of cases in the normal weight category (57.5 %) received influenza vaccine compared with the severely obese category (46.5 %).

Artificial ventilation

There were 562 cases (6.2 %) who received artificial ventilation. Unadjusted odds ratios, using normal weight as the reference, did not show difference between obese (OR 1.03, 95 % confidence interval [CI] 0.80, 1.33, $p = 0.97$) and severely obese (OR 1.14, 95 % CI 0.89, 1.46, $p = 0.30$) cases regarding need for artificial ventilation; (Table 2a). Adjusting for all clinical and demographic characteristics did not reveal a significant association between BMI and artificial ventilation. For underweight and overweight cases compared with normal weight cases, odds ratios for the unadjusted, age- and sex-adjusted, and fully-adjusted models were also non-significant.

Table 1 Characteristics of patients hospitalized with laboratory-confirmed influenza, by BMI category, 2012–2013

	Overall $N = 9048$[a] (%)	BMI categories					
		(1) Underweight (BMI < 18.5) (%)	(2) Normal (BMI 18.5 to <25) (%)	(3) Overweight (BMI 25 to <30) (%)	(4) Obese (BMI 30 to <35) (%)	(5) Severely obese (BMI ≥ 35) (%)	*p* value
Demographic characteristics							
Age group							
20–49	1496 (16.5)	62 (15.0)	431 (15.1)	396 (14.7)	230 (15.1)	377 (24.2)	**<0.01**
50–64	1966 (21.7)	74 (17.9)	465 (16.3)	510 (18.9)	401 (26.3)	516 (33.1)	
65–74	1587 (17.5)	57 (13.8)	425 (14.9)	460 (17.0)	325 (21.3)	320 (20.5)	
75–84	2007 (22.2)	92 (22.3)	620 (21.8)	716 (26.5)	329 (21.6)	250 (16.0)	
85+	1992 (22.0)	128 (31.0)	906 (31.8)	619 (22.9)	241 (15.8)	98 (6.3)	
Sex							
Male	4177 (46.2)	142 (34.4)	1337 (47.0)	1417 (52.5)	709 (46.5)	572 (36.6)	**<0.01**
Female	4871 (53.8)	271 (65.6)	1510 (53.0)	1284 (47.5)	817 (53.5)	989 (63.4)	
Race							
White	5989 (66.2)	275 (66.6)	1948 (68.4)	1844 (68.3)	971 (63.6)	951 (60.9)	**<0.01**
Black	1523 (16.8)	65 (15.7)	378 (13.3)	411 (15.2)	296 (19.4)	373 (23.9)	
Hispanic	605 (6.7)	17 (4.1)	155 (5.4)	185 (6.9)	125 (8.2)	123 (7.9)	
Other/unknown	931 (10.3)	56 (13.6)	366 (12.9)	261 (9.7)	134 (8.8)	114 (7.3)	
Comorbidities							
CVD	4354 (48.1)	163 (39.5)	1341 (47.1)	1317 (48.8)	786 (51.5)	747 (47.9)	**<0.01**
CLD	2638 (29.2)	170 (41.2)	833 (29.3)	698 (25.8)	440 (28.8)	497 (31.8)	**<0.01**
CMD	3769 (41.7)	126 (30.5)	962 (33.8)	1113 (41.2)	724 (47.4)	844 (54.1)	**<0.001**
Neuro-muscular disorder	406 (4.5)	21 (5.1)	148 (5.2)	129 (4.8)	64 (4.2)	44 (2.8)	**<0.01**
Neurologic disorder	1833 (20.3)	124 (30.0)	723 (25.4)	551 (20.4)	239 (15.7)	196 (12.6)	**<0.01**
Immuno-compromised condition	1516 (16.8)	99 (24.0)	512 (18.0)	425 (15.7)	244 (16.0)	236 (15.1)	**<0.01**
Renal disease	1718 (19.0)	62 (15.0)	527 (18.5)	526 (19.5)	331 (21.7)	272 (17.4)	**<0.01**
Asthma	1664 (18.4)	47 (11.4)	386 (13.6)	439 (16.3)	317 (20.8)	475 (30.4)	**<0.01**
Lifestyle factors							
Alcohol abuse							
Current	321 (3.6)	21 (5.1)	124 (4.4)	92 (3.4)	49 (3.2)	35 (2.2)	**<0.01**
Former	298 (3.3)	10 (2.4)	88 (3.1)	81 (3.0)	64 (4.2)	55 (3.5)	
Smoking status							
Current	1755 (19.4)	106 (25.7)	555 (19.5)	468 (17.3)	287 (18.8)	339 (21.7)	**<0.01**
Former	2551 (28.2)	102 (24.7)	783 (27.5)	781 (28.9)	452 (29.6)	433 (27.7)	
Patient care factors							
Antiviral administration[b]							
Prompt	4117 (46.1)	182 (44.7)	1254 (44.6)	1252 (47.0)	707 (46.7)	722 (47.0)	
Late	3225 (36.1)	143 (35.1)	1049 (37.3)	975 (36.6)	513 (33.9)	545 (35.5)	0.13
Influenza vaccine	4495 (53.6)	194 (50.8)	1506 (57.5)	1381 (55.4)	737 (51.5)	677 (46.5)	**<0.01**

