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ORIGINAL ARTICLE

Fractures and fall injuries after hospitalization for seasonal influenza—a national retrospective cohort study

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Abstract

Summary In this retrospective cohort study of 6604 adults, 65 years or older, admitted with seasonal influenza at Swedish hospitals, and 330,200 age- and sex-matched controls from the general population admitted for other reasons, were included. Patients with influenza had increased risk of fall injuries and fractures compared to controls.

Introduction Fractures and fall injuries often lead to disability, increased morbidity, and mortality. Older adults are at higher risk of influenza-related complications such as pneumonia, cardiovascular events, and deaths, but the risk of fractures and fall injuries is unclear. The primary objective of this study was to investigate the risk of fractures and fall injuries in older patients after admission with seasonal influenza.

Methods In this retrospective cohort study of 6604 adults, 65 years or older, admitted with seasonal influenza at Swedish hospitals (from December 1, 2015, to December 31, 2017) and 330,200 age- and sex-matched controls from the general population and admitted for other reasons, the risk of fracture or fall injury was investigated.

Results The mean (SD) age of the 6604 influenza patients was 80.9 (8.1) years and 50.1% were women. During the first year after hospital discharge, there were 680 (10.3%) patients suffering from a fracture or fall injury among the patients with influenza, and 25,807 (7.8%) among the controls, corresponding to incident rates of 141 (95% CI, 131–152) and 111 (95% CI, 110–112) fractures or fall injuries per 1000 person-years respectively, translating to a significantly increased risk of fracture or fall injury in a Cox regression model (hazard ratio (HR) 1.28 (95% CI, 1.19–1.38)), a risk that was maintained after multivariable adjustment (HR 1.22 (95% CI 1.13–1.31)).

Conclusions Older adults admitted with influenza diagnosis have an increased risk of fracture or fall injury during the first year after discharge.

Keywords Fall injuries · Fracture · Seasonal influenza

Introduction

Seasonal influenza is caused by the influenza type A or B virus resulting in acute respiratory disease which occurs in yearly epidemics during the winter season. In the USA alone, seasonal influenza was responsible for 9.2 million to 35.6 million illnesses yearly and between 140,000 and 710,000 hospitalizations yearly, in addition to the estimated yearly 36,000 deaths between 2010 and 2017 [1–4]. Older adults are at higher risk of suffering from influenza-related complications such as pneumonia, cardiovascular events, and deaths [2].

The incidence of injurious falls and osteoporosis-related fractures increases with age, primarily as a result of progressing frailty, sarcopenia, and osteoporosis [5–7]. Over one-third of persons 65 years and older experience a fall

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each year [8, 9], of which approximately 20% need medical attention, a proportion rising with age [10]. Injurious falls, including fractures and head injuries, often result in considerable disability and morbidity as well as increased mortality, complications that are particularly common after hip fracture [6, 7, 11]. The lifetime risk of hip fracture at the age of 50 years is considerable and reaches 15.8% and 28.5% in women in the USA and Sweden, respectively [12]. Hospital admission for injurious falls was the most common cause of disability in persons 70 years or older, and in 2015, there was an estimated 33,000 fall-related deaths in the USA [11, 13].

The acute phase of influenza infection commonly presents with symptoms such as a high fever, myalgia, sore throat, cough, headache, and malaise. Influenza complications include dehydration, bacterial pneumonia, and exacerbation of underlying chronical diseases, such as cardiovascular disease, diabetes, chronic obstructive pulmonary disease, and asthma [3]. Older adults are particularly vulnerable and have higher risk of mortality and of developing complications and which affect quality of life and activity of daily living (ADL) over long time periods. In the USA, state-level influenza severity and city-level influenza mortality have been associated with higher rates of substantial declines in ADL in nursing home residents [14]. Many of these negative outcomes can be prevented with the widespread use of vaccination in older adults [3]. Furthermore, the use of neuraminidase inhibitor treatment early in the infection is known to reduce the likelihood of severe outcomes [15].

Commonly observed symptoms among influenza patients such as dizziness, fatigue, and unsteady gait are also known risk factors for falls in the elderly [16, 17]. However, as a result of the absence of studies with individual patient data and prospective follow-up, it is yet unknown whether or not influenza increases the risk of injurious falls and fractures in older adults. An increased risk of these potentially serious complications will have a tremendous negative impact on public health and health systems, given the enormous number of affected persons globally.

The primary objective of this study was to investigate if the risk of fracture and fall injury is increased in older patients admitted with seasonal influenza at Swedish hospitals, compared to age- and sex-matched controls admitted for other causes.

