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Causal Inference from Observational Data with Time-Dependent Confounding: Application of Marginal Structural Models for Multi-Category Exposures

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INTRODUCTION

Time-dependent confounder is a variable that is associated with current exposure and future outcome, predicted by previous exposure, and predicts current exposure (Fig. 1) [1]. In usual-care "real-world" setting, drug effects are time-dependent, and are affected by time-dependent confounders. In such situation, conventional statistical methods in retrospective database studies produce biased estimates of exposure effect, because they fail to account for the time-dependent nature of the confounders and exposures [2]. Moreover, lack of randomization in observational designs prevents bestowing causal interpretations upon observed associations. Marginal Structural Models (MSM) technique was developed in 1997 as a new class of causal models and practical application of MSM was first introduced in 2000 [3-5].

MSM technique creates at each point of time a pseudo-population of counterfactuals (a hypothetical population in which all patients seem as exposed and unexposed to the drug), in which, time-invariant and time-dependent confounders are balanced, and therefore, causal association between the exposure and the outcome is the same as in the original study population [5-6]. The pseudo-population is created by weighting every patient in the population by the inverse of the conditional probability of being exposed to the treatment that the patient actually received. The technique compares two counterfactuals: outcome if the entire study population is exposed to the treatment and outcome if the entire study population is not exposed to the treatment. Thus, it gives valid causal interpretations between the exposure and the outcome. Nonetheless, causal inference from MSM is contingent upon inherent assumptions of exchangeability, positivity, consistency, and correct modeling for weighting and analysis models [7-9]. The following rules for confounding abatement are termed the causal effect identifiably assumptions [9]:

- Exchangeability: lack of unmeasured confounding is referred to as conditional exchangeability, where all the variables explaining exposure and outcome are included in the analysis. This assumption can be assessed by conducting sensitivity analyses [7].
- Positivity: experimental treatment assumption is referred to positivity, which implies the presence of positive probability for patients to receive each exposure category for a set of covariates, including prior exposure and confounding history. This assumption is testable [8].
- Consistency: consistency refers to the outcome for every exposed patient equals the outcome if the patient had remained exposed, and the outcome for every unexposed patient equals the outcome if the patient had remained unexposed.

CONSTRUCTING MSM

Marginal structural modeling involves two consecutive steps: estimating stabilized inverse probability weights by propensity scoring (exposure selection and censoring models) and conducting weighted repeated measures analysis by generalized estimating equations (outcome analysis model) [9]. Binary logistic regression is used for binary exposure [5,10], and multinomial logistic regression with the generalized logit link is used for multi-category exposure [11-12]. Similarly, binary logistic regression or generalized linear model is used to estimate censoring probabilities. Weighted generalized estimating equation is used to estimate the hazard ratio for the causal association between the exposure and the outcome for each patient at every time weighted by the stabilized weights. The final model includes time-dependent exposure, but not time-dependent confounders. The estimates and 95% confidence intervals from MSM can be compared with corresponding measures from Cox proportional hazards model with time-varying exposures to elucidate whether time-dependent confounding does exist in exposure-outcome assessment. If the confidence intervals between both methods overlap, time-dependent confounding doesn't exist, conditioned upon fulfilling MSM assumptions, including absence of unmeasured confounders.

THEORETICAL BASIS FOR CAUSAL INFERENCE FROM MSM

Exposure propensity scores (EPS) technique was developed in 1983 as a mean to account for confounding by indication (especially confounding by disease severity) in the presence of measured confounding variables [10]. The score is defined as the likelihood of a patient being exposed to treatment given a set of measured confounders; on average, exposure groups with similar scores are expected to have similar baseline information with respect to confounding variables. Thus, a quasi-randomization state is achieved [13]. The inverse of the EPS for exposure groups yields the inverse probability of treatment weighted (IPTW), which creates weights for each patient at each unit of time based on the propensity scores. The weights are interpreted as the number of copies for each observation that are required to form a pseudo-population of counterfactuals in which no time-dependent confounding exists [5].

