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MAJOR ARTICLE

Rates of Severe Influenza-Associated Outcomes Among Older Adults Living With Diabetes—Influenza Hospitalization Surveillance Network (FluSurv-NET), 2012–2017

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Background. Diabetes mellitus (DM) is common among older adults hospitalized with influenza, yet data are limited on the impact of DM on risk of severe influenza-associated outcomes.

Methods. We included adults aged ≥65 years hospitalized with influenza during 2012–2013 through 2016–2017 from the Influenza Hospitalization Surveillance Network (FluSurv-NET), a population-based surveillance system for laboratory-confirmed influenza-associated hospitalizations conducted in defined counties within 13 states. We calculated population denominators using the Centers for Medicare and Medicaid Services county-specific DM prevalence estimates and National Center for Health Statistics population data. We present pooled rates and rate ratios (RRs) of intensive care unit (ICU) admission, pneumonia diagnosis, mechanical ventilation, and in-hospital death for persons with and without DM. We estimated RRs and 95% confidence intervals (CIs) using meta-analysis with site as a random effect in order to control for site differences in the estimates.

Results. Of 31 934 hospitalized adults included in the analysis, 34% had DM. Compared to those without DM, adults with DM had higher rates of influenza-associated hospitalization (RR, 1.57 [95% CI, 1.43–1.72]), ICU admission (RR, 1.84 [95% CI, 1.67–2.04]), pneumonia (RR, 1.57 [95% CI, 1.42–1.73]), mechanical ventilation (RR, 1.95 [95% CI, 1.74–2.20]), and in-hospital death (RR, 1.48 [95% CI, 1.23–1.80]).

Conclusions. Older adults with DM have higher rates of severe influenza-associated outcomes compared to those without DM. These findings reinforce the importance of preventing influenza virus infections through annual vaccination, and early treatment of influenza illness with antivirals in older adults with DM.

Keywords. diabetes mellitus; influenza; influenza hospitalization; severe influenza outcomes.

In most years in the United States (US), millions of people are infected with influenza virus [1, 2]. While most people experience minor symptoms following influenza virus infection, some develop severe illness, leading to hospitalization, intensive care unit (ICU) admissions, mechanical ventilation, and even death [3–6]. Influenza-associated hospitalizations are more common in older adults [5, 7] and people with certain chronic medical conditions [8–10].

Data from a national cross-sectional survey showed that 23 million US adults, and about 21% of adults aged ≥65 years, live with diabetes mellitus (DM) [11]. DM is a common comorbidity among patients hospitalized with influenza [9, 12, 13]. Understanding the impact of DM on rates of severe influenza-associated outcomes is important for informing preventive strategies, including influenza vaccination and early diagnosis and treatment of influenza with approved antivirals for people with DM. However, studies investigating the relationship between DM and risk of influenza and severe outcomes have shown mixed results. While some studies reported increased risk of severe influenza-associated outcomes

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among people with DM [14–17], others did not find an association [12, 18].

Additionally, population-level estimates of rates of severe influenza-associated outcomes among people with DM are limited both in the US and globally. The aim of this analysis was to estimate rates and relative risk of influenza-associated hospitalization, pneumonia, ICU admission, mechanical ventilation, and in-hospital death among adults aged ≥65 years with and without DM in the US during the 2012–2013 through 2016–2017 influenza seasons.

METHODS

Data Sources

Influenza Hospitalization Surveillance Network.

We used data from the Centers for Disease Control and Prevention's (CDC) Influenza Hospitalization Surveillance Network (FluSurv-NET) collected during the 2012–2013 through 2016–2017 influenza seasons. Detailed descriptions of the FluSurv-NET surveillance system are published elsewhere [19, 20]. In brief, FluSurv-NET conducts population-based surveillance for laboratory-confirmed influenza-associated hospitalizations in select counties in 13 states, representing approximately 9% of the US population. The FluSurv-NET catchment population is similar to the US population in age, sex, and race/ethnicity distribution. During the 2012–2013 through 2016–2017 influenza seasons, 14 FluSurv-NET sites comprising 77 counties within California, Colorado, Connecticut, Georgia, Maryland, Michigan, Minnesota, New Mexico, New York (2 sites), Ohio, Oregon, Tennessee, and Utah participated in FluSurv-NET surveillance. For this analysis, we included patients who were aged ≥65 years at the time of the influenza-associated hospitalization.

