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ORIGINAL RESEARCH

Seasonality of Influenza-Like-Illness and Acute Cardiovascular Events Are Related Regardless of Vaccine Effectiveness

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BACKGROUND: Influenza has been identified as a trigger for stroke and myocardial infarction (MI) with prior studies demonstrating that influenza vaccination may decrease risk of stroke and MI.

METHODS AND RESULTS: We used data from the New York Department of Health Statewide Planning and Research Cooperative System to evaluate whether annual variability in influenza vaccination effectiveness (VE) would be associated with cardiovascular events. Daily and monthly counts of outpatient and inpatient visits for influenza-like illness (ILI), stroke, and MI were identified using *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes; VE data for each year are publicly available. We identified pertinent lags between ILI, stroke, and MI using prewhitening cross-correlation functions and applied them to autoregressive integrated moving average time series regression models. Time series forecasting systems assessed correlations among ILI, stroke, and MI, and the effect of VE on these relationships. Cross-correlation functions indicated stroke events increased 1 month after increases in ILI rates; MIs increased immediately. Accounting for seasonality and lag, peaks in ILI rates were significantly related to peaks in stroke (*P*=0.04) and MI (*P*=0.01). Time forecasting analyses indicated no relationship between VE and cardiovascular events.

CONCLUSIONS: We identified that seasonality of cardiovascular events may be associated with seasonality in ILI, though VE did not modify this relationship.

Key Words: cardiovascular disease ■ heart attack ■ influenza ■ stroke ■ vaccine effectiveness

The morbidity and mortality associated with acute cardiovascular disease are high; heart disease is the leading cause of death in the United States and stroke is the leading cause of long-term adult disability.[1–4] Incident myocardial infarction (MI) and stroke are highly prevalent, with ≈735 000 MI and 795 000 stroke events each year in the United States.[1–4] Although the mortality associated with stroke and MI has decreased, the morbidity associated with these diseases remains high, with a huge cost burden of ≈$17.5 billion per year for direct stroke costs and $11.3 billion for direct MI costs.[3,4] Identifying modifiable risk factors and demonstrating the reduction of stroke and MI risk through

risk reduction efforts is therefore a high priority.[5] One such modifiable risk factor, influenza-like illness (ILI), accounts for the majority of respiratory tract infections, the most common cause of infection in adults, and has been associated with short-term stroke and MI risk in several studies.[6–15]

A seasonal pattern of higher occurrence during winter months is shared by influenza, stroke,[16–18] and MI,[19–22] suggesting a potential interrelationship between these health outcomes. Influenza vaccination reduces the incidence, morbidity, and mortality associated with ILI.[23–26] In addition to reducing the risk of influenza, the influenza vaccine has been identified as a potential

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CLINICAL PERSPECTIVE

What Is New?

- Rates of acute cardiovascular events in New York State increase during times of high influenza rates.
- Specifically, we found that the timing of the stroke events after influenza related illness differs with an increased risk window of 30 days, whereas the risk of myocardial infarction is close in time to the influenza-related illness event.
- Annual influenza vaccine effectiveness rates did not modify this association.

What Are the Clinical Implications?

- Importance of vaccine for protection against both influenza and cardiovascular events should be further examined, particularly among individuals over the age of 65, whom we identified as a high-risk group for influenza-related events.

Nonstandard Abbreviations and Acronyms

ARIMA	autoregressive integrated moving average
ILI	influenza-like illness
MI	myocardial infarction
SPARCS	New York Department of Health Statewide Planning and Research Cooperative System
VE	vaccine effectiveness

protective factor for acute cardiovascular events, with several previous studies suggesting a reduction in risk of stroke and MI as a result of vaccination.[27,28] Recent reports indicate that incidence of stroke and MI is significantly reduced in the first 59 days following influenza vaccination, particularly among the elderly.[27,28]

The influenza vaccine is not similarly protective every year. Since the 2004 to 2005 influenza season, the Centers for Disease Control and Prevention has provided estimates of the effectiveness of the influenza vaccination. Vaccine effectiveness (VE) is an estimate of the reduction in risk of disease among vaccinated people attributed to vaccination in real-world conditions.[29]

We examined the distribution of ILI, stroke, and MI during 10 consecutive influenza seasons of fluctuating VE using data from all New York state hospitalizations and an ecological time series regression modeling approach. We hypothesized seasonal influenza rates would be positively associated with seasonal stroke and MI rates, and these relationships would be influenced by the year-to-year variability in influenza VE.

