Practice of Epidemiology

Restriction of Pharmacoepidemiologic Cohorts to Initiators of Medications in Unrelated Preventive Drug Classes to Reduce Confounding by Frailty in Older Adults

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Nonexperimental studies of the effectiveness of seasonal influenza vaccine in older adults have found 40%–60% reductions in all-cause mortality associated with vaccination, potentially due to confounding by frailty. We restricted our cohort to initiators of medications in preventive drug classes (statins, antiglaucoma drugs, and β blockers) as an approach to reducing confounding by frailty by excluding frail older adults who would not initiate use of these drugs. Using a random 20% sample of US Medicare beneficiaries, we framed our study as a series of nonrandomized “trials” comparing vaccinated beneficiaries with unvaccinated beneficiaries who had an outpatient health-care visit during the 5 influenza seasons occurring in 2010–2015. We pooled data across trials and used standardized-mortality-ratio–weighted Cox proportional hazards models to estimate the association between influenza vaccination and all-cause mortality before influenza season, expecting a null association. Weighted hazard ratios among preventive drug initiators were generally closer to the null than those in the nonrestricted cohort. Restriction of the study population to statin initiators with an uncensored approach resulted in a weighted hazard ratio of 1.00 (95% confidence interval: 0.84, 1.19), and several other hazard ratios were above 0.95. Restricting the cohort to initiators of medications in preventive drug classes can reduce confounding by frailty in this setting, but further work is required to determine the most appropriate criteria to use.

confounding factors (epidemiology); frail elderly; frailty; influenza vaccines

Abbreviations: CI, confidence interval; HR, hazard ratio; SMR, standardized mortality ratio.

Nonexperimental studies of the effectiveness of seasonal influenza vaccine in older adults have found 40%–60% reductions in all-cause mortality associated with seasonal influenza vaccination (1–6). These associations are larger than plausible given that only about 10% of winter deaths in older adults can be attributed to influenza (7), and the inverse associations are most pronounced before the start of influenza season, when there is little to no biological effect of vaccination because of a lack of circulating influenzavirus (6, 8). Uncontrolled confounding by frailty is the most plausible explanation for the strong inverse association observed between influenza vaccination and mortality prior to the influenza season (6, 8–10).

Frailty is a physiological state of increased vulnerability to stressors and reduced ability to recover homeostasis (11). Frailty thus reflects a decrease in physiological reserves and an accumulation of deficits across multiple physiological systems (11, 12).

When making treatment recommendations, physicians consider patients’ underlying health status, including comorbidity, disability, and frailty. For example, frail patients may be less likely to initiate preventive therapies due to a more pressing main medical condition (e.g., metastatic cancer) or a lack of expected long-term benefit due to a poor short-term prognosis (13–15). Furthermore, frailty has been associated with many adverse events in older adults, including hip fracture, hospitalization, and death (11, 16, 17). Because frailty affects both treatment initiation and outcomes, it is a potential confounder in nonexperimental studies addressing medical interventions.

Most routinely collected data, including administrative health-care claims data, lack clinical assessment of frailty. It is thus not possible to control for frailty directly. When assessing the effectiveness of seasonal influenza vaccine in older adults, researchers have generally taken an indirect approach to reducing

confounding by frailty. For example, restriction of the cohort has been used to make study populations more homogeneous with regard to potential confounders (18). Jackson et al. (19) restricted their study population to older adults who had serum creatinine laboratory results, and they obtained an adjusted odds ratio of 0.93 in an influenza season where the predominant circulating strain was omitted from that year's trivalent inactivated vaccine. McGrath et al. (20) restricted their sample of adult patients on hemodialysis based on a range of survival and health-care utilization criteria, and they obtained adjusted hazard ratios ranging from 0.45 to 0.96 before the start of influenza season, with hazard ratios closer to the null resulting from more severe restrictions.

Use of medications in certain preventive drug classes has been identified as a marker for low short-term mortality risk in older adults (21). We restricted our cohort to initiators of medications in certain preventive drug classes as a novel approach to reducing confounding by frailty under the assumption that frail older adults would be unlikely to initiate use of these drugs. We tested the performance of our restriction approach in estimating the association of influenza vaccination with all-cause mortality, using death prior to the influenza season as a negative control outcome (6, 22).

METHODS

Study design and population

We conducted a retrospective cohort study focused on the time periods before the 2010–2011, 2011–2012, 2012–2013, 2013–2014, and 2014–2015 influenza seasons using a random 20% sample of all Medicare beneficiaries aged 65 years or older with simultaneous fee-for-service Parts A, B, and D coverage in at least 1 calendar month between 2009 and 2014. Using national influenza surveillance data from the Centers for Disease Control and Prevention, we defined the start of each influenza season as the beginning of the first week in which $\geq 10\%$ of tested isolates were positive for influenzavirus. This corresponded to November 21, 2010; January 29, 2012; November 11, 2012; November 24, 2013; and November 9, 2014, for the 5 influenza seasons of interest.

We emulated the design proposed by Hernán et al. (23) for analyzing observational studies like randomized experiments, framing our study as a series of nonrandomized “trials” comparing beneficiaries who were vaccinated with those who had an outpatient health-care visit on the same day and were unvaccinated up to this time point (Figure 1). A new trial began on each day with at least 1 eligible vaccination and at least 1 eligible unvaccinated outpatient visit. The earliest trial started on September 1 of a given year, with the latest possible trial on the day before the start of the influenza season. Because this study design allows a beneficiary to participate in multiple trials, we refer to the unit of analysis as a person-trial. Note that the same person could contribute an unvaccinated person-trial and, later, a vaccinated one.

Both an “uncensored” approach and a “censored” approach were implemented (Figure 1). We describe the approaches as uncensored and censored to indicate whether person-time was censored when a treatment change occurred during follow-up. The uncensored approach was analogous to an intention-to-treat approach, where vaccinated person-trials contributed

exposed person-time and unvaccinated person-trials contributed unexposed person-time from their index date until death or the start of the influenza season. Unvaccinated person-trials were not censored if the person was later vaccinated.

