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METHODS

The meaning of confounding adjustment in the presence of multiple versions of treatment: an application to organ transplantation

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Abstract

Causal inference for treatments with many versions requires a careful specification of the versions of treatment. Specifically, the existence of multiple relevant versions of treatment has implications for the selection of confounders. To illustrate this, we estimate the effect of organ transplantation using grafts from donors who died due to anoxic drug overdose, on recipient graft survival in the US. We describe how explicitly outlining the target trial (i.e. the hypothetical randomized trial which would answer the causal question of interest) to be emulated by an observational study analysis helps conceptualize treatment versions, guides selection of appropriate adjustment variables, and helps clarify the settings in which causal effects of compound treatments will be of value to decision-makers.

Keywords Compound treatments · Treatment versions · Transportability · Generalizability · Transplantation

Introduction

The aim of many observational studies is to estimate the causal effect of an "exposure" or "treatment" on an outcome. However, the treatment of interest may have multiple versions. For example, the treatment "surgery" has several versions defined by the experience and skills of the surgeon. These versions include "surgery performed by a very experienced surgeon", "surgery performed by a very inexperienced surgeon", and all others in between. We refer to treatments with multiple versions as compound treatments [1].

Causal inference for compound treatments requires a careful specification of the versions of treatment when the versions have different causal effects. For example, the effect of "surgery" differs for versions defined by surgeon's ability, the effect of "in vitro fertilization" differs for versions defined by egg donor's age, the effect of "blood transfusion" differs for versions defined by whether the blood donor was a drug user, and the effect of "antiretroviral therapy" differs for versions defined by the combination of specific antiretroviral drugs. In these cases, we say that the versions are relevant for the causal effect of interest [2]. In other cases, the causal effect of treatment does not depend on the treatment version. For instance, the treatment "integrase inhibitor therapy" has several versions defined by the manufacturer of the pill, but the effect of a particular integrase inhibitor will arguably be the same regardless of where the pills are manufactured. Therefore, we do not typically think of drug manufacturers as relevant versions of treatment.

In this paper we discuss how the existence of multiple relevant versions of treatment has implications for the selection of confounders. As an example, we consider the effect of

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transplantation of organs from donors who died from opioid overdose versus from other donors. This is a timely issue because the US opioid epidemic has increased the number of organs for transplant from individuals who died from opioid overdose [3, 4], but there are concerns about infectious disease transmission and opioid-induced organ toxicity [5–10]. A recent study found no differences between transplantation using organs from donors who died due to drug overdose and transplantation using organs from those who died from other causes [11]. This analysis adjusted for both donor and recipient characteristics, but did not explicitly link the adjustment to the existence of different treatment versions of transplantation as defined by the characteristics of the donor [12, 13].

Here, we present an analysis of the same data with explicit consideration of treatment versions. We estimate the effect of transplantation from donors with and without drug overdose cause of death and demonstrate how the concept of target trial [14] is helpful to conceptualize treatment versions and make decisions about adjustment variables.

The target trial

Many causal analyses from observational data can be viewed as an attempt to emulate the (hypothetical) randomized pragmatic trial that would estimate the causal effect of interest—the target trial. By explicitly outlining the protocol of the target trial investigators are more likely to recognize and avoid methodologic pitfalls and common biases [14–16].

In particular, the randomized assignment in the target trial is emulated via confounding adjustment in observational analyses. If all confounders were appropriately measured and adjusted for (an untestable condition), then the observational analysis would be indistinguishable from the analysis of a truly randomized trial. As we explain below, this connection between confounding adjustment and emulation of randomization helps us decide what variables can be considered confounders in the presence of multiple versions of treatment. Therefore, the first step to select confounders is to specify the target trial that the observational analysis is trying to emulate.

Consider first a target trial in which individuals eligible for kidney transplantation are randomly allocated to either a graft from a donor who died from opioid overdose or to a graft from a donor who died from other causes. Each treatment arm of such a trial encompasses several relevant versions of the treatment. For example, the arm "transplantation of an organ from a donor who died from opioid overdose" includes the versions "transplantation of an organ from a donor who died from opioid overdose *at age 20*" and "transplantation of an organ from a donor who died from opioid overdose *at age 70*".