METHODS

Study Population and Design

We analyzed data from the New York Department of Health Statewide Planning and Research Cooperative System (SPARCS) for years 2004 to 2015. SPARCS, established in 1979, collects information on ≈98% of all hospitalizations in nonfederal acute care facilities regardless of insurance status. SPARCS contains patient-level detail on demographic characteristics, diagnoses, and treatments for each hospital inpatient stay and outpatient (ambulatory surgery, emergency department, and outpatient services) visit. A time-trend ecological study design to assess the trends in ILI, stroke, and MI hospitalizations over a 10-year period was conducted. Time-trend ecologic studies assess variations in aggregate exposures and outcomes over time within the same population. Patients aged ≥18 years who were hospitalized for either a stroke, MI, or ILI were included in this study. For the purpose of analysis, events were aggregated into daily counts based on admission date in order to develop raw time series for all stroke, ischemic stroke only, hemorrhagic stroke only, MI, and ILI. The Columbia University Irving Medical Center Institutional Review Board approved this study. The requirement for consent was waived due to the public and deidentified nature of the data.

Event Ascertainment

Stroke was defined using *International Classification of Diseases, Ninth Revision* (*ICD-9*) codes 433.x1 ("x," the fourth digit, can vary to specify a specific arterial distribution), 434 (excluding 434.x0), 436, or 431 present at any diagnostic position. Ischemic stroke was defined using *ICD-9* codes 433.x1 ("x," the fourth digit, can vary to specify a specific arterial distribution), 434 (excluding 434.x0), or 436 present at any diagnostic position. Hemorrhagic stroke was defined with *ICD-9* codes 430-431 present at any diagnostic position.[30] Cases were excluded if any "traumatic brain injury" (*ICD-9-CM* code 800–804, 850–854) or "rehabilitation care" (*ICD-9-CM* code V57) was present as the primary diagnosis.[8] We further excluded patients with subarachnoid or subdural hemorrhages. Primary analyses used the definition for all-cause stroke (ischemic and hemorrhagic), and secondary analyses looked at stroke type. MI was defined as *ICD-9* code 410 present at any diagnostic position. Because the specific serological diagnosis of influenza itself is not validated in SPARCS, we used influenza-like illness (ILI) as a surrogate and

defined using *ICD-9* codes previously validated for influenza surveillance.[31] A full list of *ICD-9* codes are included in Tables S1 and S2. The corresponding *ICD-10* codes were used where appropriate. ILI, stroke, and MI cases were extracted from SPARCS inpatient and emergency department data.

Vaccine Effectiveness

Influenza VE data for each year are available publicly from the Centers for Disease Control and Prevention and methods have been previously described.[32] Briefly, the Centers for Disease Control and Prevention obtains data from outpatient and inpatient cases of laboratory-confirmed influenza and compares the strains included in the vaccine to the strains currently circulating in the population.

Statistical Analysis

Prewhitening Cross-Correlation Function

Identifying lags, a period of time between the exposure of interest (ILI) and the outcome (stroke or MI), and eliminating common time trends shared by the variables are initial steps to ensure associations are not due to common temporal patterns. We applied a prewhitening filter with cross-correlation functions to assess potential correlations between rates of ILI and cardiovascular disease as a strategy to eliminate temporal patterns.[33] Once the lags of rates of cardiovascular disease after ILI were estimated using the cross-correlation functions function, we applied these lagged values to a series of time series regression models.

