Evaluation of obesity as an independent risk factor for medically attended laboratory-confirmed influenza

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Background The relationship between obesity and susceptibility to influenza infection in humans is unclear. Morbidly obese people were at an increased risk of complications from 2009 pandemic H1N1 influenza [A(H1N1)pdm09].

Objective The goal of this study was to determine whether medically attended, laboratory-confirmed influenza is independently associated with obesity in adults with acute respiratory illness.

Patients/Methods Adults ≥20 years with a medical encounter for acute respiratory illness were recruited from a population cohort during the 2007–2008 (*n* = 903), 2008–2009 (*n* = 869), and 2009 pandemic (*n* = 851) season. Nasopharyngeal swabs were tested for influenza by real-time reverse-transcription polymerase chain reaction. Body mass index (BMI) was calculated using data from the electronic medical record. Logistic regression evaluated the association between influenza and obesity, adjusting for gender, vaccination, age, and high-risk medical condition.

Results Influenza was detected in 50% of patients in 2007–2008, 15% in 2008–2009, and 14% during the 2009 pandemic. Predominant seasonal viruses in this population were A/H3N2 in 2007–2008, and A/H1N1 and B in 2008–2009. Mean (±SD) BMI was 30·58 (±7·31) in patients with influenza and 30·93 (±7·55) in test-negative controls during all seasons. Mean BMI of patients with influenza did not vary by season. After adjusting for confounders, neither obesity nor extreme obesity were associated with influenza by season or for all years combined (OR 0·95: 95% CI 0·75, 1·20 and 1·10: 0·80, 1·52, respectively, for obesity and extreme obesity, all years).

Conclusions Obesity was not associated with medically attended influenza among adults with acute respiratory illness in this population.

Keywords Body mass index, influenza, obesity.

Introduction

Obesity has been associated with dysregulation of the immune system, including decreased response to tetanus[1] and hepatitis B[2] vaccination, reduced seroprotection from the 2009 H1N1 influenza vaccine,[3] alterations in CD4+ and CD8+ T cell subsets,[4] abnormalities in inflammatory cytokine levels and transcript levels in peripheral blood mononuclear cells (PBMC),[5] and suppressed mitogen-induced lymphocyte proliferation.[6] Sheridan et al.[7] recently described the timing of obesity-related immune dysfunction, reporting an initially robust antibody response to influenza vaccination among obese individuals, but a subsequent greater decline in antibodies 12 months post-vaccination. Seroconversion following weight reduction,[8] and improvement in both *ex vivo* and *in vivo* measures of T cell mediated immune function after 6 months of caloric restriction in overweight adult humans[9] add to the evidence that a high body mass index (BMI) impairs immune response.

While the evidence linking obesity and immune response in general is quite robust, there are few studies related to obesity and laboratory-confirmed influenza in humans. The most existing research has studied the association between influenza infection and obesity in animal models. In one study, obese mice had a 6·6-fold higher mortality rate after influenza infection, accompanied by reduced natural killer cell cytotoxicity and delayed pro-inflammatory cytokine expression.[10] Subsequent work in mice has suggested that obesity may impair the recruitment of dendritic cells, which, along with macrophages, are involved in initiating and modulating the immune response to influenza infection.[11] Most recently, O'Brien et al.[12] found that obesity

impairs regeneration of damaged epithelium in lungs of influenza-infected mice, contributing to the severity of influenza infection.

Studies conducted during the 2009 H1N1 influenza pandemic have suggested that obesity contributed to morbidity and mortality after infection with this virus. A recent report described the clinical characteristics of 10 patients with A(H1N1)pdm09 infection and acute respiratory distress syndrome and found that 90% of patients had a BMI over 30 kg/m^2, indicating the presence of obesity; 70% had a BMI ≥ 40 kg/m^2 indicating morbid obesity.[13] Moreover, extreme obesity (BMI ≥ 40) has been independently associated with hospitalization and death due to A(H1N1)pdm09 infection.[14,15] Pooled odds ratios from China, Thailand, Spain, the Netherlands, and the United States indicate that worldwide, obesity was also associated with severe disease and increased risk of death among hospitalized individuals during the 2009 pandemic.[16] These reports, along with the well-documented immune dysfunction associated with obesity, make it plausible that *in vitro* and *in vivo* findings from animal studies translate into an increased risk of influenza infection or more severe outcomes in obese individuals. The goal of the present study was to determine whether medically attended, laboratory-confirmed influenza is independently associated with obesity among adults seeking medical care for an acute respiratory illness.

