MAJOR ARTICLE

Statin Treatment and Mortality: Propensity Score-Matched Analyses of 2007–2008 and 2009–2010 Laboratory-Confirmed Influenza Hospitalizations

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Background. Annual influenza epidemics are responsible for substantial morbidity and mortality. The use of immunomodulatory agents such as statins to target host inflammatory responses in influenza virus infection has been suggested as an adjunct treatment, especially during pandemics, when antiviral quantities are limited or vaccine production can be delayed.

Methods. We used population-based, influenza hospitalization surveillance data, propensity score-matched analysis, and Cox regression to determine whether there was an association between mortality (within 30 days of a positive influenza test) and statin treatment among hospitalized cohorts from 2 influenza seasons (October 1, 2007 to April 30, 2008 and September 1, 2009 to April 31, 2010).

Results. Hazard ratios for death within the 30-day follow-up period were 0.41 (95% confidence interval [CI], .25–.68) for a matched sample from the 2007–2008 season and 0.77 (95% CI, .43–1.36) for a matched sample from the 2009 pandemic.

Conclusions. The analysis suggests a protective effect against death from influenza among patients hospitalized in 2007–2008 but not during the pandemic. Sensitivity analysis indicates the findings for 2007–2008 may be influenced by unmeasured confounders. This analysis does not support using statins as an adjunct treatment for preventing death among persons hospitalized for influenza.

Keywords. immunomodulatory agents; influenza; influenza mortality; pandemic; pandemic H1N1; statins.

Influenza epidemics are responsible for substantial annual morbidity and mortality in the United States. Annual mean hospitalizations have been estimated at 128 719 (range, 88 431–208 324) between 2005 and 2011 [1] and 226 054 (range, 54 523–430 960) between 1979 and 2001 [2]. Deaths have been estimated to range between 3349 (1986–1987) and 48 614 (2003–2004) annually [3]. Influenza-associated mortality in pandemic years can be higher still and typically shifts toward younger age groups [4]. This result was especially evident during the 2009 pandemic because cross-protective immunity to the pandemic strain was present among older adults [5]. During the recent 2009 influenza pandemic, 87% of the deaths occurred in persons <65 years of age, with children and young adults and middle-aged adults having rates of hospitalization and death 4 to 7 times and 8 to 12 times greater, respectively, than estimates from the years 1976–2001 [6].

The best available strategy to prevent and control influenza is through influenza vaccination. In the United

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States, all persons ≥6 months of age are recommended to receive influenza vaccine annually. However, influenza vaccine effectiveness can vary from season to season, depending on the match between the vaccine influenza strains and the circulating strains and host factors. In addition, during influenza pandemics, the development and deployment of an influenza vaccine may be delayed. Influenza antiviral therapy for persons with severe influenza illness or who are at risk for complications is an important adjunct intervention to the influenza vaccination program, reducing morbidity and mortality during seasonal or pandemic influenza [7–12]. Nonetheless, there is always the possibility of widespread circulation of an influenza virus strain resistant to available antiviral agents, and, in a pandemic situation, the risk of antiviral shortages is ever present. The use of immune-modulating drugs, particularly statins, has been postulated as an additional tool for the treatment and prophylaxis of influenza, especially in countries where influenza vaccine and antiviral agents are not readily available [13, 14].

Statins have wide-ranging down-regulatory effects on inflammatory and immune mechanisms [15–17], and there is some evidence that statin treatment may beneficially alter the clinical course of some infectious diseases [18–21]. To date, no randomized clinical trials have been conducted to address whether statins could reduce complications of influenza, although some observational studies have suggested protective effects [22–25]. A study by Vandermeer et al [23], using data from a population-based influenza surveillance system, found a protective effect of statin use on mortality among patients hospitalized with laboratory-confirmed influenza during the 2007–2008 influenza season. Nonetheless, due to the observational nature of the study, biases could potentially explain this association, even after controlling for confounders.

We sought to repeat the 2007–2008 influenza season analysis of Vandermeer et al [23] and to analyze the 2009 influenza A (H1N1) pandemic data from the same surveillance platform to study the possible association between influenza-associated mortality and statin treatment. In this analysis, we take into account potential treatment indication biases through the use of propensity score-matched analysis.

