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Andrew Algimantas Revis Date

Obesity and 2009 Pandemic Influenza A (H1N1)

By

Andrew Algimantas Revis

MPH

Epidemiology

Dr. Michael Goodman

Faculty Thesis Advisor

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By

Andrew Revis

B.S.

University of Illinois, Urbana-Champaign

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Faculty Thesis Advisor: Dr. Michael Goodman

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Abstract

Obesity and 2009 Pandemic Influenza A (H1N1)

By Andrew Revis

Many patients with 2009 pandemic influenza A (H1N1) infection were noted to be obese, however it is not yet clear whether obesity is a an independent risk factor for severe disease. Using surveillance data, we analyzed demographic and clinical characteristics of Georgia residents ≥ 20 years of age hospitalized with 2009 H1N1 infection to assess whether obesity was associated with ICU admission after controlling for demographic factors and comorbidities. In the multivariate model, a BMI ≥45 was significantly and independently associated with ICU admission (OR, 2.56; 95% CI 1.02—6.45). Hispanic ethnicity (OR, 3.30; 95% CI 1.28—8.54) was also found to be independently associated with an increased likelihood of ICU admission due to 2009 H1N1 infection. Black non-Hispanic race was significantly and inversely associated with ICU admission (OR, 0.57; 95% CI, 0.34—0.97). The proportion of patients admitted to an ICU significantly increased with increasing BMI category (*P* trend = 0.02). More studies are needed to clarify which outcomes are related to obesity, and to what extent.

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I. Introduction

Influenza epidemics in the United States occur annually during the winter months. The influenza virus can affect persons of any age group, but rates of infection are consistently highest among children. Those aged ≥ 65 years, children under the age of two, and persons of any age with underlying medical conditions are also at high risk for influenza-associated hospitalization and death [1] [2]. On average, influenza epidemics have been associated with approximately 36,000 annual deaths between 1990 and 1999 and approximately 226,000 hospitalizations between 1979 and 2001 [3] [4] [5].

Influenza A can cause epidemic disease in humans. Influenza A viruses are categorized into subtypes based on two surface antigens: hemagglutinin (H) and neuraminidase (N). The inherent variability and segmented genome of the influenza A virus gives it the ability to form new strains, which have the potential of causing pandemics.

Since the global H1N1 influenza virus pandemic of 1918, influenza virus gene reassortment has been known to occur in both human and animal viruses. Such reassortant viruses caused the global pandemics of 1957 (H2N2) and 1968 (H3N2) [6].

On April 15th, 2009, the first human case of novel H1N1 infection was identified in the United States in Southern California and was quickly followed by additional cases that required hospitalization [7] [8] [9]. By May, the virus was determined to be the cause of respiratory illnesses that spread across North America and many other areas of the world. The virus spread rapidly and on June 11, 2009, the World Health Organization raised its pandemic level to the highest category, Phase 6 [10].

The 2009 pandemic influenza A (H1N1) virus was genetically distinct from any other human influenza A (H1N1) viruses in circulation since 1977. Molecular studies of the novel virus genome showed that it was derived from multiple reassortment events and from viruses which had been circulating in pigs for decades [5] [11]. The precise evolutionary pathway of this virus is unclear due to the lack of surveillance data from swine, but the simplest interpretation of the available data is that the progenitor of this pandemic originated in pigs and that these reassortments of swine lineages may have occurred years before their emergence in humans [7] [12] [9].

Influenza viruses are able to infect everyone; however, certain age groups are affected disproportionately [1] [2] [13] [14] [15] [16]. An unusual feature of the 2009 pandemic was that hospitalization rates and deaths among persons aged <65 years exceeded those observed during typical winter seasonal influenza epidemics [17] [18] [19]. Furthermore, the estimated number of hospitalizations and deaths among adults aged ≥65 years was below that observed in most seasonal epidemics. This difference has been attributed to partial or full immunity among older persons, presumably as a result of their exposure to the genetically similar influenza A viruses.

Early reports of novel influenza A in North America noted that a number of severely affected cases were obese [20] [17] [21] [22] [18] [23] [24]. It is unknown whether this represents a new at-risk group specific to the novel H1N1 influenza infection.

