Causal Mechanisms for Influenza Inoculations

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1 Introduction

In many health applications, conducting randomized experiments can be difficult because of ethical issues. For example, if we want to learn about the effect of influenza vaccines on hospitalization, it would be unethical to randomly select some patients to receive the vaccine and withhold the vaccine from others. Hence, encouragement designs are often used to change the vaccine uptake in one group without affecting vaccine usage in the other group, and then to tease apart the effect of the vaccine on hospitalization by comparing the two groups.

We perform a re-analysis of one such study, McDonald et al. (1992; henceforth 'the MacDonald study') [6], who studied the effect of computer reminders for influenza vaccination on morbidity during influenza epidemics. The study design had physician-patient pairs, with physicians randomly chosen to receive reminders when patients with scheduled appointments were eligible for influenza vaccination. The study found that the patients whose physicians received the reminders (the treatment group) had significantly less morbidity, measured in terms of a few different outcomes, than those whose physicians did not (the control group), and concluded that the most likely explanation for this difference was the receipt of the vaccination by the treatment group.

With these sorts of encouragement designs, there is often a noncompliance problem–not every patient who has physician that is reminded will actually be administered the vaccine, and some patients that have physicians that are not reminded will still be administered the vaccine.

The general solution to this problem is to use an instrumental variables approach, which involves an outcome (morbidity), a treatment (vaccine administration), and an instrument which affects the treatment and affects the outcome only through the treatment. In this setup, the randomized reminders to physicians are the natural choice for the instrument.

The assumption that the instrument affects the outcome only via the treatment and not through some other path is called 'exclusion restriction'. Hirano et al. (2000; henceforth 'the Hirano study') [5] gave a commentary on the MacDonald study [6] in which they said that this exclusion restriction assumption might be violated for certain subgroups. For example, upon receiving a reminder to vaccinate, physicians might also provide extra health-related guidance or medication for patients that are older and have pre-existing respiratory conditions. If this is the case, then the instrument (the reminders) would affect the outcome (morbidity) via an path (vaccination in addition to other health advice/medications) that includes more than just the treatment (vaccination). They concluded, via a Bayesian analysis, that vaccination likely had no effect on morbidity.

We re-investigate this study to see how non-Bayesian methods from the course STATS 209 at Stanford perform relative to the results of MacDonald and Hirano.

First, we repeat the instrumental variable analysis but only for the subgroup for which we do not suspect a violation of the exclusion restriction assumption. Then, we re-frame this study as an observational study by including the instrument as another covariate and assessing the effect of the treatment on the outcome. A major assumption of an observational study is that there are no unobserved variables that simultaneously affect both the treatment and the outcome. The two major types of estimators in the observational study paradigm are matching estimators and inverse propensity weighting estimators. We explore each of

these in addition to estimation via logistic regression, since that is commonly used for binary outcomes in epidemiology [3].

2 Data and Exploratory Analysis

The MacDonald study considers patients who participated in three-year randomized trials of preventive-care reminders, from 1978 to 1980, affiliated with a large urban public teaching hospital. We use 2681 individuals observed in the 1980 run of the study, similar to Hirano. Each patient i is associated with the treatment variable $D_i \in \{0, 1\}$ indicating receipt of vaccine and a binary encouragement $Z_i \in \{0, 1\}$ indicating whether that physician of patient i was reminded to vaccinate the patient. The outcome of interest is $Y_i \in \{0, 1\}$, indicating flu-related hospitalization during the winter.

In the initial study, the authors of the Hirano study incorporated two covariates: age and chronic obstructive pulmonary disease (COPD), which is a lung disease that causes breathing-related problems. We examine several additional variables available in the dataset: a discrete variable age and binary variables for sex, race, diabetes, heart disease, renal disease, and liver disease. We do not have information about what the binary encoding for race and sex means, so we will refer to them as 'race 1', 'race 0', 'sex 1', and 'sex 0'.