In the censored approach, we more accurately assigned follow-up time to exposure categories by accounting for exposure changes taking place during follow-up. In the context of seasonal influenza vaccination, exposure changes occur in only one direction (i.e., unvaccinated to vaccinated) and are simpler than in other settings, where lack of effectiveness, side effects, or sudden changes in indication may cause a person to switch medications, for example. Therefore, in the censored approach, we censored unvaccinated person-trials if the person was later vaccinated, so that the exposed person-time was assigned only to the vaccinated person-trial. The first 14 days of follow-up for a vaccinated person-trial were also considered unexposed person-time (to allow sufficient time for an immune response). Follow-up for both vaccinated and unvaccinated person-trials was additionally censored at disenrollment (since disenrollment would obscure later vaccinations).

We required beneficiaries to be ≥ 66 years of age, have ≥ 12 months of prior continuous fee-for-service enrollment in Medicare Parts A, B, and D, and have a nonmissing race variable in their enrollment files as of their index date (vaccination or outpatient visit) in order for a person-trial to be eligible. The 12 months prior to the index date served as a baseline covariate assessment period.

Exposure and outcome

The exposure of interest was seasonal influenza vaccination as defined using Current Procedural Terminology, Healthcare Common Procedure Coding System, and *International Classification of Diseases, Ninth Revision, Clinical Modification*, codes (see Web Table 1, available at <https://academic.oup.com/aje>). The date associated with the earliest assignment of one of the codes was considered the date of vaccination. Current Procedural Terminology codes 99201–99205 (office/outpatient visit, new patient) and 99211–99215 (office/outpatient visit, established patient) were used to identify the index outpatient visits for unvaccinated person-trials. The outcome was all-cause mortality based on dates of death from Medicare's enrollment files.

Covariates

We assessed a range of covariates during the 12-month baseline period (Web Table 1). Information on age, sex, and race was taken from Medicare's demographic variables. Our list of comorbid conditions began with the components of Gagne et al.'s (24) combined comorbidity score and was supplemented with additions from the literature and a set of frailty predictors (1, 2, 4, 6, 8, 25). Comorbidity was defined using Current Procedural Terminology and Healthcare Common Procedure Coding System procedure codes and *International Classification of Diseases, Ninth Revision, Clinical Modification*, diagnosis and procedure codes. We also assessed health-care use, including number of outpatient visits and number of hospitalizations, and use of several preventive services such as colonoscopies and fecal occult blood tests. Prescription drug-use variables were based on the

Figure 1. Schematic of the seasonal influenza vaccination setting used to test restriction of a Medicare cohort to initiators of preventive drug classes to reduce confounding by frailty, United States, 2009–2014. A) Study design under the uncensored approach. One trial begins on each day before influenza season, with the exposed group consisting of beneficiaries who were vaccinated on that day (square) and the unexposed as those who had an outpatient health-care visit on that day without a prior vaccination (circle). The dashed lines after vaccination and solid lines after outpatient visits represent follow-up time, which is censored at death (none depicted) or the day before the start of influenza season. Since beneficiaries could contribute to multiple trials, either by having multiple eligible outpatient visits (not shown) or by being vaccinated after an eligible outpatient visit (e.g., beneficiary 4 in trial 2 is also an exposed beneficiary in trial 4), we refer to the unit of analysis as a person-trial. A beneficiary's follow-up time could contribute simultaneously to multiple unexposed person-trials and 1 exposed person-trial. B) Study design under the censored approach. This is similar to the uncensored approach in panel A except that the first 14 days after vaccination are considered unexposed person-time (represented by a solid line for 14 days and dashed lines afterwards) and that an unexposed beneficiary's follow-up time is censored when vaccination occurs (e.g., beneficiary 4 in trial 2 is no longer followed in trial 2 and becomes an exposed beneficiary in trial 4). Follow-up time was also censored at disenrollment (not shown).

14 drug classes with potentially paradoxical associations with mortality that were identified by Glynn et al. (21) in their non-hospitalized sample and additionally included bronchodilators and oral and inhaled corticosteroids (1, 2, 4, 6, 8). All were defined using the Anatomical Therapeutic Chemical Classification System and a crosswalk to National Drug Codes.

Identification of preventive drug initiators

Initiation of use of statins, antiglaucoma drugs, or β blockers was identified during the 30 days before each person-trial's index visit. Person-trials were considered initiators if the person filled a prescription after 11 months of no use, defined as no claims for dispensed prescriptions. We tested both a strict

definition of initiation, in which the person-trial had to be naive to the entire class of drugs, and a looser definition, in which previous use of other drugs within the class was allowed (effectively including switching or augmenting medications within a given drug class). We thought that frail patients would be unlikely to switch or augment use of medications within preventive drug classes and that including switchers and augmenters would improve sample size. Each drug class was again defined using Anatomical Therapeutic Chemical Classification System codes.

Analysis

To control confounding, we created standardized mortality ratio (SMR) weights (26). Propensity scores for influenza

vaccination were estimated using separate logistic regression models for all person-trials, as well as those considered to be statin initiators, β -blocker initiators, and antiglaucoma drug initiators under both definitions of initiation (drug and class). The models included all baseline covariates, including demographic factors, comorbidity, health-care use, and prescription drug use.

We used SMR-weighted Cox proportional hazards models to estimate hazard ratios for the association between seasonal influenza vaccination and all-cause mortality before the start of the influenza season. Data from all trials were pooled together, and then the models stratified by influenza season. The robust variance estimator was used to account for beneficiaries' potential contributions to multiple trials and the weighting.

