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Using Double Negative Controls to Adjust for Healthy User Bias in a Recombinant Zoster Vaccine Safety Study

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Abstract

Unmeasured confounding is a major concern in many epidemiologic studies that are not randomized. Negative control methods can detect and reduce confounding by leveraging the proxies of the unmeasured confounders, including negative control outcomes (NCO) and exposures (NCE). An NCO is presumably unaffected by the exposure of interest but would be associated with unmeasured confounders; an NCE presumably does not affect the outcome of interest but would be associated with unmeasured confounders. A recently proposed double negative control method leverages both NCO and NCE for unmeasured confounding bias. To demonstrate this relatively new methodology in pharmacoepidemiologic studies, we re-analyzed data from a prior safety study of Recombinant Zoster Vaccine (RZV). The prior study compared risk of safety outcomes of RZV versus unvaccinated comparators, using logistic regression with propensity score adjustment. We identified NCOs and NCEs that could be used to adjust for unmeasured confounding bias that could arise if RZV recipients are incomparable to the

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comparators due to unmeasured factors. The double negative control analysis yielded relative risk estimates slightly closer to 1.0 than those reported previously, providing additional evidence of RZV safety that is less vulnerable to unmeasured confounding.

Keywords

Vaccine safety monitoring; proximal causal inference; unmeasured confounding; vaccine effectiveness

Introduction

Unmeasured confounding is a major concern in pharmacoepidemiologic studies in older adult populations. If not accounted for, unmeasured confounding may lead to profoundly misleading causal conclusions. For example, influenza typically accounts for fewer than 10% of all deaths among the elderly each winter, but observational studies have reported that influenza vaccination reduces all-cause winter mortality among the elderly by up to 50%, clearly demonstrating substantial bias^{1,2}. Many sources of bias may contribute to unmeasured confounding. A well-documented source is healthy-user bias: users of a preventive service are more likely than nonusers to engage in other health-promoting behaviors that lead to better health outcomes. In observational studies of hormone replacement therapy (HRT) on cardiovascular diseases for women during menopause, researchers found that HRT users tend to be higher educated, have a better risk factor profile, and do more leisure exercise than nonusers pre-menopause, suggesting at least part of the estimated benefits of HRT may have been due to unadjusted pre-existing characteristics³. Adherence bias is source of unmeasured confounding bias, which is caused by the association between adherence to the treatment and the health outcome. In a meta-analysis to study drug adherence and mortality, good adherence to placebo was found to be associated with lower mortality in eight studies (pooled odds ratio: 0.56; 95% CI: 0.50–0.63), indicating that the estimated treatment effect may generally be biased if one does not account for different adherence between treatment arms⁴. Other forms of potential unmeasured confounding bias include prevention bias, survivor bias, and so on⁵. These biases can be difficult to control, especially when using clinical health care data sources such as electronic health records (EHR)⁶.

Negative control methods have emerged as a popular way to detect unmeasured confounding, but the newer negative control methods for reducing and correcting for unmeasured confounding are less used^{7,8}. These methods utilize measured proxies of unmeasured confounders: 1) a negative control outcome (NCO) that is a priori known not to be causally affected by the exposure of interest, and 2) a negative control exposure (NCE) that is a priori known not to causally affect the outcome of interest. NCOs and NCEs are selected such that they are subject to the same source of unmeasured confounding as the primary outcome and exposure. As such, conditional on measured covariates, an observed association between the NCO and the exposure or between the NCE and the outcome may indicate the presence of unmeasured confounding bias, which is sometimes referred to as a “falsification test” or “bias indicator analysis”^{9–15}. As an example of negative control,

consider a study of influenza vaccine effectiveness against mortality in older adults. To quantify potential confounding bias, researchers used all-cause mortality during the period prior to influenza season (i.e., a time period when influenza is not yet circulating and so no effect of vaccine can exist) as the NCO. The large size of the estimated risk ratio (RR=0.39, 95% CI 0.33–0.47 before the influenza season) suggested that confounding bias may have impacted the vaccine effectiveness estimates of the primary outcome¹⁵. However, the type of “bias indicator analysis” does not answer all questions about unmeasured confounding, but only whether unmeasured confounding is present. For example, if the primary analysis found a significant association, but the bias indicator analysis revealed the existence of confounding, it is unclear what the true effect size is and whether it remains the same direction once the bias is corrected. On the other hand, if the primary analysis did not find a significant association and the bias indicator analysis revealed presence of unmeasured confounding, the sign and magnitude of the true effect size also remains unclear. Therefore, it is important to not only detect the unmeasured confounding, but also account for the confounding in effect estimation.

Recombinant Zoster Vaccine (RZV) is a 2-dose vaccine for preventing herpes zoster and its complications (Shingrix[®], GlaxoSmithKline)^{16,17}. Post-licensure observational studies have examined RZV safety among adults aged 50 and above^{18,19}. However, the previous analyses did not systematically address potential unmeasured confounding.