We suspect that COPD and age will affect both the receipt of vaccine and hospitalization status. We are unsure of whether the other covariates will do the same. To avoid data dredging, we will include all of the other covariates in our analyses as well.

We then make exploratory plots of the distribution of covariates across the outcome values. We see in Figure 1 that patients that were hospitalized were more like to have COPD and diabetes, be slightly older, and be of sex 1.

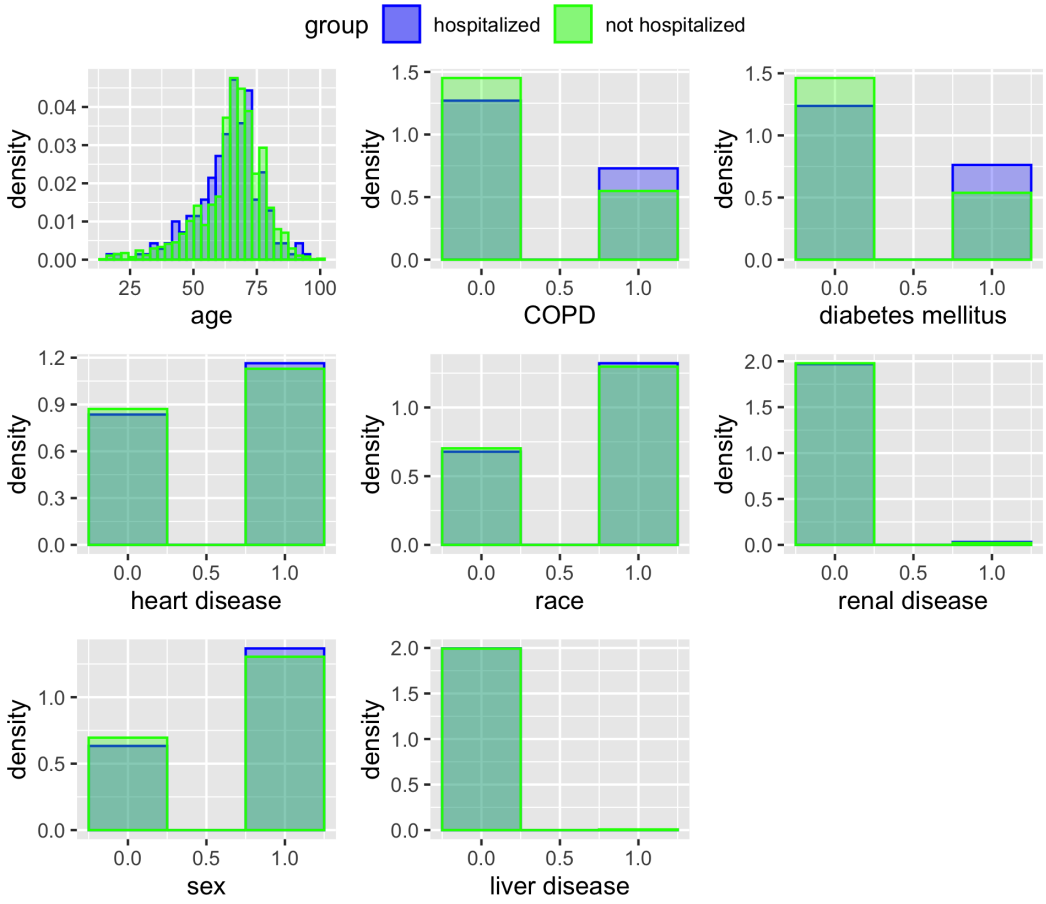

Figure 1: Distributions of covariates across hospitalized and non-hospitalized units.

So it will indeed be important to consider excluding the subgroups that have COPD and are old for instrumental variables.