Therefore, if the target trial were conducted and found that those receiving a transplant from an overdosed donor lived longer, then we would learn that receiving an organ from an overdosed donor is, on average, the preferred option. However, because overdosed donors tend to be younger than other donors [3], we would not learn whether receiving an organ from an overdosed donor is the best option because drug overdose is somehow beneficial or just because receiving an organ from a younger donor (regardless of overdose) is generally better.

From a practical standpoint, the above distinction may be moot: the decision to use organs from overdosed donors would be, on average, best, regardless of why it is the best decision. However, the dependence of the treatment effect on the versions of treatment would be problematic if the distributions of versions of treatment were to change in the population (e.g. if the average age of overdosed donors increased over time) or if we wanted to transport the effect from our population to another population with a different donor age distribution. To overcome this potential problem, we are often interested in the effects of different versions of treatment. Estimating those effects would require a different target trial.

We now describe two different target trials of overdosed versus non-overdosed donors, and then describe how their emulation using observational data requires adjustment for different sets of confounders.

Target trial #1: single randomization

Eligibility criteria Individuals aged 18 or older in the United States who are waitlisted to undergo liver or kidney transplantation between 2006 and 2016. Potential recipients are eligible for randomization at the time when a compatible organ is available.

Treatment strategies Transplantation with a liver or kidney graft from either (1) a donor who died from anoxic drug overdose or (2) a donor who died from other causes. All donors are required to be brain-dead and HIV, hepatitis C, and hepatitis B seronegative. This target trial requires the simultaneous availability of two compatible organs, one from a donor who died from anoxic drug overdose, and one from a donor who died from other causes.

Outcomes Graft failure, defined as retransplantation, death due to any cause, or, for kidney transplants, permanent return to dialysis.

Follow-up Recipients are followed from the date of randomization until graft failure, death, loss to follow-up as reported by individual transplant programs, or September 1st, 2017, whichever occurs first.

Causal contrast Intention-to-treat effect which, if full adherence is achieved, equals the per-protocol effect.

Statistical analysis For each organ type, graft survival curves by treatment group. The curves can be estimated via the Kaplan–Meier method, or if standardization for some

Table 1 Baseline characteristics of transplant recipients by organ and anoxic drug overdose status of donor, Scientific Registry of Transplant Recipients, 2006–2016

