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Statistical Primer: Propensity-score matching and its alternatives

Short title: Propensity score matching.

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SUMMARY

Propensity score (PS) methods offer certain advantages over more traditional regression methods to control for confounding by indication in observational studies. While multivariable regression models adjust for confounders by modelling the relationship between covariates and outcome, PS methods estimate the treatment effect by modelling the relationship between confounders and treatment assignment. Therefore, methods based on the PS are not limited by the number of events and their use may be warranted when the number of confounders is large, or the number of outcomes is small. The PS is the probability for a subject to receive a treatment conditional on a set of baseline characteristics (confounders). PS is commonly estimated by logistic regression and it is used to match patients with similar distribution of confounders so that difference in outcomes gives unbiased estimate of treatment effect. The present review summarises basic concepts of PS matching and provides guidance in implementing matching and other methods based on the PS such as stratification, weighting and covariate adjustment.

Key words: statistics; propensity score; matching; weighting; stratification

INTRODUCTION

Randomized trials are deemed to be the most scientifically rigorous study design to investigate the efficacy of treatment while minimizing systematic bias. In fact, subjects are randomly assigned to treatment or control groups thus allowing an equal distribution between the two groups of measured and unmeasured confounders (variables that influences both the dependent variable and independent variable causing a spurious association, referred to as covariates in regression context) [1]. However, randomized trials can be difficult to conduct, and observation studies can provide important evidence. In observational studies, subjects in treatment and control groups likely differ for confounders and differences in outcomes can reflect differences in baseline conditions rather than a real treatment effect. Matching each subject in the treatment group with subjects in the control group with comparable baseline confounders is an intuitive way to minimize confounding in observational studies. However, matching simultaneously on few confounders is a very complex process and often results in a very limited number of similar matches. An alternative method is matching based on the propensity score (PS) [2]. The PS is the probability of a subjects to receive a treatment T conditional on the set of confounders (X) and it is commonly estimated via logistic regression. The purpose of estimating PS is to simplify the matching process by collapsing all confounders into a single value. Matching patients with similar estimated PS creates approximate balance for all the confounders and difference in outcomes within groups with similar PS gives unbiased estimate of treatment effect [3,4]. PS matching can circumvent few limitations of standard multivariable regression modelling [5] (Table 1) and it has increasingly appeared in cardiovascular researches [6]. This paper presents provides a guidance in implementing PS based methods to foster transparency and consistency and to facilitate study findings interpretation.

PROPENSITY SCORE METHODS

Four different PS-based methods exist: 1) Matching: matches one or more control cases with a propensity score that is (nearly) equal to the propensity score for each treatment case; 2) Stratification (subclassification): divides sample into strata based on rank-ordered propensity scores and comparisons between groups are performed within each stratum; 3) Weighting: weights cases by the inverse of propensity score. Similar to use of survey sampling weights are used to ensure samples are representative of specific populations; 4) Regression adjustment: includes propensity scores as a covariate in a regression model used to estimate the treatment effect.

PS method should be primarily chosen based on the estimand of interest which depends on the research question and the target population. The most common estimands are the "average effect of the treatment on the treated" (ATT), which is the effect for those in the treatment group, and the "average treatment effect" (ATE), which is the effect on all individuals (treatment and control). The ATE is of more interest if every treatment potentially might be offered to every subject while ATT is preferable when patient's characteristics are more likely to determine the treatment received. Matching can estimate only the ATT; weighting can estimate either the effects based on how weights are defined; stratification can estimate either effect based on how strata are weighted; finally, covariate adjustment can estimate only marginal effect but neither ATT nor ATE. When estimating treatment effect on binary outcomes (odds ratio), matching results in estimates with less bias than stratification or covariate adjustment. IPTW should be used for estimating risk differences particularly when the interest is in estimating ATE [7]. When estimating treatment effect on time-to-event outcomes, matching and IPTW result in less biased estimates than stratification or covariate adjustment (Figure 1) [8]. Based on the above

considerations, we propose an algorithm for selecting PS methods (Figure 1). Currently, several programs can perform PS analysis but they are primarily written in R or consist of special macros in Stata or SPSS (Supplementary Table 1). We recommend the use of the following R packages: *MatchIt or nonrandom* matching; *nonrandom* for stratification and *twang* for weighting.

