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Title

Causal inference from experiment and observation

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Abstract (166 words), main text including tables (about 4198 words), 6 tables, 29 references, supplementary material with data and Stata code.

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Abstract

Results from well conducted randomized controlled studies should ideally inform on the comparative merits of treatment choices for a health condition. In the absence of this, one attempts to use evidence from the impact of treatment when administered according to decisions of the physicians and the patients (observational evidence). Naïve comparisons between treatment options using observational evidence will lead to biased results. Under certain conditions however, it is possible to obtain valid estimates of the comparative merits of different treatments from observational data. Causal inference can be conceptualised as a framework aiming to provide valid information about causal effects of treatments using observational evidence. It can be viewed as a missing data problem in which each patient has two outcomes: the observed outcome under the treatment actually received and a counterfactual (unobserved) outcome *had* the patient received a different treatment. Methodological developments over the last decades clarified the appropriate conditions and methods to obtain valid comparisons. This article provides an introduction to some of these methods.

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Introduction: Making causal statements about relative treatment effects

Let us start with a simple example by presenting the following (fictional) information on 800 patients with acute depression who received treatment A and another 800 patients with acute depression who got treatment B (table 1) for a complete six-month follow-up.

Table 1: Observed 6-months relapse for patients with acute depression receiving either treatment A or B.

	Treatment A			**Treatment B**		
	Number of patients	Relapses	Percent with relapse	Number of patients	Relapses	Percent with relapse
Total	***800***	***40***	***5.0%***	***800***	***81***	***10.1%***

We are now invited to make a statement which treatment is more efficacious i.e. is associated with less chances of relapse. As we had previously attended some courses in clinical epidemiology we refuse to answer directly the question. Instead we ask what type of study this was that produced these data.
We want to know this because our answer depends on the study design.

- If the data is coming from a randomized trial with complete adherence and complete 6-months follow-up, we will probably say that treatment A is more efficacious.
- If the data results from two different clinics in which patients with acute depression were treated then we would not be sure what to prefer as the difference between the two clinics might be confounded by the differences in patient characteristics across the two clinics. We therefore would ask for more information, for example the distributions of the initial depression severity or concomitant conditions in these two groups of patients.

Ideally we would like to know the answers to the following two questions:

- For those who had received treatment A, how many would have relapsed if they had received treatment B?
- For those who had received treatment B, how many would have relapsed if they had received treatment A?

We would then clearly prefer treatment A, if for all 1600 patients the 6-months relapse rate under treatment A is lower than under treatment B. This statement is an **example of a causal statement**. We could be even more precise in our causal statement: The 6-months relapse rate under treatment A would be 5.1% lower than under treatment B, if we can argue that the relapse rate observed for those who

received treatment A reflects the relapse rate if everyone would have received treatment A, and similarly for those who received treatment B (and ignoring issues about statistical uncertainty). But of course, we are now discussing relapse results of hypothetical situations which we will never observe. The idea to discuss hypothetical results from hypothetical situations was introduced several decades ago by Fisher, Neyman and Rubin (1-3) and more recently formalized by Pearl, Hernan and Robins (4, 5). With all these rather long 'if'-statements involving, we start to feel the need for some more formal notation (5, 6):

- Let Y denote the binary outcome for a patient having relapsed within 6 months (yes; Y=1, no; Y=0).
- Let Tr denote the treatment someone has actually received or *could have* received (Tr=A or Tr=B).
- Let $Y_{Tr=A}$ denote the (*potential or observed*) outcome for a patient **if** (s)he would have received treatment A, similarly $Y_{Tr=B}$ denotes the (*potential or observed*) outcome for a patient **if** (s)he would have received treatment B. In some publications subscripts are used (7), as here, sometimes superscripts ($Y^{Tr=A}$ or $Y^{Tr=B}$) to denote the potential outcomes of an individual (5).
- Let Pr[ ] denote the probability that something happened or the proportion of situations in which something happened; so Pr[Y=1|Tr=A] denotes the proportion of patients who relapsed among those who actually received treatment A.