Time Series Forecasting

Time series regression models (autoregressive integrated moving average: ARIMA) and time series forecasting systems were used to assess the interrelationship of ILI, stroke, MI, and VE. Because of previous studies showing different lag between ILI and stroke and ILI and MI, we did not model a combined cardiovascular outcome.[34]

ARIMA models were established for all stroke and MI incidence, and we ascertained the best fit models through the autocorrelation function. Using this best fit ARIMA model, the lag of the independent variable was added as a dynamic regressor in the time series forecasting system. By examining the residuals of the forecasting model, we assessed the relationship between VE and event rates. In years with a higher VE, the forecasted stroke rate would be expected to be greater than the actual number of stroke cases for that season. Similarly, in seasons in which the VE is lower, the forecasted stroke rate would be expected to be less than the actual data. Likewise, examining the residuals of

the best fit ARIMA model for MI rate for each influenza season and comparing the vaccine effectiveness to the sine of the residuals allows us to examine the relationship between the influenza vaccine effectiveness and the rate of MI.

Subgroup Analyses

We performed analyses stratified by age (18–64, and ≥65 years) to further examine the effect of age on the association among ILI, VE, and event rates. We then repeated the analyses stratified by race (Black and not Black).

Time series ARIMA models were fit for each age group and each racial group.

All analyses were performed using R Version 3.4.1 and packages (stats, forecast, tseries, ggplot2).

RESULTS

The total number of ILI, stroke, and MI cases from January 2004 through September 2015 are reported in Figure 1. Admissions for ILI ranged from 5639 in 2004 to 57 993 in 2009 with a steady increase in emergency department admissions from 2009 to 2014. The dramatic increase in ILI cases in 2009 was in large part due to the 2009 H1N1 influenza pandemic.[35] Admissions for stroke ranged from 40 844 in 2004 to 44 691 in 2014 with a fairly consistent admissions rate. Admissions for MI ranged from 65 270 in 2004 to 53 079 in 2014 with a steady decrease in the number of admissions each year. VE from the 2004 to 2005 through the 2014 to 2015 influenza seasons varied from 10% to 60%, with an average effectiveness of 40%.[36–41]

Cross-Correlation Function

In crude analyses, stroke hospitalizations appeared to increase soon after increases in ILI, whereas spikes of MI hospitalizations occurred rapidly, often within 7 days of ILI events (Figure 2). The cross-correlation function for all stroke yielded a lag, or time delay, of 1 month, suggesting that the risk of stroke is highest 30 days after an ILI event. The cross-correlation function for MI yielded a significant lag of zero, suggesting that there is no time delay between an ILI event and an MI event.

Stroke Hospitalization After ILI

When first testing influenza in the ARIMA model for all stroke, with no time delay (lag of zero), ILI was not a predictor of stroke. Accounting for seasonality and a 1-month lag as indicated in cross-correlation functions models, peaks in ILI rates were significantly associated with peaks in stroke hospitalizations (P=0.04;
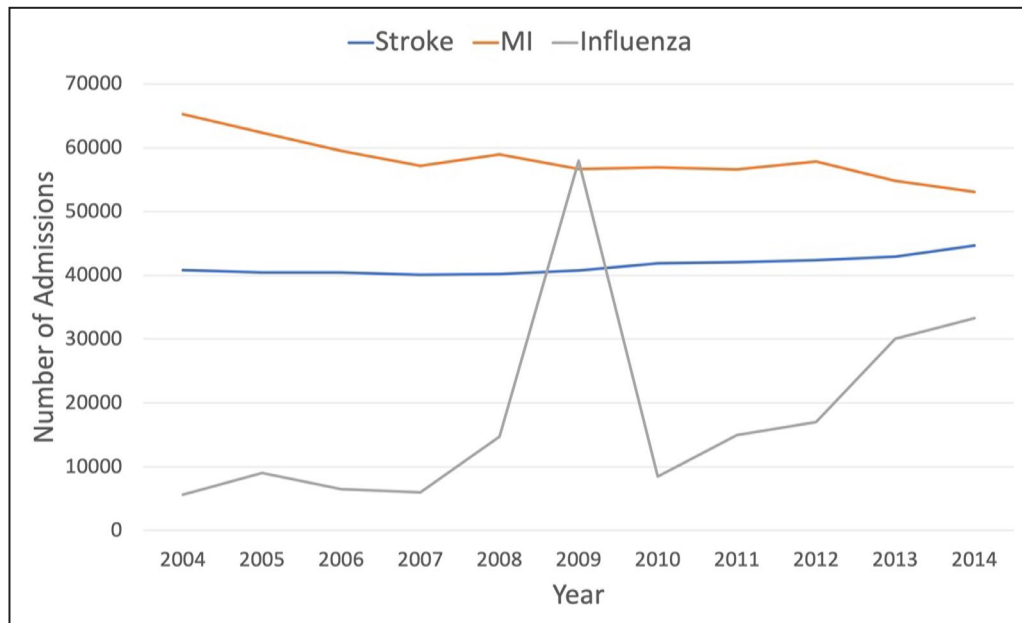
Figure 1. **Number of admissions per year for influenza-like illness, stroke, and myocardial infarction.**
MI indicates myocardial infarction.

