

Epidemiology of severe influenza outcomes among adult patients with obesity in Detroit, Michigan, 2011

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We conducted a retrospective cohort study to evaluate the impact of obesity on influenza disease severity. Individuals with obesity were more likely to have lower pulmonary disease manifestations [OR = 1.97 (95% CI 1.05, 3.69), $P = 0.03$] and to be admitted to an inpatient ward [OR = 2.93 (95% CI 1.50, 5.71), $P = 0.002$] when compared with non-obese individuals. Among admitted individuals,

persons with obesity were more likely to require a lengthy hospital stay [OR = 3.86 (95% CI 1.03, 14.42), $P = 0.045$]. Five of the six deaths in study subjects occurred in persons with obesity.

Keywords Body mass index, influenza – human, obesity.

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Influenza is a major cause of morbidity and mortality in the United States, despite the availability of effective vaccines and antivirals. In recent studies of the changing epidemiology of influenza since the emergence of H1N1, several investigators have reported notably severe outcomes of influenza illness among individuals with obesity. Previous studies have found that obese individuals with influenza A/H1N1 (A/H1N1) more frequently require mechanical ventilation and longer ICU stays¹ and have increased risk of death.^{2,3} Michigan has a particularly high obesity prevalence of 31.3% among adults, the fifth highest in the United States.⁴ Our study reviewed detailed symptom and clinical outcome data in adult patients to evaluate the impact of obesity on influenza disease severity in a metropolitan Detroit population with a high rate of obesity.

The study

We conducted a retrospective cohort study using a convenience sample of patients at least 18 years of age admitted to the emergency or inpatient ward of one of the seven hospitals in the Detroit Medical Center (DMC) system with a positive clinical laboratory confirmation of influenza from January 1 through March 31, 2011. All hospitals were located in the metropolitan Detroit area. Influenza diagnosis was determined by influenza A/H1N1 (2009) strain-specific qualitative

RT-PCR (Simplexa, Focus Diagnostics, Cypress, CA, USA) in 160 cases and by immunochromatographic lateral flow immunoassay (QuickVue, Quidel, San Diego, CA, USA) in 13 cases by the DMC clinical microbiology laboratory. Relative virus quantity was estimated by comparing the RT-PCR cycle threshold (C_t) of the samples analyzed based on the PCR assay above. Residual nasal specimens were collected if available for further testing for the presence of an H275Y mutation conferring oseltamivir resistance. Testing was performed by the University of Washington Molecular Virology Laboratory. Total nucleic acid was extracted using a QIAmp DNA Mini Kit (Qiagen, Valencia, CA, USA) and tested by allele-specific PCR on an ABI 7300 real-time PCR machine to differentiate between mutant and wild-type strain as previously described.⁵

Data were abstracted retrospectively from patient medical records using a standardized data collection form and included patient demographics, medical history, tobacco use, vaccination history (if available), symptoms, duration of illness, and clinical course. Patient characteristics and clinical outcomes were compared between individuals with obesity [defined as body mass index (BMI) ≥ 30] versus individuals without obesity (BMI 18.5–29.9). Only two individuals in our study met the definition of underweight (BMI < 18.5), and these patients were excluded from the analysis. Pregnant women were classified based on weight

measurement prior to the second trimester. Women with no pre-pregnancy or first-trimester weight recorded were excluded. The relationship between patient characteristics or outcomes and increasing weight was evaluated by comparing increasing BMI categories (overweight: BMI 25.0–29.9; obesity class I: BMI 30.0–34.9; obesity class II: BMI 35.0–39.9; obesity class III: BMI \geq 40) to normal-weight individuals (BMI 18.5–24.9).⁶ Variables were compared between categories using univariate logistic regression models for dichotomous variables and linear regression models for continuous data, with weight category as the dependent variable. Modification of the association with severe outcomes by oseltamivir prescription was evaluated through inclusion of an interaction term in the regression model.

A total of 161 patients were studied. In comparison with the reference category, there were more men who fell into the class III obesity group. The mean ages of the patients ranged from 40 to 46 years. There was no significant difference between BMI categories for the presence of diabetes, dialysis, pregnancy, or tobacco use. Among the 142 patients for whom vaccination data were available, there was no difference in vaccination rate in the previous 2 years (Table 1).