We were primarily interested in comparing the association between influenza vaccination and all-cause mortality before the influenza season in all person-trials and those considered initiators of statins, antiglaucoma drugs, and β blockers. These associations served as a negative control—we would expect a null association between influenza vaccination and all-cause mortality in the absence of widespread influenza circulation, so any observed association should be due to confounding. Creating the negative control by evaluating the association of interest before influenza season (instead of introducing another outcome) is particularly advantageous because the confounding structure before influenza season and the confounding structure during influenza season should be the same. If restriction of the study population resulted in hazard ratios closer to 1.0, it would be considered an improvement in confounding control.

RESULTS

In total, we identified 6,210,203 vaccinations and 15,739,665 unvaccinated outpatient visits over the 5 influenza seasons of interest. The median follow-up time was 51 days, and the total available follow-up time was 3,268,282 person-years. Table 1 presents the unweighted baseline characteristics of the nonrestricted cohort. Participants in vaccinated person-trials tended to be white (88.8% vs. 85.0%) and to have less metastatic cancer (1.6% vs. 3.7%), complicated diabetes (11.8% vs. 15.6%), heart failure (18.4% vs. 24.8%), use of loop diuretics (17.8% vs. 22.7%), and use of narcotic analgesics (21.6% vs. 29.0%), in comparison with those in unvaccinated person-trials. SMR weighting improved the balance of measured baseline covariates between vaccinated and unvaccinated groups (Table 1).

Among these person-trials, we identified 111,494 statin initiators, 32,309 antiglaucoma drug initiators, and 136,247 β -blocker initiators using the strict definition. These numbers increased to 192,079 statin initiators, 71,763 antiglaucoma drug initiators, and 210,710 β -blocker initiators once switchers and augmenters within the same drug class were included. Baseline characteristics of these initiators were similar regardless of which definition of initiation was used, so only those for the strict definition are shown in Table 2. Web Table 2 shows the baseline characteristics of participants once switchers and augmenters were included; the largest changes were an increase in baseline β -blocker use from 59.3% to 70.8% in the antiglaucoma group and an increase in baseline heart

failure from 39.2% to 45.0% in the β -blocker group. Baseline differences between initiators and the nonrestricted cohort were related to the indication for treatment (Table 2). For example, statin initiators and β -blocker initiators had higher prevalences of heart failure, cardiac arrhythmia, and stroke or brain injury than the nonrestricted cohort. Antiglaucoma drug initiators were less likely to be white (76.6% vs. 86.1%) and had a higher prevalence of insulin use (9.8% vs. 7.0%) and diabetes with complications (20.6% vs. 14.5%).

Restriction of the study population to preventive drug initiators improved the balance of baseline covariates between vaccinated and unvaccinated person-trials relative to the nonrestricted cohort. Figure 2 shows the balance of the 10 most imbalanced baseline covariates in the nonrestricted cohort across all groups. Restriction to antiglaucoma drug initiators and β -blocker initiators, regardless of whether switchers and augmenters were included, improved the balance of all 10 baseline covariates. Restriction to statin initiators improved the balance of 6 of these baseline covariates but worsened it for cardiac arrhythmia, heart failure, number of hospitalizations, and electrocardiograms. SMR weighting improved the balance of measured baseline covariates between vaccinated and unvaccinated groups in each group of initiators (Web Tables 3 and 4).

Across all groups, crude mortality rates were similar regardless of whether the uncensored approach or the censored approach was used. Table 3 only shows crude mortality rates obtained under the uncensored approach, but crude mortality rates obtained under the censored approach are available in Web Table 5. Crude mortality rates were also similar regardless of whether switchers and augmenters were included.

Table 3 shows that crude mortality rates in unvaccinated person-trials were consistently higher than those in vaccinated person-trials. In the nonrestricted cohort, the crude mortality rate in unvaccinated person-trials was 1.9 deaths per 100 person-years higher than that in vaccinated person-trials. Among the preventive drug initiators, the rate differences were similar, with only antiglaucoma drug initiators showing a marked reduction in the difference between unvaccinated and vaccinated person-trials—the crude mortality rate in unvaccinated person-trials was 1.2 per 100 person-years higher than that in vaccinated person-trials among antiglaucoma drug initiators and was 0.5 per 100 person-years higher among antiglaucoma drug initiators, switchers, and augmenters. The crude mortality rate ratios in the preventive drug initiator groups, ranging from 0.73 in statin initiators, switchers, and augmenters to 0.91 in antiglaucoma drug initiators, switchers, and augmenters, were closer to 1.0 than the crude mortality rate ratio of 0.69 in the nonrestricted cohort.

Additionally, the crude mortality rate was highest among the β -blocker groups. When evaluating initiators with an uncensored approach, it was 10.0 per 100 person-years and 12.3 per 100 person-years for vaccinated and unvaccinated person-trials, respectively, as compared with 4.2 per 100 person-years and 6.1 per 100 person-years for all vaccinated and unvaccinated person-trials (Table 3).

Table 4 presents results from the proportional hazards models estimating the association between influenza vaccination and all-cause mortality before the start of influenza season. Since short-term mortality prior to the influenza season should

Table 1. Baseline Characteristics of 21,949,868 Person-Trials in the Seasonal Influenza Vaccination Setting (Comparing Unvaccinated Person-Trials With Vaccinated Person-Trials) Used to Test Restriction of a Medicare Cohort to Initiators of Preventive Drug Classes to Reduce Confounding by Frailty, US Medicare Data, 2009–2014

