Obesity and Influenza

Seema Jain and Sandra S. Chaves
Influenza Division, National Center for Immunization and Respiratory Diseases, Centers for Disease Control and Prevention, Atlanta, Georgia

(See the article by Kwong et al, on pages 413–421.)

The association between obesity and influenza was first noted during the early phase of the 2009 influenza A(H1N1) pandemic, when data from many countries around the world indicated that obese persons were disproportionately represented among influenza-associated hospitalizations and deaths [1–6]. Obese (body mass index [BMI] ≧30 kg/m²) or morbidly obese patients (BMI ≧40 kg/m²) appeared to be at increased risk of influenza-associated intensive care unit (ICU) admission and death [7–9]. Furthermore, obese patients hospitalized with 2009 H1N1 infection admitted to an ICU had longer duration of mechanical ventilation, as well as ICU and hospital length of stay compared with those who were not obese [10]. Because certain chronic medical conditions (including cardiovascular and metabolic diseases) that place persons at risk for influenza-related complications are highly correlated with obesity [11], attempts to tease apart the independent contribution of obesity to influenza disease severity have been challenging.

In this issue of Clinical Infectious Diseases, Kwong and colleagues [12] explore the relationship between obesity and seasonal influenza. They used a series of Canada’s cross-sectional population-based health surveys (conducted either by phone or in person) covering 12 influenza seasons to create a retrospective cohort of individuals; data from the surveys, including self-reported height and weight, were linked to multiple administrative data sets. Risk of hospitalization, the primary outcome, was estimated based on ICD-9 and -10 coded data related to an admission code for acute and chronic respiratory diseases. The analysis includes adults aged 18–64 years old from Ontario, Canada, and excludes pregnant and breastfeeding women. Influenza seasons were defined based on virologic sentinel surveillance data. Logistic regression models were used to estimate risk of respiratory hospitalization during influenza seasons by BMI categories, adjusting estimates by predefined covariates such as age, sex, socioeconomic status, and presence of comorbidities. The authors also conducted sensitivity analyses to assess the association between BMI and hospitalization due to external causes of injury during influenza seasons, as well as the association of BMI and respiratory hospitalizations during periods when influenza viruses were not circulating.

Kwong and colleagues [12] demonstrate that persons who are obese are at increased risk for respiratory hospitalizations during seasonal influenza periods; for persons with severe obesity (BMI≧ 35), the association was present for those with and without diagnosed chronic medical conditions. Their findings are strengthened by their sensitivity analyses showing that, during influenza seasons, obese persons had increased odds for all hospitalizations but not those due to external injury. Importantly, they did not find an association between obesity and risk of hospitalization due to respiratory illness during non-influenza seasons. In addition, the use of electronic administrative databases and the linkage of these data sets to national surveys is novel, demonstrating the usefulness of electronic sources of data.

Because the analysis relied on administrative data sets, there may be medical conditions that were not ascertained. For example, diabetes, which is highly correlated with obesity [11] and also considered a high-risk condition for influenza-associated complications [13], goes undiagnosed in an estimated 40% of the US adult population [14]. Moreover, neurological disorders were not among comorbidities included in their analysis, even though such conditions are a well-recognized risk factor for influenza-associated complications [13]. Comorbidities that are not accounted for in these analyses (either because they are undiagnosed or undocumented in medical records) could lead to an overestimation.
of the independent effect of obesity on influenza as these comorbidities could help explain, partially or completely, influenza severity among persons who are obese.

In another study conducted during the 2009 H1N1 pandemic, Morgan et al [15] evaluated the risk of hospitalization by BMI controlling for presence of comorbidities and used the case-cohort approach comparing cases of 2009 H1N1 hospitalizations to a cohort of the US population estimated from the National Health and Nutrition Examination Survey (NHANES). Similar to Kwong and colleagues, Morgan et al found that morbidly obese adults with and without recognized chronic medical conditions were more likely to be hospitalized with 2009 H1N1 infection than those who were not obese. The authors acknowledged that they were unable to control for chronic medical conditions associated with influenza severity that were not accounted for in NHANES such as immunosuppression, neurological disorders, and hematological conditions that could have overestimated the impact of obesity on influenza.

While the relationship between obesity and infection [16], including pneumonia [17], has been reported prior to the 2009 H1N1 pandemic, Kwong and colleagues [12] are the first to investigate an association between obesity and seasonal influenza. There are multiple plausible explanations for the association between obesity and influenza. In animal models, pathophysiological processes for a proinflammatory state related to obesity have been explored, including decreased tumor necrosis factor, microvascular inflammation, and thrombosis, but it is unclear if these results can be directly extrapolated to humans [16]. When infected with influenza, diet-induced obese mice had higher mortality, immune dysregulation, and more lung pathology compared with lean controls [18]. One explanation could be that adipose tissue produces adiponectin, an adipokine, which reduces macrophage activity and cytokine production and contributes to a proinflammatory state in obesity and may predispose to infection [19]. Obesity has also been related to impaired T and B cell function, although studies have been inconclusive [16]. In addition to immunological explanations described in animal models, mechanical dysfunction due to obesity itself may also explain increased risk for complications due to lower respiratory tract infection. Excess weight reduces functional residual capacity as adipose tissue that has accumulated around the rib cage and abdomen can decrease lung compliance and may increase the risk of airway closure and ventilation-perfusion mismatch [20]. These mechanical dysfunctions due to obesity can also explain the difficulties of managing and weaning obese patients who require mechanical ventilation [21].

In the United States, the Advisory Committee on Immunization Practices added morbid obesity to the list of conditions that are considered to increase the risk of influenza-related complications, including hospitalization and death [13], and for which prompt empiric influenza antiviral treatment is recommended during influenza seasons [22]. These recommendations were based on the growing body of evidence showing a potential association between morbid obesity and influenza severity. While the findings from Kwong and colleagues help substantiate these guidelines, further investigation on the independent association between obesity and influenza is warranted as the data could be useful in prioritizing groups for vaccination in settings where resources are limited. Future studies done prospectively could help elucidate the interplay between comorbidities, obesity, and influenza, particularly if chronic medical conditions are measured systematically.

Worldwide, annual influenza epidemics result in an estimated 3–5 million cases of severe illness and 250 000–500 000 deaths every year [23]. The 2008 World Health Organization estimates indicated more than 500 million adults were obese [24]. Vaccination is the primary tool to prevent influenza infection and should be encouraged in patients who are obese or morbidly obese, with or without presence of recognized comorbidities.

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