Steps in propensity score based analysis

The following are the basic steps for removing the effects of confounding from the treatment effect: 1) Decide on confounders for which balance must be achieved; 2.Estimate the distance measure (e.g., propensity score); 3) Condition on the distance measure (e.g., using matching, weighting, or subclassification); 4) Assess balance on the covariates of interest; PS-based analysis is an iterative process and alternative PS-based methods should be attempted until a well-balanced sample is attained; 5) Estimate the treatment effect in the conditioned sample

Selection of confounders

Confounders (X) used for the PS model must not be influenced by the treatment (T) and they should be measured (observed) before T is given. Possible explanation for the treatment assignment should be provided including physician preference, local policies or temporal change in practice. Pre-existing conditions in control units for whom a given treatment is not applicable and these subjects must be removed from the study population. A non-parsimonious selection of confounders is recommended to reduce residual bias [3,4]. However, the inclusion of many confounders can reduce the number of good matches and therefore decreased the precision. A reasonable approach is to include both confounders related to outcome and treatment assignment if the sample size is large and to concentrate on variables believed to be strongly related to the outcome if the sample is small.

PS calculation

The great majority of applications of PS have used logistic regression to estimate the score [3,4] with treatment assignment used as dependent variable and all selected confounders forced as covariates. Other approaches such as classification, regression trees and neural networks can also be considered. In building the PS, consideration of interaction terms is recommended [9]. The predictive ability of model including should not represent a limitation in building the PS model. In fact, the PS model is not employed for inferential purposes, but simply for creating a balancing score and therefore the common practice of reporting the C-statistic as a measure of the adequacy of a PS is questionable [10]. A very high C-statistic can indicate non-overlap in the distribution of PS between treated and untreated subjects and suggests an inability to make comparisons between treated and untreated subjects. Additionally, a high C-statistic cannot be taken as evidence that PS included every important confounder.

Matching

Two commonly selected matching methods are the nearest neighbor matching and optimal matching [3,4]. Nearest neighbor relies on a greedy algorithm which selects a treated participant at random and sequentially moves through the list of participants and matches the treated unit with the closest match from the comparison group. The optimal matching algorithm minimizes the overall distance across matched groups.

Several options exist to increase the quality of matches: matching with replacement and matching with caliper adjustment. In matching with replacement, a control participant could be paired multiple times if that person's PS provides the closest match to multiple intervention participants. Matching with replacement requires the standard errors to be estimated using more complex methods, e.g. sandwich estimators as data are no longer

independent and results in precision loss. Caliper matching uses a prespecified distance within which matches are considered acceptable. If the best match is outside of the caliper distance, the matches are not included in the final set. The designated distance is usually a fraction of a standard deviation of the logit of the PS (e.g., 0.20 *standard deviation*) [9]. Monte Carlo simulations have shown that compared to other methods, caliper matching results in estimates with less bias compared with optimal and nearest neighbor matching and shows the best performance when assessed using mean squared error; matching with replacement does not have superior performance compared with caliper matching without replacement [11]. Finally, the number of comparison units selected for each treated unit should be >1 when there are few good matches in the control groups for each treated unit as a higher ration increases precision. However, if there is a limited number of comparison units, a ratio>1 can selected bad matched thus leading to bias.

Stratification

Stratification sub-classifies the individuals based on quantiles of the propensity scores [12]. The outcomes of the individuals are then compared within each of the strata, and a common estimator of the treatment effect is derived by combining the results over the five strata. A common practice is to divide the propensity score into 5 strata; this has been shown to eliminate 90% of the bias from measured confounders. Stratification approximates matching without running the risk of losing unmatched patients. Another advantage of the stratification technique is that it allows the calculation of both ATE and ATT. Stratum-specific estimates of effect are weighted by the proportion of subjects who lie within that stratum. Thus, when the sample is stratified into n equal-size strata, stratum-specific weights of 1/n are commonly used when pooling the stratum-specific treatment effects, allowing one to estimate the ATE. The use of stratum-specific weights that are equal

to that proportion of treated subjects that lie within each stratum allow one to estimate the ATT. The disadvantages of stratification are that it reduces biases less than the other methods in particular with survival analysis [8]. Another disadvantage is the complexity of pooling the strata effects (e.g. use the Cochran-Mantel-Haenszel method).

