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CONTROLLING CONFOUNDING BY FRAILTY WHEN ESTIMATING INFLUENZA VACCINE EFFECTIVENESS USING PREDICTORS OF DEPENDENCY IN ACTIVITIES OF DAILY LIVING

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Abstract

Purpose—To improve control of confounding by frailty when estimating the effect of influenza vaccination on all-cause mortality by controlling for a published set of claims-based predictors of dependency in activities of daily living (ADL).

Methods—Using Medicare claims data, a cohort of beneficiaries >65 years of age was followed from September 1, 2007, to April 12, 2008, with covariates assessed in the 6 months before follow-up. We estimated Cox proportional hazards models of all-cause mortality, with influenza vaccination as a time-varying exposure. We controlled for common demographics, comorbidities, and healthcare utilization variables, and then added 20 ADL dependency predictors. To gauge residual confounding, we estimated pre-influenza season hazard ratios (HRs) between September 1, 2007 and January 5, 2008, which should be 1.0 in the absence of bias.

Results—A cohort of 2,235,140 beneficiaries was created, with a median follow-up of 224 days. Overall, 52% were vaccinated and 4% died during follow up. During the pre-influenza season period, controlling for demographics, comorbidities, and healthcare use resulted in a HR of 0.66 (0.64, 0.67). Adding the ADL dependency predictors moved the HR to 0.68 (0.67, 0.70). Controlling for demographics and ADL dependency predictors alone resulted in a HR of 0.68 (0.66, 0.70).

Conclusions—Results were consistent with those in the literature, with significant uncontrolled confounding after adjustment for demographics, comorbidities, and healthcare use. Adding ADL dependency predictors moved HRs slightly closer to the null. Of the comorbidities, healthcare use

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variables, and ADL dependency predictors, the last set reduced confounding most. However, substantial uncontrolled confounding remained.

Keywords

Confounding; Frail elderly; Influenza vaccines

INTRODUCTION

Non-experimental studies of influenza vaccine effectiveness in older adults have commonly reported strong protective associations such as 50% reductions in all-cause mortality.^{1–6} These results conflict with other evidence – the protective associations are far larger than the 10% of winter deaths among older adults that are attributable to influenza,⁷ and they are present (and strongest) prior to the start of the influenza season, when we would expect little to no effect of vaccination due to a lack of circulating influenza virus.^{6,8}

As a result of these logical inconsistencies, it has been proposed that uncontrolled confounding by frailty may explain the strong protective association that has been observed between influenza vaccination and mortality.^{6,8–11} Frailty, defined as a physiologic state of decreased reserves and resistance to stressors, increases vulnerability to adverse outcomes.¹² Its clinical phenotype includes wasting, loss of endurance, decreased balance and mobility, slowed performance and relative inactivity, and decreases in cognitive function.¹² Frailty has been associated with a range of adverse outcomes such as hip fracture, disability, hospitalization, and death.^{12–14} Frail individuals close to death are less likely to receive preventive therapies for various reasons, such as a focus on the patient's main medical problem or lack of expected benefit.^{15–17} Therefore, frailty is likely a potential confounder for a wide range of treatment-outcome associations, including the association between influenza vaccination and all-cause mortality in older adults.

Unfortunately, measurements of frailty usually require an extensive geriatric assessment and, consequently, are generally not captured within administrative healthcare databases. An alternative approach to control for frailty is to adjust for a proxy (e.g. disability). These proxies would be distinct constructs related to frailty, but not completely overlapping – not all frail individuals are disabled, for instance.^{12,18} While measurements of these proxies would be preferred for improving confounding control, they are also generally not available in administrative healthcare databases. We instead use a claims-based operational definition developed by Faurot *et al.* using Medicare data. They published an algorithm that predicts dependency in activities of daily living (ADL) as a proxy for frailty when utilizing healthcare claims data.¹⁹ Using multivariable logistic regression with backwards elimination, they identified a set of predictors which discriminated between individuals with and without ADL dependency better than the Charlson comorbidity index (C-statistic of 0.845 vs. 0.78) and was associated with elevated mortality (Hazard ratio of 7.97 comparing those with 40% predicted probability of ADL dependency with those with <5% probability). We refer to their predictors as predictors of ADL dependency since frailty and disability are distinct constructs and an operational definition developed against a measure of frailty would be preferred over one developed against a measure of disability.