3 A Modified Instrumental Variable Approach

3.1 Key Assumptions

As stated above, instrumental variable (IV) regression is useful in studies with cases of noncompliance. The IV method relies on three fundamental assumptions for its validity in observational studies. The first is the relevance assumption, which states that instrument Z (reminders to physicians) causally affects treatment D (vaccine administration). The second condition is monotonicity, ensuring that none of the patients are 'defiers,' i.e., there are no people who would accept vaccination if their physician did not receive encouragement but would refuse it if their physician did in fact receive the encouragement. It is reasonable to assume that these first two assumptions holds; the first is tested from the coefficient of the first stage of two stage least squares; this was done in the Hirano study, so we leave it out. The third assumption exclusion restriction; it posits that instrument Z must only influence the outcome Y through its impact on treatment D. We stated above that this assumption might be violated for certain subgroups of the population–in particular, for those that have respiratory diseases and are old, as their physicians might take extra protective measures for the patients beyond just vaccination. In these cases, the change in hospitalization rate may not be due to the vaccination alone, but rather also due to unobserved additional variables like extra medical care and health precautions. Thus, the estimates of the IV regression are potentially biased unless these factors are accounted for.

3.2 Covariate Analysis

Randomization of physician reminder assignments ensures balance in pre-treatment variables between non-assignment and assignment groups. Consequently, in this study, patients with reminded physicians and those with non-reminded physicians exhibit approximately the same characteristics before vaccination. However, it is crucial to note that the randomization does not inherently guarantee balance in sub-samples stratified by the treatment.

	Means				
	Flu Shot $D_i = 1$	No Flu Shot $D_i = 0$	t-stat.	df	p-value
Age	66.9	64.7	4.2893	1385	0.0000***
COPD	0.3408	0.2625	3.8938	1153.2	0.0001***
Diabetes	0.2849	0.2765	0.4350	1216	0.6637
Heart Disease	0.5964	0.5660	1.4312	1237	0.1526
Renal Disease	0.0140	0.0131	0.1816	1192	0.8559
Liver Disease	0.0028	0.0033	-0.2021	1314	0.8399
Race	0.6439	0.6587	-0.7216	1216	0.4707
Sex	0.6355	0.6793	-2.1221	1195	0.0340**

$^{*}\, p < 0.1,\ ^{**}\, p < 0.05,\ ^{***}\, p < 0.01$

Table 1: Summary Statistics of Covariates

Table 1 displays the means of each covariate for individuals who received vaccination and those who did not. Notably, individuals diagnosed with COPD are more likely to receive the influenza vaccine than those without it, regardless of whether their physicians received reminders for inoculation. We also find that older patients are more likely to receive the vaccines. This confirms that perhaps the health status of a patient is related to both the physician reminder and the outcome.

Consequently, in order to have a valid instrument, we focus on a subsample that excludes old patients and patients with COPD. Age 60 typically marks the start of a declining immune system [9], so we use that as the threshold above which individuals are excluded. We also vary that threshold to be between ages 54 and 64 as a sensitivity check.

3.3 Outcomes

We conducted instrumental variables regression using the two-stage least-squares (TSLS) estimation for two models: one without covariates and one controlling for non-respiratory diseases, sex, and race. We find the estimated effect of the influenza vaccine on flu-related hospitalizations to be insignificant for both models. This means that the data provides little

evidence for the efficacy of the influenza vaccine among young individuals that do not have COPD.

Age cutoff point	Estimate	SE	t-stat.	p-value
64	0.0156	0.2384	0.0653	0.9479
62	-0.0000	0.2352	-0.0003	0.9997
60	0.1734	0.2719	0.6376	0.5242
58	0.1965	0.3174	0.6190	0.5363
56	0.2583	0.2900	0.6270	0.5312
54	0.1814	0.2893	0.6270	0.5312

Table 2: IV estimates at different age cutoff points

4 An Observational Study

We now frame this problem as an observational study by including the encouragement indicator as a covariate. The observational study paradigm rests on the assumption that there is no unobserved confounder (i.e., no unobserved variable that simultaneously affects both treatment and outcome). Thus, for each of the methods detailed below, we also perform a sensitivity analysis to assess the feasibility of this assumption for the respective method.