Previous studies have reported the association between obesity and severity of disease in pandemic 2009 influenza A (H1N1) infection [25] [26]; however it is not yet clear whether obesity is a risk factor for severe disease, or if there is confounding resulting from other comorbidities. The purpose of the current study is to investigate whether obesity is associated with ICU-

admissions in adults hospitalized for pandemic 2009 influenza A (H1N1) after controlling for other factors such as patient demographic characteristics and other chronic medical conditions.

II. Methods

Data for this research were obtained from the Georgia Emerging Infections Program. The Emerging Infections Program (EIP) was established by the Centers for Disease Control and Prevention in 1995 to provide a national resource for infectious disease surveillance and response, conduct applied epidemiologic and laboratory research, identify measures to prevent and control emerging infectious diseases, and strengthen national public health infrastructure. The EIPs are a network of state health departments and their collaborators in local health departments, public health laboratories, and clinical laboratories; infection control professionals; healthcare providers; and academic institutions.

The Georgia Emerging Infections Program began active surveillance for laboratory-confirmed, hospitalized cases of influenza in children <18 years of age in 2003-04 in response to a particularly severe season. Surveillance was expanded in 2005-06 to include adults ≥18 years of age. The surveillance system uses reports from hospital laboratories, admissions, infection prevention specialists, as well as databases of reportable conditions. Chart reviews of all cases are conducted to collect clinical and epidemiologic information. This public health surveillance project represents a collaboration involving state health department officials, academic institutions, EIP staff, and the Influenza Division, CDC.

Active surveillance for laboratory-confirmed influenza hospitalizations is conducted in the eight counties of Georgia's Health District 3 (Clayton, Cobb, DeKalb, Douglas, Fulton, Gwinnett, Newton, and Rockdale counties), population 3,833,277 [27].

For the purposes of this study, a case was defined as a person who is: 1) a resident of Health District 3; 2) 20 years of age or older; and 3) admitted to a catchment area hospital within 14 days of a positive influenza test between April 15, 2009 and April 30, 2010. Pregnant women were excluded from analyses because they have different definitions of normal BMI and because their criteria for hospitalization and ICU admission are different from the general population. There must have been evidence (i.e., a laboratory report in the current hospital record, a written note in the admission H&P of an influenza positive test before admission, a laboratory report from another hospital, report from infection control practitioner, or a verbal report from a primary care provider's office) of a positive influenza test by at least one of the following methods: viral culture, immunofluorescence antibody staining (Direct [DFA] or indirect [IFA]), reverse transcriptase polymerase chain reaction (RT-PCR), a commercially available rapid diagnostic test for influenza, serologic testing, or a positive, unspecified influenza test noted in the medical chart (e.g., a written note in the admission H&P or discharge summary).

Hospitalization was defined as an admission to an inpatient ward of a hospital. Patients who were admitted to and discharged from the hospital on the same day were still considered hospitalized. Emergency room, outpatient visits, and observation wards were not considered hospitalizations. If a person was admitted to an inpatient ward directly following an emergency room or an outpatient visit, the date of admission was defined as the date the patient was admitted to the ward, and not the date the patient was first seen. Patients with a hospital admission more than 14 days after positive influenza test and patients with nosocomially-acquired influenza—defined as a positive influenza test from a specimen collected more than 3 days after initial hospital admission—were not included in these analyses.

For this analysis, the primary outcome measure was ICU admission. Patient race and ethnicity were grouped into three categories: (1) non-Hispanic White, (2) non-Hispanic Black, or (3) Hispanic. We used BMI [height (m)/weight $(kg)^2$] as a measure of relative weight. Obesity was defined as a BMI ≥30 in accordance with the National Institutes of Health (NIH) classification. We divided BMI into categories of <18.5 kg/m^2, 18.5–24 kg/m^2, 25–29 kg/m^2, 30-34 kg/m^2, 35-44 kg/m^2, and ≥45 kg/m^2. If height or weight were not reported in the data collected and the chart specifically made note of obesity, then a patient was assigned the 30-34 kg/m^2 BMI category. A calculated BMI always took precedence over any note made in the patient's chart.