Table 1). We tested various ARIMA models for fit and found that the best fit ARIMA model included 2 autoregressive coefficients, 1 moving average coefficient, and 1 seasonal moving average coefficient (ARIMA (2,1,1)(0,1,1)12), indicating that seasonality and a 1-month lag were important components in the time series modeling of influenza as a predictor of all stroke. This indicates that ILI is associated with stroke, regardless of the seasonality of both events, but that the risk period for stroke after ILI is within 30 days of the ILI event. The rate of stroke is increasing up to 30 days after the ILI event, with the peak at 30 days and a subsequent decline after 30 days. When investigating ischemic and hemorrhagic stroke separately, there appeared to be a similar relationship with a 1-month lag of both stroke subtype peaks after ILI peaks ($P=0.12$ and $P=0.19$, respectively), though these results were not statistically significant.

Time forecasting analysis did not support a relationship between VE and stroke hospitalization rates, as variation in vaccine effectiveness did not correspond to forecasted predictions of stroke rates. As shown in Figure 3, the residual forecast shows the residual error, or the difference between what is expected and what was predicted for stroke cases based on seasonal VE rates. The figure illustrates that the variation of the residuals stays much the same across all years of data, indicating that that after accounting for influenza VE and seasonality, there are no statistical differences in the observed versus expected stroke cases. Therefore, our models indicated no statistically significant association between annual VE rates, ILI, and stroke. Furthermore,

the ILI cases remained significantly associated with stroke cases with a lag of 30 days in the VE models.

Myocardial Infarction Hospitalization After ILI

When first testing ILI in the ARIMA model for MI, with no time delay (within 0–7 days or lag of zero), ILI was associated with MI ($P=0.01$; Table 1). We tested various ARIMA models for fit and found that the best fit ARIMA model consisted of 1 moving average coefficient, and 1 seasonal moving average coefficient (ARIMA (0,1,1)(0,1,1)12), indicating that seasonality with no time lag was the important component in the time series modeling of ILI as a predictor of MI. This indicates that ILI is associated with MI regardless of seasonality, but there is no time delay in the association between ILI and MI. Time forecasting analysis did not support a relationship between VE and MI hospitalization rates, as variation in VE did not correspond to forecasted predictions of MI rates. Similar to what was seen in stroke hospitalizations, we saw that after accounting for influenza VE and seasonality, there are no statistical differences in the observed versus expected MI cases, indicating no relationship between VE, ILI, and MI (data not shown).