In observational studies, there are two umbrella approaches that one may use. The first is to do some sort of matching based on covariates, and the second is to use some variation of inverse propensity score weighting (IPW). For the latter, an estimator calculated using IPW alone may have high variance if the propensity scores are near 0 or 1, so we will instead use the Augmented IPW (AIPW) estimator, which is more robust.

4.1 Matching

Our first approach to estimating the effect of vaccines on hospitalizations as if we had observational data is to use matching. We first generate three datasets employing different matching procedures, and then estimate the average effect on the treated in each of these datasets.

In our three 'specifications', we match based on all covariates. This is because we believe all of them are plausibly related to some degree to both getting the vaccine and being hospitalized.

The specifications differ in the procedure using to match observations. The first dataset was created by conducing 1:1 matching and setting a caliper of 0.1σ. The second dataset is the result of 1:2 matching. We explore matching each treatment to more than one control as this can reduce variance.[1] Finally, because the 1:2 dataset exhibited imbalance in chronic obstructive pulmonary disease rates (*copd* variable), we created a third dataset that penalized imbalance in *copd*. These datasets were created using functions 'pairmatch' from R package 'optmatch' [4] and 'addcaliper' and 'addalmostexact' from R package 'DOS2' [7].

After matching, we estimated the average treatment effect on the treated. Because the canonical difference-in-means estimator can suffer severe bias in matching contexts ([1]), we estimated the bias-adjusted version provided by Abadie and Imbens (and its associated variance estimator). In addition, we conducted a sensitivity analysis using Huber-Maritz M statistics. More precisely, we used function 'senmv' from the R package 'sensitivitymv' to compute the large sample approximation to the upper bound on the one sided P-value testing the null hypothesis of no treatment effect versus the alternative hypothesis of a reduction in the outcome variable.

The different matching procedures were overall successful in reducing covariate imbalance, as we can see in Figure 2. Before matching, most covariates exhibit imbalance across treatment status. The largest imbalances are for receiving the reminder (which indicates that the intervention was relevant), and - as highlighted before - age and suffering from chronic obstructive pulmonary disease. After matching, these differences decrease dramatically. At the same time, there are slight differences in imbalance patterns across datasets. As

[1] Our original idea was to pair each treatment observation to 5 control observations ($k = 5$). However, the ratio of controls to treatments in our dataset is lower than 3, and the R package *optmatch* [4] is not prepared to set $k > \frac{n_{Z=0}}{n_{Z=1}}$ out-of-the-box. Due to time-constraints, we decided to set $k = 2$