In this study, we evaluated the potential of predictors of ADL dependency in controlling confounding by frailty when estimating influenza vaccine effectiveness in a population of Medicare beneficiaries from 2007 to 2008. Any change in estimate towards the null prior to the influenza season would be evidence of improved confounding control and would support the potential of these predictors in other non-experimental study settings where frailty is a concern.

METHODS

STUDY DESIGN AND POPULATION

We conducted a retrospective cohort study of the 2007–2008 influenza season using Medicare claims data. The 2007–2008 influenza season had several attractive characteristics (e.g. no pandemic influencing vaccination behavior) which, when combined with the large number of Medicare beneficiaries available, made it a fine test setting to evaluate the ADL dependency predictors.

We began with a random 20% sample of all Medicare beneficiaries age 65 and older with simultaneous fee-for-service Parts A, B, and D coverage in at least one calendar month between 2007 and 2013. From this sample, we constructed a cohort of all beneficiaries who had a non-missing race variable, were 66 years of age or older as of September 1, 2007, and were continuously enrolled in simultaneous fee-for-service Parts A, B, and D coverage between March 1, 2007 and September 1, 2007. These six months prior to the index date served as the baseline covariate assessment period during which comorbidities, healthcare use, and other variables were evaluated. Members of the cohort were followed from the index date until death, disenrollment from Medicare, or the end of influenza season, whichever occurred earliest.

Follow-up was divided into two time periods – a pre-influenza season period and an influenza season period – based on the start and end of the 2007–2008 influenza season as defined using national influenza surveillance data from the U.S. Centers for Disease Control and Prevention. The beginning of the first week when 10% of tested isolates were positive for influenza was defined as the start of influenza season while the end of the last week when 10% of tested isolates were positive for influenza was defined as the end of influenza season. This definition resulted in a start and end date for the 2007–2008 influenza season of January 6, 2008 and April 12, 2008, respectively.²⁰ Figure 1 shows the temporal study design. The study protocol was approved by the institutional review board at the University of North Carolina at Chapel Hill.

EXPOSURE, OUTCOME, AND COVARIATE ASSESSMENT

The exposure of interest was receipt of seasonal influenza vaccination during the follow-up period, as defined using Current Procedural Terminology (CPT), Healthcare Common Procedure Coding System (HCPCS), and International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes (Appendix 1). The date associated with the earliest occurrence of one of the codes was taken as the date of vaccination but an individual's exposure status was not changed until 14 days had passed to allow sufficient

time for an immune response. The primary outcome was all-cause mortality between September 1, 2007 and the end of influenza season (April 12, 2008). Dates of death were taken from Medicare enrollment data files.

A range of covariates were assessed during the 6-month baseline period (Appendix 1). Age, sex, and race were available from Medicare's demographic variables. The individual components of Gagne *et al.*'s combined Charlson-Elixhauser comorbidity score were assessed as represented in Table 2 of their paper,²¹ and supplemented with additional comorbidities controlled for in the literature.^{2-4,6,8} These baseline comorbidities were defined using CPT, HCPCS, and ICD-9-CM codes. Healthcare use variables included the number of outpatient visits, number of hospitalizations, and several preventive services such as colonoscopies and fecal occult blood tests; all were defined with CPT, HCPCS and ICD-9-CM codes, except the number of hospitalizations, which used a count of inpatient hospital admissions in the Medicare Provider Analysis and Review files.

In addition to these covariates, we also assessed a set of ADL dependency predictors.¹⁹ This set of predictors included 20 covariates, several of which (heart failure, psychiatric illness, and dementias) overlapped with components of the combined Charlson-Elixhauser comorbidity score. When both the comorbidities and ADL dependency predictors were included in the same model, we combined those that overlapped to avoid using strongly correlated predictors. For example, rather than include two dementia covariates, we combined the Charlson definition and the ADL dependency definition.