Materials and methods

Study design

We conducted prospective surveillance for influenza in a defined cohort of individuals with medically attended acute respiratory illness during two influenza seasons and the 2009 pandemic to estimate influenza vaccine effectiveness.[13] A case–control analysis was employed with laboratory-confirmed influenza cases and test-negative controls with non-influenza respiratory illness.[13] Use of the test-positive case versus test-negative control methodology for estimating vaccine effectiveness has the advantage of controlling for factors associated with both illness and the propensity to seek care when ill.[17] On the basis of differences that we have found between vaccinated and non-vaccinated individuals and on the known differences in health care utilization between obese and non-obese individuals,[18] we applied the test-negative control methodology to the current analysis to reduce bias.

Participants and setting

Community-dwelling individuals with a medical encounter for acute respiratory illness were recruited during the 2007–2008 influenza season (January–March 2008), the 2008–2009 season (January–March 2009), and during the 2009 pandemic period (May–November 2009). Because

the standard definitions for obesity differ for individuals <20 years of age, we limited this analysis to adults ≥20 years old. The source population included community-dwelling residents of 14 zip-codes surrounding Marshfield, Wisconsin. This population and the enrollment procedures have been previously described and used to estimate the effectiveness of influenza vaccines for several seasons.[19–21]

Briefly, among persons in our source population meeting residency criteria, those presenting for an outpatient or inpatient health care visit with at least one of the following symptoms – feverishness, chills, or cough – <8 days in duration were screened, enrolled, and tested for influenza by study staff. Outpatient areas in which recruitment occurred included general internal medicine, family practice, medical/pediatrics, general pediatrics, and urgent care. Clinicians providing care had no role in recruiting, identifying, or testing patients for inclusion in this study. The study procedures were reviewed and approved by the Marshfield Clinic Institutional Review Board, and all participants provided consent for influenza testing.

Variables and data sources

The primary outcome variable was medically attended, laboratory-confirmed influenza. A nasopharyngeal swab was obtained from all participants. Swabs were placed in M4 viral transport media, and total nucleic extractions were performed using the Roche MagNA® Pure Total Nucleic Acid Kit (Roche Diagnostics, Indianapolis, IN, USA) on 200 μl of clinical sample. Real-time reverse-transcriptase PCR (rRT-PCR) was performed on nucleic acid extracts using the Roche LightCycler® 480 Real-Time PCR System (Roche Diagnostics). All rRT-PCR protocols, probe, and primer sequences for the detection and characterization (subtyping) of influenza were provided by CDC. The rRT-PCR test has been shown to have a substantially higher sensitivity compared with either viral culture or rapid antigen testing.[22] A positive result for influenza was defined by a crossing threshold of <40 cycles.[23,24]

We conducted a secondary analysis among influenza cases only to examine serious influenza-related outcomes, defined as pneumonia or hospital admission within 30 days after symptom onset. An episode of influenza-related pneumonia required all of the following in a participant with laboratory-confirmed influenza: physician diagnosis of pneumonia, antimicrobial treatment for pneumonia, and an opacity or infiltrate on chest X-ray that was not known to be chronic.[21] A physician (EAB) reviewed all cases of pneumonia and all hospital admissions.

The primary exposure variable was obesity as defined below. BMI was calculated as weight/height,^{2} using height and weight measurements from the electronic medical record. We have previously shown that over 90% of the

patients at our clinic have weight measured annually, and 75% have height measured annually.[25] We utilized height and weight measurements obtained closest to the study enrollment date for calculating BMI. If height was not measured at the same visit as weight, then any adult (> age 20) height was used. Weights were used only if taken within 30 days before or after study enrollment. The calculated BMI value was categorized as underweight (BMI < 18·5), normal (BMI 18·5–24·9), overweight (BMI 25·0–29·9), obese (BMI 30·0–39·9), or extremely obese (BMI ≥ 40) according to NIH guidelines.[26] BMI was analyzed both as a categorical and as a continuous variable.