We identified hospitalized patients with laboratory-confirmed influenza through active review of notifiable disease databases and hospital and laboratory records, including laboratory logs of diagnostic testing for influenza, patient medical records, and infection control logs. We included patients who were residents of the FluSurv-NET surveillance catchment area who were hospitalized during 1 October–30 April of each season and had a positive influenza test no more than 14 days prior to admission or during hospitalization. For this analysis, we excluded patients with possible hospital-acquired influenza, defined as a positive influenza test ≥3 days after hospital admission. Laboratory testing for influenza was performed at the discretion of healthcare providers or based on facility testing policies, and laboratory confirmation was defined by a positive influenza test result using any of the following methods: rapid antigen testing, real-time reverse transcription polymerase chain reaction, viral culture, and direct or indirect fluorescent antibody staining.

Trained surveillance staff used a standardized case report form to conduct medical chart abstractions for identified patients. DM status for each patient was obtained through review of problem lists and history and physical examination notes from hospital medical records. FluSurv-NET does not collect information on indicators of DM control such as hemoglobin A1C or medications used to treat DM; thus, these data were not available for the current analysis. Data on patient demographics, smoking status, chronic underlying medical conditions, influenza vaccination status, community-acquired pneumonia, and in-hospital outcomes (ICU admissions, mechanical ventilation, and in-hospital death) were also abstracted. Pneumonia was defined as evidence of air space opacity, consolidation, lobar infiltrate, or pleural effusion in a chest radiograph taken during the first 3 days of hospital admission, and either a documentation of pneumonia on the discharge summary or a discharge diagnosis of pneumonia based on *International Classification of Diseases, Ninth Revision, Clinical Modification* (*ICD-9-CM*) or *International Classification of Diseases, Tenth Revision, Clinical Modification* (*ICD-10-CM*) codes (481–487, 510, 513, or 997.31).

The CDC determined that this activity met the requirement for public health surveillance; therefore, CDC Institutional Review Board (IRB) approval was not required. FluSurv-NET sites obtained human subjects and ethics approvals from their respective state health departments and academic partner IRBs as needed. The requirement for informed consent was waived per 45 Code of Federal Regulation part 46.

Centers for Medicare and Medicaid Services.

We used data from the Centers for Medicare and Medicaid Services (CMS) to obtain estimates of the proportion of adults aged ≥65 years with and without DM in each FluSurv-NET county. CMS reports county-level prevalence of selected chronic conditions by age group on an annual basis. Data used for the prevalence estimates were obtained from CMS administrative enrollment and claims data from the Medicare fee-for-service program [21]. If the claims data indicated that a beneficiary was treated for a specific chronic condition, CMS considered the beneficiary to be living with that chronic condition when calculating the prevalence of the chronic condition in the population. CMS used *ICD-CM* codes recorded in the claims data to classify beneficiary conditions. For all claims for services that occurred before 1 October 2015, CMS used *ICD-9-CM* for the classification and *ICD-10-CM* was used thereafter. (See Supplementary Appendix A for specific *ICD-9-CM* and *ICD-10-CM* codes that CMS used to define DM.) County-specific prevalence of DM was obtained by dividing the total number of beneficiaries in the county with DM by the total number of beneficiaries in the fee-for-service population in the county.

Statistical Analysis

Among patients hospitalized with influenza, we calculated frequencies and percentages of demographic characteristics, underlying medical conditions, current influenza vaccination status, antiviral treatment, and in-hospital outcomes by DM status.

To estimate the rate of each influenza-associated outcome (hospitalization, ICU admission, mechanical ventilation, pneumonia, and in-hospital death) by DM status, we first calculated the respective denominator populations using prevalence data from CMS and the National Center for Health Statistics' (NCHS) vintage bridged-race postcensal population estimates for the counties included in FluSurv-NET surveillance. We multiplied the CMS-estimated proportion of adults aged ≥65 years with and without DM in each FluSurv-NET county by the NCHS-estimated population of adults aged ≥65 years residing in that county during each season to obtain the yearly number of adults aged ≥65 years with and without DM in the FluSurv-NET catchment counties.

We summed the estimated population denominators for the participating counties within each site in a given season to obtain denominators by site for each season. We calculated the rate of each influenza-associated outcome by dividing the number of hospitalized FluSurv-NET patients with each outcome by the calculated catchment population of each FluSurv-NET site in a given season to obtain site-specific rates for each season. Rates were calculated for persons with and without DM. Rate ratios (among those with DM vs without DM) were calculated for each site per season by dividing the calculated rates in those with DM by rates in those without DM for each of the 5 influenza-associated outcomes. All rates and rate ratios were unadjusted for potential confounders such as age, race/ethnicity, sex, additional comorbidities, and vaccination status because these data were not available at the population level through CMS for adults with and without DM.