With the exception of age (continuous), race (white/black/other), number of outpatient visits (discrete count), number of hospitalizations (discrete count), mammogram (binary with an interaction term with sex), and prostate-specific antigen test (binary with an interaction term with sex), all covariates were modeled as binary variables.

STATISTICAL ANALYSIS

We used Cox proportional hazards models to estimate hazard ratios comparing vaccinated and unvaccinated individuals with respect to all-cause mortality. Vaccination status was modeled as a time-varying covariate, with all individuals starting follow-up on September 1, 2007 as unvaccinated.

Four models were run during the pre-influenza season time period and, separately, the influenza season time period (i.e. among those who survived to the start of influenza season). The first was an unadjusted model. The second controlled for age, sex, and race. The third added covariates for healthcare use, and comorbid conditions from the combined Charlson-Elixhauser score and the literature. The fourth added the ADL dependency predictors. If the addition of the ADL dependency predictors moved the HR closer to 1.0, then it would be considered an improvement in confounding control. Because there was likely overlap in the ability to control confounding between the ADL dependency predictors and the other comorbidities and healthcare variables, we also conducted sensitivity analyses where the different sets of variables were added in different orders.

Results from the pre-influenza time period were used to quantify residual bias. The association between influenza vaccination and all-cause mortality should be null before the start of the influenza season because there is little influenza circulation during that time period and influenza vaccination should only have an effect when influenza is circulating. Any difference from the expected null result would be a marker of residual bias. Results from the influenza season, on the other hand, estimated the effect of influenza vaccination on all-cause mortality during a time period when an actual effect (5–10% reduction in all-cause mortality⁷) could be expected.

RESULTS

The cohort consisted of 2,235,140 beneficiaries, followed for a total of 1,320,438 person-years (median follow up: 224 days). In this cohort, 1,172,206 (52%) were vaccinated during follow-up, with a median time-to-vaccination of 66 days. Almost all (98%) vaccinations were administered more than 14 days before the start of influenza season. A total of 93,393 (4%) beneficiaries died during follow-up, with 54% of the deaths occurring before the start of the influenza season.

We present cohort characteristics by vaccination status in Table 1. The cohort was 65% female and 85% white, with a mean age of 77 years. Most baseline covariates had similar prevalence in the vaccinated and unvaccinated groups. A smaller proportion of vaccinated individuals than unvaccinated individuals were black (5.3% vs. 11.8%). Dementia (5.6% vs. 8.1%) was less prevalent in vaccinated individuals than unvaccinated individuals, while hypertension (66.0% vs. 58.9%) and lipid abnormalities (54.7% vs. 43.0%) were more prevalent. Healthcare use was more common in vaccinated individuals than unvaccinated individuals, with higher prevalence of mammograms (15.5% vs. 9.9%), and cancer screening (22.0% vs. 15.0%).

Most deaths occurred during unexposed person-time – 64,404 deaths in 836,466 person-years (unadjusted rate = 77.0 per 1,000 person-years). Only 28,989 deaths occurred during 483,973 person-years of exposed person-time (59.9 per 1,000 person-years).

Results of the models estimating the effect of influenza vaccination on all-cause mortality are shown in Table 2. Hazard ratios before influenza season were further from the null than those during influenza season. Before influenza season, the unadjusted hazard ratio was 0.61 (95% Confidence Interval: 0.60, 0.63), and the age, sex, and race-adjusted hazard ratio was 0.59 (0.57, 0.60). Adjustment for comorbidities and healthcare use resulted in a hazard ratio of 0.66 (0.64, 0.67) and further addition of the ADL dependency predictors to the model moved the hazard ratio to 0.68 (0.67, 0.70).