We classified individuals as having a chronic medical condition if they had ≥2 visits to the Marshfield Clinic during the prior calendar year with an ICD-9-CM diagnosis code for an underlying chronic disease conferring elevated risk for influenza complications.[19] Influenza vaccination status was determined by a real-time, internet-based immunization registry (http://www.recin.org) that captures 95% of all influenza vaccinations in the study population.[27] Subjects were considered immunized beginning 14 days after receipt of vaccine because this is when antibodies that provide protection against influenza develop.[19] Subjects who received the vaccine <14 days prior to symptom onset were considered non-vaccinated.

Statistical methods

Descriptive statistics were calculated and distributions were examined for all variables of interest. Influenza cases and test-negative controls were compared by *t*-test (continuous variables) or chi-square (categorical variables) procedures. Univariate logistic regression was used to examine the association between obesity and medically attended, laboratory-confirmed influenza. Using a multivariable logistic regression model, we evaluated the association between rRT-PCR confirmed influenza and obesity, adjusting for gender, influenza vaccination status, age, and presence of any high-risk medical condition. This set of pre-specified potential confounders was included in all models. We determined the odds of being a case in each BMI group (underweight, overweight, and obese groups), relative to the normal weight BMI group (referent group). As a secondary analysis among influenza cases only, we used multivariable logistic regression to evaluate the association between obesity (both as a dichotomous variable, BMI ≥ 30, and as a multicategory variable as described in Table 1) and serious outcome (yes/no), adjusting for gender, influenza vaccination status, age, and the presence of any high-risk medical condition.

If more than one enrollment per subject occurred within the same influenza season, we included data from only the first enrollment based on the rationale that BMI would not change substantially within a 12-week enrollment period.

For the analyses of multiple seasons combined, a subject was counted more than once if multiple enrollments occurred across study periods, but only one data point was used per season. *P* values <0·05 were considered to be statistically significant. Analyses were conducted using SAS 9.1/SAS Enterprise Guide 4.1 (SAS Institute Inc., Cary, NC, USA).

Results

Of 6,874 subjects enrolled during the three study periods, 2927 (43%) were ≥20 years old; of these, 2623 (90%) were included in the present case–control analysis. Subject characteristics by study period are summarized in Table 1. There were only three individuals with BMI < 18·5 in 2007–2008, six in 2008–2009, and five during the pandemic period; data for this BMI category are not shown. There were no differences in mean overall age (45 ± 17 years), BMI (30·8 ± 7·5), BMI category (23% normal weight, 28% overweight, 37% obese, and 11% severely obese), or high-risk status (24%) by study period. The duration of time from illness onset to when an individual sought medical attention did not vary by study period or by BMI category, with a mean of 2½–3½ days in all analyses. More men (38%) participated in 2007–2008, and there were more cases in the 2007–2008 season (50%), compared with the other two study periods. There were 10 pneumonia diagnoses in 2007–2008, three in 2008–2009, and six during the 2009 pandemic; the remaining serious outcomes each season were attributed to hospitalizations. These were combined into a single measure ("serious outcome") for analysis because of the small numbers in our population.

For the 2007–2008 and 2008–2009 seasons, Marshfield Clinic providers and local vaccination clinics used trivalent inactivated influenza vaccine (TIV) for >96% of vaccines administered. During the 2009 pandemic period, only four participants received the monovalent H1N1 vaccine at least 14 days prior to symptom onset, and all tested negative for influenza by rRT-PCR.[21] Eleven participants during the pandemic period were vaccinated 1–13 days prior to symptom onset (median 7 days, range 1–13 days).

In 2007–2008, 9% (85/903) of subjects were extremely obese (BMI ≥ 40); 12% (107/869) and 11% (93/851) of subjects were extremely obese in 2008–2009 and during the 2009 pandemic, respectively. Among cases only, 10% (46/454) were extremely obese in 2007–2008; 11% (15/132) in 2008–2009, and 14% (17/119) during the 2009 pandemic.