Materials and methods

Study design

This retrospective cohort study used national registers in Sweden to identify patients with a first influenza diagnosis where a seasonal virus was identified (ICD-10 J10) from a hospital admission occurring between December 1, 2015 (when influenza became an infectious disease compulsory to report in Sweden), and December 31, 2017 (Fig. 1). Influenza patients diagnosed in primary care or outpatient visits to the hospital were not included. Patients 65 years or older were studied in Sweden; this group is offered and recommended seasonal vaccination due to its vulnerability [18]. For each influenza patient, fifty population controls without an influenza diagnosis and admitted for any other reason within a year before or after its case were matched according to sex and birth year. The risk of incident fractures and fall injuries within a year from discharge was analyzed. The study was approved by the Swedish Ethical Review Authority.

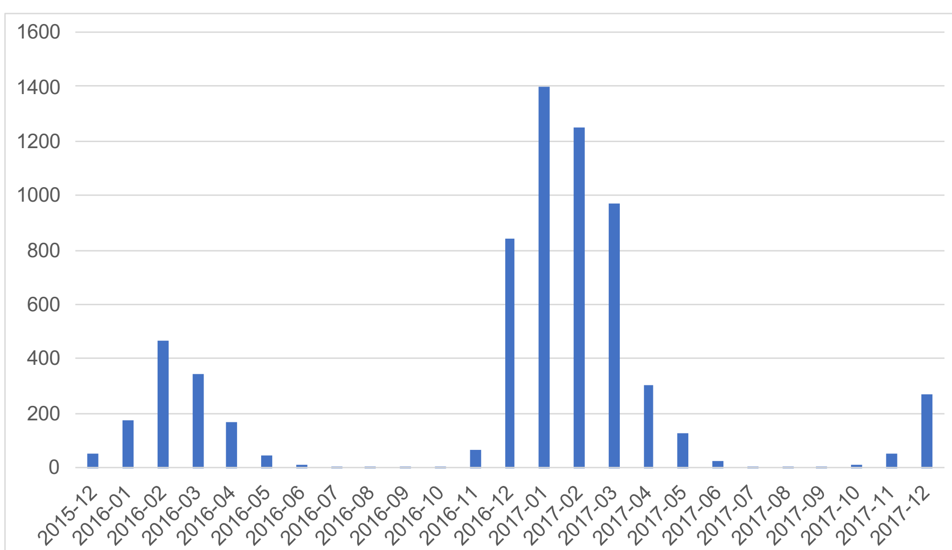


Fig. 1 Number of patients with influenza admitted per month. Distribution of baseline month for the influenza patients

Data sources

The Swedish Patient Register was used to retrieve diagnoses for influenza (inpatient visits only), comorbidities, and fractures and fall injuries (both inpatient and outpatient visits). Medication data was retrieved from the Swedish Prescribed Drug Register and data on socioeconomics and death from Statistics Sweden. All Swedes are assigned a unique personal identification at birth or at the time of immigration, enabling linkage between the different registers.

Definition of outcomes

To define incident events after discharge, register data were used. All fracture and fall injury diagnoses from hospital visits were collected (Appendix Table 1 in the Supplementary material). In order to exclude revisits, the data was refined in four steps. First, fracture diagnoses with a simultaneous code indicating a revisit (Z09, Z47, Z48) were discarded. Second, hip fracture diagnoses (S72.0–S72.2) without a simultaneous code for surgical procedure (NFB, NFC, or NFJ) were discarded. Third, a washout period of 5 months was used; i.e., if a fracture diagnosis referring to the same skeletal site was repeated within 5 months, the latter diagnosis was excluded. The washout period length has been defined using an x-ray-verified dataset in order to maximize accuracy [19]. A fall injury was defined as a fall (W00–W19) on the same date as an injury (S00-T14), and in order to avoid overlap with the fracture outcome, the fall had to occur at an occasion without a fracture diagnosis. For inpatient visits, the date of arrival to the hospital was used. Fall injury thus refers to a non-skeletal fall injury severe enough to seek hospital care.

Statistical analyses

A number of covariates representing previous illnesses and medications with presumed impact on a patient's comorbidity and risk of fracture or injurious falls were selected (Table 1). Charlson comorbidity index was calculated to summarize and quantify comorbidity [20]. The patients admitted with influenza were compared to age- and sex-matched controls admitted for other reasons. To assess differences in baseline characteristics, standardized differences were calculated. Incident rates and incident rate differences per 1000 person-years were calculated to enable comparison of periods with different lengths. Patients were followed for a year, and the follow-up time was censored for the event in question, death, emigration, or end of study (December 31, 2017). Cox regression models were used to calculate hazard ratios. In contrast to logistic regression, Cox regression uses the length of each individual's follow-up period. The Cox assumption of proportional hazards was tested using a time-dependent Cox model with a linear interaction term between time and group variable for influenza. The primary outcome was the combined outcome, during the first year after influenza diagnosis, of a first fracture or fall injury, and secondary outcomes included any fracture, hip fracture, fall injury, and death. Interaction and subgroup analyses were performed stratified by sex and age group. Specific sensitivity analyses were performed with adjustments for diabetes and chronic pulmonary diseases as well as subgroup analysis of patients without prior fall injury or fracture. Statistical analyses were performed using IBM® SPSS® software, version 26 and Stata version SE 16.0 for Mac. p values lower than 0.05 were considered significant. For interaction terms, p values lower than 0.10 were considered significant.