Inverse probability of treatment weighting

PS can also be used as inverse weights in estimates of the ATE, known as inverse probability of treatment weighting (IPTW) [13]. The weight of each participant is calculated using 2 variables: T (indicator of the participant's treatment status being 0 if in the control arm and 1 if in the treatment arm) and PS of each participant. The weight (w) of the participant [wATE = T/PS + (1-T)/(1-PS)] is equal to the inverse of the probability of receiving the treatment the participant received. In this approach, the contributions of the study subjects are weighted by 1/propensity score for experimental patients and by 1/(1−PS) for control patients. However, a different set of weights permit estimation of the average treatment effect in the treated (ATT): wATT: T+PS(1-T)/(1-PS). Treated subjects receive a weight of 1. Thus, the treated sample is being used as the reference population to which the treated and control samples are being standardized. Moreover, for settings with more than two treatments, IPSW with PS estimated via generalized boosted models can be implemented using those scores to estimate weights and causal effects. The advantages of using IPSW are that it retains all the patient data and reduces bias more than stratification and covariate adjustment [8].

Covariate adjustment

The PS can be used as a covariate in adjusting the treatment effect for baseline differences. Its advantage is that the PS itself can include many covariates along with interactions; this allows for the subsequent covariate regression model to be more parsimonious, including

only the relevant covariates along with the propensity-score variable. However, a formal assessment of balance between treatment groups is not possible. Moreover, it produces more biased estimates [8] and wrong assumptions about the functional relationship of PS and outcome (linearity, proportional hazards etc.) may then directly lead to biased estimates.

Balance check

The quality of the matches is based on the comparison of confounders distribution in the matched sample [14]. The use of hypothesis tests and p-values to compare balance is not appropriate because there are no inferences being made in relation to a population. They also conflate changes in balance with changes in statistical power. Standardized biases (also known as standardised mean difference) are recommended to assess the balance of covariates between the two groups. The standardized mean difference compares the difference in means in units of the pooled standard deviation [14]. A value higher that 0.10 (10% in case it is reported as percentage) is commonly considered index of residual imbalance. Lack of balance can indicate the need to add higher order or non-linear terms. Interaction terms should also be considered, in particular between the most unbalanced covariates. The analysis can also be restricted only to those subjects with PS that overlap with other group (common support) [15]. Graphical diagnostics can be helpful for getting a quick assessment of the covariate balance in presence of many covariate. The first step is to examine the distribution of the PS in the original and matched groups and PS overlapping using mirrored histogram (Figure 2 A) while a Love-plot of the standardized differences of means (Figure 2 B), gives us a quick overview of whether balance is adequate.

Estimation of treatment effect

Matched data should be analysed using procedures for matched analyses, such as paired t tests for continuous variable while McNemar's test, conditional logit or mixed effect (matched pairs as random effect) logistic regression can be used for binary outcomes. For time to event outcomes (survival) stratified log-rank test, stratified Cox model or mixed effect Cox model are required [3]. Data can also be analysed using a standard regression in the matched sample that includes a treatment indicator and the variables used in the PS model (double robust), where the regression adjustment is used to "clean up" small residual covariate imbalance between the groups. Methods for paired samples provide better estimates [16] and non-paired methods can be presented as sensitivity analysis.

Propensity score and missing data

In presence of missing data, multiple imputation can be used to create completed datasets from which PS can be estimated. There are two proposed methods [17]: 1) averaging of propensity scores after multiple imputation, followed by causal inference; or 2) causal inference using each set of propensity scores from the multiple imputations followed by averaging of the causal estimates. It is advisable to include the outcome in the imputation model.

REPORTING

Despite the use of this analytical approach has particularly increased in clinical research, current reporting is often inadequate and ambiguous and this result in problems with study reproducibility and interpretation. To improve consistency and reproducibility, a set of items to be reported has been recommended [18] (Supplementary Table 2). These items should be then integrated with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) categories for reporting observational studies [19].

EXAMPLE

In available randomized trials off-pump failed to improve hospital mortality when compared to on-pump in coronary artery bypass grafting (CABG). However, patients enrolled in randomized studies are highly selected and at low-risk. Whether off-pump can provide survival benefit in high risk patients in the real-world practice remains unclear. Here we implemented PS matching to compare hospital mortality after off-pump vs. on-pump in high risk patients (EuroSCORE ≥6) undergoing isolated first time CABG using Bristol Heart Institute (United Kingdom) database.