Cases and control subjects are compared in Table 2. Mean ± SD BMI was 30·58 ± 7·31 in patients with influenza and 30·93 ± 7·55 in controls across all study periods (Figure 1); BMI increased slightly with increasing age (Figure 2). Mean BMI of subjects with influenza did not vary

Table 1. Descriptive Characteristics, by Season and Body Mass Index (BMI) Category

	All[†]	BMI 18·5–24·9	BMI 25–29·9	BMI 30–39·9	BMI ≥ 40	*P*-value
2007–2008	n = 903	n = 207	n = 262	n = 346	n = 85	
Age, years[‡]	46 ± 17	41 ± 18[a]	48 ± 17[b]	48 ± 17[b]	42 ± 14[a]	<0·0001
BMI, wt/ht2[‡]	30·6 ± 7	22·5 ± 2[a]	27·4 ± 1[b]	34·3 ± 3[c]	45·9 ± 5[d]	<0·0001
Male[§]	342 (38)*	55 (27)[a]	117 (45)[b]	152 (44)[b]	18 (21)[a]	<0·0001
Vaccinated[§]	368 (41)	76 (37)	117 (45)	148 (43)	26 (31)	NS
High risk[§,¶]	217 (24)	33 (16)[a]	61 (23)[a,c]	99 (29)[b]	24 (28)[b,c]	0·01
Case status[§]	454 (50)*	105 (51)	133 (51)	170 (49)	46 (54)	NS
Serious outcome[§,††]	26 (6)	6 (6)	8 (6)	10 (6)	2 (4)	NS
Days illness onset to swab[§]	3·2 ± 1·9	3·2 ± 1·9	3·2 ± 1·9	3·2 ± 1·9	2·7 ± 1·8	NS
2008–2009	n = 869	n = 194	n = 253	n = 309	n = 107	
Age, years[‡]	44 ± 17	40 ± 17[a]	45 ± 18[b]	47 ± 16[b]	44 ± 14[a,b]	0·002
BMI, wt/ht2 [‡]	31·0 ± 8	22·6 ± 2[a]	27·4 ± 2[b]	34·3 ± 3[c]	46·3 ± 6[d]	<0·0001
Male[§]	281 (32)	45 (23)[a]	106 (42)[b]	106 (34)[c]	23 (22)[a]	<0·0001
Vaccinated[§]	410 (47)	91 (47)	114 (45)	156 (50)	48 (45)	NS
High risk[§,¶]	201 (23)	32 (16)[a]	48 (19)[a,b]	78 (25)[b]	40 (37)[c]	0·0001
Case status[3]	132 (15)	35 (18)	42 (17)	40 (13)	15 (14)	NS
Serious outcome[§,††]	8 (6)	4 (11)	2 (5)	2 (5)	0 (0)	NS
Days illness onset to swab[§]	3·6 ± 2·0	3·6 ± 2·0	3·6 ± 2·0	3·6 ± 2·0	3·3 ± 2·1	NS
2009p H1N1	n = 851	n = 186	n = 234	n = 333	n = 93	
Age, years[‡]	45 ± 16	40 ± 15[a]	46 ± 17[b,c]	48 ± 16[b]	42 ± 13[a,c]	<0·0001
BMI, wt/ht2[‡]	30·8 ± 7	22·5 ± 2[a]	27·3 ± 1[b]	34·2 ± 3[c]	45·4 ± 5[d]	<0·0001
Male[§]	284 (33)	39(21)[a]	94 (40)[b]	127 (38)[b]	23 (25)[a]	<0·0001
Vaccinated[§,‡‡]	2 (<1)*	0	0	1 (<1)	1 (<1)	NS
High risk[§,¶]	207 (24)	24 (13)[a]	48 (21)[a,b]	91 (27)[b]	42 (45)[c]	<0·0001
Case status[§]	119 (14)	25 (13)	37 (16)	39 (12)	17 (18)	NS
Serious outcome[§,††]	6 (5)	1 (4)	2 (5)	1 (3)	2 (12)	NS
Days illness onset to swab[§]	3·2 ± 2·0	3·2 ± 2·2	3·1 ± 2·2	3·3 ± 2·0	3·1 ± 1·6	NS

Across rows, comparisons significant at the 0·05 level are indicated by different letters; overall *P*-value for model is shown in last column.

*P < 0·05, versus other 2 study periods.

[†]Total number of all subjects and cases includes individuals with BMI < 18·5: 3 in 2007–2008; 6 in 2008–2009; 5 during 2009 pandemic (data not shown).

[‡]Mean ± standard deviation.

[§]n (%).

[¶]Defined by ≥2 clinic visits during prior calendar year with ICD-9 CM diagnostic code for an underlying chronic disease conferring elevated risk of influenza complications.[19]

[††]Diagnosis of X-ray confirmed pneumonia or hospitalization in a 30-day period following study enrollment; % represents % of cases.