The outcomes not observed; that is $Y_{Tr=B}$ in patients who received A and $Y_{Tr=A}$ in patients who received B, are called **counterfactual outcomes**. Table 2 illustrates this; for those patients who received treatment A, we are able to observe $Y_{Tr=A}$, but not $Y_{Tr=B}$, similarly for those who received treatment B, we observe $Y_{Tr=B}$ but not $Y_{Tr=A}$. The information we have allows us to calculate the proportion of relapses among patients indeed receiving treatment A, and those indeed receiving treatment B, i.e. Pr[Y=1|Tr=A] and Pr[Y=1|Tr=B]. We can conceptually define an **individual causal effect** for each of the 1600 persons in table 1. For example, we can define the difference between the outcomes under different treatments $Y_{Tr=B} - Y_{Tr=A}$; or assume that there is no difference in the treatment outcome i.e. $Y_{Tr=B} = Y_{Tr=A}$ for each of the 1600 patients. Again, note that we are not able to observe any of these individual causal effects. But perhaps we can make statements about the **population causal effect**. By that we mean the proportion of patients who would relapse if *all* 1600 would have received treatment B, compared with the relapse risk if *all* patients would have received treatment A, or (using our notation) estimate $Pr[Y_{Tr=B} =1] - Pr[Y_{Tr=A} =1]$. Unlike individual causal effects, it is possible - under certain conditions - to estimate population causal effects.

Table 2: Data and counterfactual outcomes for the 10 first patients with treatments (Tr) A and B. The dichotomous outcome (relapse) is denoted with Y. The counterfactual outcomes are denoted with "?".

Person	Treatment received (Tr)	Outcome Y **observed**	$Y_{Tr=A}$	$Y_{Tr=B}$
1	A	0	0	?
2	B	1	?	1
3	B	0	?	0
4	A	1	1	?
5	A	0	0	?
6	A	0	0	?
7	B	1	?	1
8	B	0	?	0
9	B	0	?	0
10	B	0	?	0

Exchangeability allows to estimate population causal effects

Let us revisit the situation in table 1 and assume the table gives the results of a well conducted randomized study with complete follow-up. Apparently the randomization was 1:1 as 800 patients received treatment A, and 800 treatment B. The average of the counterfactual outcomes of the 800 patients who received A had they received B is simply the average observed outcome of those 800 patients who did receive B; in other words the two groups, A and B, are exchangeable. Therefore those who received treatment A are a perfect random sample of all 1600 patients and the relapse rate we observe among those who received treatment A, $Pr[Y=1|Tr=A]$, estimates (up to sampling uncertainty) what would have happened if all would have received treatment A, i.e. $Pr[Y_{Tr=A}=1]$. The same argument can be made for those who indeed received treatment B. They are a perfect random sample of all, and therefore $Pr[Y=1|Tr=B] = Pr[Y_{Tr=B}=1]$. The random treatment assignment allows to estimate (on average) what would have been if those receiving A would have received B, by looking at those who actually received B. We get an *average* estimate for the question marks in table 2 by using the treatment results from the other group.

The exchangeability terms refers to the fact that the relapse risk under the possible treatment choices A or B among those who actually received A (i.e. $Pr[Y_{Tr=A}=1|Tr=A]$ and $Pr[Y_{Tr=B}=1|Tr=A]$) equals the risk under the possible treatment choices A or B among those who actually received B (i.e. $Pr[Y_{Tr=A}=1|Tr=B]$ and $Pr[Y_{Tr=B}=1|Tr=B]$). Randomisation produces exchangeability and hence functions of the observed average outcomes can be interpreted as causal effects of the treatments.