The distributions of BMI and demographic and clinical characteristics were compared in ICU and non-ICU cases using χ^2 statistics. The association between BMI and ICU was further examined using multivariate logistic regression models controlling for age, race/ethnicity, sex, and underlying conditions. In order to control for underlying conditions in the multivariate analyses, we developed a co-morbidity index based on the number of documented conditions. The co-morbidity index was divided into three ordinal categories: ≥2 conditions, 1 condition, or none. Multivariate analysis was performed using BMI the categories of: underweight, normal weight, overweight, obese class I (BMI 30-34 kg/m^2), BMI 35-44 kg/m^2, and an upper threshold of BMI ≥45 kg/m^2. We used SAS v9.2 for all analyses.

III. Results

Between April 15th, 2009 and April 30th 2010 we identified 470 patients with confirmed pandemic H1N1 influenza infection that met our inclusion criteria. Of those, 391 (83%) had both measured height and weight which we used to calculate BMI. In addition, we were able to estimate a BMI category for 8 (2%) patients whose charts noted "Obesity" or "Morbid Obesity." Thus, our final dataset included 399 patients assigned to a BMI category.

Of the 399 patients in the final dataset, 108 (27%) were between 20-34 years of age, 127 (32%) were between 35-49 years of age, and 164 (41%) were ≥50 years of age. One-hundred and ninety-two (48%) patients were male. Of the 392 patients for whom race and ethnicity data were available, 166 (42%) patients were white non-Hispanic, 194 (50%) patients were black non-Hispanic, and 24 (6%) patients were of Hispanic origin, and eight patients (2%) were self-identified as Asian (Table 1). Patients self-identified as Asian were excluded from analysis. Of the 399 adults aged 20 years or older with known BMI, 10 (3%) were classified as underweight (BMI <18.5 kg/m^2), 106 (27%) were classified as normal weight (18.5 ≤ BMI < 25), 89 (22%) were classified as overweight (25 ≤ BMI < 30), and 194 (49%) were classified as obese (BMI ≥ 30). Among the obese patients, 47 (12%) were morbidly obese (BMI ≥ 40 kg/m^2).

One-hundred and three patients (24%) were admitted to an intensive care unit (ICU). In bivariate analyses of ICU admission and underlying co-morbidities, patients admitted to the ICU were more likely than those not admitted to have renal disease (N = 19 [18%], $P = 0.04$), a diagnosis of obesity (N = 59 [57%], $P = 0.047$), NIH recognized class II obesity (N = 20 [19%], $P = 0.02$), and a BMI ≥45 kg/m^2 (N = 12 [12%], $P = 0.02$). Patients who identified as Hispanic were more likely to be admitted to the ICU than the non-Hispanic Whites (N = 14 [14%], $P = 0.003$).

Three-hundred forty-one (85%) patients received antiviral treatment. Among patients where the date of antiviral treatment started was available (N = 243), then median time from admission until initiation of antiviral therapy was 1 day (range 12 days prior to admission to 9 days after admission). Additionally, patients admitted to an ICU were less likely than patients not admitted to have received antiviral treatment within 48 hours of admission (N = 50 [65%], *P* = 0.003) (Table 3).

In the multivariate model (Table 4), a BMI ≥45 was significantly and independently associated with ICU admission (OR, 2.56; 95% CI 1.02—6.45). Hispanic ethnicity (OR, 3.30; 95% CI 1.28—8.54) was also found to be independently associated with an increased likelihood of ICU admission due to 2009 H1N1 infection. Black non-Hispanic race was significantly and inversely associated with ICU admission (OR, 0.57; 95% CI, 0.34—0.97). The proportion of patients admitted to an ICU significantly increased with increasing BMI category (*P* trend = 0.02).

IV. Discussion

Our data indicate the proportion of patients admitted to an ICU increases with the increase in BMI category. A BMI≥45 was significantly associated with an increased risk of ICU admission independent of other factors. Another important predictor of ICU admission was race. We found that Hispanic H1N1 patients were more likely to be admitted to an ICU whereas non-Hispanic Black patients had a lower probability of ICU admission compared to their non-Hispanic White counterparts.