[‡‡]Vaccine was not available in the community until late in the enrollment period during the pandemic study period.

by season. Across all study periods combined, cases were slightly younger than control subjects; a lower percentage of cases (versus controls) were vaccinated or had a high-risk medical condition.

In adjusted logistic regression models (Table 3), obesity did not predict influenza in any of the study periods, or when all years were combined (0·95: 0·75, 1·20 and 1·10: 0·80, 1·52, for obese and extremely obese groups, respectively). Results were similar regardless of whether BMI was examined as a continuous or categorical variable. In the secondary analysis among cases only, there also was no association between obesity and serious outcome: Adjusted odds ratios for serious outcome were 0·63: 0·23, 1·73 (2007–2008); 0·28: 0·47, 1·66 (2008–2009); and 1·06: 0·98, 1·15 (2009 pan-

demic). In 2007–2008 only, women and people with high-risk medical conditions were less likely to test positive for influenza (0·69: 0·52, 0·91 and 0·58: 0·41, 0·83, respectively); in 2007–2008 and 2008–2009, unvaccinated individuals were more likely to be diagnosed as influenza cases (1·56: 1·16, 2·10 and 1·95: 1·27, 2·99, respectively) (data not shown).

Discussion

Previous studies have described an association between obesity and respiratory illness in humans, but these have been conducted either in hospitalized patients [15] or in children,[28] or have used non-influenza outcome measures such as community-acquired pneumonia.[29] Our study

Table 2. Subject characteristics by case/control status

	Influenza cases	Test-negative controls	*P*-value
2007–2008	*n* = 454	*n* = 447	
Age, years[*]	44 ± 16	48 ± 18	0·001
Body mass index (BMI), wt/ht²[*]	31 ± 7	31 ± 7	NS
Male[†]	190 (42)	150 (34)	0·01
High-risk condition[†]	79 (17)	137 (31)	<0·0001
Vaccinated[†]	149 (33)	218 (49)	<0·0001
2008–2009	*n* = 132	*n* = 738	
Age, years[*]	41 ± 12	45 ± 17	0·01
BMI, wt/ht²[*]	30 ± 7	31 ± 8	NS
Male[†]	41 (31)	240 (33)	NS
High-risk condition[†]	20 (15)	181 (25)	0·02
Vaccinated[†]	42 (32)	368 (50)	0·0002
2009pH1N1	*n* = 119	*n* = 732	
Age, years[*]	41 ± 14	46 ± 16	0·003
BMI, wt/ht²[*]	31 ± 8	31 ± 7	NS
Male[†]	37 (31)	247 (34)	NS
High-risk condition[†]	27 (23)	180 (25)	NS
Vaccinated[†]	0	2 (<1)	NS
All years	*n* = 705	*n* = 1917	
Age, years[*]	43 ± 15	46 ± 17	<0·0001
BMI, wt/ht²[*]	31 ± 7	31 ± 8	NS
Male[†]	268 (38)	637 (33)	0·02
High-risk condition[†]	126 (18)	498 (26)	<0·0001
Vaccinated[†]	248 (35)	920 (48)	<0·0001

[*]Mean ± SD.
[†]*n* (%).
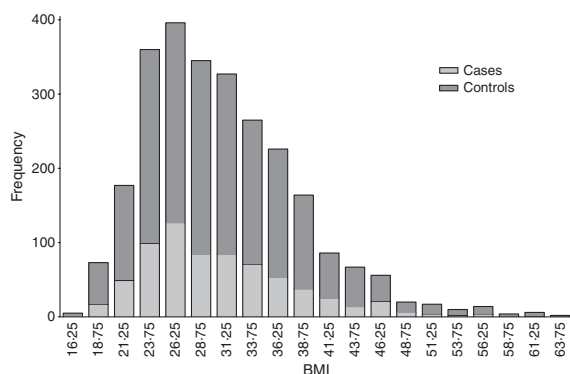
Figure 1. Body mass index (BMI) distribution by case–control status. Mean BMI of cases was 30·58 ± 7·31 kg/m² and of controls was 30·93 ± 7·55 kg/m².

demonstrates for the first time that among community-dwelling adults seeking outpatient medical care for an acute respiratory illness, obesity is not a risk factor for laboratory-confirmed influenza.