Table 3 presents hazards ratios as comorbidities, healthcare use, and ADL dependency predictors were added to pre-influenza season models in different orders. All models included age, sex, and race. As a first addition to the model, comorbidities moved the HR to 0.62 (0.61, 0.64), healthcare use moved the HR to 0.61 (0.59, 0.62) and ADL dependency predictors moved the HR to 0.68 (0.66, 0.70). Compared to the model with ADL

dependency predictors alone, only the full model moved the HR as close to the null. The models pairing two sets of predictors yielded slightly HRs slightly further from the null.

Similar results were seen during influenza season (Table 2). The unadjusted hazard ratio was 0.72 (0.70, 0.73) and the age, sex, and race-adjusted hazard ratio was 0.68 (0.67, 0.69). Adjustment for comorbidities and healthcare use resulted in a hazard ratio of 0.73 (0.72, 0.74) and the addition of the ADL dependency predictors moved the hazard ratio to 0.78 (0.76, 0.79).

DISCUSSION

In our retrospective cohort study, when ADL dependency predictors were added to an adjustment set consisting of demographics, comorbidities, and healthcare use covariates, hazard ratios estimating the effect of influenza vaccination on all-cause mortality moved slightly toward the null before influenza season and toward an expected 5–10% reduction during influenza season. This suggests a very modest improvement in confounding control, above what was achieved using an adjustment set of commonly used demographics, comorbidities, and healthcare use variables. The ADL dependency predictors were unable to completely address the confounding that was present and substantial confounding remained - influenza vaccination was associated with a 32% reduction in all-cause mortality before the influenza season, a time period when no effect would be expected.

The additional analyses, which varied the order in which comorbidities, healthcare use variables, and the ADL dependency predictors were added to models, showed that controlling for the ADL dependency predictors reduced residual confounding more than controlling for either comorbidities or healthcare use variables. Adding comorbidities, healthcare use variables, or both to models including the ADL dependency predictors did not move the HR closer to 1.0, showing that there is no net improvement from comorbidities or healthcare use variables once the ADL dependency predictors are already adjusted for. This suggests that the ADL dependency predictors reduce confounding by frailty in the same way that the commonly used comorbidities and healthcare use variables do, which makes sense given that the ADL dependency predictors consist of other comorbidities and healthcare use variables.

Overall, our results are generally consistent with those published in the literature. All of the models resulted in associations between influenza vaccination and large reductions in all-cause mortality, and adjustment for covariates identified *a priori* was largely ineffective, as has been seen previously.^{6,8,22} Where previous studies have used adjustment sets of around 25 covariates, we started with 20 comorbidities based on the combined Charlson-Elixhauser comorbidity score, which was shown to predict mortality better than either comorbidity score individually,²¹ and supplemented those covariates with five covariates from the literature, three demographic covariates, eight healthcare use covariates, and 20 ADL dependency predictors. In spite of this comprehensive adjustment set, influenza vaccination was associated with a 32% reduction in all-cause mortality before the influenza season.

It is not surprising that adding the 20 frailty predictors identified by Faurot *et al.*¹⁹ improved confounding control slightly but did not move our hazard ratios to 1.0. Faurot *et al.* used dependence in activities of daily living as a proxy for frailty, and they noted that control for confounding by frailty is likely to be only partially achieved.¹⁹ While ADL dependence may serve as a proxy for frailty, they are not equivalent. Even a perfect representation of ADL dependence would not completely capture frailty and its confounding.

Strengths of this study include its use of a large cohort of older adults, which allowed adjustment for many variables. The adjustment set used in this study was more comprehensive than those used in previous studies and included additional variables identified in the literature as being associated with mortality. Furthermore, the tested ADL dependency predictors were developed in a similar Medicare population, so their application should be appropriate. Use of the influenza vaccination setting to test the ability of the ADL dependency predictors was also a strength, as mortality prior to the influenza season served as a negative control outcome – observed associations between influenza vaccination and all-cause mortality during that time period were indicative of residual confounding.²³