Characteristic	Liver		Kidney	
	From donor with anoxic drug overdose		From donor with anoxic drug overdose	
	Yes	No	Yes	No
Recipient characteristic				
No. patients	2511	45,593	4564	75,721
Age (y), mean (SD)	54.7 (10.8)	54.9 (10.5)	51.5 (13.5)	53.0 (13.4)
BMI (kg/m^2), mean (SD)	28.5 (6.0)	28.5 (5.9)	28.4 (5.7)	28.1 (5.5)
Time on dialysis (y), mean (SD)	–	–	4.0 (3.3)	4.1 (3.4)
Gender (%)				
Male	1727 (68.8)	30,367 (66.6)	2724 (59.7)	44,879 (59.3)
Female	784 (31.2)	15,226 (33.4)	1840 (40.3)	30,842 (40.7)
Race (%)				
Asian	100 (4.0)	2194 (4.8)	242 (5.3)	4995 (6.6)
Black	222 (8.8)	4257 (9.3)	1443 (31.6)	24,553 (32.4)
Multiracial	12 (0.5)	224 (0.5)	22 (0.5)	270 (0.4)
Native American	18 (0.7)	278 (0.6)	56 (1.2)	800 (1.1)
Pacific Islander	4 (0.2)	71 (0.2)	23 (0.5)	332 (0.4)
White	2155 (85.8)	38,569 (84.6)	2778 (60.9)	44,771 (59.1)
Liver disease diagnosis (%)			–	–
Cholestatic	240 (9.6)	3978 (8.7)		
Non-cholestatic	1610 (64.1)	28,480 (62.5)		
Fulminant hepatic failure	100 (4.0)	2132 (4.7)		
Malignant neoplasm	433 (17.2)	8564 (18.8)		
Metabolic	58 (2.3)	1104 (2.4)		
Other	70 (2.8)	1335 (2.9)		
Renal disease diagnosis (%)	–	–		
Cystic			399 (8.7)	6351 (8.4)
Diabetes			1132 (24.8)	20,347 (26.9)
Glomerulonephritis			894 (19.6)	14,162 (18.7)
Hypertension			1188 (26.0)	19,556 (25.8)
Other			951 (20.8)	15,305 (20.2)
Previous transplant (%)	166 (6.6)	2687 (5.9)	595 (13.0)	10,194 (13.5)
Functional status (%)				
Req. no assistance	798 (31.8)	17,146 (37.6)	3982 (87.2)	67,058 (88.6)
Req. some assistance	1122 (44.7)	18,699 (41.0)	581 (12.7)	8563 (11.3)
Req. no assistance	591 (23.5)	9748 (21.4)	1 (0.02)	100 (0.1)
Medical condition (%)				
Hospitalized in ICU	401 (16.0)	6601 (14.5)	–	–
Hospitalized not in ICU	567 (22.6)	8721 (19.1)		
Not hospitalized	1543 (61.4)	30,271 (66.4)		
On ventilatory or perfusion support (%)	226 (9.0)	3835 (8.4)	–	–
Last MELD score (%)			–	–
<15	62 (2.5)	1034 (2.3)		
15–19	202 (8.0)	5233 (11.5)		
20–24	532 (21.2)	11,469 (25.2)		
25–29	607 (24.2)	11,107 (24.4)		
30–34	405 (16.1)	6109 (13.4)		
≥ 35 or fulminant	703 (28.0)	10,641 (23.3)		
Year of transplant (% of year's total)				
2006	103 (2.5)	4076 (97.5)	180 (2.7)	6465 (97.3)

Table 1 (continued)

Characteristic	Liver		Kidney	
	From donor with anoxic drug overdose		From donor with anoxic drug overdose	
	Yes	No	Yes	No
2011	233 (5.3)	4199 (94.7)	431 (5.8)	7002 (94.2)
2016	509 (10.4)	4388 (89.6)	926 (11.3)	7265 (88.3)
Donor characteristic				
Age (y), mean (SD)	32.7 (10.6)	43.0 (17.1)	32.4 (10.4)	39.4 (17.0)
Height (cm), mean (SD)	172.7 (9.8)	171.1 (11.0)	172.2 (11.6)	167.6 (19.8)
Weight (kg), mean (SD)	83.2 (19.3)	81.2 (20.7)	83.7 (20.9)	78.9 (25.4)
Gender (%)				
Male	1434 (57.1)	26,779 (58.7)	2620 (57.4)	44,429 (58.7)
Female	1077 (42.9)	18,814 (41.3)	1944 (42.6)	31,292 (41.3)
Race (%)				
Asian	22 (0.9)	1224 (2.7)	35 (0.8)	2076 (2.7)
Black	147 (5.9)	8961 (19.7)	260 (5.7)	12,436 (16.4)
Multiracial	2 (0.1)	95 (0.2)	5 (0.1)	162 (0.2)
Native American	13 (0.5)	179 (0.4)	25 (0.5)	358 (0.5)
Pacific Islander	3 (0.1)	111 (0.2)	7 (0.2)	231 (0.3)
White	2324 (92.6)	35,023 (76.8)	4232 (92.7)	60,458 (79.8)
History of cocaine use (%)				
Yes	1082 (43.1)	5465 (12.0)	1980 (43.4)	9522 (12.6)
History of other drug use (%)				
Yes	2033 (81.0)	14,175 (31.1)	3673 (80.5)	23,789 (31.4)
Smoking ≥ 20 pack-years (%)				
Yes	559 (22.3)	11,141 (24.4)	997 (21.8)	17,399 (23.0)
Alcohol use ≥ 2 drinks/d (%)				
Yes	505 (20.1)	6375 (14.0)	952 (20.9)	12,960 (17.1)
Hypertension (%)				
Yes	454 (18.1)	17,161 (37.6)	781 (17.1)	22,604 (29.9)
Diabetes (%)				
Insulin dependent	56 (2.2)	2768 (6.1)	82 (1.8)	2254 (3.0)
Non-insulin dependent	55 (2.2)	2931 (6.4)	111 (2.4)	3809 (5.0)
History of myocardial infarction (%)				
Yes	28 (1.1)	1841 (4.0)	52 (1.1)	2180 (2.9)
Non-local shared organ (%)	764 (30.4)	12,978 (28.5)	1281 (28.1)	20,317 (26.8)
No. of HLA B mismatches (%)	–	–		
One			1169 (25.6)	17,920 (23.7)
Two			2886 (63.2)	48,060 (63.5)
No. of HLA DR mismatches (%)	–	–		
One			2164 (47.4)	33,246 (43.9)
Two			1466 (32.1)	25,814 (34.1)