Subgroup Analyses

We hypothesized that these effects might be stronger in some age groups than in others and conducted a stratified analysis where we ran the same models as described previously, but limiting the populations to certain age groups. We did not incorporate the previous VE analyses because those were not associated
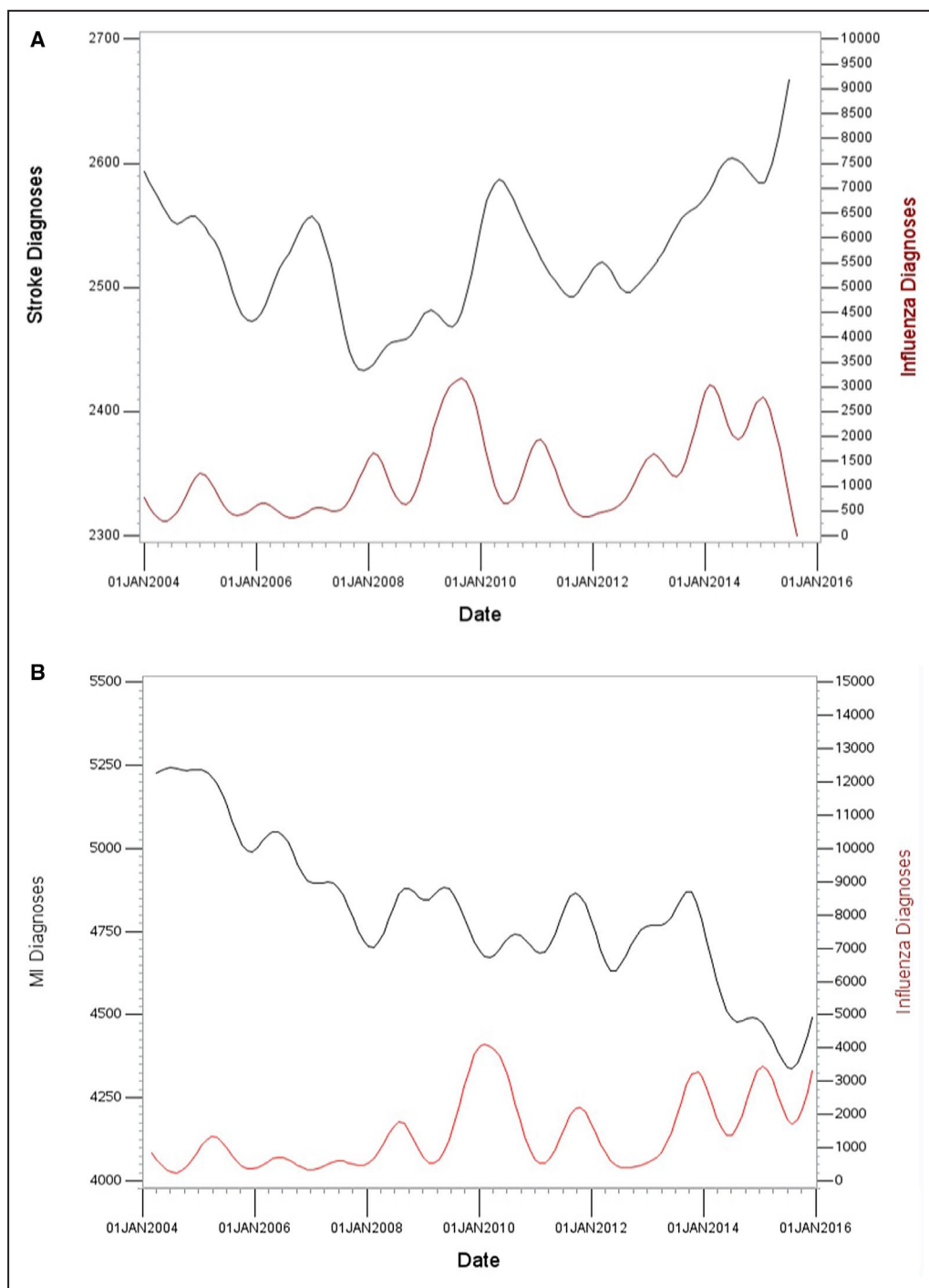
Figure 2. Monthly incidence of acute cardiovascular events and influenza-like illness from 2004 to 2015.
A, Monthly incidence of stroke and influenza-like illness; **B**, Monthly incidence of myocardial infarction an

with the forecasted predictions. We did not find the correlation between ILI and stroke differed in people <65 versus ≥65 years old. Interestingly we found an age effect for MI. After stratifying by age for MI rates, there was a significant association between ILI and MI among those ≥65 years, but the association between ILI and MI among those under 65 was not statistically significant (Table 2). We then stratified by racial groups to evaluate if there was a difference in the associations among certain racial groups. There was no race effect between ILI and stroke (*P* value for Black: 0.3979, *P* value for non-Black: 0.8861). In

Table 1. Association of ILI Rates and Cardiovascular Event Rates in the Forecasting Models

Model Parameter	Estimate	SE	P Value
Stroke			
Moving average*	0.773	0.10	<0.0001
Accounting for the yearly seasonality	0.888	0.22	<0.0001
Influenza with a time delay of 30 d	15.423	7.40	0.0399
MI			
Moving average*	0.686	0.07	<0.0001
Accounting for the yearly seasonality	0.891	0.23	0.0002
Influenza with no time delay	2.97E-06	1.15E-06	0.0111

ILI indicates influenza-like illness; and MI, myocardial infarction.