Analyses to address potential bias

First, the starting dates of the controls' follow-up were matched to the cases' starting date, to minimize any potential effects of temporal variations. Second, multivariable adjustment using baseline characteristics was added to the regression models comparing influenza patients with matched controls. The multivariable adjustment included known risk factors for fall injuries and fractures, as presented in Table 1, except for the 10 most common diagnoses for admission.

Role of the funding source

The funding sources did not take part in the study design; in the collection, analysis, and interpretation of data; in the writing of the report; nor in the decision to submit the paper for publication.

Results

The present study included 6604 patients 65 years or older admitted with influenza followed for 4814 person-years, and 330,200 age- and sex-matched controls admitted for other reasons and followed for 232,433 person-years. The mean (SD) age of the influenza patients was 80.9 (8.1) years, 50.1% were women, and the mean (SD) Charlson comorbidity index was 2.5 (2.3). All the controls were exactly matched according to age and sex, and the mean difference between the discharge date (baseline) of the influenza patients and the controls was 1.3 days. There were 522 (7.9%) influenza patients with prescribed neuraminidase inhibitors collected from the pharmacy 2 weeks prior to or after baseline compared to 700 (0.2%) among the controls. While the mean Charlson comorbidity index was similar in the groups, it was less common among the influenza patients to be admitted for fracture or fall injury than among the controls and more common in those to be admitted with pneumonia, type 2 diabetes, or chronic obstructive pulmonary disease. The