Characteristic	Unvaccinated Person-Trials, % (n = 15,739,665)	Unvaccinated Person-Trials (Weighted), % (n = 6,166,140 ^a)	Vaccinated Person-Trials, % (n = 6,210,203)
Age, years ^b	76.0 (7.3)	76.8 (7.6)	76.9 (7.6)
Male sex	37.4	36.4	36.2
Race			
White	85.0	88.8	88.8
Black	7.8	5.1	5.1
Other	7.2	6.1	6.1
Comorbidity			
Asthma	12.1	9.4	9.3
Pneumonia	9.1	7.0	6.9
AIDS	0.1	0.1	0.1
Alcohol abuse	0.6	0.4	0.4
Cardiac arrhythmias	30.6	24.2	23.9
Coagulopathy	7.0	4.5	4.4
Chronic pulmonary disease	29.7	23.9	23.6
Deficiency anemias	32.0	25.1	25.0
Diabetes, complicated	15.6	11.9	11.8
Fluid and electrolyte disorders	20.0	15.0	14.9
Hemiplegia or paraplegia	1.5	1.2	1.2
Hypertension	82.5	78.7	78.5
Liver disease	3.6	2.5	2.4
Any malignancy	20.9	15.7	15.5
Metastatic solid tumor	3.7	1.6	1.6
Pulmonary circulation disorders	4.9	3.5	3.4
Peripheral vascular disorder	24.9	19.7	19.7
Renal failure	17.4	13.8	13.6
Weight loss	2.2	1.6	1.6
Lipid abnormality	75.8	73.7	73.4
Vertigo	17.4	12.7	12.5
Arthritis	59.2	50.3	50.1
Bladder dysfunction	14.6	11.3	11.2
Heart failure	24.8	18.6	18.4
Psychiatric illness	13.6	11.4	11.4
Hypotension or shock	7.0	5.0	5.0
Stroke/brain injury	9.7	7.6	7.5
Dementia	13.7	13.5	13.7
Parkinson disease	2.3	2.0	2.0
Weakness	13.9	11.6	11.7
Skin ulcer	7.4	5.1	5.0
Paralysis	2.6	2.1	2.1

Table continues

Table 1. Continued

Characteristic	Unvaccinated Person-Trials, % (n = 15,739,665)	Unvaccinated Person-Trials (Weighted), % (n = 6,166,140 ^a)	Vaccinated Person-Trials, % (n = 6,210,203)
Health-care use			
No. of hospitalizations ^b	0.5 (1.0)	0.3 (0.8)	0.3 (0.8)
No. of outpatient visits ^b	13.6 (10.2)	9.4 (6.8)	9.2 (7.6)
Electrocardiogram	31.3	22.8	22.4
Colonoscopy	11.5	10.0	10.0
Fecal occult blood test	10.0	9.6	9.5
Mammogram	27.1	28.9	28.8
Prostate-specific antigen test	20.9	19.6	19.4
Pneumococcal vaccination	6.0	6.1	6.1
Cancer screening	37.7	39.9	39.8
Podiatric care	14.7	12.3	12.3
Rehabilitation care	11.3	9.1	9.0
Home oxygen	7.1	5.5	5.4
Ambulance transport	18.4	14.2	14.2
Wheelchair	2.7	2.1	2.0
Hospital bed	1.6	1.2	1.2
Prescription drug use			
Antiarrhythmic agents	9.9	6.9	6.8
Antiglaucoma	9.9	9.3	9.3
Anxiolytic agents	11.2	9.4	9.4
β blockers	48.3	44.2	44.0
Bronchodilators	17.3	14.8	14.8
Calcium channel blockers	32.5	30.1	29.9
Digitalis glycosides	5.0	3.9	3.9
Inhaled corticosteroids	10.1	8.7	8.6
Insulin	7.5	5.8	5.8
Lipotropics	58.2	59.0	58.7
Loop diuretics	22.7	18.0	17.8
Narcotic analgesics	29.0	21.8	21.6
NSAIDs	27.0	22.0	21.9
Oral corticosteroids	23.0	17.6	17.3
Potassium replacements	15.6	12.9	12.9
Thiazide diuretics	24.4	24.7	24.7
Vasodilators	10.8	8.4	8.3

Abbreviations: AIDS, acquired immunodeficiency syndrome; NSAIDs, nonsteroidal antiinflammatory drugs.

^a Weighted number of person-trials.

^b Values are expressed as mean (standard deviation).

not be affected by influenza vaccination, we assumed that a hazard ratio of 1.0 was the true unconfounded estimate.

With the uncensored approach, the crude and weighted hazard ratios for the nonrestricted cohort were 0.70 (95% confidence interval (CI): 0.69, 0.71) and 0.85 (95% CI: 0.84, 0.86), respectively. Restriction resulted in weighted hazard ratios that were closer to the null for all groups. Among statin initiators, the weighted hazard ratio was 1.00 (95% CI: 0.84, 1.19); among

β-blocker initiators, switchers, and augmenters, the weighted hazard ratio was 0.99 (95% CI: 0.90, 1.09); among β-blocker initiators, the weighted hazard ratio was 0.98 (95% CI: 0.87, 1.12); and among antiglaucoma drug initiators, switchers, and augmenters, the weighted hazard ratio was 0.98 (95% CI: 0.79, 1.23). The reduction in bias relative to the nonrestricted cohort ranged from 24.6% among statin initiators, switchers, and augmenters to 99.4% among statin initiators.

Table 2. Baseline Characteristics of Person-Trials According to Type of Medication Use (Statin Initiators, Antiglaucoma Drug Initiators, and β -Blocker Initiators) as Compared With the Nonrestricted Cohort, US Medicare Data, 2009–2014