*This indicates there is a statistically significant seasonal variation in the cases of stroke and MI.

analyses of race and MI, ILI was a significant predictor in the ARIMA model for MI among non-Black (P value: 0.0107) but was not significant in the ARIMA model for Black. This indicates that among non-Black populations there is an association between ILI and MI, whereas there is no association between influenza and MI in Black populations.

DISCUSSION

This time series analysis highlights the relationship among ILI, stroke, and MI. In this study, influenza incidence rates were associated with stroke incidence rates, regardless of the seasonality trends, but only when the lag of 1 month was accounted for in the time series model. Furthermore, the relationship was consistent regardless of VE for those years. Of note, in the years with increased VE, the overall rates of ILI, stroke, and MI were nominally lower, but the association between ILI and stroke and between ILI and MI remained the same. In the analysis of ILI and MI the time series models indicated that ILI is associated with MI events regardless of seasonality and that the risk of MI is within 7 days after the ILI event.

The results between ILI and stroke and between ILI and MI were not attenuated by VE when the VE was incorporated into the forecasting model. In addition, VE was not directly associated with ILI in this population. Despite this, in years with increased VE we did see overall reductions in the absolute risk of ILI, and subsequent stroke and MI, but the overall association between ILI and stroke or MI was not influenced by VE.

In subgroup analyses we found that the association between ILI and stroke was consistent across age groups and racial groups, regardless of VE. The significant lag of 30 days between ILI and stroke occurred within each age stratum, and the VE each year did not affect the direct ILI and stroke relationship. This was in contrast to the pronounced association between ILI and MI in the elderly population indicating a high-risk population. There were differences in the ILI and MI association across racial groups, with a significantly relationship seen only in the non-Black population. The results of the MI analyses are similar to a prior study that identified an association between ILI and MI with no time delay; however, in contrast, we additionally found an association between ILI and stroke with stroke occurring within 30 days after ILI.[34] Of note, the prior study did not investigate a time delay between ILI and stroke, and
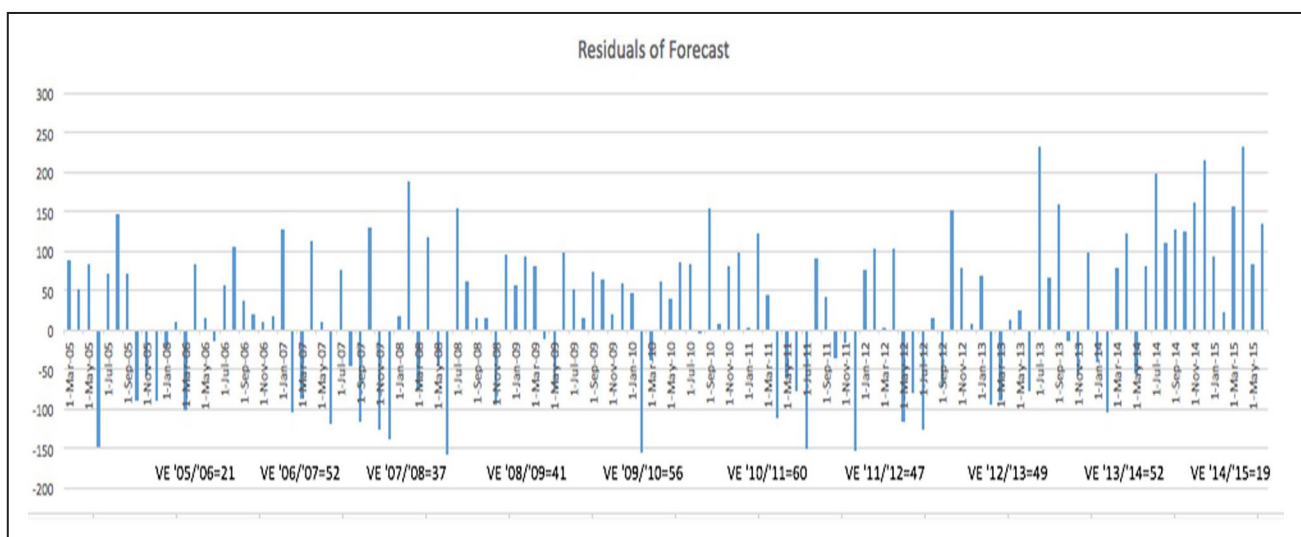
Figure 3. Seasonal vaccine effectiveness and the ARIMA model residuals.
The residual forecast shows the residual error, or the difference between what is expected and what was predicted. The figure illustrates that after accounting for vaccine effectiveness, there are no statistical differences in the observed vs expected stroke cases. ARIMA indicates autoregressive integrated moving average; MI, myocardial infarction; and VE, vaccine effectiveness.

