A Method/Macro Based on Propensity Score and Mahalanobis Distance to Reduce Bias in Treatment Comparison in Observational Study

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ABSTRACT

In observational studies, investigators usually do not have the same control over the treatment assignment as they do with randomized controlled studies. As a result, the treatment and control groups may have a large difference on their observed covariates. These differences could lead to bias in estimating treatment effects. There are several propensity score based methods that could reduce the bias caused by these differences and make the two groups comparable. One method is the nearest available Mahalanobis metric matching within the calipers defined by the propensity score. This paper will present and demonstrate the matching algorithm based on this method. A macro is developed to implement the matching algorithm; a growth hormone observational study is used as an example to demonstrate the bias before the match and percentage of bias reduction after the match.

Key words: observational study, propensity score, Mahalanobis distance

INTRODUCTION

In observational studies, unlike controlled randomized clinical studies, frequently there are large differences in participants’ characteristics between treatment and control (or another treatment) groups. These differences may lead to bias in the direct comparison of treatment effect, especially when there is a strong relationship between these characteristics and the outcome variable. Traditionally covariates adjustment and various matching algorithms were used to reduce the bias; however, in many situations these methods are not adequate to address the issue. For example, using a model with a large number of covariates may lead to inefficient estimates of the treatment effect. Propensity score, defined as the conditional probability of receiving a particular treatment ($Z_i = 1$) versus control or another treatment group ($Z_i = 0$) given the study participants’ covariates, $X_i$, $\Pr(Z_i = 1 \mid X_i = x_i)$ was first introduced by Rosenbaum and Rubin in 1983, and now is commonly used as a building block in many methods of bias reduction in the analysis of observational data. Matched pairing, stratification (sub-classification) and covariance adjustment are the three commonly used propensity score based techniques. Propensity score can be estimated from a logit model using PROC LOGISTIC procedure in SAS/STAT.

Mahalanobis distance is the distance between two $N$ dimensional points scaled by the statistical variation in each component of the point. For example, if $X$ and $Y$ are two points from the same distribution with covariance matrix $C$, then the Mahalanobis distance can be expressed as $D(X, Y) = (X - Y)C^{-1}(X - Y)$. When the covariance matrix is the identity matrix, Mahalanobis distance specializes to the Euclidean distance. Mahalanobis Metric Matching was used as one method of matching observations based on Mahalonobis distance for bias reduction in observational studies.

Matching is a method of sampling from a large reservoir of potential candidates in one group to produce a group of modest size in which the distribution of covariates is similar to that in another group. Various methods were developed by combining ideas of matching and propensity score. Specifically, propensity scores can be used to construct matching cohorts using three methods: (i) Nearest available matching on the estimated propensity score, (ii) Mahalanobis metric matching including the propensity score and (iii) the nearest available Mahalanobis metric matching within calipers defined by the propensity score. All three methods are useful techniques with different properties. The first method is simple and incurs less computation. Lori developed and presented two macros based on the first method. The second method has the effect of “equal percent bias reducing” (EPBR). The third method produces the best balance for the covariates between two treatment groups, and is considered to be superior to the other two methods.
In this paper we present a SAS macro that was developed to implement the third method listed above - the nearest available Mahalanobis metric matching within calipers defined by the propensity score - and use the macro to illustrate the methodology.

Data from a growth hormone study - a large observational study, is used throughout the paper. The objective of the study is to evaluate long-term safety outcomes in growth hormone deficiency (GHD) adult patients received with treatment A compared with treatment B. A total of 2430 (1988 in treatment group A, 442 in treatment group B) GHD adult patients were enrolled in the study. It has been determined based on expert’s opinion that 37 variables at baseline may be related to making decision on treatment assignment; therefore these variables were included in logit model to estimate propensity score. Five of these variables, including age, status of diabetic insipidus, onset of disease (adult=1, other=0) and cause of GH deficiency (1=tumor/adenoma, 0=no) and logit of propensity score were considered as key variables for treatment choice and were used in computing the Mahalanobis distance. One quarter of standard deviation of logit of propensity score (about 0.23) was used as a caliper.

MATCHING ALGORITHM

The matching algorithm and macro proposed in the paper are illustrated in Chart 1.