Lack of exchangeability

Exchangeability would be clearly violated if participants differ considerably across the two treatments in characteristics that are related to the outcome of interest. Such a case can occur when one treatment is preferentially been given more often to patients with more severe depression. Let's assume both treatments are equally effective, i.e. the population causal risk difference is zero, i.e. $Pr[Y_{Tr=A}=1]= Pr[Y_{Tr=B}=1]$. Treatment B is given exclusively in clinic B which receives patients within more severe symptoms who have a higher risk to relapse after treatment. This then leads to a higher observed relapse rate in those who receive treatment B than in those who receive treatment A (administrated in clinic A), i.e. $Pr[Y=1|Tr=B] > Pr[Y=1|Tr=A]$, and the observed difference does not correspond to the population causal risk difference.

Let us suppose that the data in table 1 reflects such an observational study where patients are treated in two different clinics and admission to each of the clinics depends on patient characteristics. Table 3 now presents the 6-months relapse results for the two group of patients stratified by sex, age group and severity of depression symptoms at study enrolment. Those treated in clinic B are more often males (510 of 800) compared to clinic A (400 of 800), and in clinic B patients are on average older (510 were 60+) compared to patients in clinic A (280 were 60+), and finally clinic B had more patients with severe depression symptoms (400 patients) than clinic A (200 patients). Within each of the eight subgroups (by sex, age and symptoms severity level) we observe the same relapse rate between the two clinics.

Table 3: Observed 6-months relapse for patients with depression receiving either treatment A or B stratified by sex, age group and severity of symptoms at study enrolment.

			Treatment with A in clinic A			**Treatment with B in clinic B**		
			Number of patients	Relapses	Percent with relapse	Number of patients	Relapses	Percent with relapse
Total	Age	Severity	800	40	5.0%	800	81	10.1%
Men	<60	Low	200	4	2.0%	50	1	2.0%
	<60	High	60	6	10.0%	100	10	10.0%
	60+	Low	100	5	5.0%	200	10	5.0%
	60+	High	40	10	25.0%	160	40	25.0%
Women	<60	Low	200	2	1.0%	100	1	1.0%
	<60	High	60	3	5.0%	40	2	5.0%
	60+	Low	100	4	4.0%	50	2	4.0%
	60+	High	40	6	15.0%	100	15	15.0%

We see that the information looks different when we stratify the data into these subgroups. Can we conclude that relapse rate after treatment with A is equivalent to that with B? Being equivalent would mean that if all had been treated with A we would expect the same results as if all would have been treated with B. To be able to conclude this equivalence we need to assume that within these eight subgroups exchangeability is fulfilled. This is equivalent to assume that within the eight subgroups the "assignment" to clinic A or B is **"as randomized"** (although not in 1:1 randomisation ratio but in a ratio that is changing from subgroup to subgroup). This also implies that we are assuming that there is no further important variable which was not assessed. This also known as the assumption of no unmeasured confounding.

How to obtain the population causal effect from observational data

First, we need to assume exchangeability within the subgroups which is called **conditional exchangeability** (7). Once we assume conditional exchangeability, we have different choices for comparing the relapse rates between treatments. Many might suggest to use a **logistic regression model for relapse** including as predictors age, sex and severity in addition to treatment. The coefficient for treatment of such a logistic regression model makes implicit comparisons of patients of the same sex, age and depression severity. Some would suggest to use Mantel-Haenszel methods (8) or a propensity score matching procedure (9). Another approach is what basic epidemiology books describe as **direct standardization** (7): Calculate the expected relapse in all 1600 patients (in the 8 subgroups) first using the observed relapse of clinic A and a then using the observed relapse of clinic B. Then compare the two expected relapse rates in all 1600 patients. The difference between the two expected relapse rates under A and B will yield and estimate of the population causal effect (under the assumption of conditional exchangeability within the subgroups). A bit more work is then needed to obtain an appropriate 95% confidence interval for the causal effect. Instead of doing the direct standardization calculation steps as just described, we could approach the calculations by using the so called **inverse probability of treatment weights**.