Bold *p* values indicate a statistically significant Chi square test of homogeneity

CVD cardiovascular disease, *CLD* indicates chronic lung disease, *CMD* indicates chronic metabolic disorder

[a] Row totals may not sum to total sample size due to missing data

[b] Prompt antiviral administration indicates patients who received antiviral treatment on day 1 of hospital admission. Late antiviral administration indicates patients who received antiviral treatment between day 2 and up to and including day 5

Table 2 Unadjusted and adjusted associations between BMI category and indicators of influenza severity

	Unadjusted OR (95 % CI)	OR (95 % CI) adjusted for sex and age (as categorical)	OR (95 % CI) adjusted for all covariates in Table 1
a. Unadjusted and adjusted associations between BMI category and artificial ventilation, n = 9014			
Underweight	1.10 (0.73, 1.67)	1.12 (0.74, 1.71)	1.09 (0.71, 1.71)
Normal weight	1	1	1
Overweight	0.90 (0.72, 1.13)	0.86 (0.69, 1.08)	0.89 (0.69, 1.15)
Obese	1.02 (0.80, 1.33)	0.92 (0.72, 1.20)	1.06 (0.80, 1.41)
Severely obese	1.13 (0.89, 1.46)	0.96 (0.75, 1.25)	1.03 (0.77, 1.38)
b. Unadjusted and adjusted associations between BMI category and ICU admission, n = 9017			
Underweight	1.12 (0.85, 1.47)	1.13 (0.86, 1.49)	0.99 (0.74, 1.34)
Normal weight	1	1	1
Normal	0.83 (0.72, 0.97)	0.80 (0.70, 0.94)	0.80 (0.69, 0.95)
Obese	0.97 (0.82, 1.15)	0.90 (0.76, 1.08)	0.90 (0.75, 1.09)
Severely obese	1.01 (0.86, 1.20)	0.91 (0.77, 1.09)	0.85 (0.70, 1.03)
c. Unadjusted and adjusted associations between BMI category and radiographic-confirmed pneumonia, n = 8769			
Underweight	1.29 (1.04, 1.60)	1.34 (1.09, 1.66)	1.30 (1.04, 1.64)
Normal weight	1	1	1
Overweight	0.82 (0.74, 0.92)	0.83 (0.74, 0.93)	0.87 (0.77, 0.99)
Obese	0.73 (0.64, 0.84)	0.77 (0.68, 0.89)	0.79 (0.69, 0.92)
Severely obese	0.72 (0.63, 0.83)	0.83 (0.72, 0.96)	0.88 (0.76, 1.04)

Intensive care unit

There were 1396 cases (15.5 %) who were admitted to the ICU. Unadjusted OR (Table 2b) for ICU admission among obese and severely obese cases compared with normal weight cases were not significantly different (OR 0.97, 95 % CI 0.82–1.15, $p = 0.73$; OR 1.01, 95 % CI 0.86–1.20, $p = 0.87$). The odds ratios for the fully-adjusted model revealed a non-significant trend towards a protective effect of obesity and severe obesity on ICU admission (adjusted odds ratio [aOR] 0.90, 95 % CI 0.75, 1.09, $p = 0.28$; aOR 0.85, 95 % CI 0.70, 1.03, $p = 0.10$). There was a significant protective effect of overweight on ICU admission compared with normal weight group, that remained even after adjusting for all covariates (aOR 0.81, 95 % CI 0.69, 0.95, $p < 0.01$).

Community-acquired pneumonia

There were 2854 cases (32.6 %) with radiographic-confirmed pneumonia. Unadjusted odds ratios demonstrated reduced odds of radiographic-confirmed pneumonia among obese and severely obese cases (OR 0.73, 95 % CI 0.64, 0.84, $p < 0.01$; OR 0.72, 95 % CI 0.63, 0.83, $p < 0.01$ respectively) compared to normal weight cases (Table 2c). After adjusting for all clinical and demographic characteristics, there was a significantly protective effect of being overweight (aOR 0.87, 95 % CI 0.77, 0.98, $p = 0.02$) or obese (aOR 0.80, 95 % CI 0.69, 0.92, $p < 0.01$) in terms of having radiographic-confirmed pneumonia. The severely obese tended to have a lower odds of radiographic-confirmed pneumonia, but this did not achieve statistical significance (aOR 0.89, 95 % CI 0.76, 1.04, $p = 0.13$). The odds of radiographic-confirmed pneumonia were higher among underweight patients compared to normal weight patients both before and also after multivariate adjustment (aOR 1.31, 95 % CI 1.04, 1.64).