To account for FluSurv-NET site differences in the aggregated data, we used random effects meta-analysis models to pool the calculated rates and rate ratios for each outcome for all seasons combined and for each season individually, controlling for FluSurv-NET sites. The random-effects models were implemented in R (version 3.6.0) using the Metafor function [22]. All other analyses were conducted using SAS version 9.4 (SAS Institute, Cary, North Carolina). We report rates and rate ratios and associated 95% confidence intervals (CIs) by season and for the 5 seasons combined.

RESULTS

A total of 31 934 adults aged ≥65 years hospitalized with laboratory-confirmed influenza during the 2012–2013 through 2016–2017 influenza seasons were included in this analysis. The median age was 80 years (interquartile range, 72–87 years), 55.4% were female, 68.7% were White, and 94.2% had 1 or more underlying conditions (Table 1). In total, 10 863 (34%) had DM. Antiviral treatment was prescribed for 88% and 87% of the patients with DM and without DM, respectively. The proportions with select underlying conditions and vaccination status among patients with and without DM (respectively) are as follows: cardiovascular disease (68.5% vs 57.6%), renal disease (35.6% vs 19.9%), obesity/extreme obesity (41.7% vs 22%), and receipt of current season influenza vaccine (58.4% vs 56.1%).

Controlling for site differences, the pooled influenza-associated hospitalization rate per 100 000 person-years from 2012–2013 through 2016–2017 was 276 (95% CI, 230–330) in those with DM and 181 (95% CI, 150–217) in those without DM (Table 2). From 2012–2013 through 2016–2017, the pooled rates per 100 000 person-years of each of the other influenza-associated outcomes among those with and without DM, respectively, were as follows: ICU admission, 42 vs 23; pneumonia, 64 vs 42; mechanical ventilation, 17 vs 9; and in-hospital death, 11 vs 7.

The pooled rate ratio of each influenza-associated outcome among people with DM vs those without DM were as follows: influenza-associated hospitalization, 1.57 (95% CI, 1.43–1.72); ICU admission, 1.84 (95% CI, 1.67–2.04); pneumonia, 1.57 (95% CI, 1.42–1.73); mechanical ventilation, 1.95 (95% CI, 1.74–2.20); and in-hospital death, 1.48 (95% CI, 1.23–1.80). In each of the 2012–2013 through 2016–2017 influenza seasons, the rates of influenza-associated hospitalization, ICU admission, pneumonia, and mechanical ventilation were significantly higher among those with DM than among those without DM (Table 3).

DISCUSSION

This analysis was conducted to estimate rates of severe influenza-associated outcomes among adults aged ≥65 years with and without DM in the US. We found that among adults aged ≥65 years hospitalized with influenza from 2012–2013 through 2016–2017 and reported to FluSurv-NET, more than one-third had DM. On average, there were 276 influenza-associated hospitalizations per 100 000 person-years in adults aged ≥65 years with DM within the FluSurv-NET catchment areas. Across all seasons, the rate of influenza-associated hospitalizations in people with DM was almost 60% greater than in those without DM. Furthermore, the rates of ICU admission, pneumonia, mechanical ventilation, and in-hospital death in those with DM were higher than the rates in those without DM. Variability in rates of severe outcomes across the 5 influenza seasons may have been due in part to differences in circulating influenza virus types and subtypes [23], severity of the influenza season [24], and vaccine effectiveness [25].

Previous studies have shown that DM may increase the risk of severe outcomes of influenza [12, 26]. One study conducted

Table 1. Demographic and Clinical Characteristics of Adults ≥65 Years of Age Hospitalized With Influenza, With and Without Diabetes Mellitus—Influenza Hospitalization Surveillance Network (FluSurv-NET), 2012–2017