The prevalence of obesity in the US has been increasing dramatically [28]. According to the Behavioral Risk Factor Surveillance System, the prevalence of obesity between 1991 and 1998 increased in all 50 states, in both men and women, and across all age groups [29]. In 1991, only four states had obesity rates of 15% or higher, but by 1998, 37 states had exceeded that level. The National Health and Nutrition Examination Surveys (NHANES) show that the prevalence of obesity rose gradually from 1960 to 1980, but in the period from the second survey (NHANES II: 1976 to 1980) until the third (NHANES III: 1988 to 1994), it increased dramatically, from 14.5% to 22.5% [30 31 32]. The increase in obesity prevalence noted in the NHANES surveys was evident in both men and women, for all age categories, and across race-ethnic groups.

The increasing rates of obesity across the US highlight the growing importance of understanding the role of this condition with respect to influenza pathogenesis. Seasonal influenza viruses are known to cause disease among all age groups; however, certain age groups are typically affected disproportionately when compared to others [1 13 14 15 16 33]. Although in our study obesity was associated with H1N1 severity, it has not been shown to increase the risk of

severe seasonal influenza [34 35 36 37]. The association between seasonal influenza and obesity in human studies could have been obscured by an underreporting of obesity or a focus on the co-morbidities associated with obesity (e.g., asthma, diabetes, and CVD) or by the disproportionate numbers of frail elderly individuals affected, who account for most deaths from seasonal influenza and who are often underweight [38].

The current study adds to a growing literature suggesting an association between obesity and the risk of severe outcome pertaining to pandemic H1N1 infection. During the 2009 pandemic, almost half of Georgia residents ≥20 years of age hospitalized with 2009 H1N1 infection were obese. The prevalence of BMI ≥30 in adults in this analysis (49%) was 1.8 times that estimated for all adults in Georgia (27.2%) and 1.5 times that estimated for all adults in the United States (33%) [30 29]. The prevalence of BMI ≥40 (12%) was 1.9 times higher than the estimated prevalence in the United States (6.2%), and the prevalence of BMI ≥45 was 6.8 times higher than national estimates (7.5% vs 1.1%) [29].

Researchers have previously described obese persons as requiring hospitalization and critical care for 2009 H1N1 infection. Early in the pandemic, 9 of 10 severely ill adults requiring intensive care in Michigan had a BMI ≥30 kg/m^2; of these, 7 had a BMI ≥40 kg/m^2. Clinicians were urged to be aware of the potential for severe complications of novel H1N1 infection, particularly in extremely obese patients [20]. Another study of hospitalized patients in Australia and New Zealand found that among 611 critically ill patients with confirmed pandemic H1N1 influenza A infection, 26% had a body-mass index greater than 35 kg/m^2 [23]. A national study involving more than 200 hospitalized patients found that 26% with BMI information had a BMI ≥40 kg/m^2 [17]. Among cases of 2009 H1N1 infection requiring intensive care, a BMI ≥30 kg/m^2

was found in 35 (74%) of 47 patients in Utah [21], 10 (31%) of 32 patients in Spain [24] 21 (36%) of 58 patients in Mexico [22], and 56 (33%) of 168 patients in Canada [18]. Diabetes and BMI ≥30 were the most frequently identified underlying conditions among adult case patients who died from 2009 H1N1 infection during the 2009 pandemic worldwide [23 34].