baseline covariates is appropriate, via a discrete-time hazards model (e.g. a pooled logistic model with monthly periods) with a flexible function of time (restricted cubic splines with five knots), an indicator for treatment group, product terms for treatment and follow-up time, and the baseline covariates [17–19]. The 95% confidence intervals for 5-year survival probabilities can be calculated using a percentile-based nonparametric bootstrap.

Target trial #2: double randomization

The target trial described above does not distinguish between effects due to the drug overdose and the donor's other characteristics (e.g. age, history of drug use that may affect the liver or kidney) that are unequally distributed between overdosed and non-overdosed donors. To isolate the effect of drug overdose, we would need to conduct a different target

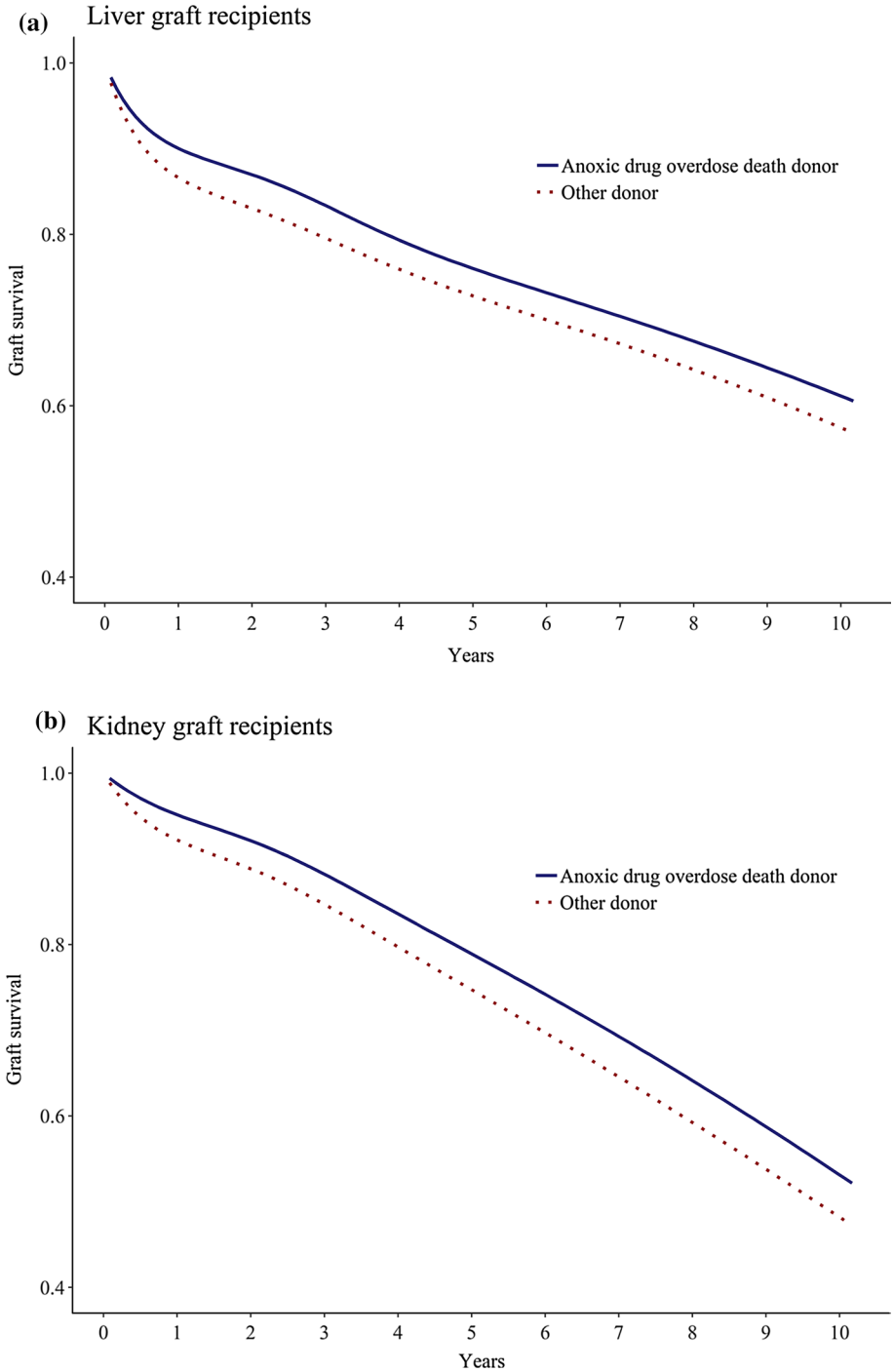

Fig. 1 Target trial #1—standardized survival curves for recipients of anoxic drug overdose donor grafts, and recipients of grafts from other donors

trial with the same protocol as the first target trial, except that the donor would be randomly assigned to death from either anoxic drug overdose or other causes.

Such a trial is of course unethical and will never be conducted, but this hypothetical trial is precisely the one that answers the question "what would be the causal effect of transplant from an overdosed donor if the characteristics of overdosed and non-overdosed donors were the same?"