Table 2. Model Parameter Estimates, Standard Errors, and *P* Values for the Relationship Between ILI and Cardiovascular Events, Stratified by Age and Race

	Stroke			MI		
	Influenza Coefficient Estimate	SE	*P* Value	Influenza Coefficient Estimate	SE	*P* Value
Age group, y						
18–45	−0.00001	0.00	0.4885	0.00000	0.00	0.6067
46–64	−0.01156	0.01	0.2021	0.00002	0.00	0.2195
65+	0.00001	0.00	0.1168	0.00006	0.00	<0.0001
Race						
White	0.00001	0.00	0.8861	0.00004	0.00	0.0107
Black	0.00001	0.00	0.3979	0.0059	0.01	0.3344

ILI indicates influenza-like illness; and MI, myocardial infarction.

our models with no time delay had similar results to their reports. It was only after the models incorporated the time delay between ILI and stroke that our results diverged from what has been reported in the literature.

Prior studies highlighted the association of ILI, stroke, and MI rates with the winter season.[34] The literature on the temporal trends of stroke and MI have found consistent increases in stroke and MI occurrence during the winter months, with the hypotheses for the mechanism behind this relationship unclear. By applying the cross-correlation technique in the ARIMA modeling, this allowed us to examine the association between peaks in ILI and stroke and peaks of ILI and MI while removing any association that could have resulted from the similarities in the seasonality of these 3 events. These findings provide an explanation for the seasonality of stroke seen during the winter months.

Our findings were consistent with previous reports indicating the risk of stroke after ILI is greatest up to 30 days after the ILI event and reports indicating the risk of MI is closer in time to the initial ILI event.[42] The timing of stroke after ILI has been reported in case-crossover studies and showed greatest risk of stroke within the 30-day period after an ILI event.[42]

The role of VE in these associations remains unclear. Influenza VE varies season to season as the virus undergoes antigenic drift and shift and the circulating strains of the virus alter. While the potential to become infected with influenza even after vaccination remains, the symptoms experienced may be less severe if vaccinated. In the years with increased VE, the rate of influenza is only slightly decreased, but the association between ILI and stroke and between ILI and MI remains. This was in contrast to prior studies that highlighted a direct effect of influenza vaccinations on the decreased risk of stroke or MI after ILI in those who were vaccinated.[27,28] It is possible that VE did not have a direct effect on the relationship between ILI and acute

cardiovascular events because influenza and ILI accounts for a relative small proportion of cardiovascular disease risk. It is also possible that effects of VE on secondary outcomes, such as stroke and MI, are limited because many individuals may not get vaccinated.

This study had several limitations. First, this was an ecological study, and so we cannot extrapolate our findings to the individual level. In addition, we were unable to adjust for potentially important individual confounders such as hypertension and diabetes status. Although we know the overall VE for each year, a key limitation of this design is the inability to account for influenza vaccination prevalence as we had no data on individual level details on vaccine usage. This study did not show an association between VE and the rates of either stroke or MI, but this could be because of the increased risk of ILI, and subsequent stroke or MI, in people who are not vaccinated. The effectiveness of the vaccine is useful only when the vaccine is used. In years with increased VE we did see overall reductions in the absolute risk of ILI, and small decreases in subsequent stroke and MI, but the overall association between ILI and stroke or MI was not significantly influenced by VE. This study was conducted using New York state administrative hospitalization data, but the VE data were not specific to New York. Rather the VE was calculated based on national rates reported to the Centers for Disease Control and Prevention. The strains of the virus circulating in New York can differ from those circulating nationally and vaccine uptake could also differ in New York. This could cause the vaccine effectiveness in New York to differ from the national average. Future work incorporating vaccination information is needed to elucidate the role of the influenza vaccine in reducing stroke or MI risk.