METHODS

Study Setting and Population

This study was conducted with data from the Centers for Disease Control and Prevention's (CDC) Emerging Infections Program (EIP) influenza hospitalization surveillance. The EIP influenza hospitalization surveillance system collects data on persons hospitalized with laboratory-confirmed influenza from October 1 through April 30 of the following year, because influenza typically circulates in the fall to spring months in the northern hemisphere. The exception to this was the 2009 influenza pandemic, in which hospitalization data were collected from September 1, 2009 through April 30, 2010. The EIP network comprises selected counties in 10 US states (California, Colorado, Connecticut, Georgia, Maryland, Minnesota, New Mexico, New York, Oregon, and Tennessee) and includes a catchment area of approximately 23 million people.

Cases were identified through active surveillance from reports from hospitals and review of infection control logs or hospital laboratory lists. Ascertainment of cases was based on laboratory testing ordered by attending healthcare providers for clinical purposes. Cases included patients (1) ≥18 years of age, (2) residing within the EIP catchment area, (3) admitted to a catchment area hospital, and (4) admitted within 14 days of a positive influenza test either by viral culture, real-time reverse transcription polymerase chain reaction, immunofluorescence antibody staining (indirect or direct), rapid influenza diagnostic test, or any test of unknown type recorded in the medical chart. Patients possibly infected with influenza virus during hospitalization (positive influenza test >3 days after admission) were excluded as case subjects.

Data Collection

Demographic, epidemiologic, and clinical information were collected from chart reviews. Influenza vaccination status was determined from the medical chart, primary care provider, or via phone interview (of patient or proxy). Patients were considered vaccinated for influenza if a vaccine had been administered >2 weeks before hospitalization, regardless of whether the patient had seasonal vaccine, H1N1 monovalent vaccine (for the 2009 pandemic), both seasonal and monovalent vaccine, or unknown vaccine type. If antivirals were administered at any point during the course of illness, a patient was considered treated. Age was categorized into 5 groups (18–34, 35–44, 45–54, 55–64, and ≥65 years). Race and ethnicity were determined by chart review or by self-report during patient interviews for vaccination status information. Race was categorized into 3 groups (White, Black, and other), and ethnicity was categorized as Hispanic or non-Hispanic. Race and ethnicity were analyzed separately. Underlying health conditions of interest included asthma, chronic cardiovascular disease (excluding hypertension), chronic metabolic disease, renal disease, chronic lung disease, immunosuppressive disorders (including cancer diagnosis in the 12 months before hospital admission), seizure disorders, history of lymphoma or leukemia, blood disorders, neuromuscular disorders, obesity, and cognitive dysfunction. We combined all underlying chronic disease variables other than cardiovascular disease, chronic metabolic disease, chronic lung disease, renal disease, and asthma into a variable for "other chronic diseases." Height and weight were collected during the 2009 pandemic but not during the 2007–2008 influenza season. Height and weight were used to determine body mass index (BMI), which was used to categorize patients as underweight (BMI <18.5), normal weight (BMI 18.5–24.9), overweight

(BMI 25.0–29.9), obese (BMI 30.0–39.9), or morbidly obese (BMI ≥40).

The exposure of interest was statin treatment, either before or during hospitalization, which was determined from hospital records. Data on statin dose or frequency of administration were not collected. Death within 30 days of a positive influenza test was the outcome of interest. Mortality after hospital discharge was determined by linkage of hospitalization data with the Social Security Death Index (SSDI) by state. Linkage was done using Registry Plus™ Link Plus (version 2.0), a probabilistic record linkage program. Mortality during hospitalization was determined through chart review and data linkage with SSDI data.

This study was submitted for review and approved by the institutional review boards serving the CDC and participating states.

Analysis

Propensity scores were used to predict the probability of treatment with statins. The use of propensity scores in observational studies facilitates similar distributions of baseline characteristics between treated and untreated groups, reducing potential treatment selection bias [26]. Logistic regression models were iteratively assessed to determine the balance of covariate proportions between statin treatment groups in the subsequent matched samples. The best and final model was the one that balanced covariates between treatment groups, as determined by standardized differences <0.10. The final logistic regression model for the 2007–2008 matched sample included age, sex, race, ethnicity, cardiovascular disease, chronic metabolic disease, chronic lung disease, renal disease, asthma, and vaccination status as covariates. The final logistic regression model for the 2009–2010 matched sample included age; sex; race; cardiovascular disease; chronic metabolic disease; chronic lung disease; renal disease; weight category; long-term care residence; vaccination status; and interaction terms for age and race, age and sex, and age and cardiovascular disease. After calculation of propensity scores, a greedy matching algorithm was used to identify 1 untreated patient for each treated patient in the respective matched samples [27].