A target trial with two randomization points—the donor's cause of death and the recipient's organ assignment—would allow us to determine whether a different outcome distribution between transplants from donors who died from drug overdose or from other causes is due to the donor's cause of death or to the donor's characteristics. More generally, a trial with two or more randomizations allows us to compare the effects of different versions of treatment.

Table 2 Standardized 5-year graft survival in target trials 1 and 2

	Treatment arm	
	Anoxic drug overdose graft	Other graft
Liver graft recipients		
Target trial #1 survival % (95% CI)	75.8 (73.8–77.7)	72.6 (72.1–73.0)
Difference	3.2 (1.1–5.2)	
Target trial #2 survival % (95% CI)	72.3 (69.8–74.8)	72.7 (72.3–73.2)
Difference	−0.5 (−2.9 to 2.1)	
Kidney graft recipients		
Target trial #1 survival % (95% CI)	78.5 (77.1–80.0)	74.3 (74.0–74.7)
Difference	4.2 (2.6–5.7)	
Target trial #2 survival % (95% CI)	75.5 (73.7–77.1)	74.5 (74.1–74.9)
Difference	1.0 (−0.9 to 2.7)	

Emulation of the target trials

Data source

We emulated the two target trials described above using the Scientific Registry of Transplant Recipients (SRTR). The SRTR data system includes data on all donors, wait-listed candidates, and transplant recipients in the US, submitted by the members of the Organ Procurement and Transplantation Network (OPTN). The Health Resources and Services Administration (HRSA), US Department of Health and Human Services provides oversight to the activities of the OPTN and SRTR contractors.