In this article, we will showcase the double negative control approach, which leverages both NCEs and NCOs to correct the unmeasured confounding bias^{7,20,21}. We will re-analyze the EHR data from a prior RZV safety study¹⁸, re-calculate the relative risk estimates for the associations between RZV and selected safety outcomes and confidence intervals using the double negative control method, and compare them to a propensity score adjusted regression method used in the prior study.

METHODS

Data acquisition and study design

We used data from a prospective post-licensure RZV safety study conducted through the Vaccine Safety Datalink (VSD), a collaboration between thirteen healthcare systems and the Centers for Disease Control and Prevention¹⁸. EHR data on immunizations, medical utilizations, and demographics were captured on adults aged 50 and older who either received RZV or had a qualifying annual well-visit at one of seven VSD-participating managed care organizations (MCO): Kaiser Permanente of Northern California, Oakland, California; Kaiser Permanente of Southern California, Pasadena, California; Kaiser Permanente Northwest, Portland, Oregon; Kaiser Permanente Washington, Seattle, Washington; Kaiser Permanente Colorado, Denver, Colorado; Marshfield Clinic Research Foundation, Marshfield, Wisconsin; and HealthPartners, Bloomington, Minnesota. The study began in January 2018, when RZV usage began at some VSD sites, and continued for two years until December 2019. Each MCO’s institutional review board approved this study; additional informed consent was not required.

Primary exposure and comparator groups

The primary exposure group, hereafter referred to as the “RZV recipients”, was composed of adults aged 50 and older who received at least one dose of RZV (representing >99% of all doses RZV vaccine doses received during study period), as identified by Administered Vaccine (CVX) code 187, at the participating MCOs during the surveillance period. The comparator group, referred to as “well-visit comparators,” included adults aged 50 years and older who, during the study period, sought care at participating MCOs for an annual well-visit and did not receive RZV on or before the well-visit date. Annual well-visits were identified by ICD-10-CM diagnosis codes Z00.00 and Z00.01. If an individual had more than one eligible well-visits during the surveillance period, one representative visit was selected per study year (2018 and 2019). Individuals were excluded from the well-visit comparator group if they had unknown gender information or had more than three well-visits during the surveillance period (as this high frequency could either be an error or reflective of unusual health-seeking behavior). In sensitivity analyses, we used a subset of the well-visit group composed of those who also had received a documented influenza vaccine in the year prior to their well-visit, referred to as the “well-visit + flu shot comparators”; this was the main comparator group used in the original RZV safety study¹⁸.

We chose well-visit comparators instead of the well-visit + flu shot comparators as our primary comparator group because the differences in healthcare-seeking behaviors between RZV recipients and well-visit comparators were expected to be greater than the differences between RZV recipients and the well-visit + flu shot subset in the original RZV safety study¹⁸. Specifically, well-visit comparators exhibited the lowest frequencies of healthcare-seeking behaviors among the three comparator groups (e.g., having an optometry or ophthalmology visit in the prior year). Therefore, we hypothesized that unmeasured confounding would be more severe when using the well-visit comparators, allowing us to better demonstrate the benefits of correcting such bias using the double negative control method.

Safety outcomes

We selected four safety outcomes: stroke, acute myocardial infarction (MI), pneumonia, and gout, defined using ICD-10-CM diagnoses codes assigned by healthcare providers to outpatient (OP), emergency department (ED), urgent care (UC), or inpatient (IP) hospital encounters. Each outcome was assessed on Day 1 (i.e., the day after the index RZV vaccination or well-visit date) through Day 42. Outcomes were excluded if any of the ICD-10-CM codes for the same outcome were recorded during the 365 days prior to the index date to avoid inclusion of follow-up appointments for events that occurred prior to the index. Table 1 details the complete list and definitions of the safety outcomes.

These safety outcomes were chosen according to clinical significance, potential for unmeasured confounding, and biological plausibility. The relevance of an outcome was determined based on the safety profiles of prior vaccines as well as data from pre-licensure studies of RZV²². We aimed to correct unmeasured confounding primarily due to healthcare-seeking behavior, so we sought to prioritize safety outcomes that were determined to have a greater susceptibility to confounding by healthcare-seeking behavior

through a combination of expert opinion and prior literature^{18,23–25}. We chose to investigate only the more common safety outcomes because performance of the statistical methods used in this analysis has not been fully examined in settings with extremely rare outcomes²⁶.

Potential confounders

Baseline characteristics were captured during the 365 days prior to the index RZV vaccination or well-visit date. Selected covariates included age in years at vaccination or well-visit date, MCO site, sex, and indicators of healthcare-seeking behavior including dermatology visits in the past year (yes/no), optometry/ophthalmology visits in the past year (yes/no), receipt of influenza vaccine in the prior year (yes/no), and any prior history of Zoster Vaccine Live (Merck and Co., etc.) (ZVL) vaccination (yes/no). In the double negative control method, if a variable is included as the negative control exposure (e.g., dermatology visit), then it is not included as the confounder. When studying cardiovascular safety outcomes, i.e., acute MI and stroke, we additionally adjust for prior histories of comorbid conditions, including diabetes, hypertension, hyperlipidemia, and ischemic conditions (ischemic heart disease, transient ischemic attack, or prior stroke). Table S1 in Appendix S1 details all covariates included in the analysis defined using ICD-10-CM, CVX, or department codes.