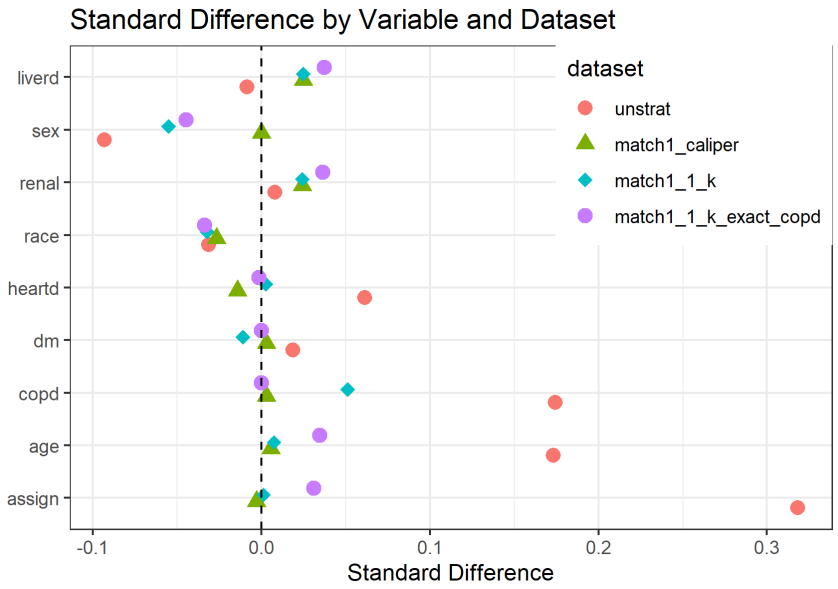

Figure 2: Covariate Imbalance Pre and After Matching

	ATT	CI	Sensitivity p-val	# of pairs
1:1	0.020	[-0.007, 0.048]	0.99	716
1:2	-0.002	[-0.038, 0.033]	1	716
1:2 with exact COPD	-0.001	[-0.036, 0.034]	1	1432

Table 3: Average Treatment on the Treated - Matching estimation

expected, the 1:1 dataset is the one with the lowest degree of imbalance. While 1:2 matching might help lower variance, the quality of matches in that dataset is reduced. Additionally, introducing the penalty on *copd* imbalance helps attain perfect balance in that variable, but at the cost of increasing imbalances in other covariates. Most noticeably, we see increases in imbalance on the 'reminder' and 'age' variables. This suggests that attaining perfect balance for *copd* could come at the cost of introducing other sources of bias.

We present our estimations in Table 3. The estimation conducted using the 1:1 matching procedure has a positive sign, which implies that getting the vaccine *increases* hospitalizations. In contrast, the estimations conducted in the two versions of 1:2 matching are in the expected direction. However, we must note that in all cases, the null result is within the 95% confidence interval and p-values are extremely large. This means that regardless of the matching procedure we employ, evidence strongly suggests that getting the vaccine does not have an impact on hospitalizations.

4.2 AIPW

The AIPW estimator has an important 'double robustness' property, where it relies on either the propensity score model or the outcome mean model to be correctly specified, and is robust to either one (but only one) of those models being misspecified. It is also more efficient than ordinary least squares for nonlinear data. While it is more difficult to interpret because of its complexity, it provides significant improvements over IPW with the double robustness property. We use the 'AIPW' R package [10] to compute the numerical value of the estimator.

	Estimate	SE	N
Risk of treatment	0.0859	0.0107	716
Risk of control	0.0862	0.0061	2145
Risk difference	-0.0003	0.0122	2861
Risk ratio	0.9966	0.1418	2861

Table 4: Results from the AIPW estimator.

From Table 4 we see that the risk difference is very small and the risk ratio is almost 1. Thus it appears that the vaccine treatment did not have any sizeable effect on the outcome of hospitalization.

Figure 3 shows the distributions of propensity scores and inverse propensity weights, respectively.

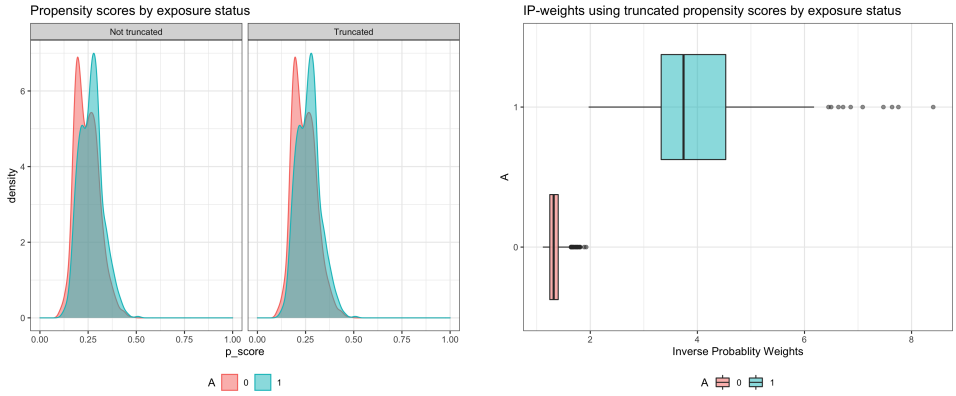

Figure 3: Left: Distribution of propensity scores. Right: Distribution of inverse propensity weights. A refers to the treatment assignment (i.e., receipt of vaccine).