Use of inverse probability of treatment weights

The idea behind the use of inverse probability of treatment weights (IPTW) is to create two "**pseudopopulations**" of patients of the same total size as the one observed. In one pseudopopulation all receive treatment A, in the other all receive treatment B. Then, the probability (risk) of relapse in the two pseudopopulations will be compared.

Let us illustrate the idea by looking only at one subgroup; that of men of age 60+ with high severity depression in table 3. In total there are 200 participants in this subgroup; 40 treated with A and 160 with

B. So, a men of age 60+ with high severity depression has 1 in 5 probability to be treated with A and 4 in 5 to be treated with B. To calculate what would have happened to 200 patients if they were all treated with A, we multiply the 40 patients (and their 10 observed relapses) indeed treated at clinic A by a factor of 5 which is the inverse of the probability to receive A. So, out of 200 patients, 50 would relapse if they were all treated with A. To obtain the number of relapses had all 200 patients received B, we multiply the observed relapse rate in B (40 in 160) with a factor 5/4=1.25 (the inverse of the probability to receive B). So, again 50 patients would relapse if all 200 had been treated with B.

Therefore we can get the results of the direct standardization by the following steps.

1) Within each subgroup for which exchangeability can be assumed, calculate the probability to receive the treatment (s)he has indeed. Denote these with Pr[Tr as received | subgroup],
2) Calculate IPTW =1 / Pr[Tr as received | subgroup]
3) Calculate the observed event rate within each subgroup Pr[Y=1| Tr as received in subgroup]
4) Within each subgroup multiply IPTW with the number of patients in the subgroup and with the number of events. This will reconstruct what we expect if all would have had treatment A compared to if all would have had treatment B.
5) Sum the events and number of patients across subgroups in the pseudopopulations for A and B. Use these numbers to estimate the causal relative treatment effect.
6) Obtain a 95% confidence interval for the causal relative treatment effect by using robust standard errors (5, 10, 11) .

Table 4 gives the IPTW weights for each of the 8 subgroups that are used to create the two pseudopopulations. 161 patients would relapse out of 1600 patients who could have received A; the same for B and hence the risk difference is zero.

Table 4: Data, inverse probability of treatment weights (IPTW) and pseudopopulations for treatments A and B.

			Observed data						
			Treatment with A			Treatment with B			
Sex	***Age***	***Severity***	***Patients***	***Relapses***	***IPTW weights***	***Patients***	***Relapses***	***IPTW weights***	**Total**
Men	<60	Low	200	4	1.25	50	1	5	250
	<60	High	60	6	2.67	100	10	1.6	160
	60+	Low	100	5	3	200	10	1.5	300
	60+	High	40	10	5	160	40	1.25	200
Women	<60	Low	200	2	1.5	100	1	3	300
	<60	High	60	3	1.67	40	2	2.5	100
	60+	Low	100	4	1.5	50	2	3	150
	60+	High	40	6	3.5	100	15	1.4	140
		All	***800***	***40***		***800***	***81***		***1600***
			Pseudopopulations						
			If all patients were treated with A			**If all patients were treated with B**			
Men	<60	Low	250	5		250	5		500
	<60	High	160	16		160	16		320
	60+	Low	300	15		300	15		600
	60+	High	200	50		200	50		400
Women	<60	Low	300	3		300	3		600
	<60	High	100	5		100	5		200
	60+	Low	150	6		150	6		300
	60+	High	140	21		140	21		280
		All	***1600***	***121***		***1600***	***121***		**3200**

The steps outlined above can be easily be done using standard statistical software. The probabilities in step 1 can be obtained from a logistic regression with receiving treatment A (or B) as the outcome (See the supplementary material on how this can be done in Stata). Step 2 is simple and steps 3) und 6) can be done again with a logistic regression or other generalized linear models which allow for using robust standard errors (5, 10, 11).

Table 5 presents the results from the different approaches to analyse the data of table 3 and obtain an odds ratio for relapse between the two treatments. A naïve crude analysis, not accounting for the different patient profiles in clinic A and B, results in a clearly higher odds for relapse in clinic B compared to clinic A. The various ways to account for the differences in patient characteristics and obtain causal effects do not show remarkable differences in the estimated odds ratio.