Negative control outcomes and exposures

Negative control variables are measured proxies of the unmeasured confounder. The key criteria of negative control variables and assumptions under which the double negative control method is viable are detailed in Shi et al.⁷ and listed in Appendix S2. Most importantly, the selected negative control variables should satisfy the negative control independence assumptions (NCEs are assumed to have no direct effect on the outcome, and NCO are assumed not to be directly affected by the exposure) and U-relevance assumption (both NCE and NCO are associated with the unmeasured confounder, i.e., healthcare-seeking behavior). Figure 1 shows the directed acyclic graph (DAG) of a scenario where the variables satisfy the required conditions. Shi et al. provided a more comprehensive list of DAGs with valid negative controls⁷.

We identified a list of potential NCEs and NCOs (See Table S2 in Appendix S1), presumably associated with subjects' healthcare-seeking behavior, based on literature review and input from subject-matter experts^{18,25,27–30}. For example, previous dermatology visits are a potential NCE because a dermatology visit is unlikely to cause the safety outcomes in the study, but having prior dermatology visits may reflect more active healthy behaviors. The primary goal of the search is to ensure that the selected negative control variables satisfy the required conditional independence assumptions while potentially being relevant to the unmeasured healthcare-seeking behavior (U-relevant). We did not analyze the two extremely rare negative controls, ingrown nail and lipomas, from the candidate list. We then employed a data-driven procedure to select the negative control pairs (NCE and NCO) that are most likely to be U-relevant for each of the four safety outcomes in our analysis. For each safety outcome, let X denote the primary exposure (RZV vs. well-visit comparator), Y denote the presence of the outcome (e.g., stroke), and C denote a vector of observed covariates (e.g., age and gender). Let Z and W denote a candidate NCE (e.g., dermatology visit in the prior

year) and NCO (e.g., hip fracture in the 42 days following vaccination), respectively. In our study, X , Y , Z , and W are all binary. The statistical significance of Z in a logistic regression model of W on X , Z , C and the statistical significance of $\widehat{W}$ in a logistic regression model of Y on X , $\widehat{W}$, C were then evaluated, where $\widehat{W}$ is a prediction of W based on the logistic regression of W on X , Z , C . The negative control pairs with a p-value greater than 0.05 in either model was excluded. This data-driven procedure allows us to check if a specific pairing of Z and W were both strongly associated with the unmeasured confounder whose confounding effect can thus be identified. The final negative control pair for each safety outcome was selected based on the following two criteria: 1) both NCE and NCO were considered plausible to satisfy the required negative control independence assumptions and U-relevance assumption by the subject matter expert; and 2) greater marginal significance of Z in logistic regression model of W on X , Z , C and of $\widehat{W}$ in a logistic regression model of Y on X , $\widehat{W}$, C . We summarize the procedure in Figure 2. More details and rationale of the selection approach are in Appendix S3. Table 1 lists the considered negative control pairs. The selected NCE and NCO for the safety outcomes were dermatology visit and epistaxis respectively for all four safety outcomes.

Statistical analyses

To demonstrate the impact on estimated vaccine effectiveness of an approach that attempts to correct for unmeasured confounding bias, we applied the following methods: 1) the propensity score adjusted regression analysis used in the original RZV safety study¹⁸, and 2) the double negative control approach^{7,20,21}. Both approaches were employed for all four safety outcomes of interest. We used both methods to estimate a marginal RR and 95% confidence intervals for each target outcome among RZV recipients versus well-visit (or well-visit + flu) comparators¹⁸. The propensity score method, as the main analytical method in Nelson et al.¹⁸, used logistic regression to model the association between each safety outcome and receipt of RZV vaccination, flexibly adjusting for the propensity of receiving RZV using cubic splines. The average risk of safety outcomes in the RZV and well-visit groups were then estimated by standardization and marginal RR was then computed³¹.

The double negative control method incorporated the same healthcare-seeking behavior proxy variables (i.e., that were used in the propensity score adjustment method in the original RZV study) as negative control variables, acknowledging that the proxies were imperfect measures of the unmeasured confounders. For simplicity, let U be an unmeasured confounder (e.g., healthcare-seeking behavior). See Table 1 the finalized negative control pair in the primary analysis. Let $Y(x)$ denote the potential outcome had the individual received RZV ($x=1$) or not ($x=0$). For a pair of binary negative control variables Z (i.e. NCE) and W (i.e. NCO), the average risk of potential outcome $Y(x)$ conditional on the measured confounders C , denoted by $E[Y(x)|C]$ was estimated using Equation (1) as below:

$$E[Y(x)|C] = \frac{E(Y|X = x, Z = 0, C) - E(Y|X = x, Z = 1, C)}{P(W = 0|X = x, Z = 0, C) - P(W = 0|X = x, Z = 1, C)} \times \frac{P(W = 1|C)}{P(W = 0|C)} \quad (1)$$

We gave a formal derivation of Equation (1) in Appendix S4 of the Web Material.