Variable	Total (N = 31 934)	Adults With DM (n = 10 863)	Adults Without DM (n = 21 071)
Sex			
Male	14 253 (44.6)	5232 (48.2)	9021 (42.8)
Female	17 681 (55.4)	5631 (51.8)	12 050 (57.2)
Age, y			
Median (IQR)	80 (72–87)	78 (71–84)	81 (73–88)
65–74	10 174 (31.9)	4185 (38.5)	5989 (28.4)
75–84	11 107 (34.8)	4036 (37.2)	7071 (33.6)
≥85	10 653 (33.4)	2642 (24.3)	8011 (38)
Race/ethnicity			
Non-Hispanic White	21 939 (68.7)	6638 (61.1)	15 301 (72.6)
Non-Hispanic Black	3508 (11)	1656 (15.2)	1852 (8.8)
Non-Hispanic American Indian/Alaska Native	110 (0.3)	51 (0.5)	59 (0.3)
Non-Hispanic Asian/Pacific Islander	1719 (5.4)	746 (6.9)	973 (4.6)
Non-Hispanic multiracial	26 (0.1)	11 (0.1)	15 (0.1)
Hispanic/Latino	1634 (5.1)	803 (7.4)	831 (3.9)
Unknown	2998 (9.4)	958 (8.8)	2040 (9.7)
Smoking status			
Current smoker	3252 (10.2)	992 (9.1)	2260 (10.7)
Former smoker	12 274 (38.4)	4341 (40)	7933 (37.7)
Never smoker/unknown	16 408 (51.4)	5530 (50.9)	10 878 (51.6)
Vaccination in the current season[a]			
No	9861 (30.9)	3303 (30.4)	6558 (31.1)
Yes	18 156 (56.9)	6339 (58.4)	11 817 (56.1)
Unknown	3917 (12.3)	1221 (11.2)	2696 (12.8)
Antiviral treatment[b]			
No	3705 (11.6)	1238 (11.4)	2467 (11.7)
Yes	28 028 (87.8)	9600 (88.4)	18 428 (87.5)
Unknown	201 (0.6)	25 (0.2)	176 (0.8)
Any underlying medical condition (including DM)			
No	1641 (5.1)	…	1641 (7.8)
Yes	30 074 (94.2)	10 863 (100)	19 211 (91.2)
Unknown	219 (0.7)	…	219 (1)
Cardiovascular disease			
No	12 351 (38.7)	3424 (31.5)	8927 (42.4)
Yes	19 583 (61.3)	7439 (68.5)	12 144 (57.6)
Renal disease			
No	23 866 (74.7)	6997 (64.4)	16 869 (80.1)
Yes	8068 (25.3)	3866 (35.6)	4202 (19.9)
Chronic lung disease			
No	21 482 (67.3)	7455 (68.6)	14 027 (66.6)
Yes	10 452 (32.7)	3408 (31.4)	7044 (33.4)
Neurologic/neuromuscular disease			
No	22 195 (69.5)	7712 (71)	14 483 (68.7)
Yes	9739 (30.5)	3151 (29)	6588 (31.3)
Immunosuppression			
No	27 315 (85.5)	9382 (86.4)	17 933 (85.1)
Yes	4619 (14.5)	1481 (13.6)	3138 (14.9)
Classification of weight status			
Underweight	1420 (4.5)	230 (2.1)	1190 (5.7)
Normal/healthy	10 093 (31.6)	2327 (21.4)	7766 (36.9)
Overweight	9426 (29.5)	3223 (29.7)	6203 (29.4)
Obese	7366 (23.1)	3452 (31.8)	3914 (18.6)
Morbidly obese	1794 (5.6)	1076 (9.9)	718 (3.4)
Unknown	1835 (5.8)	555 (5.1)	1280 (6.1)
Intensive care unit admission			
No	27 250 (85.3)	9136 (84.1)	18 114 (86)

Table 1. Continued

Variable	Total (N = 31 934)	Adults With DM (n = 10 863)	Adults Without DM (n = 21 071)
Yes	4488 (14.1)	1701 (15.7)	2787 (13.2)
Unknown	196 (0.6)	26 (0.2)	170 (0.8)
Developed pneumonia			
No	24 541 (76.9)	8378 (77.1)	16 163 (76.7)
Yes	7393 (23.2)	2485 (22.9)	4908 (23.3)
Received mechanical ventilation			
No	29 999 (93.9)	10 159 (93.5)	19 840 (94.2)
Yes	1700 (5.3)	664 (6.1)	1036 (4.9)
Unknown	235 (0.7)	40 (0.4)	195 (0.9)
Outcome of hospitalization			
Died	1206 (3.8)	387 (3.6)	819 (3.9)
Discharged	30 609 (95.9)	10 472 (96.4)	20 137 (95.6)
Unknown	119 (0.4)	4 (0)	115 (0.6)
Influenza season			
2012–2013	5525 (17.3)	1828 (16.8)	3697 (17.6)
2013–2014	2771 (8.7)	1011 (9.3)	1760 (8.4)
2014–2015	10 534 (33)	3496 (32.2)	7038 (33.4)
2015–2016	2988 (9.4)	1087 (10)	1901 (9)
2016–2017	10 116 (31.7)	3441 (31.7)	6675 (31.7)
Site			
California	4192 (13.1)	1506 (13.9)	2686 (12.8)
Colorado	3009 (9.4)	851 (7.8)	2158 (10.2)
Connecticut	2611 (8.2)	811 (7.5)	1800 (8.5)
Georgia	2129 (6.7)	742 (6.8)	1387 (6.6)
Maryland	3518 (11)	1283 (11.8)	2235 (10.6)
Michigan	807 (2.5)	286 (2.6)	521 (2.5)
Minnesota	3955 (12.4)	1224 (11.3)	2731 (13)
New Mexico	952 (3)	335 (3.1)	617 (2.9)
New York	4109 (12.9)	1397 (12.9)	2712 (12.9)
Ohio	1869 (5.9)	758 (7)	1111 (5.3)
Oregon	2181 (6.8)	780 (7.2)	1401 (6.7)
Tennessee	1474 (4.6)	500 (4.6)	974 (4.6)
Utah	1128 (3.5)	390 (3.6)	738 (3.5)