Characteristic	Statin Initiators, % (n = 111,494)	Antiglaucoma Drug Initiators, % (n = 32,309)	β -Blocker Initiators, % (n = 136,247)	Nonrestricted, % (n = 21,949,868)
Age, years ^a	75.5 (7.0)	77.1 (7.3)	76.4 (7.3)	76.3 (7.4)
Male sex	39.7	39.0	40.6	37.1
Race				
White	82.9	76.6	84.2	86.1
Black	8.9	12.7	8.2	7.1
Other	8.2	10.7	7.5	6.9
Comorbidity				
Asthma	12.8	13.0	13.2	11.3
Pneumonia	11.3	9.7	14.8	8.5
AIDS	0.2	0.2	0.1	0.1
Alcohol abuse	0.9	0.6	1.2	0.5
Cardiac arrhythmias	36.8	30.4	49.3	28.7
Coagulopathy	7.8	7.0	10.0	6.3
Chronic pulmonary disorder	33.8	30.0	36.3	28.0
Deficiency anemias	33.7	34.4	38.4	30.0
Diabetes, complicated	17.1	20.6	16.3	14.5
Fluid and electrolyte disorders	24.9	21.0	31.8	18.5
Hemiplegia or paraplegia	3.9	1.8	2.4	1.4
Hypertension	87.6	84.2	89.7	81.4
Liver disease	3.8	3.6	4.5	3.3
Any malignancy	18.3	18.6	21.6	19.3
Metastatic solid tumor	2.6	2.5	4.4	3.1
Pulmonary circulation disorders	7.1	5.6	8.5	4.5
Peripheral vascular disorder	29.7	27.0	30.1	23.5
Renal failure	19.8	19.3	22.0	16.3
Weight loss	3.2	2.3	4.7	2.0
Lipid abnormality	86.7	76.4	77.5	75.1
Vertigo	21.1	18.7	22.3	16.0
Arthritis	59.2	59.5	60.5	56.6
Bladder dysfunction	14.6	15.0	16.1	13.7
Heart failure	33.2	26.0	39.2	23.0
Psychiatric illness	15.3	13.6	15.9	13.0
Hypotension or shock	9.9	7.5	13.0	6.5
Stroke/brain injury	18.0	11.4	14.6	9.1
Dementia	16.9	16.0	17.0	13.7
Parkinson disease	2.1	2.0	2.3	2.2
Weakness	17.5	15.5	19.6	13.3
Skin ulcer	7.5	8.1	8.1	6.7
Paralysis	5.9	3.1	3.9	2.5

Table continues

Table 2. Continued

Characteristic	Statin Initiators, % (n = 111,494)	Antiglaucoma Drug Initiators, % (n = 32,309)	β -Blocker Initiators, % (n = 136,247)	Nonrestricted, % (n = 21,949,868)
Health-care use				
No. of hospitalizations ^a	0.8 (1.2)	0.5 (1.1)	0.9 (1.2)	0.4 (1.0)
No. of outpatient visits ^a	12.7 (9.9)	14.2 (11.1)	13.2 (9.9)	12.3 (9.7)
Electrocardiogram	50.3	32.2	58.7	28.8
Colonoscopy	11.0	10.7	11.7	11.1
Fecal occult blood test	9.6	10.2	9.8	9.9
Mammogram	24.7	25.4	23.0	27.6
Prostate-specific antigen test	22.0	21.4	22.0	20.5
Pneumococcal vaccination	7.3	5.9	7.1	6.0
Cancer screening	36.2	36.3	34.5	38.3
Podiatric care	13.3	16.2	13.6	14.0
Rehabilitation care	14.5	11.8	15.3	10.7
Home oxygen	7.6	7.3	8.5	6.6
Ambulance transport	28.3	19.8	32.7	17.2
Wheelchair	3.3	3.0	3.7	2.5
Home hospital bed	1.9	2.0	2.3	1.5
Prescription drug use				
Antiarrhythmic agents	10.7	10.0	13.0	9.0
Antiglaucoma	8.8	100.0	12.4	9.7
Anxiolytic agents	11.1	10.6	11.1	10.7
β blockers	55.9	59.3	100.0	47.1
Bronchodilators	17.9	17.5	18.6	16.6
Calcium channel blockers	35.0	34.9	37.5	31.7
Digitalis glycosides	5.3	4.8	6.5	4.7
Inhaled corticosteroids	10.0	10.4	10.7	9.7
Insulin	8.6	9.8	8.3	7.0
Lipotropics	100.0	59.0	59.1	58.4
Loop diuretics	24.0	23.4	27.8	21.3
Narcotic analgesics	28.5	28.1	30.8	26.9
NSAIDs	26.3	30.5	26.6	25.5
Oral corticosteroids	23.0	22.6	25.0	21.4
Potassium replacements	16.1	15.7	19.0	14.8
Thiazide diuretics	24.9	24.2	25.9	24.4
Vasodilators	16.9	11.6	15.7	10.1

Abbreviations: AIDS, acquired immunodeficiency syndrome; NSAIDs, nonsteroidal antiinflammatory drugs.

^a Values are expressed as mean (standard deviation).

With the censored approach, the crude and weighted hazard ratios for the nonrestricted cohort were 0.60 (95% CI: 0.59, 0.62) and 0.74 (95% CI: 0.73, 0.75), respectively. Restriction resulted in weighted hazard ratios that were closer to the null, except in statin initiators, switchers, and augmenters, in whom the weighted hazard ratio was 0.72 (95% CI: 0.61, 0.84). Among antiglaucoma drug initiators, the weighted hazard ratio was 0.90 (95% CI: 0.57, 1.43). The change in bias relative to the nonrestricted cohort ranged from an increase of 12.2% among statin initiators, switchers, and augmenters to a reduction of 66.4% among antiglaucoma drug initiators.

For all groups, weighted hazard ratios in the uncensored approach were closer to the null than weighted hazard ratios in the censored approach. This was expected because in the uncensored approach, follow-up time after someone in an unvaccinated person-trial became vaccinated contributed to both exposure groups, making them more similar to each other, whereas in the censored approach, follow-up time for an unvaccinated person-trial was censored when vaccination occurred, so that vaccinated person-time was assigned only to the exposed group. Including switchers and augmenters did not have a consistent effect on the weighted hazard ratios. In most situations, inclusion

Figure 2. The 10 most imbalanced baseline covariates between vaccinated and unvaccinated person-trials in a nonrestricted Medicare cohort, as measured by the standardized absolute mean difference, and their balance after restriction of the cohort to specific groups of preventive drug initiators, United States, 2009–2014. The vertical solid line and the vertical dashed line indicate standardized absolute mean differences of 0 and 0.1, respectively.

of switchers and augmenters resulted in lower weighted hazard ratios, but antiglaucoma drugs (hazard ratios of 0.93 to 0.98) and β blockers (hazard ratios of 0.98 to 0.99) in the uncensored approach were an exception to this trend.