The χ^2 test was used to assess differences in characteristics between the statin treatment groups in the unmatched cohort. Categorical variables were transformed to indicator variables to facilitate assessment of balance of covariates between statin treatment groups after matching. Standardized differences [26] were used to evaluate measured baseline covariate distributions between statin treatment groups in the matched cohorts. McNemar's test for matched pairs was used to assess the difference in proportion of deaths between treated and untreated groups. We used Cox proportional hazards models with robust standard errors, stratified on matched pairs, to determine the effect of statin treatment on mortality within 30 days of a positive influenza test. We used the method described by Rosenbaum [28] for survival outcomes for determining the sensitivity of point estimates to hidden bias. We conducted statistical analysis using SAS software (version 9.3; SAS Institute, Cary, NC), and OpenEpi (version 2.3.1) was used for post hoc sample size calculation [29].

RESULTS

Baseline Characteristics Before Matching

Table 1 shows demographic and clinical characteristics of treatment groups before matching, for both the 2007–2008 influenza season (statin treatment group N = 1013, nontreatment group N = 2030) and the 2009 pandemic (statin treatment group N = 980, nontreatment group N = 3458) cohorts. In the 2007–2008 cohort, the statin treatment group was older, with a greater proportion of males, a greater proportion of whites, and a higher prevalence of chronic medical conditions (with the exception of asthma and "other chronic diseases") compared with the nontreatment group.

In the 2009 pandemic cohort, the statin treatment group compared with the nontreatment group was older, with a greater proportion of males and whites. The statin treatment group had a higher prevalence of cardiovascular disease, chronic metabolic disease, chronic lung disease, and renal disease, but not of other chronic conditions. The statin treatment group also had a greater proportion of persons considered obese and morbidly obese.

Influenza vaccination was more prevalent among those in the statin treatment group, for both cohorts. There was no significant difference between the proportion of those treated with antivirals for either cohort.

Baseline Characteristics After Matching

After matching on propensity score (Table 2), both the 2007–2008 and 2009 pandemic matched samples were balanced on treatment groups. For all covariates, the standardized differences after matching were <0.10 for both cohorts.

Mortality Outcomes, Point Estimates

There were 670 pairs in the 2007–2008 sample. For 21 pairs, the treated case subject died within 30 days, but the untreated case subject did not. There were 51 pairs in which the untreated case subject died within 30 days but the treated subject did not. For 1 pair, both the treated and untreated case subjects died, and for 597 pairs, neither case subject died. The results of McNemar's test indicate that the 30-day mortality rates between the treated (3.28%) and untreated (7.76%) groups were significantly different ($P < .001$).

There were 439 pairs in the 2009–2010 cohort sample. For 17 pairs, the treated case subject died within 30 days but the untreated case subject did not. There were 23 pairs in which the untreated case subject died within 30 days but the treated subject did not. For 4 pairs, both the treated and untreated case subjects died, and for 395 pairs, neither case subject died. The results of McNemar's test indicate that the 30-day mortality

Table 1. Characteristics of the 2007–2008 and 2009–2010 Hospitalized Cohorts by Statin Treatment[a]