Data are presented as No. (%) unless otherwise indicated. The χ^2 test *P* values comparing those with and without DM were all <.01 except for pneumonia (*P* = .40).

Abbreviations: DM, diabetes mellitus; IQR, interquartile range.

[a]Received current season influenza vaccine at least 2 weeks prior to hospitalization. Influenza Hospitalization Surveillance Network (FluSurv-NET), 2012–2013 through 2016–2017.

[b]This includes treatment with oseltamivir (Tamiflu), zanamivir (Relenza), or peramivir (Rapivab).

during the 2009 influenza A(H1N1) pandemic demonstrated that DM may double the risk of influenza-associated death and increase the odds of influenza-associated ICU admission by 4.29 times compared with those without DM [15]. From a pathophysiologic standpoint, animal models have demonstrated that glycemic variability, which is associated with markers of oxidative stress and hyperinflammation, may increase severity of influenza infection [27]. Our findings support the current evidence that DM increases the risk of severe influenza-associated outcomes in adults aged ≥65 years in the US.

The majority of people with DM have at least 1 additional chronic comorbidity [28–30]. Commonly reported comorbidities among persons with DM include hypertension, chronic kidney disease, cardiovascular disease, and obesity [28–30]. FluSurv-NET data previously demonstrated that during the 2010–2011 through 2017–2018 influenza seasons, almost 12% of adults hospitalized with influenza experienced an acute cardiovascular event, with acute heart failure and acute ischemic heart disease being the most commonly reported [31]. DM, cardiovascular diseases, chronic kidney disease, and obesity, among other factors, were shown to independently increase the risk of acute heart failure and acute ischemic heart disease [31]. In the present analysis, we were unable to determine the prevalence of comorbidities among people with and without DM residing in the FluSurv-NET catchment area (source population); however, among the hospitalized FluSurv-NET patients, we found that the prevalence of cardiovascular disease, obesity, and chronic renal disease was higher among those with DM compared with those without DM. Future studies should assess whether accompanying comorbidities further increase the risk of severe influenza-associated outcomes in people with DM.

Table 2. Rates of Hospitalization, Intensive Care Unit Admission, Pneumonia, Mechanical Ventilation, and In-Hospital Death Among Adults With and Without Diabetes Mellitus—Influenza Hospitalization Surveillance Network (FluSurv-NET) and Centers for Medicare and Medicaid Services, 2012–2017

DM Status and Influenza Season	Hospitalization Rate	ICU Admission Rate	Pneumonia Rate	Mechanical Ventilation Rate	In-Hospital Death Rate
With DM					
Influenza season					
All 5 seasons	276 (230–330)	42 (35–51)	64 (53–77)	17 (14–20)	11 (9–13)
2012–2013	223 (185–267)	38 (30–47)	51 (41–62)	16 (13–21)	8 (6–11)
2013–2014	123 (102–148)	24 (19–30)	38 (30–46)	10 (8–13)	5 (4–8)
2014–2015	395 (329–473)	58 (47–71)	87 (72–106)	24 (20–29)	15 (12–19)
2015–2016	121 (100–145)	23 (18–28)	33 (27–41)	9 (7–12)	5 (4–7)
2016–2017	366 (306–439)	56 (46–68)	87 (72–106)	21 (17–25)	15 (12–19)
Without DM					
Influenza season					
All 5 seasons	181 (150–217)	23 (19–28)	42 (34–51)	9 (8–10)	7 (6–9)
2012–2013	150 (124–181)	21 (17–25)	37 (30–45)	8 (6–9)	7 (4–9)
2013–2014	72 (59–87)	13 (10–16)	20 (16–25)	6 (5–7)	4 (3–5)
2014–2015	262 (217–316)	32 (26–39)	61 (50–74)	13 (11–16)	10 (8–13)
2015–2016	69 (57–83)	11 (9–13)	18 (15–22)	5 (4–6)	3 (2–4)
2016–2017	233 (193–281)	30 (24–36)	52 (43–64)	10 (8–12)	9 (7–12)

Data are presented as rates per 100 000 (95% confidence interval). Data source: Influenza Hospitalization Surveillance Network (FluSurv-NET), 2012–2013 through 2016–2017.