Logistic regression was used to estimate the conditional mean of both the target outcome $E(Y|X = x, Z = z, C)$ and the negative control outcome $P(W = 1|X = x, Z = z, C)$ for $x, z = (0, 1)$. The conditional probability $P(W = 1|C)$ was estimated by the relationship $P(W = 1|C) = \sum_{z,x=0,1} P(W = 1|Z = z, X = x, C)P(Z = z|X = x, C)P(X = x|C)$, where the conditional probabilities $P(Z = z|X = x, C)$ and $P(X = x|C)$ were also estimated by logistic regression. We do not directly use regression models to estimate $P(W = 1|C)$ because such a model may be incompatible with the regression models for $P(W = 1|Z = z, X = x, C)$, causing model misspecification bias. The marginal mean potential outcome $E[Y(x)]$ was then computed by standardization. We computed the marginal RR as the ratio of marginal mean potential outcome estimates, i.e. $RR = E[Y(1)]/E[Y(0)]$. To calculate standard error, we computed the sandwich variance using standard estimating equation theories, incorporating the uncertainty from all intermediate modeling steps in the calculation of RR³².

Sensitivity analyses

To assess the robustness of our approach against different choices of comparator groups and negative controls, we performed two sensitivity analyses. First, we repeated the primary analysis but used the well-visit + flu shot comparators instead of the full well-visit comparators. Since receipt of influenza vaccine was used to define the well-visit + flu shot comparator group, 'receipt of influenza vaccine in the prior year' was not used in the vector of measured confounder C . For the double negative control method, we used the same NCE (dermatology visit in the prior year) and NCO (epistaxis) as the primary analysis. Second, the list of candidate negative control variables may have different sampling errors that could affect the point estimates and standard errors in finite samples. To assess the impact of the choice of one double negative control pair over another, we calculated estimates and confidence intervals for pneumonia using four feasible negative control pairs and one cardiovascular target outcome (acute MI) using ten feasible negative control pairs from Step 3 in Figure 1.

RESULTS

Table 2 details baseline characteristics of RZV recipients, well-visit comparators, and well-visit + flu shot comparators. A total of 650,701 participants received at least one dose of RZV in the two-year study period. There were 1,869,067 well-visits indexed in the study period and 1,089,165 well-visits for which the study participant had also received an influenza vaccine in the prior year. RZV recipients were, on average, slightly older than well-visit comparators. They were more likely to seek preventive care such as vaccinations, dermatology visits, and optometry/ophthalmology visits. They were more likely to have a record of comorbid conditions such as hypertension and hyperlipidemia, within the past year. The distribution of gender was similar across groups, although a slightly higher proportion of women received RZV compared to men. As hypothesized, the prevalence of many healthy user indicators (prior Zoster vaccination, prior pneumonia vaccination, optometry/ophthalmology visits in the past year, and dermatology visits in the past year) of the well-visit + flu shot comparator group fell in between those of the RZV recipients

and the well-visit comparators. The proportion of participants from each MCO site in the well-visit + flu shot comparator group was approximately the same as in the well-visit group, suggesting that influenza vaccination rates were relatively consistent across sites.

Table 3 shows RR estimates and confidence intervals for associations between RZV receipt and the four target safety outcomes for both the propensity score-adjusted approach and the double negative control method. Using the well-visit comparator group, the propensity score-adjusted analyses estimate the RR for acute MI, stroke, gout, and pneumonia to be 0.78 (95% CI: 0.70, 0.90), 0.83 (95% CI: 0.71, 0.96), 1.10 (95% CI: 1.03, 1.16) and 0.81 (95% CI: 0.71, 0.90), respectively. This suggests a potential protective effect of RZV on acute MI, stroke, and pneumonia, and a potential harmful effect on gout. The results of the double negative control method are similar, with the estimated RRs for acute MI, stroke, gout, and pneumonia to be 0.83 (95% CI: 0.72, 0.96), 0.89 (95% CI: 0.76, 1.04), 1.09 (95% CI: 1.02, 1.16) and 0.90 (95% CI: 0.80, 0.99), respectively. Notably, the negative association of RZV with stroke is not statistically significant. In general, the double negative control approach yielded comparable or slightly attenuated RR estimates, validating the conclusions of the previous analysis.

We present the results of the sensitivity analyses for the impact of different comparator groups and negative control pairs in Appendix S5 of the Web Materials. The choice of the well-visit comparators versus the well-visit + flu shot comparators did not remarkably alter our conclusion. For example, the propensity score adjusted logistic regression estimated the RR for acute MI to be 0.80 (95% CI: 0.68, 0.94) while the double negative control method estimated the RR to be 0.84 (95% CI: 0.71, 1.00). For acute MI and pneumonia, the choices of different negative control outcome variables mostly produced similar point estimates of RR but some negative control pairs may produce wider confidence intervals which covered one, likely due to increased standard errors. For example, with cataract as NCE and epistaxis as NCO, the estimated RR for acute MI is 0.84 (95% CI: 0.68, 1.06).