There are several limitations of this study. First, some exposure misclassification is expected since some vaccinations are likely to have been obtained free of charge without presentation of insurance information or as part of bundled services in care settings. We did in fact observe relatively low vaccination coverage of 52%, in comparison with CDC estimates for the 2007–2008 influenza season that put coverage at 72%.²⁴ Exposure misclassification would be expected to cause bias towards the null and, therefore, obscure the degree of confounding by frailty. Furthermore, we tested this specific set of ADL dependency predictors in only one setting in which confounding by frailty is suspected. The confounding control offered by these predictors may differ between influenza seasons and among exposure-outcome associations studied. Finally, we evaluated covariates only during the six-month baseline and ignored any changes during follow-up; however, adjustment for covariates in a time-dependent manner did not substantially reduce confounding in a study of influenza vaccination in adult hemodialysis patients.²²

We conclude that addition of one specific set of ADL dependency predictors to an adjustment set including commonly used demographics, comorbidities, and healthcare use variables showed modest improvements in confounding control in a study of influenza vaccination and all-cause mortality. When considered separately, the ADL dependency predictors contributed more to confounding control than did the included comorbidities or healthcare use variables. Neither comorbidities nor healthcare use variables led to further improvements once the ADL dependency predictors were controlled for. Influenza vaccination was still associated with a 32% reduction in all-cause mortality during a time period in which no effect would be expected, indicating that the addition of the ADL dependency predictors was unsuccessful in addressing the confounding present in this setting.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

- Non-experimental studies of influenza vaccine effectiveness in older adults have commonly reported strong protective associations that may be caused by uncontrolled confounding by frailty.
- Consistent with previous studies, controlling for commonly used demographics, comorbidities, and healthcare use variables resulted in a strong protective association between influenza vaccination and all-cause mortality, even before the start of the influenza season when no association would be expected.
- Controlling for a set of predictors of dependence in activities in daily living (ADL) reduced uncontrolled confounding more than controlling for commonly used comorbidities or healthcare use variables.
- Adding the ADL dependency predictors to commonly used comorbidities and healthcare use variables reduced confounding only slightly, and substantial residual confounding remained.

Figure 1.
Study design schematic

Characteristics of 2,235,140 Medicare beneficiaries during the six months prior to cohort entry on Sep 1, 2007, according to vaccination status at the end of follow-up.

Table 1

Characteristic	Vaccinated N=1,173,363		Unvaccinated N=1,062,400		Total N=2,235,140	
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%
Age, years	76.9 (7.5)		76.2 (7.9)		76.6 (7.7)	
Male sex		33.7		35.6		34.6
Race						
White		88.8		79.9		84.6
Black		5.3		11.8		8.4
Other		5.9		8.3		7.0
Healthcare Use						
Number of outpatient visits	4.7 (4.4)		3.4 (4.0)		4.1 (4.3)	
Number of hospitalizations	0.2 (0.6)		0.2 (0.6)		0.2 (0.6)	
Electrocardiogram	12.7		11.3		12.0	
Colonoscopy	6.0		4.5		5.3	
Fecal occult blood test	6.1		4.2		5.2	
Mammogram	15.5		9.9		12.9	
Prostate-specific antigen test	12.3		10.2		11.3	
Pneumococcal Vaccination	1.6		1.1		1.3	
Comorbidities						
Asthma	6.2		4.9		5.6	
Pneumonia	4.3		4.9		4.6	
Congestive heart failure	14.8		15.2		15.0	
Dementia	5.6		8.1		6.8	
Chronic pulmonary disease	18.2		16.6		17.5	
Hemiplegia or paraplegia	0.8		1.2		1.0	
Any malignancy	11.8		9.6		10.8	
Metastatic solid tumor	1.1		1.3		1.2	
AIDS	0.1		0.1		0.1	
Cardiac arrhythmias	17.3		14.7		16.1	