	2007–2008 Cohort			2009–2010 Cohort		
Variables	Statin Treatment N = 1013	No Statin Treatment N = 2030	*P* Value	Statin Treatment N = 980	No Statin Treatment N = 3458	*P* Value
Age categories			<.0001			<.0001
18–34	10 (0.99)	308 (15.17)		29 (2.96)	1284 (37.13)	
35–44	27 (2.67)	200 (9.85)		79 (8.06)	595 (17.21)	
45–54	76 (7.50)	296 (14.58)		258 (26.33)	783 (22.64)	
55–64	149 (14.71)	245 (12.07)		297 (30.31)	452 (13.07)	
≥65	751 (74.14)	981 (48.33)		317 (32.35)	344 (9.95)	
Sex			<.0001			.04
Female	514 (50.79)	1189 (58.57)		542 (55.31)	2039 (58.96)	
Male	498 (49.21)	841 (41.43)		438 (44.69)	1419 (41.04)	
Race			<.0001			.0008
White	706 (69.69)	1240 (61.08)		564 (57.55)	1770 (51.19)	
Black	133 (13.13)	404 (19.90)		186 (18.98)	813 (23.51)	
Other	37 (3.65)	67 (3.30)		60 (6.12)	165 (3.12)	
Hispanic	45 (4.44)	130 (6.40)	.13	103 (10.51)	548 (15.85)	.001
Admitted from LTCF	118 (11.64)	283 (13.94)	.067	63 (6.46)	137 (3.97)	.001
Underlying Conditions						
Cardiovascular Disease	669 (66.04)	667 (32.86)	<.0001	457 (46.63)	432 (12.49)	<.0001
Chronic Metabolic Disease	526 (51.92)	557 (27.44)	<.0001	587 (59.89)	652 (18.85)	<.0001
Chronic Lung Disease	308 (30.40)	439 (21.63)	<.0001	285 (29.08)	514 (14.86)	<.0001
Renal Disease	231 (22.80)	250 (12.32)	<.0001	208 (21.22)	232 (6.71)	<.0001
Asthma	124 (12.24)	353 (17.39)	.0002	236 (24.08)	1067 (30.86)	<.0001
Other Chronic Conditions[b]	269 (26.55)	625 (30.79)	.016	241 (24.59)	825 (23.85)	.63
Body Mass Index						<.0001
Underweight	—	—		11 (1.47)	103 (4.16)	
Normal	—	—		137 (18.29)	690 (27.89)	
Overweight	—	—		177 (23.63)	582 (23.52)	
Obese	—	—		260 (34.71)	742 (29.99)	
Morbidly obese	—	—		164 (21.90)	357 (14.43)	
Vaccinated (Yes)	629 (62.09)	884 (43.55)	<.0001	280 (28.57)	704 (20.36)	<.0001
Antivirals (Yes)[c]	564 (55.68)	1112 (54.78)	.67	825 (84.18)	2885 (83.43)	.52

Abbreviations: LTCF, long-term care facility.

[a] Data shown as frequency and (%). Missing or unknown values not shown. Unknowns excluded from χ^2 analysis.

[b] Other chronic diseases is a combination of any underlying chronic illnesses mentioned in patient medical records other than cardiovascular disease, chronic metabolic disease, chronic lung disease, renal disease, asthma, and obesity.

[c] Any antivirals administered during the course of illness.

rates between the treated (4.78%) and untreated (6.15%) groups were not significantly different ($P = .43$).

Cox proportional hazards models with robust standard errors were fit to the matched samples, stratified on matched pairs. The sole predictor variable for the models was statin treatment. The hazard ratios for death within the 30-day follow-up period was 0.41 (95% confidence interval [CI], .25–.68; $P < .001$) for the 2007–2008 sample and 0.77 (95% CI, .43–1.36; $P = .37$) for the 2009 pandemic sample.

We tested post hoc whether logistic regression on the unmatched 2009 pandemic cohort would have resulted in a significant point estimate for an effect of statins on mortality. We used a logistic model with backward deletion (and all first-order covariates). Because statin treatment was not a covariate selected through stepwise selection, we forced statin treatment into the final model. In a final model that included age, sex, and renal disease as covariates, the adjusted odds ratio (OR) for statins was not significant (OR = 0.74; 95% CI, .52–1.07).

Sensitivity Analysis

A sensitivity parameter and corresponding bounds were calculated for the observed point estimate from the 2007–2008 matched sample. The results (gamma = 1.47; maximum *P* value = .049) indicate that the point estimate is sensitive to hidden bias.

Table 2. Standardized Differences for the Matched Samples and Unmatched Cohorts[a]