The majority of study patients (81%) had influenza A. Inpatient encounters were more common among individuals with class I and class III obesity (Table 2). When compared with all non-obese individuals, individuals with obesity (classes I through III) were more likely to require hospital admission: [OR = 2.93 (95% CI 1.50, 5.71), $P = 0.002$]. Among hospitalized patients ($n = 101$), individuals with obesity were more likely to require a lengthy hospital stay (>7 days): [OR: 3.86 (95% CI: 1.03, 14.42), $P = 0.045$]. Individuals with obesity more often presented with lower

pulmonary disease manifestations (defined as wheezing, rales/crackles, hypoxia, infiltrate, consolidation): [OR = 1.97 (95% CI 1.05, 3.69), $P = 0.03$] and rhinorrhea [OR = 2.19 (95% CI 1.10, 4.34)]. No significant differences were found in the rates of fever, headache, lymphocytopenia, myalgia, cough, sore throat, or 30-day readmission. Five of the six influenza-related deaths were in individuals with BMI > 30 ($P = 0.131$) (Table 2); however, one of these five was a pregnant woman.

A sensitivity analysis was performed excluding 16 pregnant women. Inpatient admission, the presence of lower pulmonary manifestations, and lengthy hospital stay remained significantly increased among non-pregnant obese individuals [OR: 2.98 (95% CI: 1.46, 6.07), $P = 0.003$; OR: 2.13 (95% CI: 1.10, 4.12), $P = 0.03$; OR: 4.67 (95% CI: 1.26, 17.3), $P = 0.02$, respectively]. Semi-quantitative viral load was available for 135 individuals and did not differ between BMI categories even after controlling for differences in length of illness. Influenza virus quantity was significantly higher among inpatients (linear regression coefficient 2.72; $P = 0.01$) and current tobacco users (linear regression coefficient 2.73; $P = 0.01$) after controlling for length of illness prior to sample collection.

The majority of patients were prescribed oseltamivir (Table 2). However, oseltamivir prescription did not significantly modify the association between obesity and severe influenza outcomes (lower pulmonary disease: $P = 0.39$; lengthy hospital stay: $P = 0.49$; inpatient admission: $P = 0.09$). RT-PCR testing for the H275Y mutation was performed to investigate whether severe outcomes following oseltamivir treatment may have been due to resistant H1N1 strains. Residual specimens from patients with sufficient viral load or allele-specific RT-PCR testing for the H275Y

Table 1. Demographics and patient characteristics, by body mass index (BMI) and weight category

	Obesity				
	18.5–25.0 Normal weight $n = 43$	25.0–29.0 Overweight $n = 38$	30.0–34.9 Obese class I $n = 37$	35.0–39.0 Obese class II $n = 20$	40+ Obese class III $n = 23$
Age, mean years	40	46	46	41	44
Male, no. (%)	22 (51)	27 (71)	22 (59)	14 (70)	19 (83)*
Received 2009 influenza vaccine**	4/38 (11)	5/34 (15)	5/33 (15)	3/17 (15)	0/20 (0)
Received 2010 influenza vaccine**	10/38 (26)	13/34 (38)	13/33 (39)	5/17 (29)	8/20 (40)
Diabetes, no. (%)	4 (9)	10 (26)	8 (22)	4 (20)	5 (22)
Dialysis, no. (%)	2 (5)	3 (8)	0 (0)	2 (10)	4 (17)
Pregnant, no. (%)	4 (9)	4 (11)	4 (11)	4 (20)	0 (0)
Current tobacco user, no. (%)	19 (44)	7 (18)*	13 (35)	5 (25)	9 (39)

* $P < 0.05$ for comparison to individuals with BMI 18.5–24.9.

**Vaccination data were not available for all subjects. Valid denominators and percentages are represented for these variables.