We compared data from three study periods, including the 2009 pandemic and two seasonal influenza epidemics (2007–2008, when A/H3N2 was the primary circulating virus, and 2008–2009, when A/H1N1 and influenza B both circulated). While there were minor differences between study periods in subject characteristics, there were no differences in BMI; the lack of association between obesity and influenza held true across all three study periods, for both seasonal and pandemic influenza viruses. Notably, illness rates varied substantially between seasons, with the proportion of people with laboratory-confirmed influenza more than three times higher in 2007–2008 (versus 2008–2009 and 2009 pandemic seasons).

The relationship between obesity and complications from influenza infection has received a great deal of attention because extreme obesity was observed to be present in 90% of patients hospitalized in the intensive care unit early during the course of the 2009 pandemic.[13] Obesity was later identified as an independent risk factor for death because of A(H1N1)pdm09.[15] The percentage of subjects with extreme obesity in our study ranged from 9·4% in 2007–2008 to 11% during the pandemic period; among cases only, the prevalence was 10–11% during the two seasonal influenza periods (2007–2008 and 2008–2009), and only slightly higher, 14%, during the pandemic. These proportions are

Table 3. Crude and Adjusted odds ratio (OR) and 95% confidence intervals (95% CI) for influenza case status*

	Outcome variable: influenza case							
	All years		2007–2008		2008–2009		2009 pandemic	
	Crude OR	Adjusted OR	Crude OR	Adjusted OR	Crude OR	Adjusted OR	Crude OR	Adjusted OR
Body mass index (BMI) Category								
<18·5	0·61 (0·17, 2·18)	0·69 (0·19, 2·48)	0·66 (0·11, 4·03)	0·75 (0·12, 4·69)	—	—	1·65 (0·18, 15·37)	2·04 (0·21, 19·64)
18·5–24·9 (Reference)	1·00	1·00	1·00	1·00	1·00	1·00	1·00	1·00
25–29·9	1·06 (0·83, 1·34)	1·07 (0·84, 1·37)	1·00 (0·69, 1·44)	1·03 (0·71, 1·51)	0·98 (0·60, 1·61)	1·02 (0·62, 1·70)	1·25 (0·72, 2·17)	1·40 (0·80, 2·45)
30–39·9	0·90 (0·71, 1·13)	0·95 (0·75, 1·20)	0·97 (0·69, 1·38)	1·04 (0·72, 1·49)	0·71 (0·43, 1·16)	0·77 (0·47, 1·28)	0·88 (0·51, 1·50)	1·02 (0·59, 1·78)
40+	1·00 (0·73, 1·37)	1·10 (0·80, 1·52)	1·12 (0·72, 1·99)	1·29 (0·77, 2·18)	0·73 (0·37, 1·42)	0·76 (0·38, 1·50)	1·50 (0·76, 2·94)	1·53 (0·76, 3·08)

*Adjusted for gender, influenza vaccination status, age, and the presence of any high-risk medical condition.
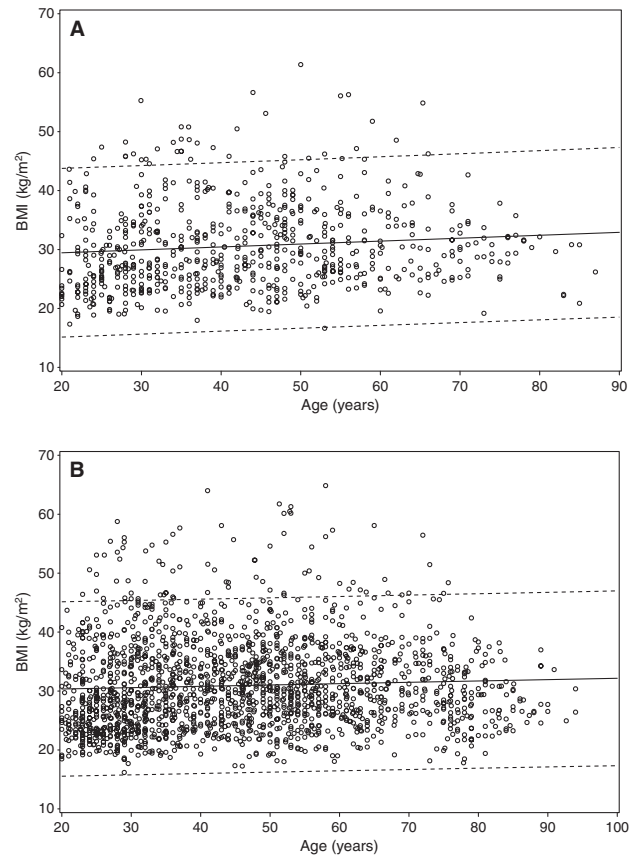