	2007–2008 Matched Sample				2009–2010 Matched Sample			
Variables	Statin Treatment N = 670	No Statin Treatment N = 670	Standardized Difference (Matched)	Standardized Difference (Unmatched)	Statin Treatment N = 439	No Statin Treatment N = 439	Standardized Difference (Matched)	Standardized Difference (Unmatched)
Age categories								
18–34	5 (0.75)	6 (0.90)	0.02	0.54	11 (2.51)	9 (2.05)	0.03	0.94
35–44	19 (2.84)	13 (1.94)	0.06	0.30	45 (10.25)	40 (9.11)	0.04	0.28
45–54	54 (8.06)	52 (7.76)	0.01	0.23	138 (31.44)	138 (31.44)	0.00	0.09
55–64	91(13.58)	95 (14.18)	0.02	0.08	123 (28.02)	129 (29.38)	0.03	0.43
≥65	501 (74.78)	504 (75.22)	0.01	0.55	122 (27.79)	123 (28.02)	0.01	0.57
Sex								
Female	350 (52.24)	379 (56.57)	—	—	245 (55.81)	252 (57.40)	—	—
Male	320 (47.76)	291 (43.43)	0.09	0.16	194 (44.19)	187 (42.60)	0.03	0.07
Race								
White	534 (79.70)	533 (79.55)	0.00	0.55	319 (72.67)	315 (71.75)	0.01	0.57
Black	107 (15.97)	108 (16.12)	0.00	0.21	96 (21.87)	101 (23.01)	0.03	0.15
Other	30 (4.48)	30 (4.48)	0.00	0.02	24 (5.47)	23 (5.24)	0.01	0.06
Hispanic	9 (1.34)	7 (1.04)	0.03	0.20	21 (4.78)	25 (5.69)	0.04	
Admitted from LTCF	92 (13.73)	104 (15.52)	0.05	0.20	27 (6.15)	32 (7.29)	0.05	0.16
Underlying conditions								
Cardiovascular Disease	422 (62.99)	433 (64.63)	0.03	0.70	173 (39.41)	163 (37.13)	0.05	0.81
Chronic Metabolic Disease	332 (49.55)	317 (47.31)	0.05	0.52	223 (50.80)	218 (49.66)	0.02	0.93
Chronic Lung Disease	209 (31.19)	208 (31.04)	0.00	0.20	134 (30.52)	140 (31.89)	0.03	0.35
Renal Disease	130 (19.40)	137 (20.45)	0.03	0.28	64 (14.58)	64 (14.58)	0.00	0.43
Asthma	76 (11.34)	68 (10.15)	0.04	0.15	120 (27.33)	113 (25.74)	0.04	0.15
Other Chronic Conditions[b]	198 (29.55)	208 (31.04)	0.03	0.09	114 (25.97)	116 (26.42)	0.01	0.02
Body Mass Index								
Underweight	—	—	—	—	6 (1.37)	4 (0.91)	0.04	0.16
Normal	—	—	—	—	88 (20.05)	89 (20.27)	0.01	0.23
Overweight	—	—	—	—	102 (23.23)	100 (22.78)	0.01	0.00
Obese	—	—	—	—	163 (37.13)	167 (38.04)	0.02	0.10
Morbidly obese	—	—	—	—	80 (18.22)	79 (18.00)	0.01	0.20
Vaccinated (Yes)	441 (65.82)	446 (66.57)	0.02	0.35	142 (32.35)	152 (34.62)	0.05	0.18
Antiviral (Yes)[c]	372 (55.52)	364 (54.33)	0.02	0.06	374 (85.19)	369 (84.05)	0.03	0.02

Abbreviations: LTCF, long-term care facility.

[a] Data shown as frequency and (%), except for standardized difference.

[b] Other chronic diseases is a combination of any underlying chronic illnesses mentioned in patient medical records other than cardiovascular disease, chronic metabolic disease, chronic lung disease, renal disease, asthma, and obesity.

[c] Any antivirals administered during the course of illness.

An unmeasured confounder that could explain a 47% difference in the odds of statin treatment between groups could explain the observed association between statin use and mortality. Sensitivity analysis for the point estimate for 2009–2010 data was not calculated due to the lack of an observed significant effect.

Post hoc Sample Size Analysis

Using the outcomes from the 2007–2008 analysis, we determined post hoc that the 2009 analysis would require at least 434 matched pairs, assuming the effect size observed for the 2007–2008 analysis would be the expected effect size observed in the 2009 sample.

DISCUSSION

In this analysis, using data from a population-based laboratory-confirmed influenza hospitalization surveillance platform, we evaluated the effects of statin use over 2 influenza seasons. We found that statins had no statistically significant effect on mortality during the 2009 pandemic season, but there was a significant statin effect on reducing mortality during the 2007–2008

influenza season. The differential impact of statin treatment on mortality between seasons could be due to differences in circulating strains, because the predominant influenza A virus subtype in 2007–2008 season was H3N2, whereas influenza A(H1N1)pdm09 virus predominated during the pandemic period. Age group-specific attack rates among different influenza subtypes can vary, and differences in immune histories by age could have an impact on the different results between the 2007–2008 season and the pandemic. Statins have been found to modulate anti-inflammatory effects [30]; whether the difference in apparent efficacy of statins between the 2 seasons could be explained by variation in age-specific immune histories or variation in the degree of cytokine dysregulation caused by the different influenza virus subtypes is an area for additional investigation. However, on further examination, the latter association was measurably sensitive to bias and therefore could reflect omissions of covariate measurement rather than an actual relationship between statin treatment and death after influenza-associated hospitalization.