Step 1. Propensity scores are computed for every subject using a logistic regression model with all possible independent variables that may have affected choosing treatment for study participants included.

Step 2. The subjects in treatment group A (the group with less study participants) are randomly ordered and the first subject from group A is selected. Subjects in group B whose propensity score is within the caliper (one quarter of standard deviation of the logit of the propensity score as suggested by Rosenbaum and Rubin2) are identified as initial matched candidates. Three situations may occur in this step: (I) No candidate is located within the caliper, then this round of matching will stop here and the next round will start (i.e. determine the match for the next subject in group A). (II) Only one candidate is identified within the caliper and this candidate is considered as final. (III) More than two candidates were identified, and then the search process will move to Step 3.

Step 3. Mahalanobis distances based on a smaller numbers of key variables and propensity score are calculated between the subject in group A and those initially selected subjects in group B. The subject with the smallest distance to the subject in group A is selected as a final matched candidate. The matched pair is then removed from the pool, and the process will repeat for the next subject in group A. All remaining subjects in group B are available for the remaining matching rounds. The matching process will repeat until the group A is exhausted.

Notice that direct computation of Mahalanobis distances involves inverting variance-covariance matrix C, which is both numerically unstable and computationally expensive. This can be avoided by transforming the raw data X into standardized X* having an identity covariance (via a spectral decomposition of C). Then the Mahalanobis distance for data-points in X will be identical to the Euclidean distance for data-points in the standardized space, X*. The computations can be implemented in SAS by a variety of ways. For example, one can use PROC IML subroutine SVD. Since some SAS users may have no access to SAS/IML software, in the macro we chose to only use SAS procedures available in the SAS/STAT software. Specifically, we use PROC PRINCOMP and PROC SCORE to obtain the principal components scores with an identity covariance matrix for all data-points and PROC FASTCLUS to compute the Euclidean distances from each observation to a specific reference point by setting it as a seed.
Chart 1 Matching Scheme

Group A

Estimate propensity score from Logistic Regression Model

Find potential candidates pool based on propensity score

If n=0
Start with next cycle

If n=1
Export the matched pair

If n>=2
Mahalanobis metric matching

Group B
RESULTS

As referenced in the Introduction, a growth hormone observational study is used here as an application example for match algorithm and the proposed macro. Table I describes the original population and contains all of covariates that were used in the multiple logistic regression model to compute propensity score. Difference between two treatment groups is evaluated using T-test for continuous variables and Chi-Square test for categorical variables. P values for majority of variables (23 out of 38) are significant at 0.05 level which means there is a significant difference between the two groups with respect to these characteristics. A direct comparison between two groups based on this study population would lead to biased and invalid inference if the outcome measure is related to any of these baseline characteristics.