Figure 2. (a, b) Association between Body mass index (BMI) and age by case–control status. (a) cases, $r = 0.10$, $P = 0.007$ and (b) controls $r = 0.05$, $P = 0.02$.

lower than that observed by Louie et al.[15] among people hospitalized with A(H1N1)pdm09, where 19% of subjects had extreme obesity, but this discrepancy might be expected because of the different study populations.

Prior to the 2009 pandemic, obesity had not been recognized as a risk factor for severe seasonal influenza in humans. Louie et al.[15] suggest that an association may have been obscured either by underreporting of obesity, obesity-related comorbidities, or by the disproportionate number of frail elderly individuals who have the highest rates of death from influenza. Others have suggested that previously identified risk factors for seasonal influenza are the same as risk factors for severe pandemic illness and that the independent role of obesity needs further study as it was not associated with A(H1N1)pdm09 influenza-associated hospitalization.[30] We suggest that the risk factors for severe complications of influenza-associated illnesses may be fundamentally different from those for less severe, non-hospitalized influenza. Although we assessed illness severity using influenza-related pneumonia or hospital admission in the 30 days following symptom onset, we observed very

few serious outcomes in our population; thus, our ability to detect the differences by weight status was limited. Our finding of few serious events is similar to those from a recent human study reporting that the 2009 influenza pandemic was relatively mild among healthy adults, most likely because of pre-existing immunity from prior seasonal A/H1N1 infections.[31] Other recent animal work has also suggested that while obesity may be a risk factor for severe A(H1N1)pdm09 infection, whether or not it is also a risk factor for other less severe or seasonal influenza viruses remains unknown.[32]

Our study has a number of strengths, including prospective enrollment of subjects from a defined population seeking medical care, use of rRT-PCR for influenza diagnosis, and availability of detailed data from the electronic medical record. We adjusted for vaccination status, for example, because in our population, consistent with vaccine coverage rates in the United States as a whole, coverage varied by age group; coverage also varied by case status. This study also has several limitations. We did not attempt to explore mechanisms for the association between obesity and laboratory-confirmed influenza. Obese individuals are likely to differ in terms of factors that influence the risk of influenza infection, including diet, physical activity, metabolism, and genetics; these should be considered in future studies. It is not known whether obesity is a risk factor for other specific non-influenza respiratory viral infections, for which we did not test. If obesity is associated with medically attended respiratory illness in general, but not specifically with influenza, that could produce a null finding because the controls should represent the background risk of exposure (in this case, obesity) in the population. If control subjects with non-influenza respiratory illness were more obese than the general population, it could bias the association between influenza and obesity toward the null (odds ratio for influenza case status would be closer to 1·00). We were not able to retrospectively identify pregnancy in the electronic medical record; some women of childbearing age could be incorrectly classified as overweight or obese when they are pregnant. This should result in non-differential misclassification, however, because cases and controls are equally as likely to become pregnant. The relationship between obesity and influenza case status could also vary by viral subtype. We enrolled few individuals with BMI ≥ 40, limiting our ability to detect differences in outcomes among the extremely obese. Lastly, the use of BMI as a measure of obesity does not provide compartment-specific information on fat mass versus lean body mass, so it is possible for different individuals with the same BMI to have different body composition. The effect of increased adipose tissue mass *per se*, on risk of influenza, cannot be determined from our results, although BMI and fat mass are highly correlated ($r = 0.94$).[33]

In summary, we did not find an association between obesity and medically attended, laboratory-confirmed influenza in our population of adults seeking care for acute respiratory illness over three influenza seasons that included both seasonal and pandemic virus circulation. In a secondary analysis, we also did not find an association between obesity and serious influenza-related outcomes (defined by pneumonia or hospitalization) among cases during this same time period. These findings are in contrast to the association between obesity and serious illness that has previously been described for pandemic illness and emphasize the potential differences in risk based on patient population, setting, and outcome measure studied. Confirmation of our findings in a larger patient population is needed to further explore public health implications for influenza prevention and treatment of individuals with obesity.

Acknowledgements

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