Table 1 Baseline characteristics

Variable		Controls $N=330{,}200$	Influenza $N=6604$	St. Diff
Age	Mean (SD)	80.7 (8.0)	80.9 (8.1)	1.7
Female sex	*n* (%)	165,350 (50.1%)	3307 (50.1%)	0
Charlson comorbidity index	Mean (SD)	2.4 (2.4)	2.5 (2.3)	7.1
= 0	*n* (%)	74,338 (22.5%)	1106 (16.7%)	−14.6
= 1 or 2	*n* (%)	135,577 (41.1%)	2808 (42.5%)	3.0
≥ 3	*n* (%)	120,285 (36.4%)	2690 (40.7%)	8.9
Length of admission, days	Mean (SD)	7.1 (14.1)	8.3 (8.3)	10.3
Admitted with pneumonia	*n* (%)	21,926 (6.6%)	1058 (16.0%)	29.9
Admitted with fracture	*n* (%)	21,506 (6.5%)	100 (1.5%)	−25.7
Admitted with fall injury	*n* (%)	12,962 (3.9%)	168 (2.5%)	−7.8
Number of admissions last 5 years	Mean (SD)	4.1 (4.2)	5.2 (5.9)	21.3
Rural residency, ≥ 200 per km^2	*n* (%)	84,748 (25.7%)	2095 (31.7%)	13.4
Non-Nordic citizenship at birth	*n* (%)	19,627 (5.9%)	554 (8.4%)	9.5
Osteoporosis (M80-M81)	*n* (%)	21,055 (6.4%)	452 (6.8%)	1.9
Secondary osteoporosis	*n* (%)	19,148 (5.8%)	525 (7.9%)	8.5
Osteoporosis medication last year	*n* (%)	13,558 (4.1%)	309 (4.7%)	2.8
Calcium or vitamin D last year	*n* (%)	33,821 (10.2%)	779 (11.8%)	5.0
Prednisolone use	*n* (%)	59,465 (18.0%)	1643 (24.9%)	16.8
Previous alcohol-related disease, 5 years	*n* (%)	8910 (2.7%)	189 (2.9%)	1.0
Previous rheumatoid arthritis, 5 years	*n* (%)	9141 (2.8%)	276 (4.2%)	7.7
Previous fracture	*n* (%)	123,086 (37.3%)	2411 (36.5%)	−1.6
Multiple (≥ 2 occasions last 5 years)	*n* (%)	22,921 (6.9%)	410 (6.2%)	−3.0
Recent (last year)	*n* (%)	46,757 (14.2%)	598 (9.1%)	−16.0
Previous fall injury	*n* (%)	85,155 (25.8%)	1915 (29.0%)	7.2
Multiple (≥ 2 occasions last 5 years)	*n* (%)	17,928 (5.4%)	413 (6.3%)	3.5
Multiple (≥ 4 occasions last 5 years)	*n* (%)	2971 (0.9%)	75 (1.1%)	2.4
Recent (last year)	*n* (%)	26,235 (7.9%)	520 (7.9%)	−0.3
Parkinson's disease (G20)	*n* (%)	6090 (1.8%)	160 (2.4%)	4.0
Knee replacement	*n* (%)	13,656 (4.1%)	119 (1.8%)	−13.8
Hip replacement	*n* (%)	12,366 (3.7%)	124 (1.9%)	−11.3
Fall-related medications last year				
Opioids (N02A)	*n* (%)	65,182 (19.7%)	990 (15.0%)	−12.6
Antiepileptics (N03A)	*n* (%)	17,416 (5.3%)	487 (7.4%)	8.6
Anti-Parkinson drugs (N04)	*n* (%)	9738 (2.9%)	263 (4.0%)	5.7
Antipsychotics (N05A)	*n* (%)	10,156 (3.1%)	245 (3.7%)	3.5
Anxiolytics (N05B)	*n* (%)	32,083 (9.7%)	747 (11.3%)	5.2
Hypnotics and sedatives (N05C)	*n* (%)	66,893 (20.3%)	1443 (21.9%)	3.9
Antidepressants (N06A)	*n* (%)	55,209 (16.7%)	1302 (19.7%)	7.8
Anti-dementia drugs (N06D)	*n* (%)	11,441 (3.5%)	314 (4.8%)	6.5
The 10 most common diagnoses while admitted				
Essential (primary) hypertension (I10)	*n* (%)	120,103 (36.4%)	2225 (33.7%)	−5.6
Atrial fibrillation or flutter (I48)	*n* (%)	68,098 (20.6%)	1619 (24.5%)	9.3
Type 2 diabetes mellitus (E11)	*n* (%)	44,040 (13.3%)	1122 (17.0%)	10.2
Chronic obstructive pulmonary disease (J44)	*n* (%)	21,612 (6.5%)	862 (13.1%)	22.0
Heart failure (I50)	*n* (%)	37,240 (11.3%)	925 (14.0%)	8.2
Chronic ischemic heart disease (I25)	*n* (%)	34,931 (10.6%)	686 (10.4%)	−0.6
Presence of cardiac/vascular implants/grafts (Z95)	*n* (%)	23,906 (7.2%)	421 (6.4%)	−3.4
Asthma (J45)	*n* (%)	7125 (2.2%)	294 (4.5%)	12.9
Chronic kidney disease (N18)	*n* (%)	12,698 (3.8%)	316 (4.8%)	4.6
Disorders of urinary system (N39)	*n* (%)	16,825 (5.1%)	282 (4.3%)	−3.9

Detailed definitions of variables are presented in Supplementary Table 1. Standardized differences (St. Diff.) were calculated as $(\text{mean}_{\text{influenza}} - \text{mean}_{\text{controls}})/n\ ((\text{SD}^2_{\text{influenza}} + \text{SD}^2_{\text{controls}})/2)$

influenza patients were admitted for longer durations and had more admissions during the last 5 years. Differences at baseline between the cases and controls are presented in Table 1.

During the first year after discharge, 356 influenza patients suffered from fractures of which a majority were severe, affecting the hip, spine, proximal humerus, pelvis, or skull (A in Table 2). There were also 379 influenza patients suffering from incident fall injuries, of which 43% affected the head (B in Table 2). Combined, 680 patients with influenza (10.3%) suffered from a fracture or fall injury (only first instance counted) and 25,807 (7.8%) among the controls, corresponding to incident rates of 141 (95% CI, 131–152) and 111 (95% CI, 110–112) fractures or fall injuries per 1000 person-years, respectively. Patients admitted with influenza had a significantly higher risk of fracture or fall injury (hazard ratio (HR) 1.28 (95% CI, 1.19–1.38)) than the controls, also after multivariable adjustments (Table 3, Fig. 2). In a sensitivity analysis adjusted for age, sex, chronic pulmonary diseases, and diabetes, the increased risk of fracture or fall injury was maintained (HR 1.24 (95% CI 1.15–1.34)). When excluding patients with a fracture or fall injury during the year prior to baseline, there still was an increased risk of fracture or fall injury (HR 1.34; 95% CI 1.22–1.47 adjusted for age and sex). The risk of any fracture, hip fracture, and fall injury analyzed separately was significantly and consistently higher among influenza patients than controls, though the risk of hip fracture was not significantly maintained upon multivariable adjustments (Table 3).