Figure 2 illustrates the process of attaining quasi-randomization by virtue of MSM. Suppose in a sample of 100 patients, 80 are exposed to the treatment of interest and 20 are unexposed. The conjecture of MSM is to recreate this sample in a way that would equate the selection mechanism between the exposed and the unexposed. Within the exposed group, the probability of exposure given the covariance structure $Pr(E=1|Z)$ equals 0.8, and the inverse of that probability $1/Pr(E=1|Z)$ equals 1.25. By multiplying this inverse probability—as if it was a weight—times the number of people in that group (n=80) a total sample size of 100 is obtained. The same is applied to the unexposed group, where the probability of not exposure $1-Pr(E=1|Z)$ equals 0.2, and the inverse of the probability equals 5. Similarly, a total sample size of 100 will be obtained after multiplying the inverse probability of exposure by the number of people in the unexposed group (n=20). In effect, the MSM has created two populations with selection mechanism of 50% chance, one treated and the other untreated, i.e. probability of the outcome for the counterfactual groups when treated versus the probability of the outcome for the counterfactual group when untreated $Pr[O(E=1|Z)]-Pr[O(E=0|Z)]$; where O is the outcome of interest, E is the exposure of interest ($E=1$, exposed; $E=0$, unexposed), and Z is a vector of confounding variables. This quasi-randomization approach creates selection probabilities that are the same for the exposed and the not exposed. The same principle extends to multi-category exposure groups, where probability of exposure to every treatment given the actual and counterfactual groups equals 50% (Figure 3). Actual exposure groups are in black and counterfactual groups that were created by the weighting approach are in gray.

REAL-WORLD EXAMPLE

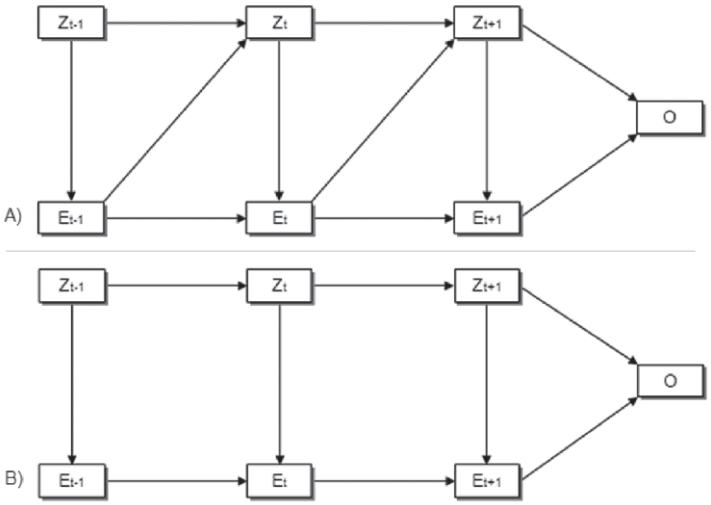
The example in the following table is abstracted from author's dissertation. A

retrospective database analysis of the UK Clinical Practice Research Datalink was conducted to assess the association between inhaled long-acting beta-agonists (LABA) as monotherapy or combination therapy with inhaled corticosteroids (ICS) and asthma related morbidities within 12 months of study drug initiation, including prescriptions for short courses of oral corticosteroids and asthma related visits for accident and emergency departments. In this study, switching between study drugs was allowed to represent real-life stepwise asthma therapy and time-dependent confounding by disease severity was measured by the following variables during 12 months before initiation of study drugs (prescription for oral corticosteroids, asthma related visits to hospitals and emergency departments, and number of prescriptions for inhaled short-acting beta-agonists), and the following variables at the initiation and during 12 months after (prescriptions for short-acting beta-agonists and number of asthma drug classes prescribed). These time-dependent confounders were measured on a monthly basis during study follow up. Among individuals with asthma aged >12 years, there was time-dependent confounding by asthma severity between LABA products and prescriptions for oral corticosteroids (confidence intervals between Cox model and MSM do not overlap); however, such confounding was not present when examining emergency department visits (confidence intervals do overlap). The findings show that LABA monotherapy is associated with worsened asthma outcomes compared to ICS/LABA combination therapy and in tandem with recommendations from regulatory agencies and asthma management guidelines, these products should not be used as monotherapy without concurrent anti-inflammation by ICS.