DISCUSSION

Restricting the study population to preventive drug initiators can reduce uncontrolled confounding by frailty when estimating the effect of seasonal influenza vaccination on short-term all-cause mortality in older adults. Estimates in the nonrestricted cohort were as expected—there was considerable confounding

in the crude models and residual confounding in the weighted models. While confidence intervals widened because of the restriction, estimates were consistently closer to the null value, except in statin initiators, switchers, and augmenters under the censored approach. Several hazard ratio estimates were above 0.95, which is a substantial improvement from the weighted estimates of 0.74 and 0.85 in the nonrestricted cohort.

The uncensored approach produced estimates closer to the null than the censored approach because the former duplicates person-time across exposure groups when unvaccinated person-trials are vaccinated. Analogs of either approach may be appropriate, depending on the study question, and restriction is feasible under both approaches. We therefore focus our discussion on

Table 3. Mortality Rates Among Adults Aged ≥ 65 Years Before Influenza Season Under the Uncensored Approach, by Vaccination Status, US Medicare Data, 2009–2014

Group	Unvaccinated Person-Trials ^a				Vaccinated Person-Trials				Crude Rate Difference (per 100 P-Y)	Crude Rate Ratio
	No. of Person-Trials	P-Y of Follow-up	No. of Deaths	Crude Mortality Rate (per 100 P-Y)	No. of Person-Trials	P-Y of Follow-up	No. of Deaths	Crude Mortality Rate (per 100 P-Y)		
Nonrestricted	15,739,665	2,378,563	144,154	6.1	6,210,203	889,719	37,430	4.2	−1.9	0.69
Statin initiators	90,976	13,699	968	7.1	20,518	3,094	171	5.5	−1.6	0.77
Statin initiators, switchers, and augmenters	155,269	23,983	1,758	7.3	36,810	5,761	303	5.3	−2.0	0.73
Antiglucoma drug initiators	25,015	3,795	225	5.9	7,294	1,076	51	4.7	−1.2	0.80
Antiglucoma drug initiators, switchers, and augmenters	55,322	8,487	446	5.3	16,441	2,459	117	4.8	−0.5	0.91
β -blocker initiators	114,761	17,049	2,099	12.3	21,486	3,173	318	10.0	−2.3	0.81
β -blocker initiators, switchers, and augmenters	178,059	26,464	3,336	12.6	32,651	4,822	519	10.8	−1.8	0.86

Abbreviation: P-Y, person-years.

^a Reference category.

Table 4. Hazard Ratios for the Association Between Influenza Vaccination and All-Cause Mortality Before Influenza Season Among Adults Aged ≥ 65 Years, US Medicare Data, 2009–2014

Group	Censored HR				Bias Reduction, %	Uncensored HR				Bias Reduction, %
	Crude HR	95% CI	Weighted HR	95% CI		Crude HR	95% CI	Weighted HR	95% CI	
Nonrestricted	0.60	0.59, 0.62	0.74	0.73, 0.75	0 ^a	0.70	0.69, 0.71	0.85	0.84, 0.86	0 ^a
Statin initiators	0.63	0.51, 0.79	0.81	0.65, 1.01	28.8	0.78	0.66, 0.93	1.00	0.84, 1.19	99.4
Statin initiators, switchers, and augmenters	0.58	0.50, 0.69	0.72	0.61, 0.84	–12.2	0.71	0.63, 0.81	0.88	0.77, 1.01	24.6
Antiglaucoma drug initiators	0.75	0.48, 1.18	0.90	0.57, 1.43	66.4	0.78	0.57, 1.09	0.93	0.66, 1.29	53.0
Antiglaucoma drug initiators, switchers, and augmenters	0.78	0.59, 1.05	0.85	0.64, 1.14	47.1	0.91	0.73, 1.13	0.98	0.79, 1.23	90.3
β -blocker initiators	0.70	0.60, 0.82	0.87	0.75, 1.02	54.0	0.82	0.72, 0.92	0.98	0.87, 1.12	90.0
β -blocker initiators, switchers, and augmenters	0.71	0.63, 0.81	0.84	0.74, 0.95	41.4	0.85	0.77, 0.94	0.99	0.90, 1.09	94.1

Abbreviations: CI, confidence interval; HR, hazard ratio.

^a Referent.

the effects of restriction on estimates in both approaches rather than the choice between the two approaches.

Since the reduction in bias varied by initiator group, the choice of restriction criteria is important. Restrictions to initiators should focus on classes of medications that generally have delayed effects and therefore would not be given to frail patients with limited life expectancy. Drugs that treat symptoms and improve quality of life might be a poor choice because their benefits could be realized in the short term. Ideally, drug classes would be selected on the basis of real-world prescribing patterns, since expectations and guidelines may differ from actual practice—this is why we used drug classes that may be artifactually associated with better short-term survival because of selective prescribing (21). Furthermore, the effect of interest should not be modified by the selected drug class or by its indications. This was not a concern in our setting because we used a negative control outcome to assess residual confounding, but effect modification could be problematic in some settings. For example, when estimating vaccine effectiveness, restricting the cohort to statin initiators might be a poor choice due to statins' potential immunomodulatory effects and reduced immune response to vaccination among statin users (27, 28).