Characteristic	Vaccinated N=1,173,363		Unvaccinated N=1,062,400		Total N=2,235,140	
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%
Pulmonary circulation disorders	1.5	1.3	1.3	1.3	1.4	1.4
Peripheral vascular disorders	13.8	13.9	13.9	13.9	13.8	13.8
Hypertension	66.0	58.9	58.9	58.9	62.6	62.6
Diabetes, complicated	7.9	7.2	7.2	7.2	7.6	7.6
Renal failure	7.0	6.3	6.3	6.3	6.7	6.7
Liver disease	1.1	1.1	1.1	1.1	1.1	1.1
Coagulopathy	2.7	2.4	2.4	2.4	2.6	2.6
Weight loss	0.7	1.2	1.2	1.2	1.0	1.0
Fluid and electrolyte disorders	8.8	9.3	9.3	9.3	9.1	9.1
Deficiency anemias	17.3	16.6	16.6	16.6	17.0	17.0
Alcohol abuse	0.4	0.6	0.6	0.6	0.5	0.5
Psychoses	4.4	5.9	5.9	5.9	5.1	5.1
ADL Dependency Predictors						
Cancer screening	22.0	15.0	15.0	15.0	18.7	18.7
Lipid abnormality	54.7	43.0	43.0	43.0	49.1	49.1
Vertigo	7.4	6.4	6.4	6.4	6.9	6.9
Arthritis	36.3	32.8	32.8	32.8	34.7	34.7
Bladder dysfunction	6.5	6.0	6.0	6.0	6.3	6.3
Podiatric care	8.4	7.9	7.9	7.9	8.2	8.2
Heart failure [†]	14.9	15.3	15.3	15.3	15.0	15.0
Psychiatric illness [‡]	16.0	18.9	18.9	18.9	17.4	17.4
Rehabilitation care	4.8	4.2	4.2	4.2	4.5	4.5
Home oxygen	4.9	4.3	4.3	4.3	4.7	4.7
Hypotension or shock	2.4	2.5	2.5	2.5	2.5	2.5
Ambulance transport	8.3	10.5	10.5	10.5	9.4	9.4
Stroke/brain injury	5.3	6.4	6.4	6.4	5.8	5.8
Dementias [§]	10.0	12.9	12.9	12.9	11.4	11.4
Parkinson's disease	1.7	1.9	1.9	1.9	1.8	1.8
Weakness	5.2	6.4	6.4	6.4	5.8	5.8

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Characteristic	Vaccinated N=1,173,363		Unvaccinated N=1,062,400		Total N=2,235,140	
	Mean (SD)	%	Mean (SD)	%	Mean (SD)	%
Skin ulcer		3.4		4.3		3.8
Paralysis		1.5		2.1		1.8
Wheelchair		2.5		3.2		2.9
Hospital bed		1.5		2.1		1.8

⁷Definition merged with Charlson Congestive Heart Failure

⁸Definition merged with Elixhauser Psychoses

⁹Definition merged with Charlson Dementia

Table 2

Hazard ratios (HR) for all-cause mortality comparing vaccinated and unvaccinated beneficiaries.

Model	Pre-influenza season		Influenza season	
	HR	95% CI	HR	95% CI
Unadjusted	0.61	0.60 – 0.63	0.72	0.70 – 0.73
Age, sex, race	0.59	0.57 – 0.60	0.68	0.67 – 0.69
+ Comorbidities, healthcare use	0.66	0.64 – 0.67	0.73	0.72 – 0.74
+ ADL dependency predictors	0.68	0.67 – 0.70	0.78	0.76 – 0.79

Table 3

Pre-influenza season hazard ratios (HR) for all-cause mortality comparing vaccinated beneficiaries with unvaccinated beneficiaries as the reference, using different combinations of comorbidities, healthcare use, and ADL dependency predictors as adjustment sets.

Model [†]	HR	95% CI
Comorbidities	0.62	0.61 – 0.64
Healthcare use	0.61	0.59 – 0.62
ADL dependency predictors	0.68	0.66 – 0.70
Comorbidities & healthcare use	0.66	0.64 – 0.67
Comorbidities & ADL dependency predictors	0.67	0.66 – 0.69
Healthcare use & ADL dependency predictors	0.67	0.66 – 0.69
Comorbidities, healthcare use, and ADL dependency predictors	0.68	0.67 – 0.70

[†] All models include age, sex, and race