Abbreviations: DM, diabetes mellitus; ICU, intensive care unit.

The results of the present analysis have implications for influenza prevention and control strategies. As the prevalence of DM and obesity in the US continues to increase [32, 33], rates of severe influenza-associated outcomes among older adults may also increase. Persons with DM should receive annual influenza vaccination [34]; prior FluSurv-NET analyses have demonstrated that influenza vaccination can attenuate disease severity among people hospitalized with influenza [6]. Data from the National Health Interview Survey showed that influenza vaccination coverage during the 2017–2018 season was 75% and 71% among adults aged ≥65 years with and without DM, respectively [35], suggesting room for improved vaccine uptake in this population. Annual influenza vaccination should be part of the routine preventive health services offered to every adult with DM. Early antiviral treatment is also recommended for confirmed or suspected influenza among persons ≥65 years as well as persons with DM or other chronic underlying conditions, regardless of hospitalization status [34]. While we were not able to specifically assess these factors, optimizing glycemic control [36, 37] among persons with DM may help reduce the risk of severe influenza-associated outcomes.

The results of the present analysis should be interpreted with the following limitations in mind. All rates and rate ratios reported in this analysis were unadjusted, so they are subject to confounding effects of other important variables, including age, race/ethnicity, sex, chronic comorbidities, and vaccination status. The FluSurv-NET catchment area covers 9% of the US population and findings may not be nationally generalizable. Methods for defining DM varied between CMS and FluSurv-NET; while CMS used *ICD* codes from insurance claims to identify DM, FluSurv-NET obtained data on DM through medical chart abstractions. The *ICD* codes that were used by CMS to define DM included conditions that may be temporary,

Table 3. Rate Ratios of Hospitalization, Intensive Care Unit Admission, Pneumonia, Mechanical Ventilation, and In-Hospital Death Among Adults With and Without Diabetes Mellitus—Influenza Hospitalization Surveillance Network (FluSurv-NET) and Centers for Medicare and Medicaid Services, 2012–2017

Influenza Season	Hospitalization	ICU Admission	Pneumonia	Mechanical Ventilation	In-Hospital Death
All 5 seasons	1.57 (1.43–1.72)	1.84 (1.67–2.04)	1.57 (1.42–1.73)	1.95 (1.74–2.20)	1.48 (1.23–1.80)
2012–2013	1.49 (1.34–1.66)	1.78 (1.51–2.10)	1.40 (1.21–1.62)	2.13 (1.66–2.72)	1.37 (.97–1.94)
2013–2014	1.74 (1.54–1.96)	1.84 (1.51–2.23)	1.79 (1.51–2.12)	1.78 (1.34–2.37)	1.45 (.94–2.21)
2014–2015	1.51 (1.36–1.66)	1.78 (1.55–2.04)	1.44 (1.28–1.62)	1.80 (1.49–2.17)	1.44 (1.10–1.87)
2015–2016	1.75 (1.56–1.97)	2.06 (1.69–2.51)	1.80 (1.52–2.13)	2.04 (1.51–2.75)	1.68 (1.11–2.57)
2016–2017	1.56 (1.41–1.72)	1.87 (1.63–2.15)	1.63 (1.45–1.84)	2.09 (1.71–2.55)	1.54 (1.19–2.00)

Data are presented as rate ratios (95% confidence intervals), which were obtained from random-effects meta-analysis models. Data source: Influenza Hospitalization Surveillance Network (FluSurv-NET), 2012–2013 through 2016–2017.