Donor's cause of death is recorded by the SRTR in categories of anoxia, cerebrovascular disease and stroke, head trauma, central nervous system tumors, or other. Mechanism of death is recorded within categories of drowning, sudden infant death syndrome, intracranial hemorrhage and stroke, death from natural causes, seizure, drug intoxication, asphyxiation, cardiovascular disease, electrical injury, gunshot wound, stab wound, blunt injury, or none of the above. Because the SRTR does not specifically identify opioid overdose as a cause of death, we used anoxic drug overdose as a proxy for opioid overdose death. The validity of anoxic drug overdose as a proxy for opioid overdose is supported by the concordance between the rise in opioid overdose death rates and the increase in anoxic drug overdose donor deaths recorded in the SRTR database, and the concordance between state-specific drug overdose death rates reported by the Center for Disease Control (CDC) and the state-specific anoxic drug overdose organ donor rates recorded in the SRTR [3, 4, 20–22]. The proportion of deceased donors with anoxic drug overdose as cause of death from 2006 to 2016 is shown in Online Resource Fig. 1. The SRTR collects data on graft failure [23].

Emulation of target trial #1

We identified 48,104 liver and 80,285 kidney graft recipients who were eligible for the emulation of the target trial (eligibility flowcharts displayed in Online Resource Figs. 2, 3). The recipients' characteristics at baseline are summarized in Table 1. The median follow-up time was 3.4 years for liver transplant recipients and 3.8 years for kidney transplant recipients. Loss to follow-up occurred for 7.0% of kidney recipients and 5.0% of liver recipients.

Because in the real-world organs from donors with and without anoxic drug overdose are not randomly assigned, we emulated the randomization by adjusting survival estimates for the following recipient characteristics: recipient age, body mass index, time on dialysis (kidney recipients only), gender, race, diagnosis, history of prior transplant, functional status, medical condition, need for ventilatory or perfusion support, model for end stage liver disease (MELD) score, and year of transplant. All continuous variables were flexibly modelled using restricted cubic splines with five knots.

After adjustment for baseline characteristics, recipients of anoxic drug overdose grafts had a lower risk of graft failure. For liver graft recipients, the standardized 5-year graft survival was 75.8% (95% CI 73.8–77.7%) for the anoxic drug overdose group and 72.6% (95% CI 72.1–73.0%) for the other group (difference: 3.2%, 95% CI 1.1–5.2%). For kidney graft recipients, the standardized 5-year graft survival was 78.5% (95% CI 77.1–80.0%) for the anoxic drug overdose group and 74.3% (95% CI 74.0–74.7%) for the other group (difference: 4.2%, 95% CI 2.6–5.7%). Standardized survival curves are displayed in Fig. 1.

That is, we estimated that 5-year graft survival is greater for transplant recipients of grafts from anoxic drug overdose donors than for transplant recipients of grafts from other donors (Table 2).