Table 2 Type of incident fracture and fall injury, first year among influenza patients

A. Type of fracture	***n* (%)**
Hip	89 (25%)
Vertebral	40 (11%)
Pelvic	32 (9%)
Proximal humerus	28 (8%)
Forearm	33 (9%)
Rib	42 (12%)
Other	32 (9%)
Lower leg	26 (7%)
Hand or foot	20 (6%)
Head	14 (4%)
Total	**356 (100%)**
B. Type of fall injury	***n* (%)**
Head injuries	
Subdural, subarachnoidal, or intracranial bleeding	26 (7%)
Concussion	18 (5%)
Lacerations	58 (15%)
Other unspecified or superficial injuries	60 (16%)
	162 (43%)
Other locations	
Lacerations	26 (7%)
Distorsions and luxations	24 (6%)
Contusions	132 (35%)
Hip	56 (15%)
Lower back and pelvic	25 (7%)
Thorax	20 (5%)
Shoulder	19 (5%)
Knee	12 (3%)
Other unspecified or superficial injuries	35 (9%)
	217 (57%)
Total	**379 (100%)**

In a multivariable Cox model analyzing the risk of fracture or fall injury, there was no significant interaction between sex and the influenza group variable ($p=0.84$), and the incidences and hazard ratios were similar for both men and women (Appendix Table 2 in the Supplementary material).

However, there was a significant interaction between the age and the influenza group variable ($p=0.08$). Subgroup analyses revealed a higher risk in influenza patients than in controls of both fracture and fall injury among patients 80 years old or older (Fig. 3, Appendix Table 3 in the Supplementary material). During the first year after discharge, 3743 influenza patients 80 years or older suffered from 456 (12.4%) fractures or fall injuries and their controls from 17 068 (9.1%), corresponding to incident rates of 181 (95% CI, 165–198) and 139 (95% CI, 137–141) fractures per 1000 person-years, respectively. Patients 80 years or older admitted with influenza had a significantly higher risk of fracture or fall injury (hazard ratio (HR) 1.31 (95% CI, 1.19–1.43)) than the controls, also after multivariable adjustments (Fig. 3, Appendix Table 3 in the Supplementary material). The risk of any fracture, hip fracture, and fall injury analyzed separately was significantly and consistently higher among influenza patients than controls (Fig. 3, Appendix Table 3 in the Supplementary material).

The 1-year mortality did not differ significantly between patients admitted for influenza compared to patients admitted for other causes, 1064 (16.1%) vs. 53 764 (16.3%), $p=0.72$, respectively, translating to a hazard ratio of 0.96 (95% CI 0.90–1.02), $p=0.15$, in an unadjusted Cox model.

Discussion

To our knowledge, this is the first study with individual patient data, demonstrating that patients 65 years or older admitted with seasonal influenza have a substantially increased risk of injurious falls and fractures during the first year after discharge than age- and sex-matched controls admitted for other reasons. A highly similar risk increase among influenza patients was observed for fall injury, any fracture, and hip fracture. Sensitivity analyses revealed

Table. 3 First-year incidence of fractures and fall injuries

	Controls	Influenza	*p* value
	330 200	6604	
Fracture or fall injury			
Patients, *n* (%)	25,807 (7.8%)	680 (10.3%)	< 0.001
Per 1000 person-years (95% CI)	111 (110–112)	141 (131–152)	< 0.001
Unadjusted Cox model, HR (95% CI)	Ref	1.28 (1.19–1.38)	< 0.001
Adjusted for age, sex, and Charlson comorbidity index, HR (95% CI)	Ref	1.25 (1.16–1.35)	< 0.001
Multivariable adjustment, HR (95% CI)	Ref	1.22 (1.13–1.31)	< 0.001
Any fracture			
Patients, *n* (%)	13,186 (4.0%)	356 (5.4%)	< 0.001
Per 1000 person-years (95% CI)	55.4 (54.4–56.3)	71.8 (64.7–79.6)	< 0.001
Unadjusted Cox model, HR (95% CI)	Ref	1.30 (1.17–1.44)	< 0.001
Adjusted for age, sex, and Charlson comorbidity index, HR (95% CI)	Ref	1.27 (1.14–1.41)	< 0.001
Multivariable adjustment, HR (95% CI)	Ref	1.24 (1.12–1.38)	< 0.001
Hip fracture			
Patients, *n* (%)	3368 (1.0%)	95 (1.4%)	0.001
Per 1000 person-years (95% CI)	13.9 (13.4–14.4)	18.7 (15.3–22.9)	0.006
Unadjusted Cox model, HR (95% CI)	Ref	1.35 (1.10–1.65)	0.004
Adjusted for age, sex, and Charlson comorbidity index, HR (95% CI)	Ref	1.29 (1.05–1.58)	0.02
Multivariable adjustment, HR (95% CI)	Ref	1.21 (0.99–1.48)	0.07
Fall injury			
Patients, *n* (%)	14,404 (4.4%)	379 (5.7%)	< 0.001
Per 1000 person-years (95% CI)	60.8 (59.8–61.8)	76.6 (69.2–84.7)	< 0.001
Unadjusted Cox model, HR (95% CI)	Ref	1.27 (1.15–1.41)	< 0.001
Adjusted for age, sex, and Charlson comorbidity index, HR (95% CI)	Ref	1.24 (1.12–1.37)	< 0.001
Multivariable adjustment, HR (95% CI)	Ref	1.20 (1.08–1.33)	0.001