DISCUSSION

Unmeasured confounding is a key concern for observational studies of preventive therapies in older adult populations conducted using EHR data, where data have been gathered for the purposes of clinical care and where confounders are not proactively measured for research purposes. We demonstrate a novel method for quantifying some sources of unmeasured confounding bias and explicitly correct for this bias in their estimation efforts, including computing confidence intervals that account for the additional uncertainty that unmeasured confounding introduces. Compared with the previously proposed single negative control counterparts, which often rely on rank preservation or equi-confounding assumptions that can rarely be justified in practice^{33,34}, the assumptions for this newer double negative control approach are mild and can be often verified by prior domain knowledge. Using data from a prior RZV post-licensure safety study¹⁸, we found that the results of traditional covariate adjustment methods mostly align with our double negative control method for the four safety outcomes under consideration, suggesting that the presence of potential unmeasured confounding may not significantly alter the causal conclusions. Our analysis demonstrates a principled approach and exemplifies the necessary steps for detecting

and correcting confounding bias for future post-market vaccine effectiveness and safety evaluation.

We hypothesized that the results of the analyses with the double negative control method versus the propensity score adjusted regression method would be more similar when using the well-visit + flu shot comparator group than when using the well-visit comparator group. This is because the well-visit + flu shot comparators may have exhibited health-seeking behavior more similar to the RZV group in the original RZV safety study, thus potentially reducing the amount of unmeasured confounding. Our results in the Appendix S5 of the Supplementary Material supported this hypothesis; estimates and confidence intervals were more similar between the double negative control analysis and the flexible propensity score regression analysis when well-visit + flu shot comparators were used than well-visit comparators.

A major advantage of the double negative control method is that it allows correction for unmeasured confounding between two independent groups, making the use of concurrent comparators a much more viable option. In vaccine safety surveillance studies, vaccinated and unvaccinated individuals are often fundamentally different, necessitating the use of self-controlled design or historical comparators, which have other important known weaknesses^{35–41}. Limitations of self-controlled study designs include susceptibility to bias when event rates are not constant within the study period⁴⁰. When using historical comparators or self-controlled design, temporal trends in the target outcome, or in diagnostic or coding practices may lead to false signaling or failure to identify a true safety signal^{35,40}. Using a concurrent comparator group avoids risk of temporal bias.

Our analysis has several limitations. The proposed approach requires correct specification of the causal diagram. A wrongly specified DAG may cause biased or numerically unstable causal effect estimates. As such, extensive input from domain experts and a careful evaluation of causal assumptions are needed to ensure the correctness of the causal DAG. We used a data-driven approach to choose appropriate double negative controls for a given outcome and exposure of interest. However, the ideal choice of negative control may not always be clear in practice. Our sensitivity analysis that used multiple different negative control pairs to estimate a particular vaccine-outcome association demonstrated that the choice of double negative control can influence the estimated comparative risk statistics from the analysis, although from our sensitivity analysis, use of different negative control variables did not lead to a reversal of an observed decrease in risk to an observed increase in risk or vice versa; the only difference was that different choices of negative control variable pairs may result in effect size estimates of varying standard errors. It is also possible that the low NCE or NCO prevalence may limit the power of detecting an association. Future simulation study research that evaluates use of the double negative control methodology under a variety of scenarios related to the choice of the negative control pair or the use of multiple negative control variables is important to gain further understanding of the method's properties. The double negative control method requires both NCE and NCO to be associated with the unmeasured confounder and can only correct bias to the extent of the association. In other words, if there exist other unmeasured confounders which are not associated with the NCE or NCO, bias due to those unmeasured confounders may remain.

In Appendix S3.2, we exemplified a case where the selected negative control variables failed to capture the bias introduced by the concerned unmeasured confounder. In such cases, the negative control method may not produce an estimator, or the resulting estimator may be numerically unstable, which further highlights the importance of domain experts' input to ensure the correctness of the proposed causal DAG. Additional model misspecification bias may arise in our method. We used a logistic regression model for $P(W=1|Z=z, X=x, C)$ and compatible regression models for $P(W=1|C)$, but further reducing the bias is possible through nonparametric regression. Negative control methods have been developed to incorporate more flexible estimation for the nuisance functions while maintaining valid inference, which require different statistical assumptions and extensive statistical programming⁴². As this manuscript aims to demonstrate the application of negative control methods in epidemiological studies, we do not pursue those directions. In our final analysis, we used a single NCE and NCO pair, but as demonstrated in Appendix S4, NC variables with multiple categories or multiple NC variables may be used to capture different facets of the unmeasured confounding. Selection of multiple negative control variables, however, is notably more challenging and shall be left for future research. Other limitations of the data that may also compromise the validity of our conclusions, including incomplete data capture due to delays in receipt of some insurance claims by MCO systems, the potential misclassification of safety outcomes, and the potential misclassification of vaccination status^{35–41}.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement:

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to patient privacy and ethical restrictions.