Table 2. Outcomes of influenza infection by weight category, no. (%)

	18.5–25.0 Normal weight n = 43	25.0–29.0 Overweight n = 38	Obesity			Odds ratio (95% CI) comparing obese (all classes) to non-obese
			30.0–34.9 Obese class I n = 37	35.0–39.0 Obese class II n = 20	40+ Obese class III n = 23	
Influenza type						
Seasonal H1N1	33 (77)	23 (61)	28 (76)	12 (60)	16 (70)	1.04 (0.53, 2.04)
H3N2	5 (12)	11 (29)	5 (14)	5 (25)	4 (17)	0.86 (0.39, 1.91)
B	5 (12)	4 (11)	4 (11)	3 (15)	3 (13)	1.14 (0.44, 2.98)
Visit type						
Emergency department	21 (49)	19 (50)	9 (24)	6 (30)	5 (22)	
Inpatient	22 (51)	19 (50)	28 (76)*	14 (70)	18 (78)*	2.93 (1.50, 5.71)
Inpatient stay > 7 days (among 101 inpatients)	1 (2)	2 (5)	6 (16)	6 (27)*	3 (13)	3.86 (1.03, 14.42)
Lower pulmonary disease	17 (40)	15 (39)*	24 (65)	10 (50)	11 (48)	1.97 (1.05, 3.69)
Prescribed antibiotics	22 (51)	16 (42)	20 (54)	8 (40)	13 (57)	1.96 (0.97, 3.96)
Prescribed oseltamivir	27 (63)	26 (68)	29 (78)	17 (85)	17 (74)	1.19 (0.64, 2.21)
Mortality	1 (2)	0 (0)	2 (5)	2 (10)	1 (4)	5.33 (0.61, 46.71)

**P* < 0.05 for comparison to individuals with BMI 18.5–24.9.

mutation were available from 47 patients with the seasonal H1N1 strain. All specimens were collected prior to the initiation of oseltamivir. All 47 specimens were found to be wild type.

Conclusions

Our study showed individuals with obesity were more likely to require hospital admission as well as a lengthy hospital stay (>7 days) when compared with non-obese individuals. Data from previous studies show obesity and morbid obesity to be disproportionately represented among hospitalizations, intensive care admissions,^{1,2} and deaths from influenza A (H1N1).² The reason for increased morbidity in obese individuals in these studies remains unclear. Through a detailed review of patient symptoms and clinical course, we found that obese individuals were more likely to have lower pulmonary disease manifestations, suggesting a potential explanation for increased morbidity among obese individuals with influenza.

Our findings of increased severity associated with obesity is consistent with worldwide reports based on the data from the 2009 H1N1 pandemic^{3,7}; however, the effect of obesity that we found is not as strong. A pooled analysis of surveillance data from 19 countries found a relative risk of 15.0 for influenza-related hospitalization in persons with obesity.³ The association between obesity and influenza severity has primarily been identified in the studies of the pandemic strain 2009 pH1N1. Corresponding data regarding

seasonal influenza infection and obesity have not found similar associations,⁸ and estimates from post-2009 influenza infections reflect the more moderate risk of obesity presented here.⁹ These discordant findings could result from differences by influenza strain. Easterbrook *et al.*¹⁰ examined strain-specific differences in mice and found increased mortality and decreased cytokine production among obese mice infected with the pandemic strain but not among the mice infected with a subsequent A/H1N1 seasonal strain.

Five of the six deaths in study subjects occurred in those who were obese and patients with obesity had high rates of inpatient admission and lower pulmonary disease (Table 2), despite oseltamivir treatment in many. An investigation of the H275Y mutation in H1N1 cases did not identify any resistant strains that may have contributed to disease severity.

Limitations of our study included our use of a convenience sample with data collected through medical record abstraction. We did not have sufficient sample size to fully explore the modifying effect of comorbid conditions on influenza severity and were limited in our ability to investigate factors that were not systematically available, including race. However, studies in mice support the hypothesis that obesity itself, outside of coincident comorbid conditions, may hamper immune response to influenza infection.^{11–13} Smith *et al.*¹² found that obese mice infected with influenza A had a 6.6-fold increase in mortality compared with lean mice, despite similar viral titers in both groups. These mice demonstrated decreases in serum leptin, cytokine response,

and NK cell activity. Increased disease severity may also be affected by decreased effectiveness of influenza vaccines in persons with obesity. The effectiveness of influenza vaccines in obesity has been evaluated in studies in mice¹⁴ and humans.^{15,16} Murine models have shown impaired immune responses, uncontrolled inflammation, and increased mortality among obese, vaccinated mice.¹⁴ In a 12-month study of antibody response to influenza vaccine, Sheridan *et al.*¹⁶ have found that persons with obesity had an initial response that was comparable to healthy-weight controls, but antibody levels in obese individuals showed a greater decrease 12 months after vaccination. In contrast, Talbot *et al.*¹⁵ have reported comparable long-term seroprotection to both H3N2 and H1N1 vaccine antigens in obese and non-obese individuals in a study of older adults. We did not find a difference in vaccination status between obese and non-obese individuals experiencing severe influenza morbidity; however, this information was obtained from the patient medical record and may be incomplete.