Discussion

We found no association between obesity (BMI from 30 to 34.99) or severe obesity (BMI $\geq$ 35) and selected seasonal influenza severity outcomes among adults hospitalized during the 2012–2013 influenza season, after controlling for comorbidities, demographic characteristics, lifestyle, and patient care factors. To our knowledge, this is the first study to use a large, multisite, population-based dataset to explore this association. We did find a slight, but significant, reduced odds of radiographic-confirmed pneumonia among obese patients compared with normal weight patients, after adjusting for all covariates. There was also a small protective effect of overweight compared with normal weight patients regarding ICU admission and radiographic-confirmed pneumonia, in unadjusted and fully-adjusted models. Underweight status was an independent risk factor for pneumonia. Our results add to a growing body of research exploring the association between weight category and severe outcomes associated with influenza during non-pandemic periods.

Our findings that obesity and severe obesity are not associated with increased odds of artificial ventilation or ICU admission suggest that BMI may play a smaller role in explaining variation in adverse outcomes among patients with seasonal influenza which may differ from that documented with influenza A(H1N1)pdm09. Another possible explanation for our findings is that obese and severely obese patients may be more likely to be admitted to hospital, even with milder disease [7]. This could lead to a larger proportion of obese subjects with less severe outcomes compared with normal weight subjects, resulting in a finding of no (or even a protective) effect of obesity on severe seasonal influenza-related outcomes.

We suggest two possible explanations for our finding of significant protective effect of overweight and obesity for radiographic-confirmed pneumonia. Firstly, overweight and obesity may be associated with unmeasured factors that influence the development of pneumonia in patients with influenza. Singanayagam et al. found that obesity (BMI $\geq$ 30) was independently associated with reduced 30-day mortality in patients hospitalized with community-acquired pneumonia and postulated that since adipose tissue can secrete adipokines with anti-inflammatory properties [7], this might provide a host defense mechanism resulting in a protective effect for influenza-associated pneumonia. In the United Kingdom, a large, retrospective cohort study has also documented an association of overweight and obesity with a decreased rate of influenza-associated pneumonia [8]. An alternative explanation is that increased body thickness of obese individuals leads to limited diagnostic image quality, poor X-ray penetration, and poor visualization [9]. These technical difficulties associated with radiographic imaging of obese individuals may lead to lower rates of radiographic-diagnosed pneumonia among obese patients.

Similar to previous findings [8], in our study, being underweighted was associated with increased risk of influenza-associated pneumonia. The relation of low BMI with increased risk of pneumonia may indicate sequelae of malnutrition (e.g., anorexia and muscle wasting), or be due to unrecognized, subclinical underlying chronic conditions (e.g., undiagnosed cancer). Underweight has also been linked to a decrease in immunity, contributing to an inability to meet the energy demands associated with the immune response to fight viral infections [10]. This could be considered as a potential modifiable risk factor associated with severe influenza.

This study had some limitations. Testing of patients was done at the discretion of the clinician, and clinicians may differentially request diagnostic tests based on patients' clinical and demographic characteristics. It is difficult to predict in which direction this potential bias could affect our findings. Also, despite the inclusion of more than 9000 cases of laboratory-confirmed influenza in our study, the number of deaths ($n = 237$) was not sufficient to investigate the association between BMI and influenza-associated mortality. Nevertheless, our study had a number of strengths. First, all cases were laboratory-confirmed which allowed us to avoid misclassification of other acute respiratory illness as influenza. Additionally, we had comprehensive data regarding patient comorbidities, vaccination status, antiviral administration, and severe in-hospital outcomes. With more than 1500 cases in the obese and severely obese categories, we had a sufficient number of severe outcomes in both obese and severely obese categories to create sound inferences of model parameters.

In conclusion, using 2012–2013 influenza season data from a large, multisite surveillance program, we found no evidence of increased odds of severe influenza-related outcomes among obese and severely obese adults hospitalized with seasonal influenza in a year when influenza A(H3N2) virus predominated. A possible association between (severe) obesity and hospitalization for strain-specific influenza viruses remains to be confirmed. The risk of influenza-associated pneumonia was higher among underweight patients with influenza. There was a decreased risk of influenza-associated pneumonia among overweight and obese patients; the reason for this is not readily apparent and requires further investigation.

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Conflict of interest No potential conflict of interest.

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