Abbreviations:

CDC	Centers for Disease Control and Prevention
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CI	confidence interval
DAG	directed acyclic graph
ED	emergency department
ICD-10-CM	International Classification of Diseases, Tenth Edition
IP	inpatient
MCO	managed care organizations
MI	myocardial infarction
NCE	negative control exposure
NCO	negative control outcome
OP	outpatient
VSD	Vaccine Safety Datalink

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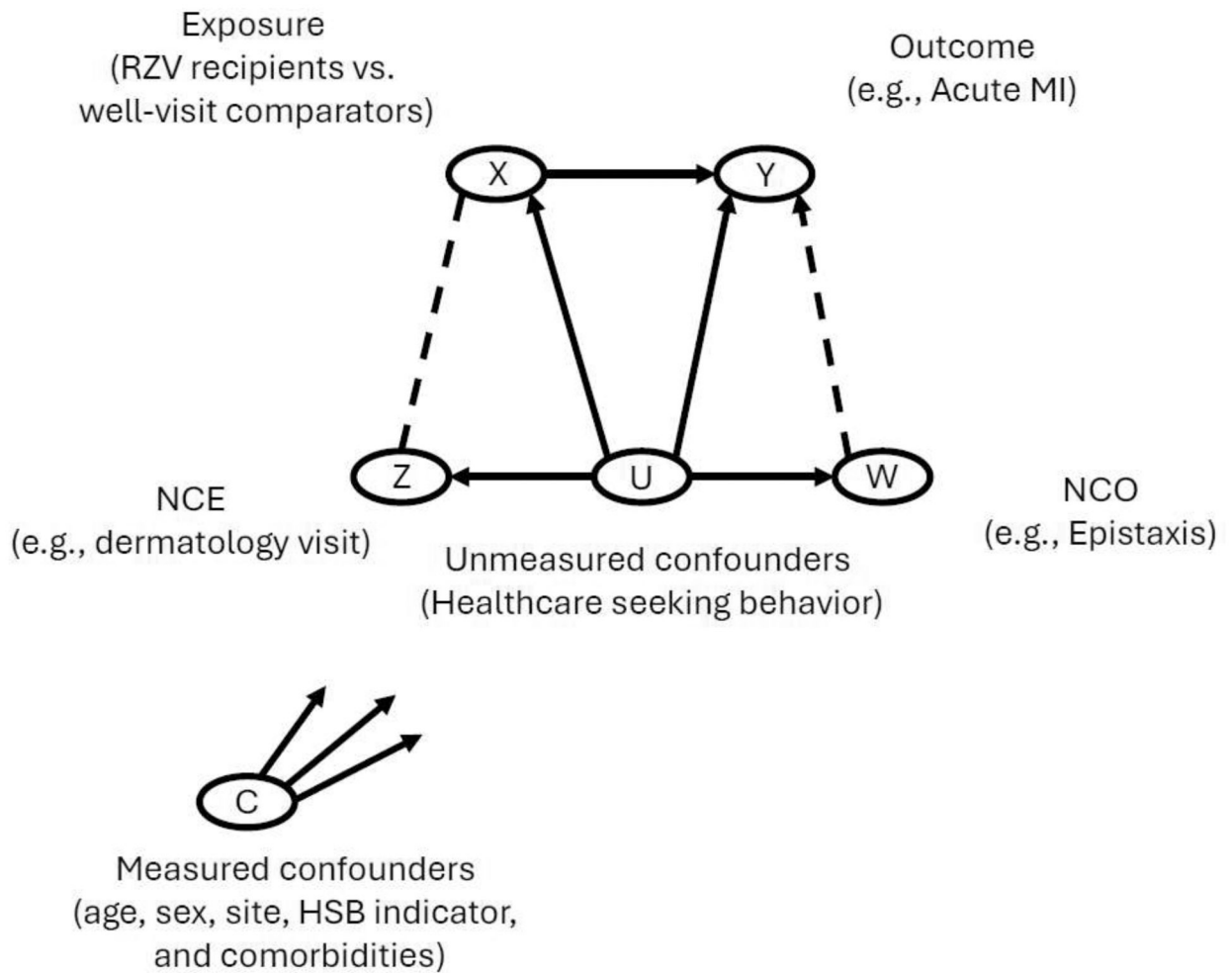
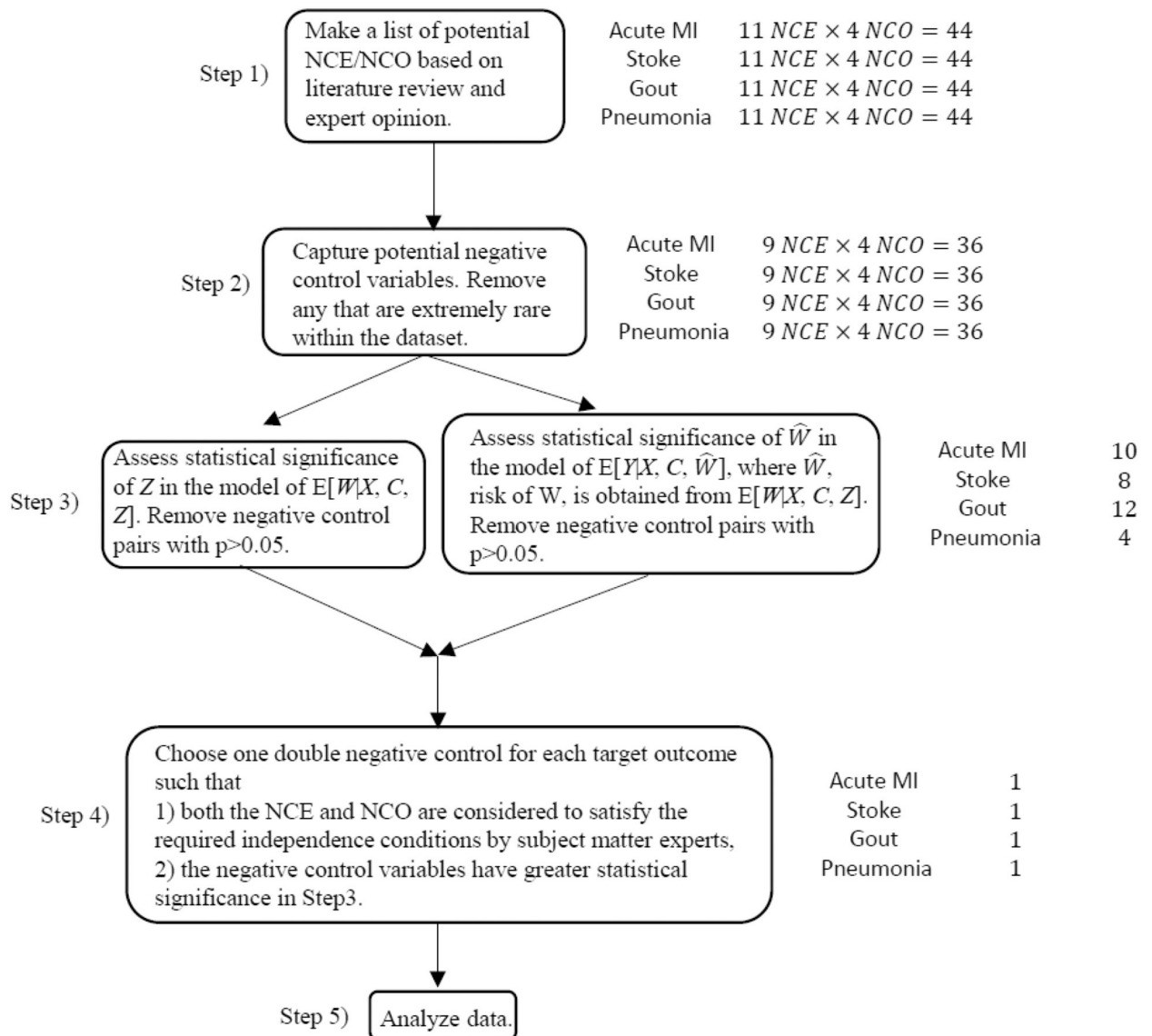