Although we did not assess immunologic response to influenza in our subjects, the severe disease outcomes observed in individuals with obesity support continued vigilance in the prevention of and treatment for influenza infection among this group. Our findings, along with those in previous studies, underline the need for larger studies to examine the mechanisms and correlates of severe influenza outcomes in obese versus non-obese patients.

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References

- 1 Diaz E, Rodriguez A, Martin-Loeches I *et al.* Impact of obesity in patients infected with 2009 influenza A(H1N1). *Chest* 2011; 139:382–386.
- 2 Morgan OW, Bramley A, Fowlkes A *et al.* Morbid obesity as a risk factor for hospitalization and death due to 2009 pandemic influenza A(H1N1) disease. *PLoS ONE* 2010; 5:e9694.
- 3 Van Kerkhove MD, Vandemaële KA, Shinde V *et al.* Risk factors for severe outcomes following 2009 influenza A (H1N1) infection: a global pooled analysis. *PLoS Med* 2011; 8:e1001053.
- 4 Centers for Disease Control and Prevention. Overweight and obesity. Available at: <http://www.cdc.gov/obesity/data/adult.html> (Accessed 17 August 2012).
- 5 Renaud C, Kuypers J, Corey L. Diagnostic accuracy of an allele-specific reverse transcriptase-PCR assay targeting the H275Y oseltamivir resistant mutation in 2009 pandemic influenza A/H1N1 virus. *J Clin Virol* 2010; 49:21–25.
- 6 National Heart Lung, and Blood Institute. Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults. Bethesda, MD: National Heart Lung, and Blood Institute, 1998 Contract No.: 98-4083.
- 7 Gonzalez-Candelas F, Astray J, Alonso J *et al.* Sociodemographic factors and clinical conditions associated to hospitalization in influenza A (H1N1) 2009 virus infected patients in Spain, 2009–2010. *PLoS ONE* 2012; 7:e33139.
- 8 Blumentals WA, Nevitt A, Peng MM, Toovey S. Body mass index and the incidence of influenza-associated pneumonia in a UK primary care cohort. *Influenza Other Respi Viruses* 2012; 6:28–36.
- 9 Myles PR, Semple MG, Lim WS *et al.* Predictors of clinical outcome in a national hospitalised cohort across both waves of the influenza A/H1N1 pandemic 2009–2010 in the UK. *Thorax* 2012; 67:709–717.
- 10 Easterbrook JD, Dunfee RL, Schwartzman LM *et al.* Obese mice have increased morbidity and mortality compared to non-obese mice during infection with the 2009 pandemic H1N1 influenza virus. *Influenza Other Respi Viruses* 2011; 5:418–425.
- 11 Gardner EM, Beli E, Clinthorne JF, Duriancik DM. Energy intake and response to infection with influenza. *Annu Rev Nutr* 2011; 31:353–367.
- 12 Smith AG, Sheridan PA, Harp JB, Beck MA. Diet-induced obese mice have increased mortality and altered immune responses when infected with influenza virus. *J Nutr* 2007; 137:1236–1243.
- 13 Smith AG, Sheridan PA, Tseng RJ, Sheridan JF, Beck MA. Selective impairment in dendritic cell function and altered antigen-specific CD8 + T-cell responses in diet-induced obese mice infected with influenza virus. *Immunology* 2009; 126:268–279.
- 14 Kim YH, Kim JK, Kim DJ *et al.* Diet-induced obesity dramatically reduces the efficacy of a 2009 pandemic H1N1 vaccine in a mouse model. *J Infect Dis* 2012; 205:244–251.
- 15 Talbot HK, Coleman LA, Crimin K *et al.* Association between obesity and vulnerability and serologic response to influenza vaccination in older adults. *Vaccine* 2012; 30:3937–3943.
- 16 Sheridan PA, Paich HA, Handy J *et al.* Obesity is associated with impaired immune response to influenza vaccination in humans. *Int J Obes* 2012; 36:1072–1077.