Sample size may also be an important consideration in selecting which restriction criteria to use. Our restricted groups ranged from 32,309 person-trials to 210,710 person-trials, but in other settings the more restrictive criteria may result in prohibitively small sample sizes. Including switchers and augmenters may substantially improve sample size, but the causes of switching and augmentation should be consistent with the goal of excluding frail people. For β blockers in our setting, the weighted hazard ratios were similar regardless of whether switchers and augmenters were included, whereas for statins, the inclusion of switchers and augmenters resulted in hazard ratios further away from 1.0. The reasons for switching and augmenting (i.e., a current treatment's lack of effectiveness or side effects) are different from those for initiation, and switchers and augmenters differ from initiators. For example, if switchers and augmenters tend to have more advanced illness, then including switchers and

augmenters might introduce sicker people subject to channeling away from seasonal influenza vaccination, much like frail people, and adversely affect confounding control. Appropriate restriction criteria will need to offer both improvements in confounding control and reasonable sample size. Finally, while we focused on preventive drug initiation, restriction based on other medical interventions may also be suitable.

Beta blockers were chosen as a candidate for restriction because they were shown by Glynn et al. (21) to be associated with a strong reduction in all-cause mortality among New Jersey Medicare beneficiaries between 1991 and 1994. However, in our study, mortality rates among β -blocker initiators were markedly higher than those in the nonrestricted cohort. This is probably a result of profound changes in the indication for β blocker use: Whereas congestive heart failure used to be a contraindication for β -blocker use, since the late 1990s β blockers have become indicated in patients with congestive heart failure based on evidence from randomized trials (29–31). The increased prevalence of patients with congestive heart failure in the population taking β blockers contributes to the increased mortality observed in our study. This suggests that researchers seeking to use this method for confounding control would need to be aware of changing prescribing practices. While a complete switchover from contraindication to indication is probably an infrequent occurrence, such a change could have a large effect on confounding control.

One strength of this study was the use of Medicare data to obtain a large sample, which facilitated investigation of restriction criteria that drastically reduced sample size. Even though restriction excluded 99% of our original sample, it resulted in tens of thousands of initiators and acceptable precision of effect estimates. Another strength was the use of the influenza vaccination setting to take advantage of a negative control outcome. With the expectation that there should be no effect of influenza vaccination on all-cause mortality before the start of the influenza season, we were able to use any observed associations as an indication of residual bias and to examine how residual bias changed as we restricted our study population. Using the negative control outcome meant that we could expect a consistent null effect across all groups, unlike the case in other settings,

where we would have to consider whether the effect of interest differed in the restricted subgroups. Furthermore, the negative control outcome was created by using the outcome of interest in a slightly earlier time period rather than identifying a secondary outcome, so we avoided introducing an alternative confounding structure. In settings where only negative control outcomes with more limitations are available, other approaches may be beneficial (e.g., negative control exposures or multiple negative control outcomes).

However, our study also had some limitations. First, it is unlikely that Medicare insurance claims captured all vaccinations that occurred. Incomplete capture would result in exposure misclassification, which, if nondifferential with respect to the outcome and confounders, would be expected to cause bias towards the null, since the observed exposure groups—mixtures of truly exposed and unexposed people—would be more similar to each other than the true exposed and unexposed groups (32). This exposure misclassification bias is in opposition to confounding by frailty, which spuriously decreases mortality risk in the vaccinated and thus moves estimates away from the null in our study. Furthermore, as noted with β blockers, the effect of restricting the cohort to any of these drug classes may change over time as prescribing patterns evolve. Our approach depends on frail patients' being channeled away from drug initiation, but this may not occur if indications and contraindications change in clinical practice. Finally, drug initiation may be a collider (a variable affected by 2 other variables), and restricting on it may induce M-bias by creating artificial associations between the variables affecting it (33, 34). For example, propensity to seek health care might affect both drug initiation and influenza vaccination (exposure), while the indication for drug initiation might affect both drug initiation and mortality (outcome). This would make drug initiation a collider, and restricting on initiation would create a path from influenza vaccination to mortality (Web Figure 1). The importance of the resulting M-bias depends on the strength and direction of effects along the newly opened path, which would be specific to the drug class considered. However, simulation studies have shown that the bias from conditioning on a collider tends to be small compared with the bias caused by an uncontrolled confounder (35, 36), which is consistent with our results showing a net improvement in confounding control in spite of restricting on a potential collider.

In this retrospective cohort study, we were able to demonstrate reductions in uncontrolled confounding by frailty by restricting our cohort to initiators of medications in specific drug classes. The degree of improvement was not consistent across all drug classes tested, and it further varied by the use of an uncensored or censored approach and by whether switchers and augmenters were included. We conclude that restriction shows promise as a study design approach for reducing unmeasured confounding by frailty in pharmacoepidemiologic studies of older adult populations, but further work is required to determine the most appropriate criteria and settings for use.

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REFERENCES

1. Nichol KL, Nordin J, Mullooly J, et al. Influenza vaccination and reduction in hospitalizations for cardiac disease and stroke among the elderly. *N Engl J Med*. 2003;348(14):1322–1332.
2. Nichol KL, Nordin JD, Nelson DB, et al. Effectiveness of influenza vaccine in the community-dwelling elderly. *N Engl J Med*. 2007;357(14):1373–1381.
3. Hak E, Nordin J, Wei F, et al. Influence of high-risk medical conditions on the effectiveness of influenza vaccination among elderly members of 3 large managed-care organizations. *Clin. Infect. Dis*. 2002;35(4):370–377.