Table 5: Comparing relapse rate under treatment B with that under treatment A using different analytical approaches to estimate causal odds-ratio while accounting for confounding by sex, age and severity of symptoms

Analytical approach	Odds Ratio for relapse (B versus A) and 95% CI
Logistic regression for relapse including only hospital (**no adjustment**)	2.14 (1.45- 3.17)
Logistic regression for relapse including sex, age and severity independently	0.98 (0.64 – 1.52)
Logistic regression for relapse including sex, age, severity with all 2-way interactions between sex, age and severity	1.0 (0.65 – 1.55)
IPTW weighted analysis with weights constructed with sex, age and severity independently in the model for the defining the weights	0.99 (0.65 – 1.51)
IPTW weighted analysis with weights constructed with all 2-way interactions between sex, age and severity in the model for the defining the weights	1.0 (0.65 – 1.53)

Advantages in using inverse probability weighting in estimating causal effects

If IPTW results are comparable to those obtained from a logistic model, why is the use of IPTW weights (or direct standardisation) needed in practice? The reason is that the use of IPTW weights can be extended to situations in which standard regression models will not allow to reconstruct an "as randomized" situation, especially if time-dependent confounding exists (5, 12, 13). This happens in observational studies with treatments that vary over time, when the treatment depends on the patients' outcome and when time-dependent confounders are present that are also affected by previous treatments. For example, estimation of the causal effect of timing of starting antiretroviral treatment would be problematic with standard regression approaches; this is because treatment decision in HIV-infected persons are based on the concentration of CD4+ lymphocytes measured in the blood (14-17). The concentration of CD4+ lymphocytes declines over time in the absence of antiretroviral treatment and there is a higher mortality risk for lower concentrations. However, the concentration of CD4+ lymphocytes is also affected by previous treatment as effective treatment increases the concentration. Methods based on using IPTW allowed researchers to estimate the causal effect where standard methods may fail to adjust appropriately for the time-changing CD4 concentrations (12, 14).

Table 6: The use of inverse probability of censoring weights when assessing 12 months vital status stroke patients being discharged from clinics

Severity of disease or risk category for death	Number of patients leaving the clinic	Patients with available follow-up information	Deaths recorded at follow-up	Percent dead at follow-up	Probability of having a follow-up	Inverse of the probability of having a follow-up
Low	400	360	72	20%	90.0%	1.11
High	600	300	150	50%	50.0%	2.00
Total	1000	660	222	34%		

The use of inverse probability weights can also be extended to address more complex situations, like for example observations with differential follow-up as encountered in a study on stroke patients in Switzerland (18). The study attempted to assess the 12 months vital status of all stroke patients being discharged from clinics in a defined region in Switzerland in 2008 (18). Table 6 shows a simplified version of the data with just one strong prognostic factor for mortality. Patients could be separated into a high and low relapse risk group based on the NIH stroke scale. Here we have 1000 patients leaving the clinic and 660 (66%) could be traced for follow-up information. However, availability of follow-up information was not the same in the low and high risk groups. Follow-up information was available in 90% for the low risk group patients and in 50% of the high risk patients. Mortality risk among those with available follow-up information was 34%, with 20% in the low risk patients and 50% in the high risk patients. Clearly, it would be inappropriate to think that this 34% mortality reflects the true mortality rate among all 1000 patients.

So how could one obtain a more realistic mortality estimate? Again, as with the data in table 3, an additional assumption about (conditional) exchangeability is needed. If one is willing to assume that within each risk group the patients with follow-up information are representative of all the patients of that risk group, one would do the following calculation to reconstruct the mortality among all 1000 patients. We expect to have a 20% mortality among all 400 low risk patients (=80 expected deaths) and a 50% mortality in high risk patients (=300 expected deaths). In total we expect 380 deaths among all 1000 patients, i.e. a mortality risk of 38%.