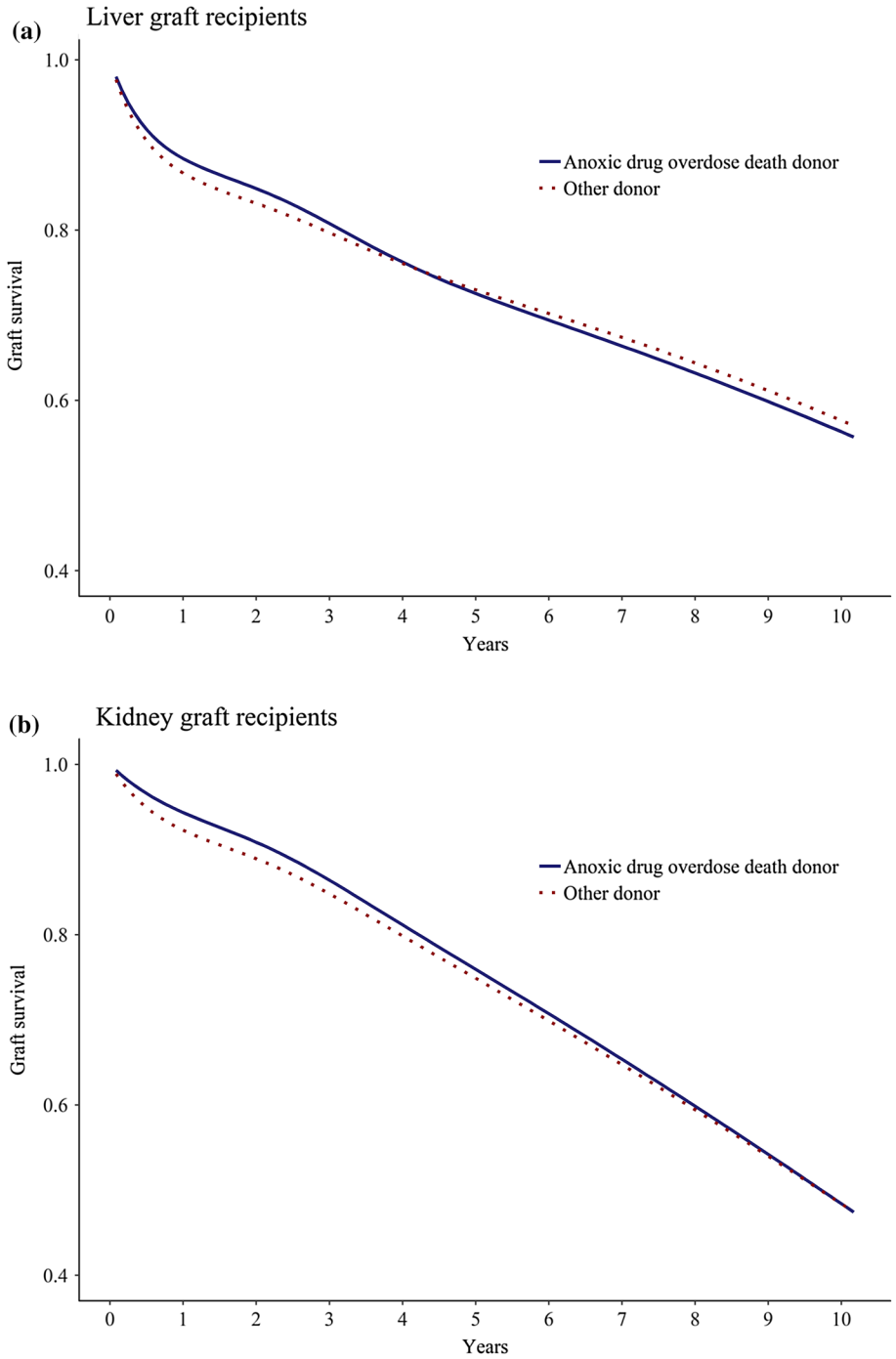

Fig. 2 Target trial #2—standardized survival curves for recipients of anoxic drug overdose donor grafts, and recipients of grafts from other donors

Emulation of target trial #2

To emulate the random assignment of donor cause of death, we additionally adjusted our analysis for the following donor characteristics: donor age, height, weight, gender, race, history of cocaine use, history of other drug use, smoking history, alcohol use, hypertension, diabetes, history of myocardial infarction, donor location relative to recipient, and number of donor-recipient HLA mismatches.

For liver graft recipients, 5-year graft survival was 72.3% (95% CI 69.8–74.8%) for the anoxic drug overdose group and 72.7% (95% CI 72.3–73.2%) for the other group (difference: −0.5%, 95% CI −2.9 to 2.1%). For kidney graft recipients, 5-year graft survival was 75.5% (95% CI 73.7–77.1%) for the anoxic drug overdose group and 74.5% (95% CI

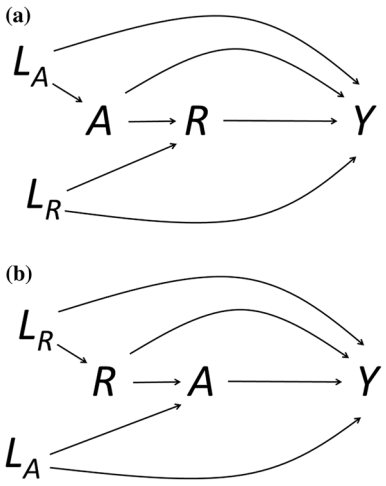

Fig. 3 **a** Causal graph in which R represents the compound treatment of interest, A represents the relevant versions of treatment, Y the outcome, L_A the confounders for the effect of A on Y, and L_R are the confounders for the effect of R on Y. Here the treatment versions are defined before the time when an individual receives the treatment of interest. **b** Causal graph in which the treatment versions are defined after an individual has begun treatment

74.1–74.9%) for the other group (difference: 1.0%, 95% CI −0.9 to 2.7%). Standardized survival curves are displayed in Fig. 2.