Table I: Group Comparisons Prior to Matching

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group A (Mean + SD)</th>
<th>Group B (Mean + SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>1988</td>
<td>442</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>46.08 (14.83)</td>
<td>54.82 (15.98)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Baseline body mass index</td>
<td>31.27 (7.02)</td>
<td>30.08 (6.22)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Baseline diastolic blood pressure</td>
<td>77.98 (10.31)</td>
<td>77.72 (10.50)</td>
<td>0.635</td>
</tr>
<tr>
<td>Baseline systolic blood pressure</td>
<td>123.07 (16.99)</td>
<td>126.90 (19.28)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Number of pituitary hormonal disorders</td>
<td>2.15 (1.28)</td>
<td>2.17 (1.14)</td>
<td>0.732</td>
</tr>
<tr>
<td>Number of smoking years</td>
<td>7.31 (11.96)</td>
<td>9.21 (13.95)</td>
<td>0.008</td>
</tr>
<tr>
<td>Logit of propensity score</td>
<td>-1.86 (0.88)</td>
<td>-1.16 (0.82)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pre-existing coronary artery disease</td>
<td>127 (6.39)</td>
<td>50 (11.31)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pre-existing diabetes insipidus</td>
<td>435 (21.88)</td>
<td>58 (13.12)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pre-existing diabetes mellitus</td>
<td>166 (8.35)</td>
<td>64 (14.48)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pre-existing hypertension</td>
<td>493 (24.80)</td>
<td>143 (32.35)</td>
<td>0.002</td>
</tr>
<tr>
<td>Pre-existing hyperlipidemia</td>
<td>808 (40.64)</td>
<td>214 (48.42)</td>
<td>0.003</td>
</tr>
<tr>
<td>Pre-existing pituitary microadenoma</td>
<td>237 (11.92)</td>
<td>36 (8.14)</td>
<td>0.024</td>
</tr>
<tr>
<td>Pre-existing pituitary macroadenoma</td>
<td>713 (35.87)</td>
<td>231 (52.26)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Onset type for GH deficienc (adult/childhood)</td>
<td>1674 (84.21)</td>
<td>391 (88.46)</td>
<td>0.023</td>
</tr>
<tr>
<td>Pre-existing pathological bone fracture</td>
<td>57 (2.87)</td>
<td>1 (0.23)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pre-existing visual impairment</td>
<td>527 (26.51)</td>
<td>147 (33.26)</td>
<td>0.005</td>
</tr>
<tr>
<td>Cause of GH deficiency (idiopathic)</td>
<td>365 (18.36)</td>
<td>48 (10.86)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cause of GH deficiency (empty sella)</td>
<td>96 (4.83)</td>
<td>12 (2.71)</td>
<td>0.055</td>
</tr>
<tr>
<td>Cause of GH deficiency (trauma-shee)</td>
<td>89 (4.48)</td>
<td>14 (3.17)</td>
<td>0.242</td>
</tr>
<tr>
<td>Cause of GH deficiency (tumor/adenoma)</td>
<td>1243 (62.53)</td>
<td>335 (75.79)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Cause of GH deficiency (Other)</td>
<td>195 (9.81)</td>
<td>33 (7.47)</td>
<td>0.149</td>
</tr>
<tr>
<td>Family history of cerebrovascular disease</td>
<td>588 (29.58)</td>
<td>141 (31.90)</td>
<td>0.359</td>
</tr>
<tr>
<td>Gender (0 = F, 1 = M)</td>
<td>1105 (55.58)</td>
<td>273 (61.76)</td>
<td>0.020</td>
</tr>
<tr>
<td>Pre-existing malignant tumor</td>
<td>91 (4.58)</td>
<td>36 (8.14)</td>
<td>0.004</td>
</tr>
<tr>
<td>Pre-existing non-functional pituitary adenoma</td>
<td>546 (27.46)</td>
<td>175 (39.59)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Pre-existing functional pituitary adenoma</td>
<td>411 (20.67)</td>
<td>93 (21.04)</td>
<td>0.846</td>
</tr>
</tbody>
</table>
Table II describes the matched population based on the matching algorithm implemented in our macro. In summary, 441 patients out of 442 (99.8%) from group B were successfully matched by patients from group A. Only 882 patients (36.3%) out of 2430 total patients will be used for the final analysis to estimate treatment effect. Difference between the matched pairs is evaluated using T-test for continuous variables and Chi-Square test for categorical ones. For none variables, there is a significant difference between two matched groups, which shows that the two matched groups are well balanced.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Group A (Mean + SD)</th>
<th>Group B (Mean + SD)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total patients</td>
<td>441</td>
<td>441</td>
<td>0.996</td>
</tr>
<tr>
<td>Age</td>
<td>54.77 (15.55)</td>
<td>54.77 (15.95)</td>
<td>0.911</td>
</tr>
<tr>
<td>Baseline body mass index</td>
<td>30.13 (6.14)</td>
<td>30.09 (6.23)</td>
<td>0.853</td>
</tr>
<tr>
<td>Baseline diastolic blood pressure</td>
<td>77.64 (10.00)</td>
<td>77.77 (10.46)</td>
<td>0.907</td>
</tr>
<tr>
<td>Baseline systolic blood pressure</td>
<td>126.50 (18.64)</td>
<td>126.89 (19.30)</td>
<td>0.761</td>
</tr>
<tr>
<td>Number of pituitary hormonal disorders</td>
<td>2.16 (1.15)</td>
<td>2.17 (1.14)</td>
<td>0.009</td>
</tr>
<tr>
<td>Number of smoking years</td>
<td>9.23 (14.11)</td>
<td>9.23 (13.95)</td>
<td>1.000</td>
</tr>
<tr>
<td>Logit of propensity score</td>
<td>-0.016 (0.18)</td>
<td>0.016 (0.18)</td>
<td>0.662</td>
</tr>
<tr>
<td>Pre-existing coronary artery disease</td>
<td>51 (11.56)</td>
<td>50 (11.34)</td>
<td>1.000</td>
</tr>
<tr>
<td>Pre-existing diabetes insipidus</td>
<td>57 (12.93)</td>
<td>58 (13.15)</td>
<td>1.000</td>
</tr>
<tr>
<td>Pre-existing diabetes mellitus</td>
<td>65 (14.74)</td>
<td>64 (14.51)</td>
<td>1.000</td>
</tr>
<tr>
<td>Pre-existing hypertension</td>
<td>147 (33.33)</td>
<td>142 (32.20)</td>
<td>0.774</td>
</tr>
<tr>
<td>Pre-existing hyperlipidemia</td>
<td>212 (48.07)</td>
<td>213 (48.30)</td>
<td>1.000</td>
</tr>
<tr>
<td>Pre-existing pituitary microadenoma</td>
<td>35 (7.94)</td>
<td>36 (8.16)</td>
<td>1.000</td>
</tr>
<tr>
<td>Pre-existing pituitary macroadenoma</td>
<td>228 (51.70)</td>
<td>230 (52.15)</td>
<td>0.547</td>
</tr>
<tr>
<td>Onset type for GH deficiency (adult/childhood)</td>
<td>388 (87.98)</td>
<td>390 (88.44)</td>
<td>0.917</td>
</tr>
<tr>
<td>Pre-existing pathological bone fracture</td>
<td>1 (0.23)</td>
<td>1 (0.23)</td>
<td>1.000</td>
</tr>
</tbody>
</table>
Table III Percent Reductions in Bias for Key Variables