We get mathematically exactly the same result (38%) if one would conduct a weighted analysis restricted to the 660 observed patients with available follow-up information, but using risk group specific weights which are 1.11 (1/0.8) and 2 (1/0.5), derived as the inverse of the probability of available follow-up

information. This is what we called an analysis using inverse probability of censoring weights. The advantages of such a weighted approach are twofold. First, it can easily be extended to more than one prognostic variable risk using multivariable logistic regression to construct the weights. Second, as discussed above with the IPTW, in almost all statistical software it is possible to conduct a weighted analysis and to obtain estimates and robust 95% confidence intervals that account for the weighting (10, 11). However, we need to remember and acknowledge the assumption that all relevant prognostic variables have been included in a correct statistical model for calculating the weights. The risk estimate derived from inverse probability of censoring weights might still be biased, if this assumption does not hold. In the Bern stroke patient study the naïve estimate of the 12-month mortality was 20.6% (95% CI: 17.6%-24.0%). When using inverse probability of censoring weights derived from a logistic regression including 8 baseline characteristics (sex, age, NIH stroke scale, diabetes, smoking, hyperlipidemia, hypertension, and Charlson Index) 12-month mortality was estimated at 27.6% (95% CI: 23.7%-31.5%). Finally, inverse probability of treatment weights and inverse probability of censoring weights can jointly be combined to obtain estimates of all patients treated one way or the other with complete follow-up (if assumptions about conditional exchangeability hold up).

Concluding remarks

In this tutorial we covered a formal definition of population causal effects using arguments on counterfactual outcomes ($Pr[Y_{Tr=A}=1]$ versus $Pr[Y_{Tr=B}=1]$ in case of binary outcome) and explained how the use of inverse probability of treatment weights and inverse probability of censoring weights plus certain exchangeability assumptions allow to calculate the difference or the (odds) ratio of $Pr[Y_{Tr=A}=1]$ and $Pr[Y_{Tr=B}=1]$. Additional methods have been developed over the last two decades to obtain causal effect estimates when not only one-time fixed treatments (like in table 3) are to be compared but long-term treatments with incomplete adherence (5, 19-22). Furthermore, some refinements to the calculation of weights (like stabilisation of the weights) are often recommended to avoid overly wide 95% confident intervals (see chapter 12 in (5)).

Although primarily used in the analysis of observational studies, methods for causal inference are also relevant to the analysis of randomized trials. The fact that exchangeability holds in a well conducted randomised experiment provides no guarantee that the intention-to-treat analysis provides an unbiased estimate of the causal effect (6, 23, 24). The outcome may not be measured for all subjects (differential loss to follow up), the treatment assignment may not reflect actual treatment received (noncompliance), unblinding of the treatment might result in differential co-treatments plus other actions. Causal inference from randomised studies in the presence of these problems requires similar assumptions and analytical methods as causal inference from observational studies (23-26).

All the concepts and methods outlined here make the implicit assumption that a subject's counterfactual outcome under one treatment version or exposure value does not depend on other subjects' treatment version. If this assumption does not hold (for example, in studies dealing with infectious diseases or educational reforms), then individual causal effects cannot be properly defined for a given person via the concept of individual potential outcomes ($Y_{Tr=B}$ versus $Y_{Tr=A}$). Some see it as a limitation that the counterfactual approach is conceptualized with "treatments" or well-defined actions but seems less helpful to other types of scientific questions on causality (27). Hernan recently responded to this (28): "The goal of the potential outcomes framework is not to identify causes or to "prove causality", as it sometimes said. That causality cannot be proven was already forcibly argued by Hume in the 18th century (29). Rather, quantitative counterfactual inference helps us predict what would happen under different interventions, which requires our commitment to define the interventions of interest." So the potential outcomes framework helps to organize our discussion and thinking when we –the medical professions, the society - are discussing what is the best way of action.

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