Figure 1:

An example of a directed acyclic graphs (DAG) illustrating assumptions for the double negative control method. The double negative control method acknowledges that measured covariates may be imperfect proxies of the unmeasured confounders and can be classified into measured confounder, negative control exposure (NCE) and negative control outcome (NCO) based on their relationship to other variables. The measured confounders C have arrows towards every other variable. The dashed line between X and Z indicates that direction of the arrow may go either way. The dashed arrow indicates W may have a causal effect on Y.

**Figure 2:**

Flow chart of principled approach to determine primary double negative controls. Notation: W , negative control outcome; Z , negative control exposure; X , exposure of interest; Y , outcome of interest; C , measured confounders. The right side shows the numbers of remaining negative control pairs under consideration after every step.

Table 1:

Operational definitions of negative control variables used in primary analysis for the Vaccine Safety Datalink, January 2018 - December 2019.

	Operational Definition ^a	Medical Setting	Pre/Post-vaccination Interval ^b
Negative Control Exposure			
Dermatology Visit	Department: DRM	IP, ED/UC, OP	1–365 days prior to index date
Negative Control Outcome			
Epistaxis	ICD10: R04.0	IP, ED/UC, OP	1–42 days after index date

^a 4-digit ICD-10 codes included those that started with those 4 digits and had any 5th digit.

^b Index date refers to the date of the indexed RZV vaccination or well-visit.

Table 2:

Baseline characteristics of the study population for the Vaccine Safety Datalink, January 2018 - December 2019.