HR hazard ratio. Multivariable adjustment included all covariates presented in Table 1, except from the 10 most common diagnoses for admission

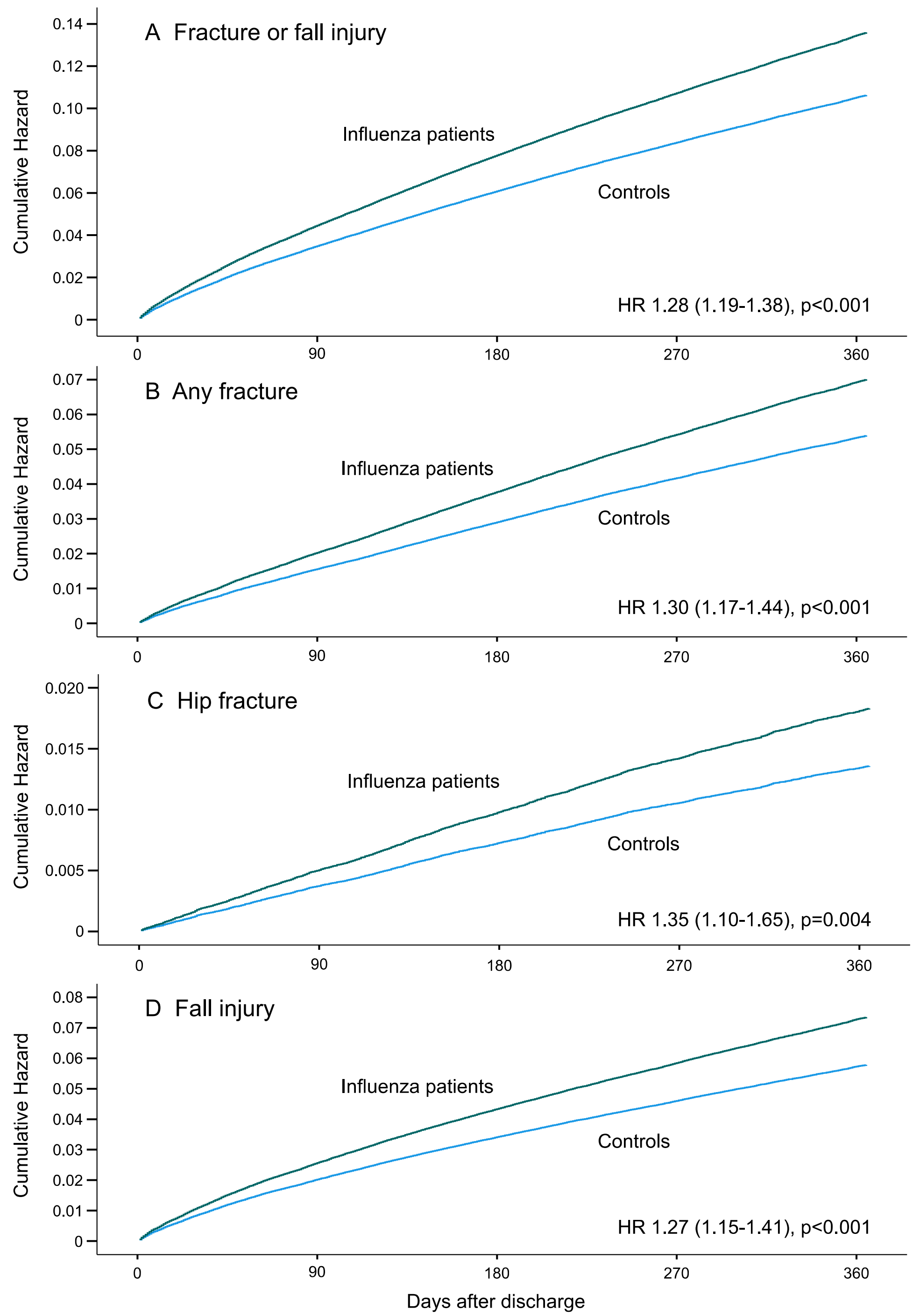
that there were no significant differences between men and women, but the risk of injurious falls and fractures was especially pronounced in the elderly, 80 years or older.