Our study also has several strengths. Unlike previous time series analyses, we were able to capture both inpatient and outpatient diagnoses for ILI.[34] Prior work in the National Inpatient Sample captured

only those ILI cases that required inpatient hospitalization, that is, the most severe cases. The use of ARIMA models allowed for the investigation of these relationships accounting for the inherent overlap in each of their respective seasonal trends. These models accounted for this and investigated if there were associations above and beyond the timing overlaps.

Our study supports prior evidence suggesting part of the time trends in stroke and MI can be attributed to the time trends of ILI. In addition, we found that the timing of the stroke events after ILI differs with an increased risk window of 30 days, whereas the risk of MI is close in time to the ILI event. This may be due to the fact that the effect of acute respiratory illness such as ILI has a more direct effect on cardiac output and function, increasing the risk of MI and other cardiac events. The effects of ILI on stroke may be more related to a subacute process such as inflammation and take longer to manifest. Furthermore, we found that people over the age of 65 explain the majority of the association between ILI and MI, indicating a high-risk group where intervention efforts could be targeted. The role of ILI and stroke did not differ by age or racial groups, but we did see different effects in the relationship between ILI and MI, with the relationship significantly only in the non-Black population. Our findings suggest that the importance of vaccination for protection against not only influenza but cardiovascular events should be further examined. Interventions to increase vaccination coverage rates need to be piloted to minimize the number of individuals experiencing influenza as well as the cardiovascular events associated with influenza and other influenza-like illnesses.

ARTICLE INFORMATION

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Dr Elkind serves on the National, Founders Affiliate, and New York City chapter boards of the American Heart Association/American Stroke Association; and receives royalties from UpToDate for chapters related to cryptogenic stroke. The remaining authors have no disclosures to report.

Supplementary Materials

Tables S1–S2

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Supplemental Material

Table S1. ICD-9 Codes used to define Stroke, and Myocardial Infarction.

	ICD-9 Codes
Ischemic Stroke	433.01, 433.11, 433.21, 433.31, 433.81, 433.91,434.01, 434.11, 434.91, 436
Hemorrhagic Stroke	430, 431, 431.0, 431.00, 432, 432.0,432.00, 432.1,432.9
Myocardial Infarction	410.00, 410.01, 410.02, 410.10, 410.11, 410.12, 410.20, 410.21, 410.22, 410.30, 410.31, 410.32, 410.40, 410.41, 410.42, 410.50, 410.51, 410.52, 410.60, 410.61, 410.62, 41070, 410.71, 410.72, 410.80, 410.81, 410.82, 410.90, 410.91, 410.92

Table S2. ICD-9 Codes used to define ILI[31]

079.89	Viral Infection NEC	466	Acute bronchitis and broncholitis
079.99	Viral Infection NOS	466.0	Acute bronchitis
460	Acute Nasopharyngitis	466.1	Acute broncholitis
462	Acute pharyngitis	466.19	Acute bronchiolitis due to other infectious organism
464	Acute Laryngitis and tracheitis	478.9	Other and unspecified diseases of upper respiratory tract
464.0	Acute Laryngitis	480	Viral pneumonia
464.1	Acute tracheitis	487	Influenza
464.10	Acute tracheitis w/o obstruction	487.0	Influenza with pneumonia
464.2	Acute Laryngotracheitis	487.1	Influenza with other respiratory manifestation
464.20	Acute Laryngotracheitis w/o obstruction	487.8	Influenza with other manifestation
465	Upper respiratory infection multiple or unspecified sites	490	Bronchitis not specified as acute or chronic
465.0	Acute laryngopharyngitis	780.6	Fever
465.8	Upper respiratory infection multiple sites	784.1	Throat pain
465.9	Upper respiratory infection of unspecified sites	786.2	Cough