That is, we estimated that, if cause of death were randomly assigned among donors, the 5-year graft survival would be approximately the same for transplant recipients of grafts from anoxic drug overdose donors compared to transplant recipients of grafts from other donors. This result suggests that the survival benefit found in target trial #1 was driven by the characteristics of donors who die from drug overdose (e.g. they tend to be younger) rather than by drug overdose itself.

Discussion

Confounding adjustment in observational studies is the procedure through which we attempt to emulate the randomized treatment assignment of randomized trials. In this paper, we describe how adjustment for confounders measured at two different times implies that we are trying to emulate a target trial with two randomization points. In our example, double adjustment for both recipient's and donor's characteristics implies the emulation of a target trial in which both the type of donor and the donor's cause of death are randomly assigned.

This conceptualization applies more generally. Consider the causal diagrams of Fig. 3, in which R represents the compound treatment, A the relevant versions of treatment, Y the outcome, and L_R and L_A the confounders for the effect of R and A, respectively. These causal diagrams are structurally equivalent to the ones used to represent controlled direct effects [2].

Our organ transplantation example is represented by Fig. 3a because the treatment versions precede the compound treatment (our estimates support the presence of an arrow from A to the outcome Y, but not from R to Y). In other cases, the treatment versions are defined after the compound treatment, as represented in Fig. 3b. For example, consider a study that compares the effect of "hernia repair using synthetic mesh" with "hernia repair using suture only" on the risk of hernia recurrence. These treatments have versions defined by the type of suture (permanent vs. absorbable) used to repair the hernia and/or secure the mesh, which is decided by surgeons after the type of mesh is selected (i.e. permanent suture may be more likely when mesh is not used to reinforce the repair). Explicitly describing the target trial to be emulated is useful for clarifying the temporal ordering of treatment decision points.

A successful emulation of a trial with several decision points requires adjustment for confounders (conditional exchangeability) and confounder overlap (positivity) at all of these points. In our example, if all donors who died of drug overdose had a history of prior drug use, the treatment version "transplantation using an organ from an opioid overdose donor *with no prior history of drug use*" would not exist in our study population and we would be unable to adjust for it.

Our analysis includes two simplifications. First, we considered only two decision points, even though there may be treatment versions defined by the experience of the transplant team, the type of equipment and instruments used, the time and day of transplantation, the location of procurement and transplantation, etc. However, many of these versions are unlikely to be relevant to the causal effect of interest. Second, we coarsened the treatment variable for recipients of grafts from donors who died of non-overdose causes into a single treatment group which may limit transportability of our effect estimate to non-US populations with different distributions of donor causes of death.

The type of target trial we attempt to emulate should be guided by the causal question of interest. For instance, policy makers deciding whether or not organs from opioid overdosed victims should be utilized in the US may be interested in the emulation of our first target trial to quantify the effect of transplantation using grafts from overdosed donors compared with transplantation of grafts from other donors. As long as the distribution of treatment versions (e.g. donor's age) is approximately constant over time, these policy makers may not be concerned with the question of whether the benefit we found is due to the drug overdose or to the other donors' characteristics. On the other hand, policy makers in other countries with different distributions of donor characteristics may be more interested in the emulation of our second target trial, which suggested that, when overdosed

donors and donors who die of other causes have similar characteristics, the utilization of grafts from overdosed donors results in graft survival that is similar to that observed when grafts from other donors are utilized. More generally, effect estimates from the emulation of trials like our second target trial can be standardized to a known distribution of participant (e.g. donor) characteristics for transportability to other settings [1].

In summary, our example illustrates how the causal question guides the conceptualization of the target trial, and how explicitly describing target trials helps guide appropriate selection of adjustment variables in observational analyses. When causal questions are poorly defined, it is difficult to conceptualize the target trial, and therefore which variables should be adjusted for and under what conditions the resulting effect estimate can be used for decision-making.

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