Study population: A total of 3424 patients with preoperative EuroSCORE ≥6 underwent isolated first time CABG from 1996 to 2015 at a single institution (Bristol). Off-pump was used in 1670 patients and on-pump was used in 1754 patients.

PS calculation: We selected 20 confounders for hospital mortality to compare the two groups (Table 2). We estimated PS for off-pump by logistic regression using linear terms, no interaction and stratification by year of surgery.

Matching process: To create matched pairs, we used caliper matching (0.20 standard deviation of logit of PS) without replacement. Matching selected 1199 pairs. Table 2 shows baseline confounders distribution in the original and matched samples.

Balance check: After matching the two groups were comparable for all confounders (SMD<0.10). Visual inspection of mirrored histogram showed adequate PS overlapping (Figure 2A) and Love plot confirmed no significance imbalance for any of covariates included (Figure 2B).

Estimation of treatment effect: In the original sample off-pump was not significantly associated to reduced mortality also in a fully adjusted multivariable logistic regression. However, in the matched sample conditional logit, at doubly robust and mixed effect logistic

regression off-pump was found to be significantly associated with reduced in-hospital mortality (Table 2) (R codes provided in Supplementary Material).

LIMITATIONS OF PS MATCHING

The main limitation of PS methods is their inability to control for unmeasured confounding. A drawback of matching is an often substantially reduced sample size since for some patients matches may not be found. This may significantly affect the study's final conclusions which then apply only to the selected subset of patients that could be matched. The PS tends to work better in larger samples. Significant imbalances of certain covariates may be unavoidable despite a well-constructed propensity score secondary to a small number of observations. As randomized studies, PS methods generate an average effect and therefore, they do not address what treatment may be right for a given patient.

CONCLUSIONS

PS methods reduce a set of confounders into a single, intuitive variable which optimizes matching and make it possible to statistically adjust when the ratio of events to confounders is low. They also may reveal cases in which the patient populations are too divergent to make meaningful comparisons. Proposed reporting guidelines should be followed to foster transparency and consistency and to facilitate study findings interpretation.

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FIGURES

Figure 1. Algorithm to select most appropriate propensity score (PS) method. ATT: average effect of the treatment on the treated; ATE: average treatment effect.

Figure 2A. Mirrored histogram showing propensity score distribution and overlapping in unmatched (white) and matched (green) in the treatment (off-pump, top) and in the control group (on-pump, bottom).

Figure 2B. Love plot showing changes in standardised mean difference before (red) and after (blue) matching (BMI: body mass index; MI: myocardial infarction; YOP: year of procedure; DMI: diabetes mellitus on insulin; PCI: percutaneous coronary intervention; PVD: peripheral vascular disease; LMD: left main disease; COPD: chronic obstructive pulmonary disease; CVA: cerebrovascular accident IABP: intra-aortic balloon pump; NYHA: New York Heart Association functional class; LV: left ventricular ejection fraction; NVD: number of vessel diseased)

Table 1. Advantages of Propensity score matching over standard multivariable regression

Problem with MV regression	Comments	Advantages with PS matching
Restricted number of confounders in the model	In MV model, numbers of confounders are limited by numbers of events. A common rule-of-thum is one covariate for every 8-10 events. This limits the application of MV model in particular in case of large number of confounders and relatively low number of events	For the calculation of PS, number of confounders used in the PS model are not limited by numbers of outcome events. The collapsing of covariates into one score allows the investigator to include all potential confounders that otherwise may not have been possible to include, and may improve statistical efficiency. Therefore, use of PS may be warranted when the number of confounders is large or the number of outcomes is small.
Invalidity of the study due to confounding by indication	Patients with contraindications to the experimental treatment (or those with absolute indications) may have no comparable exposed subjects (or unexposed subjects) for valid estimation of relative or absolute differences in outcomes. These subjects are not usually recognized with conventional response modeling and might be influential due to effect measure modification or model misspecification.	Matching on the PS focuses directly on the indications for the experimental treatment. Graphical comparison of PSs in exposed versus unexposed subjects can identify these areas of non-overlap that are otherwise difficult to describe in a multivariate setting with many factors influencing treatment decisions.
Modelling assumption	MV regression model relies on the modeling assumptions of linearity between covariates and the natural logarithm of the odds of the outcome	Matching by PS eliminates the linearity assumption between PS and outcomes.
Model design not separated from outcome analysis	Multivariable regression models adjust for confounders by modeling relationship between covariates and outcome and therefore model specification can be influenced by researcher expectation to prove the original hypothesis.	PS matching estimate the treatment effect by modelling covariates and treatment assignment. PS matching mirrors a randomized experiment because the study design (PS model and matching) is separated from the outcome analysis. This protects against actual or suspected bias on the part of the researcher