	RZV	Wellness Visit	Wellness + Flu Visit	Total
	N=650,701	N=1,869,067	N=1,089,165	N=2,519,768
Safety Outcome, N (%)				
Acute MI	328 (0.05%)	974 (0.05%)	601 (0.06%)	1,302 (0.05%)
Stroke	287 (0.04%)	826 (0.04%)	501 (0.05%)	1,113 (0.04%)
Gout	1,903 (0.29%)	4,564 (0.24%)	2,944 (0.27%)	6,467 (0.26%)
Pneumonia	517 (0.08%)	1,545 (0.08%)	1,055 (0.10%)	2,062 (0.08%)
Age Group, N (%)				
50–54	39,785 (6%)	298,638 (16%)	124,000 (11%)	338,423 (13%)
55–59	67,529 (10%)	324,672 (17%)	148,183 (14%)	392,201 (16%)
60–64	123,925 (19%)	322,079 (17%)	171,533 (16%)	446,004 (18%)
65–69	135,332 (21%)	317,421 (17%)	203,573 (19%)	452,753 (18%)
70–74	128,188 (20%)	257,261 (14%)	180,860 (17%)	385,449 (15%)
75–79	80,775 (12%)	161,275 (9%)	118,746 (11%)	242,050 (10%)
80+	75,167 (12%)	187,721 (10%)	142,270 (13%)	262,888 (10%)
MCO Site, N (%) ^a				
NCK	218,063 (34%)	903,726 (48%)	524,413 (48%)	1,121,789 (45%)
KPC	45,863 (7%)	149,318 (8%)	96,260 (9%)	195,181 (8%)
HPM	67,344 (10%)	113,213 (6%)	60,050 (6%)	180,557 (7%)
MFC	11,073 (2%)	72,225 (4%)	36,636 (3%)	83,298 (3%)
NWK	34,839 (5%)	60,121 (3%)	36,348 (3%)	94,960 (4%)
SCK	211,922 (33%)	447,690 (24%)	273,665 (25%)	659,612 (26%)
KPWA	61,597 (9%)	122,774 (7%)	61,793 (6%)	184,371 (7%)
Female, N (%)	378,475 (58%)	1,008,879 (54%)	600,488 (55%)	1,387,354 (55%)
Healthy user indicator, N (%)				
Zostavax during prior year	374,431 (58%)	746,049 (40%)	563,930 (52%)	1,120,480 (44%)
Influenza vaccine during prior year	531,022 (82%)	1,089,165 (58%)	1,089,165 (100%)	1,620,187 (64%)
OPT/OPH visit during prior year	319,407 (49%)	671,436 (36%)	458,493 (42%)	990,843 (39%)
Dermatology visit during prior year	150,559 (23%)	236,787 (13%)	168,111 (15%)	387,346 (15%)
Pneumonia vaccine during prior year	80,648 (12%)	117,319 (6%)	91,999 (8%)	197,967 (8%)
Comorbidity in Year Prior, N (%)				
Diabetes	116,932 (18%)	269,938 (14%)	186,006 (17%)	386,870 (15%)
Hypertension	283,139 (44%)	585,135 (31%)	402,577 (37%)	868,274 (34%)
Hyperlipidemia	315,577 (48%)	585,951 (31%)	411,335 (38%)	901,528 (36%)
Ischemic Heart Conditions ^b	58,787 (9%)	114,372 (6%)	82,537 (8%)	173,159 (7%)

^aNCK: Kaiser Permanente of Northern California; KPC: Kaiser Permanente Colorado; HPM: HealthPartners; MFC: Marshfield Clinic Research Foundation; SCK: Kaiser Permanente of Southern California; NWK: Kaiser Permanente Northwest; KPWA: Kaiser Permanente Washington.

^b Presence of ischemic heart disease, transient ischemic attack, or prior stroke.

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Table 3:

Relative risk of target safety outcomes between RZV vaccinees and well-visit comparators for the Vaccine Safety Datalink, January 2018 - December 2019.

Safety Outcome	Analysis Used	
	Negative Control Method	Propensity-Adjusted Analysis
Acute MI	0.83 (95% CI: 0.72, 0.96) *	0.79 (95% CI: 0.68, 0.90) *
Stroke	0.89 (95% CI: 0.76, 1.04)	0.83 (95% CI: 0.71, 0.96) *
Pneumonia	0.90 (95% CI: 0.80, 0.99) *	0.81 (95% CI: 0.72, 0.90) *
Gout	1.09 (95% CI: 1.02, 1.16) *	1.10 (95% CI: 1.03, 1.16) *

* Indicates the confidence interval does not include 1.

All analyses adjusted for sex, study site, age group (50–54, 55–59, 60–64, 65–69, 70–74, 75–79, 80+), and select healthy user indicators. Healthy user indicators were influenza vaccine in prior year (yes/no), dermatology visit in prior year (yes/no), optometry/ophthalmology visit in prior year (yes/no), and Zostavax vaccine in prior year (yes/no). If an indicator was included as a negative control exposure, that indicator was not used as a covariate. Analyses of cardiovascular outcomes (e.g., acute MI, stroke) additionally adjusted for the cardiovascular risk factors hypertension, hyperlipidemia, diabetes, and ischemic heart condition (presence of ischemic heart disease, TIA, or stroke).