<table>
<thead>
<tr>
<th>Variables</th>
<th>Bias before matching</th>
<th>Bias after Matching</th>
<th>Percent Reduction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>8.74</td>
<td>0.01</td>
<td>99.89</td>
</tr>
<tr>
<td>Pre-existing diabetes insipidus</td>
<td>8.76</td>
<td>0.22</td>
<td>97.49</td>
</tr>
<tr>
<td>Onset type for GH deficiency</td>
<td>4.25</td>
<td>0.46</td>
<td>89.18</td>
</tr>
<tr>
<td>Cause of GH deficiency (adult/childhood)</td>
<td>13.26</td>
<td>0.45</td>
<td>96.61</td>
</tr>
<tr>
<td>Logit of propensity score</td>
<td>0.70</td>
<td>0.03</td>
<td>95.71</td>
</tr>
</tbody>
</table>
**Percentage bias reduction is calculated by \((1 - D_j)/D_i \times 100\%\) where \(D_i\) and \(D_j\) are group difference in covariates means after matching and before matching, respectively.**

**CONCLUSION**

By applying the macro presented in this paper, subjects in one treatment group can be successfully matched to another treatment group using Mahalanobis metric matching within the calipers defined by propensity score method. Such matching process would in general result in two treatment groups having very similar baseline characteristics, thus treatment difference can be appropriately estimated. The source SAS code is attached in the end of this paper and SAS users could apply this macro in their own research work.

**REFERENCE**

3. Lori S Parsons, “Using SAS software to perform a case-control match on propensity score in an observational study”, SUGI 1999, 225-229,

**ILLUSTRATION OF CODE**

```sas
options macrogen mlogic mprint;
libname XXXX 'X:\XXXX'; ***Please specify the libname name and location***;
proc datasets lib=work kill;run;

proc princomp data=&data std out=out outstat=outstat noprint;
var &var;
run;
proc score data=&refdata score=outstat out=reference_point;
```
var &var;
run;

proc append data=out base=reference_point;
run;

proc fastclus data=reference_point maxc=1 replace=none maxiter=0 NOPRINT
   out=mahalanobis_to_point(drop=cluster);
   var prin:;
run;

proc sql;
   create table mahalanobis_to_point
      as select a.*
            from mahalanobis_to_point a, &refdata b
            where a.&id^=b.&id;
   quit;
proc sort data=mahalanobis_to_point;
   by distance;

data mahalanobis_to_point;
   set mahalanobis_to_point;
   by distance;
   if _n_=1;
   run;

data case_ctrl;
   set &refdata(keep=&id) mahalanobis_to_point(keep=&id);
   newid=&i;
run;

data case_ctrl_together;
   set case_ctrl_together case_ctrl;
   if &id=. then delete;
run;