Table. A real-world example.

Outcome	Model	Hazard ratio (95%Confidence interval)		
		LABA vs. ICS	Combo vs. ICS	Combo vs. LABA
Prescriptions for short courses oral steroids	Cox	1.47 (1.22-2.44)	1.00 (0.66-2.10)	0.91 (0.81-1.35)
	MSM	1.10 (1.07-1.18)	0.38 (0.12-0.66)	0.50 (0.14-0.78)
Asthma related emergency department visits	Cox	1.04 (0.32-15.0)	0.72 (0.08-5.01)	0.56 (0.11-4.12)
	MSM	1.01 (0.05-8.02)	0.41 (0.03-3.14)	0.32 (0.05-2.06)

Figure 1. Illustration of time-variable treatment with (A) and without (B) time-dependent confounding.



CONCLUSIONS

Availability of large databases with the possibility of linkage across different data sources increases researcher's ability to account for an array of confounders, including longitudinal updates of confounder values and exposure states. In addition, therapeutic modalities for most clinical conditions, especially chronic diseases, have increased in complexity to span pharmacological classes, including novel classes that are used as a second-line therapy in most disease states. Such stepwise approach of treatment is common across all chronic diseases and mostly driven by underlying disease severity and patient's response to baseline therapy. The richness of healthcare databases can be mobilized to conduct comparative effectiveness and safety research that better answer critical question arising from real-world circumstances of time-varying treatment and disease severity [14]. Although controlling a known confounder does not guarantee causal estimation, analytical approaches, e.g., MSM that treat treatments and confounders in patterns that resemble usual-care settings improve our knowledge beyond simple binary comparisons of treatment outcomes. In addition to confounding abatement, researchers who wish to test for causal relationships must also verify statistical power and sufficient variability in treatment after such abatement.

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Figure 2. Illustration of attaining quasi-randomization by virtue of MSM in a hypothetical population of size N=100 with binary exposure

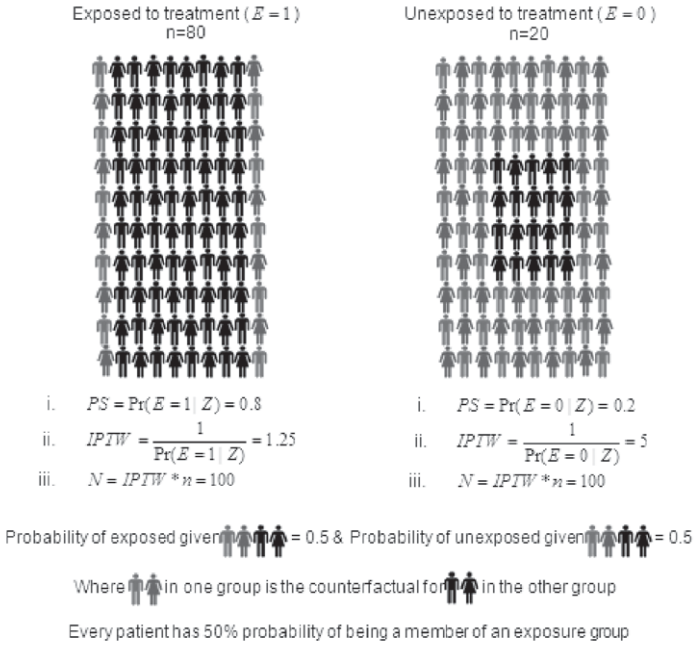

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Figure 3. Illustration of attaining quasi-randomization by virtue of MSM in a hypothetical population of size N=100 with exposure to three treatments.