Abbreviation: ICU, intensive care unit.

including drug-induced or chemically induced DM; thus, CMS claims data may have overestimated the true population prevalence of DM. For instance, DM prevalence among US adults aged ≥65 years in 2016 was about 21% based on data from the National Health Interview Survey [11], compared with 27% based on CMS data. Overestimation of DM prevalence in the underlying population would have led to underestimation of rates and relative risks for the selected outcomes among adults with DM in our analysis. If this overestimation were to be corrected, the rate ratios reported in our analysis would be expected to increase, further strengthening our conclusions. Because FluSurv-NET does not collect information on type 1 vs type 2 DM, diabetic treatment, or glycemic control among those with DM, we were unable to account for these factors in our analysis. Finally, providers may have been more likely to hospitalize people with DM, even with less severe influenza, than those without DM. This potential admission bias, which we were unable to account for, might have impacted rate ratios for influenza-associated hospitalizations among persons with and without DM.

This analysis, conducted over multiple seasons using a population-based and geographically diverse surveillance network, provides robust data to add to the evidence of the impact of DM on severe influenza-associated outcomes among adults aged ≥65 years in the US. The results could help guide public health and clinical practice in the care of diabetic patients including promoting annual influenza vaccination, advocating for patients to seek healthcare early, and encouraging healthcare providers to have a low threshold for early diagnosis and treatment of influenza.

Supplementary Data

Supplementary materials are available at *Open Forum Infectious Diseases* online. Consisting of data provided by the authors to benefit the reader, the posted materials are not copyedited and are the sole responsibility of the authors, so questions or comments should be addressed to the corresponding author.

Notes

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References

1. Rolfes MA, Foppa IM, Garg S, et al. Annual estimates of the burden of seasonal influenza in the United States: a tool for strengthening influenza surveillance and preparedness. Influenza Other Respir Viruses **2018**; 12:132–7.
2. Centers for Disease Control and Prevention. Burden of influenza. **2020**. https://www.cdc.gov/flu/about/burden/index.html. Accessed 17 March 2021.
3. Reed C, Chaves SS, Daily Kirley P, et al. Estimating influenza disease burden from population-based surveillance data in the United States. PLoS One **2015**; 10:e0118369.
4. Chow EJ, Rolfes MA, O'Halloran A, et al. Respiratory and nonrespiratory diagnoses associated with influenza in hospitalized adults. JAMA Netw Open **2020**; 3:e201323.
5. Czaja CA, Miller L, Alden N, et al. Age-related differences in hospitalization rates, clinical presentation, and outcomes among older adults hospitalized with influenza—U.S. Influenza Hospitalization Surveillance Network (FluSurv-NET). Open Forum Infect Dis **2019**; 6:ofz225.
6. Arriola C, Garg S, Anderson EJ, et al. Influenza vaccination modifies disease severity among community-dwelling adults hospitalized with influenza. Clin Infect Dis **2017**; 65:1289–97.
7. Chandrasekhar R, Sloan C, Mitchel E, et al. Social determinants of influenza hospitalization in the United States. Influenza Other Respi Viruses **2017**; 11:479–88.
8. Costantino C, Vitale F. Influenza vaccination in high-risk groups: a revision of existing guidelines and rationale for an evidence-based preventive strategy. J Prev Med Hyg **2016**; 57:E13–8.
9. Mertz D, Kim TH, Johnstone J, et al. Populations at risk for severe or complicated influenza illness: systematic review and meta-analysis. BMJ **2013**; 347:f5061.
10. Collins JP, Campbell AP, Openo K, et al. Outcomes of immunocompromised adults hospitalized with laboratory-confirmed influenza in the United States, 2011-2015. Clin Infect Dis **2020**; 70:2121–30.
11. Bullard KM, Cowie CC, Lessem SE, et al. Prevalence of diagnosed diabetes in adults by diabetes type—United States, 2016. MMWR Morb Mortal Wkly Rep **2018**; 67:359–61.
12. Van Kerkhove MD, Cooper MJ, Cost AA, Sanchez JL, Riley S. Risk factors for severe outcomes among members of the United States military hospitalized with pneumonia and influenza, 2000-2012. Vaccine **2015**; 33:6970–6.
13. Gilca R, De Serres G, Boulianne N, et al. Risk factors for hospitalization and severe outcomes of 2009 pandemic H1N1 influenza in Quebec, Canada. Influenza Other Respi Viruses **2011**; 5:247–55.
14. Goeijenbier M, van Sloten TT, Slobbe L, et al. Benefits of flu vaccination for persons with diabetes mellitus: a review. Vaccine **2017**; 35:5095–101.
15. Allard R, Leclerc P, Tremblay C, Tannenbaum TN. Diabetes and the severity of pandemic influenza A (H1N1) infection. Diabetes Care **2010**; 33:1491–3.