*** Exclude patients in case group which are selected in the Mahalanobis macro ***;

proc sql;
   create table case_temp
      as select a.*
            from case_temp a, mahalanobis_to_point b
            where a.&id^=b.&id;
   quit;
%MEND Mahalanobis;

***Set up a dataset which will contain all control patients and matched case
patients***;

data case_ctrl_together; run;

***********************************************************************
***  data --- input dataset name ***
***  class --- categorical variables included in the logistic model ***
***  yvar  --- dependent variable (1=case group, 0=control group) ***
***  xvar  --- independent variables ***
***  id    --- patient identification number ***
***********************************************************************;
%macro match(data, class, yvar, xvar, id);

***Perform logistic regression, select independent variables, and create the propensity score***;

proc logistic descending data=&data noprint;
   &class;
   model &yvar=&xvar;
   output out=propen(drop=_level_) prob=prob xbeta=logit;
run;

proc univariate data=propen noprint;
   var logit;
   output out=propen_sd std=sd;
run;

***create datasets of case and control, which contain patients from case and control groups ***;

data ctrl case;
   set propen;
      if &yvar=0 and prob ne . then do;
         rannum=ranuni(1234567);
         label rannum='Uniform Randomization Score';
         output ctrl;
      end;
      else if &yvar=1 and prob ne . then do;
         output case;
      end;
   data ctrl;
      if _n_=1 then set propen_sd(keep=sd);
      set ctrl;
run;

***sort ctrl by random number generated ***;

proc sort data=ctrl;
   by rannum;
run;

data _null_
   set ctrl;
   by sd;
   if last.sd then call symput('tot',put(_n_,8.));
run;

data case_temp;
   set case;

*** select one patient once time from dataset ctrl, and search for matched-pair in case group ***;

%let j=%eval(&tot);

%do i=1 %to &j;
   data ctrl_temp;
      set ctrl;
      if _n_=&i;
%endo;
low=logit - 0.25*sd;
up =logit + 0.25*sd;
run;

data match_temp;
  if _n_=1 then set ctrl_temp(keep=low up);
    set case_temp(drop=rannum);
  if low<=logit<=up;
run;

*************************************************************************************;
*** calculate number of patients who were included in the match dataset ***
*** 1) if there is no match found, then select next patient from case group ***
*** 2) if there is one matched, select this patient and go to next round ***
*** 3) if there are more than 1 patients, calculate Mahalanobis distance and ***
***    select the patient with smallest distance, then go to next round ***
*************************************************************************************;
proc sql;
  create table casen
    as select count(&id) as n
    from match_temp;
  quit;

data _null_;
  set casen;
  if _n_=1 then call symput('casen',put(n,8.));
run;
%if %eval(&casen)=0 %then %do;
  data case_ctrl_together;
    set case_ctrl_together match_temp(in=a keep=&id);
    if &id=. then delete;
    if a then newid=&i;
  run;
%end;
%else %if %eval(&casen)=1 %then %do;
  data match_temp1;
    set ctrl_temp match_temp;
    newid=&i;
  run;
  data case_ctrl_together;
    set case_ctrl_together match_temp1(keep=&id newid);
    if &id=. then delete;
  run;
  proc sql;
    create table case_temp
      as select a.*
      from case_temp a,  match_temp b
      where a.&id^=b.&id;
    quit;
%end;
%else %do;

***please specify the key variables (including propensity score as one key variable) which are used to calculate the mahalanobis distance ***;
%Mahalanobis(match_temp, XXXXX, ctrl_temp);
%end;
%end;

***Create test dataset that contains patients from case_control_together, and all variables and propensity scores as well***;

proc sql;
  create table test
  as select a.*, b.newid
  from propen a, case_ctrl_together b
  where a.&id=b.&id
  order by newid,&yvar;
quit;
%mend match;

*** This is the end of macro ***

ACKNOWLEDGMENT

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