We also run Double/debiased Machine Learning (DML) for causal inference, a similar method to AIPW developed by Chernozhukov et al. (2023) [2], because it has sensitivity analysis built into the software. It gives an average treatment effect estimate of 10^{-5} with a p-value of 0.997. It outputs a robustness value for the bound of 0.009. This means that omitted variables that explain more than 0.009% of 'the residual variation of the outcome and generate an additional 0.009% of variation on the average precision on the treatment regression. are sufficiently strong to make the estimated bounds include 0" [2]. This sensitivity analysis shows that it is quite feasible that there may be an unobserved confounder.

4.3 Logistic Regression

We also do an analysis using logistic regression, since it is common to use in epidemiology for assessing the effect of a treatment on a binary outcome [3]:

$$P(Y_i = 1 \mid D_i, X_i) = \frac{e^{\beta_0 + \beta_1 D_i + \beta_2^T X_i}}{1 + e^{\beta_0 + \beta_1 D_i + \beta_2^T X_i}}$$

The coefficient of the treatment D_i here is $\log \frac{P(Y_i=1|D_i=1,X_i=x)/P(Y_i=0|D_i=1,X_i=x)}{P(Y_i=1|D_i=0,X_i=x)/P(Y_i=0|D_i=0,X_i=x)}$. With our data, we find the estimate of the treatment effect to be 0.978 and the estimate of the upper confidence limit to be 1.17.

As for sensitivity analysis, we use the E-value [8], a measure of evidence for causal effects in observational studies. We find E-values of 1.17 and 2.009 for the treatment effect estimate and upper confidence limit estimate, respectively. This means that a potential unobserved confounder that was associated with both vaccination and hospitalization by a risk ratio of 1.17-fold each, above and beyond the observed confounders, could explain away the observed point estimate, but weaker confounding could not [8]. Similarly, the unobserved confounder must have an association greater than 1.91 to explain away the upper confidence limit. Importantly, this means that the unobserved confounder would have to be associated with both vaccination and hospitalization by a risk ratio of 1.17-fold each via pathways that were independent of sex, age, having COPD, having heart disease, etc. Since this E-value is fairly close to 1 (which would mean that no additional association would be needed to explain away the observed association), but we have also controlled for multiple covariates, the interpretation of its magnitude may be ambiguous. One could argue that it either is or is not very plausible that some unobserved confounder satisfies this association to explain away the point estimate. Given that the sensitivity analysis from the DML method indicated the plausibility of such an unobserved confounder, we err on the side of allowing that possibility.

So in summary, the AIPW, DML, and logistic regression methods all indicate that there is no significant effect of vaccines on hospitalization, but also that the unconfoundedness assumption, albeit impossible to test, may be violated for the study set up given the results

of the sensitivity analysis. We conclude then that it would be difficult to set up a bulletproof observational framework for this problem, but if one did study the problem this way, it might confirm the results of Hirano and of the IV analysis above.

5 Conclusion

We re-analyzed the effects of influenza vaccines on hospitalization using IV and observational study methods for causal inference. Via all methods, we found that the vaccines likely had no causal effect on hospitalization, confirming the analysis of Hirano et al. (2000) [5]. These findings underscore the importance of checking the assumptions of a model thoroughly before applying the model.

Future work could entail exploring other machine learning-based methods for teasing apart a causal effect in a scenario with potential unobserved confounders and no valid instrument. Future work could also focus on developing guidelines to help researchers check commonly-violated assumptions in different domains (e.g., psychology, epidemiology, etc.), as many assumption violations may go unnoticed because of a lack of knowledge about a domain-specific mechanisms that violate the required assumptions.

6 Code

The data and code for this project is available at https://github.com/mserramo/stats-209-final.

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