Time-dependent Propensity Score and Collider-Stratification Bias: an example of beta_2-agonist use and risk of coronary heart disease


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Background:

- In observational studies of time-varying exposure and confounders, the use of propensity score (PS) is limited to assigning weights, inverse probability of treatment weighting (IPTW) as in marginal structural models (MSMs).
- Stratification and conditioning on time confounders which are also intermediates can induce collider-stratification bias and adjust away the (indirect) effect of exposure.
- Similar bias could be expected when conditioning/stratification on time-dependent PS.

Objective:

- To explore collider-stratification and confounding bias due to conditioning or stratifying on time-dependent PS in a clinical example on the effect of inhaled short and long-acting beta_2-agonist use (SABA and LABA respectively) on coronary heart disease (CHD).

Methods:

A cohort of patients with an indication for SABA and/or LABA use was extracted from the Netherlands Medical Research University Medical Center Utrecht General Practitioner (GP) Research Network.

- Follow-up began with the first day of diagnosis of bronchitis, asthma, or COPD and ended at the occurrence of CHD, death, unregistration with the general practitioner, or end of the study, whichever occurred first.
- SABA and LABA use and potential confounders were ascertainment on 3 months interval.
- Hazard ratios (HR) were estimated using PS stratification as well as covariate adjustment using PS and compared with those of MSMs in both SABA and LABA use separately.
- In MSMs, censoring was accounted for by including inverse probability of censoring weights (IPCW).

Results:

Table 1. Estimates of Hazard Ratio for CHD Associated With Use of Inhaled SABA and LABA Using Different PS (time-dependent) methods and MSMs With Three Months Interval Approach

<table>
<thead>
<tr>
<th>Methods</th>
<th>SABA Use</th>
<th>LABA Use</th>
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<tbody>
<tr>
<td></td>
<td>HR</td>
<td>95% CI</td>
</tr>
<tr>
<td>Crude Estimate</td>
<td>0.90</td>
<td>0.63, 1.28</td>
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<tr>
<td>PS Stratification</td>
<td></td>
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<tr>
<td>Quantiles of PS</td>
<td>1.07</td>
<td>0.72, 1.60</td>
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<tr>
<td>Percentiles of PS</td>
<td>1.15</td>
<td>0.77, 1.71</td>
</tr>
<tr>
<td>Covariate adjustment</td>
<td>1.09</td>
<td>0.74, 1.61</td>
</tr>
<tr>
<td>IPTW†</td>
<td>0.92</td>
<td>0.60, 1.41</td>
</tr>
<tr>
<td>IPTW*</td>
<td>0.86</td>
<td>0.55, 1.34</td>
</tr>
<tr>
<td>Time-varying Cox Model††</td>
<td>1.03</td>
<td>0.69, 1.55</td>
</tr>
</tbody>
</table>

* Stratification based on quantiles of PS in the Cox model
** Stratification based on deciles of PS in the Cox model
*** PS were included as covariate in the Cox model
†† Stabilized treatment weight were used to fit MSMs

Conclusions:

- Regular methods to control for confounding (e.g. PS adjustment) do not adequately control for time-varying confounding.
- In this clinical example of the effects of beta2-agonist use on the risk of CHD, regular methods and methods to control for time-varying confounding (MSM) yielded different effect estimates.
- This could be due to collider-stratification bias or adjustment for intermediate effects.
- Methods such as MSMs is recommended in the presence of time-varying confounder.

References:


Authors’ Disclosure Information

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For more information on the PROTECT project please go to: Web: www.imi-protect.eu E-mail: protect_support@ema.europa.eu