4. Nordin J, Mullooly J, Poblete S, et al. Influenza vaccine effectiveness in preventing hospitalizations and deaths in persons 65 years or older in Minnesota, New York, and Oregon: data from 3 health plans. *J Infect Dis*. 2001;184(6):665–670.
5. Jefferson T, Rivetti D, Rivetti A, et al. Efficacy and effectiveness of influenza vaccines in elderly people: a systematic review. *Lancet*. 2005;366(9492):1165–1174.
6. Jackson LA, Jackson ML, Nelson JC, et al. Evidence of bias in estimates of influenza vaccine effectiveness in seniors. *Int J Epidemiol*. 2006;35(2):337–344.
7. Simonsen L, Reichert TA, Viboud C, et al. Impact of influenza vaccination on seasonal mortality in the US elderly population. *Arch Intern Med*. 2005;165(3):265–272.
8. Jackson ML, Yu O, Nelson JC, et al. Further evidence for bias in observational studies of influenza vaccine effectiveness: the 2009 influenza A(H1N1) pandemic. *Am J Epidemiol*. 2013;178(8):1327–1336.
9. Simonsen L, Viboud C, Taylor RJ, et al. Influenza vaccination and mortality benefits: new insights, new opportunities. *Vaccine*. 2009;27(45):6300–6304.
10. Nelson JC, Jackson ML, Weiss NS, et al. New strategies are needed to improve the accuracy of influenza vaccine effectiveness estimates among seniors. *J Clin Epidemiol*. 2009;62(7):687–694.
11. Fried LP, Ferrucci L, Darer J, et al. Untangling the concepts of disability, frailty, and comorbidity: implications for improved targeting and care. *J Gerontol A Biol Sci Med Sci*. 2004;59(3):255–263.
12. Fried LP, Tangen CM, Walston J, et al. Frailty in older adults: evidence for a phenotype. *J Gerontol A Biol Sci Med Sci*. 2001;56(3):M146–M156.
13. Welch HG, Albertsen PC, Nease RF, et al. Estimating treatment benefits for the elderly: the effect of competing risks. *Ann Intern Med*. 1996;124(6):577–584.
14. Redelmeier DA, Tan SH, Booth GL. The treatment of unrelated disorders in patients with chronic medical diseases. *N Engl J Med*. 1998;338(21):1516–1520.
15. Glynn RJ, Schneeweiss S, Stürmer T. Indications for propensity scores and review of their use in pharmacoepidemiology. *Basic Clin Pharmacol Toxicol*. 2006;98(3):253–259.
16. Song X, Mitnitski A, Rockwood K. Prevalence and 10-year outcomes of frailty in older adults in relation to deficit accumulation. *J Am Geriatr Soc*. 2010;58(4):681–687.
17. Woods NF, LaCroix AZ, Gray SL, et al. Frailty: emergence and consequences in women aged 65 and older in the Women's Health Initiative Observational Study. *J Am Geriatr Soc*. 2005;53(8):1321–1330.
18. Schneeweiss S, Patrick AR, Stürmer T, et al. Increasing levels of restriction in pharmacoepidemiologic database studies of elderly and comparison with randomized trial results. *Med Care*. 2007;45(10 suppl 2):S131–S142.
19. Jackson LA, Nelson JC, Benson P, et al. Functional status is a confounder of the association of influenza vaccine and risk of all cause mortality in seniors. *Int J Epidemiol*. 2006;35(2):345–352.
20. McGrath LJ, Ellis AR, Brookhart MA. Controlling time-dependent confounding by health status and frailty: restriction versus statistical adjustment. *Am J Epidemiol*. 2015;182(1):17–25.
21. Glynn RJ, Knight EL, Levin R, et al. Paradoxical relations of drug treatment with mortality in older persons. *Epidemiology*. 2001;12(6):682–689.
22. Lipsitch M, Tchetgen Tchetgen E, Cohen T. Negative controls: a tool for detecting confounding and bias in observational studies. *Epidemiology*. 2010;21(3):383–388.
23. Hernán MA, Alonso A, Logan R, et al. Observational studies analyzed like randomized experiments: an application to postmenopausal hormone therapy and coronary heart disease. *Epidemiology*. 2008;19(6):766–779.
24. Gagne JJ, Glynn RJ, Avorn J, et al. A combined comorbidity score predicted mortality in elderly patients better than existing scores. *J Clin Epidemiol*. 2011;64(7):749–759.
25. Faurot KR, Jonsson Funk M, Pate V, et al. Using claims data to predict dependency in activities of daily living as a proxy for frailty. *Pharmacoepidemiol Drug Saf*. 2015;24(1):59–66.
26. Brookhart MA, Wyss R, Layton JB, et al. Propensity score methods for confounding control in nonexperimental research. *Circ Cardiovasc Qual Outcomes*. 2013;6(5):604–611.
27. Smaldone C, Brugaletta S, Pazzano V, et al. Immunomodulator activity of 3-hydroxy-3-methylglutaryl-CoA inhibitors. *Cardiovasc Hematol Agents Med Chem*. 2009;7(4):279–294.
28. Black S, Nicolay U, Del Giudice G, et al. Influence of statins on influenza vaccine response in elderly individuals. *J Infect Dis*. 2016;213(8):1224–1228.
29. Hunt SA, Baker DW, Chin MH, et al. ACC/AHA guidelines for the evaluation and management of chronic heart failure in the adult: executive summary. A report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1995 Guidelines for the Evaluation and Management of Heart Failure). *J Am Coll Cardiol*. 2001;38(7):2101–2113.
30. Funck-Brentano C. Beta-blockade in CHF: from contraindication to indication. *Eur Heart J Suppl*. 2006;8(suppl C):C19–C27.
31. Consensus recommendations for the management of chronic heart failure. On behalf of the membership of the advisory council to improve outcomes nationwide in heart failure. *Am J Cardiol*. 1999;83(2 suppl 1):1A–38A.
32. Rothman KJ, Greenland S, Lash TL. *Modern Epidemiology*. 3rd ed. Philadelphia, PA: Lippincott Williams & Wilkins; 2008.
33. Greenland S. Quantifying biases in causal models: classical confounding vs collider-stratification bias. *Epidemiology*. 2003;14(3):300–306.
34. Greenland S, Pearl J, Robins JM. Causal diagrams for epidemiologic research. *Epidemiology*. 1999;10(1):37–48.
35. Myers JA, Rassen JA, Gagne JJ, et al. Effects of adjusting for instrumental variables on bias and precision of effect estimates. *Am J Epidemiol*. 2011;174(11):1213–1222.
36. Liu W, Brookhart MA, Schneeweiss S, et al. Implications of M bias in epidemiologic studies: a simulation study. *Am J Epidemiol*. 2012;176(10):938–948.