It has previously been reported that influenza also increases the risk of non-respiratory complications such as cardiovascular events, including myocardial infarction and stroke, as well as the risk of death [2]. In contrast, the knowledge regarding musculoskeletal complications of seasonal influenza is very limited. Symptoms commonly observed in influenza patients including dizziness, fatigue, and unsteady gait are also known risk factors for falls in the elderly [16, 17]. A recently published insurance database study found a weak association between influenza-like illness and risk of hip fracture in nursing home residents in the USA, but the analyses was limited to nursing home rates of these conditions, without individual knowledge regarding comorbidities and other relevant factors that could affect the risk of fractures or fall injuries [21]. A recent study from Israel found that hip fracture rates were associated with low temperatures and were higher in the 2-week-period following a period of high weekly rate of influenza, but individual data on influenza patients was not available [22]. Thus, available evidence suggests an increased risk of hip fractures in influenza patients but the lack of necessary data, on individual patient level, taking comorbidity and influenza diagnosis into account, prevented conclusive analyses. In contrast, the present analysis, relying on individual patient data, demonstrates that the risk of fracture and fall injury is elevated after hospital discharge.

It has previously been reported that among the 1.64 million older adults in the USA, over 70% treated in emergency departments for fall injuries were women [23]. We analyzed whether or not women would be at particularly high risk to sustain fractures or injurious falls after influenza. However, we found no interaction between sex and risk of these outcomes. Men and women had a highly similarly increased risk of fractures and injurious falls.

Influenza affects the respiratory system, commonly presents with fever, cough, myalgia, and fatigue, and can induce acute respiratory distress syndrome (ARDS), which has a high mortality rate [24]. In this study, we could not detect an increased mortality in influenza patients, but this finding

Fig. 2 Cumulative hazard of fracture or fall injury in unadjusted Cox models for patients 65 years old or older, first year after being admitted with influenza compared to controls admitted for other reasons



was most likely affected by the control group, consisting of age- and sex-matched patients admitted for other diagnoses, having considerably more comorbidity than the general population.

Prevention of influenza in older adults using high-dose influenza vaccine is effective [25], and could be used in this population in order to prevent influenza-related complications, and as indicated by the findings in this study, including also fall injuries and fractures in older adults. Among seniors in Sweden, 65 years or older, the vaccination rate for seasonal influenza is around 49% [26], providing opportunity for improvement. The results from the present study indicate that vaccination may also be effective in reducing the number of fractures and other injurious falls in this patient group.

The present study has limitations. First, the observational design prevents assessment of causality. Second, the fracture definitions were based on register data, without guarantees that all fractures were x-ray verified. Third, we did