Data from the 2007–2008 season was previously analyzed using a multivariable logistic regression model [23]. Results from that analysis showed that after controlling for demographic characteristics, underlying medical conditions, vaccination, and antiviral treatment, the use of statins reduced the odds of death (adjusted OR, 0.59; 95% CI, .38–.92). However, a limitation of observational studies is the lack of random treatment assignment, which can result in sizeable differences in the distribution of covariates between treatment groups. We sought to balance the covariates between the statin-treated and untreated groups by using propensity score analysis. Nonetheless, we also found a protective effect of statins on death among laboratory-confirmed influenza patients hospitalized during the 2007–2008 season. Questions persist about the efficacy of statin medications in reducing severe complications of influenza because we showed that our findings could be driven by unmeasured biases.

Four other studies that looked at statin use and influenza outcomes also found equivocal results. Two of them examined the impact of statins in reducing severe disease in adults hospitalized with laboratory-confirmed influenza during the 2009 H1N1 pandemic [22, 31]. Neither found a significant association between use of statins and severe disease (classified as either intensive care unit admission or death), although both were potentially hampered by small sample size. Two studies evaluating statin use during multiple influenza seasons in the decade before the 2009 pandemic found a protective effect on influenza mortality, although 1 of the studies found only a modest (10% reduction in deaths from pneumonia) effect [24, 25]. These latter 2 studies relied entirely on administrative claims data; patients identified with influenza were not laboratory-confirmed, raising concern for misclassification of outcome, and may have been additionally biased by misclassification of exposure, because both studies abstracted data on previous history of statin use but not actual use at the time of the influenza hospitalization.

Information about whether there is benefit to initiating statin use in patients without other indications for statins at the time of influenza diagnosis would certainly be of clinical and public health interest. In this context, randomized controlled trials (RCT) that address initiation of statin treatment in patients with influenza would offer clear advantages. Recent RCT data have been pessimistic regarding the role of statins in modulating inflammatory responses in infectious disease processes. One RCT observed no clinical effect of statins on 28-day mortality among patients with ventilator-associated pneumonia [32]; another showed that statins did not improve clinical outcomes among patients with acute respiratory disease syndrome associated with sepsis [33]. In contrast, a recent in vitro study showed that statin treatment can protect host cells against influenza-induced inflammation by reducing the production of tumor necrosis factor-α, interleukin-8, and interferon-γ, and therefore inhibit influenza A virus replication [34]. Further studies to evaluate the effect of immunomodulatory agents in reducing influenza-related complications may still be warranted, but they may be better suited for settings where these drugs are not used widely.

This study has several limitations. We could not determine whether a patient's statin treatment continued throughout the 30-day follow-up period because we only had medical data for the period of time the patient was hospitalized. The length of exposure to statins before hospitalization was not measured nor was the dose or frequency of statin use before or during hospitalization, which could have a possible effect on the outcome. In addition, identification of death after hospital discharge via data linkage between the SSDI and EIP data could result in an underdetection of deaths; the probabilistic linkage algorithm used is highly accurate, but it is not a match-merge of data by, for example, a unique identification number. However, there is no reason to expect that either mortality status would be misclassified or that deaths would be undetected as a result of treatment status or any particular covariate. Emerging Infections Program influenza surveillance sites do not collect detailed data on socioeconomic status or baseline functional status, and data on BMI were not collected during the 2007–2008 influenza season. Certainly, an unmeasured covariate such as insurance coverage could hypothetically increase the likelihood of statin treatment prehospitalization while simultaneously reducing the likelihood of death after hospitalization. Healthy user bias may certainly apply to the current study as well as most studies cited above [22–25, 35]. Patients being treated with statin medication have been found to have better access to preventive services such as screening services and vaccinations, and therefore they may be healthier at baseline than patients not taking statins [36]. Moreover, those with limited access to care would be more likely to be hospitalized later in the course of illness, and they

would have reduced opportunities to respond to medical interventions.

CONCLUSIONS

During an influenza pandemic, we may have very few tools to prevent and treat influenza virus infection and therefore reduce mortality, because vaccine development can occur very late in the course of the pandemic and antivirals may be in limited quantity and of unknown effectiveness to a novel strain. Our study results do not find a definite protective effect of statins on influenza-associated death. Promotion of the use of statins as part of public health pandemic preparedness or for an individual patient's benefit is not warranted based on current available data.

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