16. Walker TA, Waite B, Thompson MG, et al. Risk of severe influenza among adults with chronic medical conditions. J Infect Dis **2020**; 221:183–90.
17. Seki M, Fuke R, Oikawa N, Hariu M, Watanabe Y. Association of influenza with severe pneumonia/empyema in the community, hospital, and healthcare-associated setting. Respir Med Case Reports **2016**; 19:1–4.
18. Shah NS, Greenberg JA, McNulty MC, et al. Severe influenza in 33 US hospitals, 2013–2014: complications and risk factors for death in 507 patients. Infect Control Hosp Epidemiol **2015**; 36:1251–60.
19. Chaves SS, Lynfield R, Lindegren Lou M, Bresee J, Finelli L. The US Influenza Hospitalization Surveillance Network. Emerg Infect Dis **2015**; 21:1543–50.
20. Centers for Disease Control and Prevention. Influenza Hospitalization Surveillance Network (FluSurv-NET). **2020**. https://www.cdc.gov/flu/weekly/influenza-hospitalization-surveillance.htm. Accessed 23 April 2021.
21. Centers for Medicare and Medicaid Services. Chronic conditions. **2021**. https://www.cms.gov/Research-Statistics-Data-and-Systems/Statistics-Trends-and-Reports/Chronic-Conditions/CC_Main. Accessed 23 April 2021.
22. Wolfgang V. Conducting meta-analyses in R with the metafor package. J Stat Softw **2010**; 36:1–48.
23. Centers for Disease Control and Prevention. FLUVIEW Interactive: national, regional, and state level outpatient illness and viral surveillance. https://gis.cdc.gov/grasp/fluview/fluportaldashboard.html. Accessed 25 February 2022.
24. Biggerstaff M, Kniss K, Jernigan DB, et al. Systematic assessment of multiple routine and near real-time indicators to classify the severity of influenza seasons and pandemics in the United States, 2003-2004 through 2015-2016. Am J Epidemiol **2018**; 187:1040–50.
25. Centers for Disease Control and Prevention. CDC seasonal flu vaccine effectiveness studies. **2021**. https://www.cdc.gov/flu/vaccines-work/effectiveness-studies.htm. Accessed 25 February 2022.
26. Klekotka RB, Mizgała E, Król W. The etiology of lower respiratory tract infections in people with diabetes. Pneumonol Alergol Pol **2015**; 83:401–8.
27. Marshall RJ, Armart P, Hulme KD, et al. Glycemic variability in diabetes increases the severity of influenza. MBio **2020**; 11:1–15.
28. Al-Goblan AS, Al-Alfi MA, Khan MZ. Mechanism linking diabetes mellitus and obesity. Diabetes Metab Syndr Obes **2014**; 7:587–91.
29. Nowakowska M, Zghebi SS, Ashcroft DM, et al. The comorbidity burden of type 2 diabetes mellitus: patterns, clusters and predictions from a large English primary care cohort. BMC Med **2019**; 17:145.
30. Cornelsen L, McGowan Y, Currie-Murphy LM, Normand C. Systematic review and meta-analysis of the economic impact of smoking bans in restaurants and bars. Addiction **2014**; 109:720–7.
31. Chow EJ, Rolfes MA, O'Halloran A, et al. Acute cardiovascular events associated with influenza in hospitalized adults. Ann Intern Med **2020**; 173:605–13.
32. Hales CM, Carroll MD, Fryar CD, Ogden CL. Prevalence of obesity and severe obesity among adults: United States, 2017–2018. **2020**. www.cdc.gov/nchs/data/databriefs/db360-h.pdf. Accessed 25 August 2020.
33. Fang M. Trends in the prevalence of diabetes among U.S. adults: 1999–2016. Am J Prev Med **2018**; 55:497–505.
34. Grohskopf LA, Alyanak E, Ferdinands JM, et al. Prevention and control of seasonal influenza with vaccines: recommendations of the Advisory Committee on Immunization Practices, United States, 2021–22 influenza season. MMWR Recomm Rep **2021**; 70:1–28.
35. Hung M-C, Lu jun P, Srivastav A, Cheng YJ, Williams WW. Influenza vaccination coverage among adults with diabetes, United States, 2007–08 through 2017–18 seasons. Vaccine **2020**; 38:6545–52.
36. Marshall RJ, Armart P, Hulme KD, et al. Glycemic variability in diabetes increases the severity of influenza. MBio **2020**; 11:e02841-19.
37. Kornum JB, Thomsen RW, Riis A, Lervang HH, Schønheyder HC, Sørensen HT. Diabetes, glycemic control, and risk of hospitalization with pneumonia: a population-based case-control study. Diabetes Care **2008**; 31:1541–5.