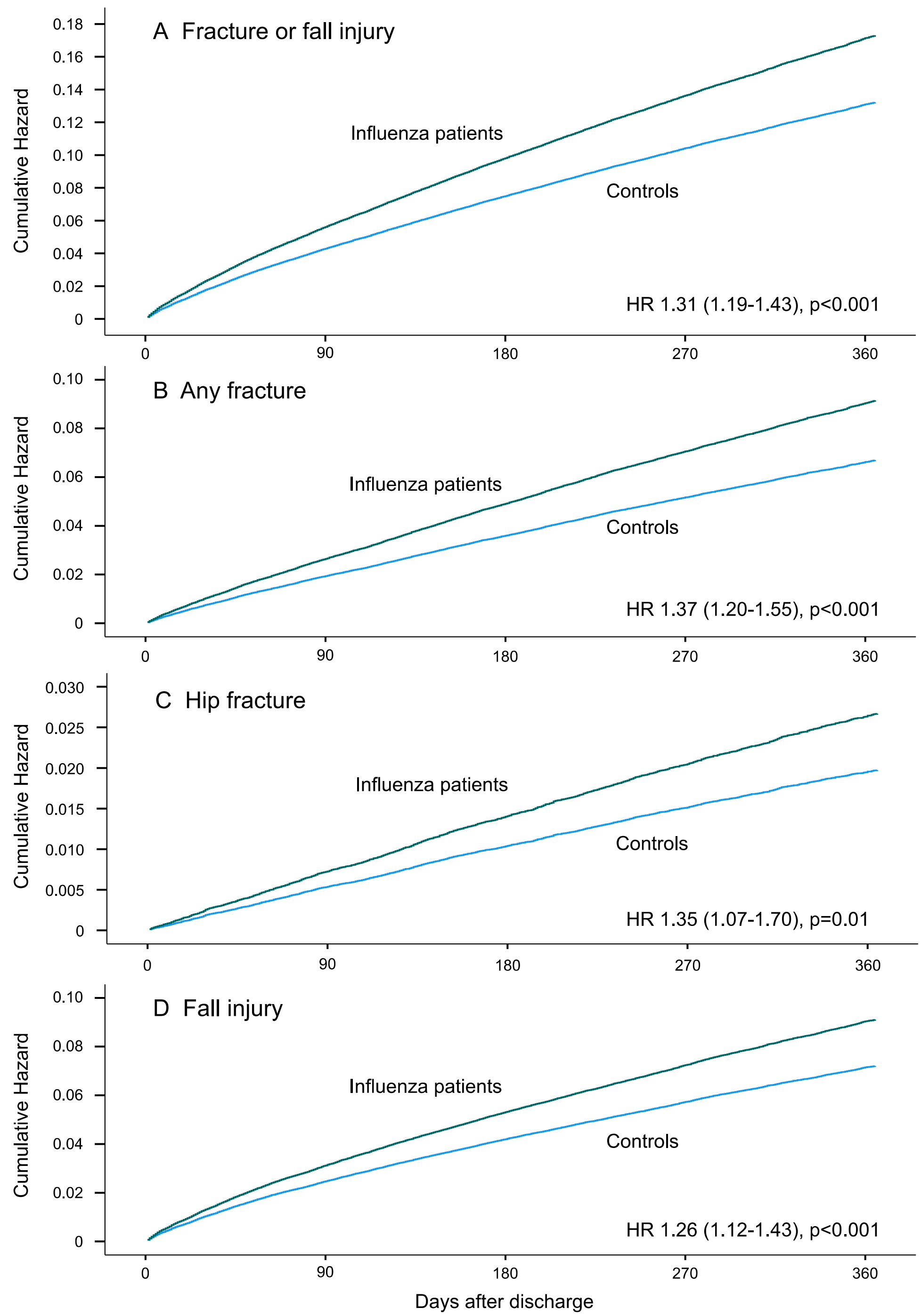


Fig. 3 Cumulative hazard of fracture or fall injury in unadjusted Cox models for patients 80 years old or older, first year after being admitted with influenza compared to controls admitted for other reasons

not have access to reliable information on trauma type; however, evidence shows that trauma type does not discriminate osteoporotic from non-osteoporotic fractures [27]. Fourth, since we did not control for influenza diagnoses in primary care, some control patients might have had influenza, which would only further underestimate the associations. Fifth, the study included only patients admitted with influenza and surviving to be discharged. Thus, by limiting the study to survivors, it is likely that the result is an underestimation of the increase in fracture and fall injury risk in influenza patients. Sixth, since only patients admitted to hospital for influenza were studied, the results may not be generalizable to all influenza patients, nor other age groups or populations with different ethnic proportions. Seventh, we were not able to study the risk of fracture or fall injury in the acute phase of influenza disease when patients most commonly present with the most severe symptoms, i.e., during the time when patients were still admitted to hospital, which most likely has resulted in an underestimation of the increased risk induced by influenza. Eighth, even though we chose to start the study after reporting of influenza cases became mandatory, it is possible that the lower prevalence in 2015–2016 is due to delayed compliance in reporting.

Strengths of this study include the large sample size, well-matched controls on both age and sex, and inclusion time, as well as the comprehensive information on risk factors for fracture and fall injuries. To our knowledge, this is the first study using individual patient data, investigating the risk of fractures and fall injury in patients admitted with influenza. In order to avoid a possible bias induced by patients contracting influenza while treated for their fracture or fall injury, we only counted these incidences after hospital discharge. This is supported by a recent investigation of in-ward transmission of influenza at a large, acute-care hospital, which found that 26% of influenza transmission was nosocomial [28]. While falling ill with influenza certainly may be a proxy for general frailty and the association is attenuated with gradual adjustment, the association remains significant even after extensive adjustment. This indicates that influenza may be an independent risk factor.

In conclusion, an increased risk of fractures and fall injuries was observed in influenza patients after discharge from hospital, in comparison to age- and sex-matched controls admitted for other reasons.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s00198-021-06068-1.

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Declarations

Conflicts of interest Dr. Axelsson has received lecture fees from Lilly, Meda/Mylan, and Amgen. Prof. Lorentzon has received lecture fees from Astellas, Amgen, Lilly, UCB Pharma, Radius Health, Meda/Mylan, GE-Lunar, and Santax Medico/Hologic. Mr Litsne has no conflict of interest.

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