In the current study, we identified a trend of increasing risk of ICU admission as BMI increases among patients hospitalized with pandemic H1N1 virus. Additionally, we noted that the morbidly obese (BMI ≥ 45 kg/m^2) patients were at marked increased risk of critical illness after adjustment for reported co-morbidities. It is plausible that obesity increases the risk of severe influenza. In addition to the mechanical stresses associated with increased body mass, obesity alters normal metabolic and physiologic pathways. Obesity can profoundly alter lung mechanics, diminish exercise capacity, augment airway resistance resulting in an increased work of breathing, and influence respiratory muscle function, control of breathing, and gas exchange [39, 40]. Researchers have previously implicated excessive weight gain with an increased risk of developing community-acquired pneumonia [41]. Obesity can also impede pulmonary function. Obese patients allocate a disproportionately high percentage of total body oxygen consumption to respiratory work, resulting in reduced functional residual capacity and expiratory volume [32]. A subsequent ventilation-perfusion abnormality may decrease ventilatory reserve and predispose the obese to respiratory failure after even mild pulmonary challenges [32 34 41 39]. Obese patients needing intensive care for acute lung injury have prolonged mechanical ventilation and hospital stay, compared with nonobese patients [42]. In addition to its effects on pulmonary function, obesity is frequently but not always associated with diabetes, hypertension, hyperlipidemia, cardiovascular disease and higher overall mortality [39 34].

Obesity has also been associated with a state of chronic, low-grade inflammation [43]. The realization that obesity is associated with an altered inflammatory profile has important implications in the pathogenesis of influenza. Adipose tissue is an active endocrine organ which secretes a variety of inflammatory mediators and obesity has been associated with an overall proinflammatory state that is thought to be responsible for insulin resistance, endothelial cell dysfunction, atherogenesis, and, ultimately, arteriosclerosis [43 44]. Additionally, impaired glucose metabolism and insulin resistance associated with obesity alters normal neutrophil function and increases the potential for infection [45]. Although undefined, it is plausible that the H1N1 influenza inflammatory response is amplified in obese patients.

The key results from our study corroborate the findings from previous research and are strengthened by our study design and use of extensive data from a large series of hospitalized H1N1 influenza patients. Ours is one of few analyses capable of assessing the independent effect of obesity on H1N1 disease severity by controlling for chronic neurologic, hematologic, nondiabetes metabolic and immunosuppressive disorders. Another strength of the current study is the inclusion of a racially and ethnically diverse patient population. In our analysis, non Hispanic H1N1 patients were more likely to be admitted to an ICU whereas non-Hispanic Black patients had a lower probability of ICU admission compared to their non-Hispanic White counterparts. These findings could be due to differences in income, insurance coverage, and need for care, as well as less commonly assessed factors such as culture, attitudes, or discrimination, which differentially influence members of racial and ethnic minority groups to seek medical care [46]. Although examining racial disparities with respect to pandemic H1N1 infection was not the intent of this study, our results certainly merit further investigation of the topic.

Our study also has several limitations. Our focus on severe disease requiring ICU admission may not reflect important presenting features in less severe cases. Although we described cases in the highest populated counties of Georgia, many more counties were not included in our surveillance program. Because our study lacked data on socioeconomic status, we were unable to assess its role in the differences in ICU admission.

In summary, obesity, a common and increasing condition worldwide, was more prevalent among adults hospitalized with 2009 H1N1 infection than it was among the adult population for Georgia and the United States. The question of whether the relation between obesity and disease severity is causal cannot be easily answered. Although obese persons may have multiple co-morbidities that contribute to the risk of severe in H1N1 influenza, persons with elevated BMI, particularly the morbidly obese, appear to be at higher risk for ICU admission due to 2009 H1N1 infection after controlling for other risk factors. Even if obesity is only a reflection of undiagnosed co-morbidities or other underlying risk factors, BMI can still serve as convenient measure for identifying adults at high risk for severe disease. This would be comparable to the recommendations for seasonal influenza immunization among the elderly because older age groups are known to be at higher risk for severe disease regardless of the underlying biological mechanism [34]. Large prospective studies are needed to further clarify which outcomes are related purely to obesity, and to what extent.