MV: multivariable; PS: propensity score

Table 2. Preoperative confounders distribution in the original and matched samples

	Off-pump (original)	On-pump (original)	SMD before matching	Off-pump (matched)	On-pump (matched)	SMD After matching
Set of Confounders	1670	1754		1199	1199	
Age, year (mean (sd))	74 (7)	73 (7)	0.158	74 (7)	74 (7)	0.004
Female n(%)	486 (29.1)	489 (27.9)	0.027	332 (27.7)	336 (28.0)	0.019
NYHA III/IVn(%)	680 (40.7)	767 (43.7)	0.061	497 (41.5)	506 (42.2)	<0.001
MI within 30 days n(%)	666 (39.9)	649 (37.0)	0.059	463 (38.6)	474 (39.5)	0.016
Prior PCI n(%)	91 (5.4)	88 (5.0)	0.019	69 (5.8)	65 (5.4)	0.030
IDDM n(%)	163 (9.8)	161 (9.2)	0.020	113 (9.4)	121 (10.1)	0.039
Smoking n(%)	164 (9.8)	177 (10.1)	0.009	115 (9.6)	120 (10.0)	0.014
Creatine >200mmol/l n(%)	99 (5.9)	102 (5.8)	0.005	70 (5.8)	65 (5.4)	0.018
COPD n(%)	254 (15.2)	266 (15.2)	0.001	195 (16.3)	182 (15.2)	0.056
CVA n(%)	111 (6.6)	126 (7.2)	0.021	77 (6.4)	90 (7.5)	0.033
PVD n(%)	440 (26.3)	450 (25.7)	0.016	334 (27.9)	311 (25.9)	0.029
NVD n(%)			0.299			0.092
1	101 (6.0)	44 (2.5)		51 (4.3)	30 (2.5)	
2	416 (24.9)	282 (16.1)		261 (21.8)	197 (16.4)	
3	1153 (69.0)	1428 (81.4)		887 (74.0)	972 (81.1)	
LMD n(%)	529 (31.7)	545 (31.1)	0.013	392 (32.7)	399 (33.3)	0.005
LVEF<30% n(%)	237 (14.2)	331 (18.9)	0.126	179 (14.9)	203 (16.9)	0.055
Cardiogenic shock n(%)	23 (1.4)	67 (3.8)	0.154	20 (1.7)	28 (2.3)	0.006
Preop IABP n(%)	59 (3.5)	77 (4.4)	0.044	49 (4.1)	54 (4.5)	0.009
Emergency n(%)	64 (3.8)	139 (7.9)	0.175	53 (4.4)	59 (4.9)	0.037
BMI (mean (sd))	27 (4)	27 (5)	0.092	27 (4)	27 (5)	0.012
YOP (mean (sd))	2006 (4)	2005 (6)	0.328	2006 (5)	2006 (5)	0.051
Performed by Trainee n(%)	411 (24.6)	437 (24.9)	0.007	294 (24.5)	293 (24.4)	0.014
Logistic EuroSCORE	10±7%	10±8%		10±7%	10±8%	
Estimation of treatment effect						
			P-value			P-value
In Hospital Mortality n(%)	54 (3.2)	75 (4.3)	0.11*	36 (3.0)	55 (4.6)	0.06*
fully-adjusted logistic OR[95%CI]	0.72[0.48-1.07]		0.10			
Conditional logit OR[95%CI]				0.66[0.43-0.99]		0.04
Doubly robust logistic OR[95%CI]				0.61[0.39-0.95]		0.03
Mixed effect logistic OR[95%CI]				0.64[0.42-0.99]		0.04

*Chi-squared test; SMD: standardized mean difference; NYHA: New York Heart Association; MI: myocardial infarction; PCI: percutaneous coronary intervention; IDDM: insulin dependent diabetes mellitus; COPD: Chronic obstructive pulmonary disease; CVA: cerebrovascular accident; PVD: peripheral vascular disease; NVD: number of vessels diseased; LMD: left main disease; LVEF: left ventricular ejection fraction; IABP intra-aortic balloon pump; BMI: body mass index; YOP: year of procedure.