V. References

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VI. Tables

Table 1: Demographic characteristics of patients hospitalized for 2009 H1N1 in Georgia, comparing adults ≥ 20 who were admitted to an ICU with those who were not admitted

	All Patients (N = 399)	ICU Patients (N = 103)	Non-ICU Patients (N = 296)	P-value
Age groups		number (%)		
20 -- 34.9	108 (27)	33 (32)	75 (25)	-
35 -- 49.9	127 (32)	34 (33)	93 (32)	-
50+	164 (41)	36 (35)	128 (43)	0.27
Sex				
M	192 (48)	47 (46)	145 (49)	-
F	207 (52)	56 (54)	151 (51)	0.6
Race or Ethnicity				
White Non-Hisp.	166 (42)	46 (45)	120 (41)	-
Black Non-Hisp.	194 (50)	41 (40)	153 (53)	-
Hispanic	24 (6)	14 (14)	10 (4)	**0.0004**

Table 2: Characteristics of patients hospitalized for 2009 H1N1 in Georgia, comparing adults ≥ 20 who were admitted to an ICU with those not admitted

MEDICAL CONDITION	**All Patients (N = 399)**	**ICU Patients (N = 103)**	**Non-ICU Patients (N = 296)**	**P-value**
		number (%)		
Any one condition	307 (77)	77 (75)	230 (78)	0.4
Asthma	97 (24)	19 (18)	78 (26)	0.11
Chronic Lung Disease	69 (17)	20 (19)	49 (17)	0.51
Chronic Metabolic Disease	90 (23)	27 (26)	63 (21)	0.3
Immunosuppression	91 (23)	20 (19)	71 (24)	0.34
Chronic Cardiovascular Disease	63 (16)	19 (18)	44 (15)	0.39
Chronic Renal Disease	50 (13)	19 (18)	31 (10)	**0.04**
Hemoglobinopathy	7 (2)	1 (1)	6 (2)	0.68
Neuromuscular Disorder	20 (5)	8 (8)	12 (4)	0.14
Neurocognitive Disorder	7 (2)	3 (3)	4 (1)	0.38
Seizure	5 (1)	2 (2)	3 (1)	0.61
Cancer	14 (4)	5 (5)	9 (3)	0.37
Leukemia or Lymphoma	9 (2)	2 (2)	7 (2)	>0.99

Table 3: Clinical characteristics of patients hospitalized for 2009 H1N1 in Georgia, comparing adults ≥ 20 who were admitted to an ICU with those who were not admitted

CLINICAL FINDINGS	**All Patients (N = 399)**	**ICU Patients (N = 103)**	**Non-ICU Patients (N = 296)**	**P-value**
		number (%)		
Discharge Diagnosis ARDS	23 (6)	21 (20)	2 (<1)	**<0.0001**
Discharge Diagnosis Pneumonia	199 (50)	73 (71)	176 (43)	**<0.0001**
Discharge Diagnosis Encephalopathy	8 (2)	6 (6)	2 (<1)	**0.005**
Required Mechanical Ventilation	64 (16)	63 (61)	1 (<1)	**<0.0001**
Secondary Bacterial Infection	27 (7)	12 (12)	15 (5)	**0.02**
Antiviral Treatment	341 (85)	94 (91)	247 (83)	0.053
≤48 h after admission	243 (77)	50 (65)	193 (81)	**0.003**

Table 4: Risk factors independently significantly associated with ICU admission for hospitalized case patients ≥20 years of age with known BMI information

	OR (95% Wald CI)	P-trend
Body Mass Index		
<18.5	1.63 (0.30 - 8.91)	-
18.5 - 24	1	-
25 - 29	1.10 (0.53 - 2.27)	-
30 - 34	1.49 (0.75 - 2.98)	-
35-44	1.61 (0.78 - 3.32)	-
≥45[1]	2.56 (1.02 - 6.45)	**0.019**
Age groups		
20 -- 34.9	1	-
35 -- 49.9	0.90 (0.48 - 1.69)	-
50+	0.66 (0.35 - 1.24)	0.2
Co-morbidity Index		
0 Conditions	1	-
1 Condition	0.74 (0.39 - 1.42)	-
≥2 Conditions	1.39 (0.74 - 2.61)	0.25
Sex		
Male	0.74 (0.44 - 1.24)	0.25
Race or Ethnicity		
White Non-Hisp.	1	Referent
Black Non-Hisp.	0.57 (0.34 - 0.97)	**0.04**
Hispanic	3.30 (1.28 - 8.54)	**0.01**