Comparison of Approaches to Select a Propensity Score Matched Control Group in the Absence of an Obvious Start of Follow Up for this Group: An Example Study on the Economic Impact of the DMP Bronchial Asthma

Vergleich von Methoden zur Selektion einer Propensity Score gematchten Kontrollgruppe in Abwesenheit eines Beginns des Follow-ups: Eine Studie zum ökonomischen Nutzen des DMP Asthma bronchiale

Authors
Josephine Jacob, Niklas Schmedt, Lennart Hickstein, Wolfgang Galetzka, Jochen Walker, Dirk Enders

Affiliation
InGef – Institut für angewandte Gesundheitsforschung
Berlin GmbH, Berlin

Key words
Propensity Score Matching, claims data, disease management program, health care costs, mortality, start of follow-up

Schlüsselwörter
Beginn Follow-up, Propensity Score Matching, Sekundärdaten, Disease Management Programm, Leistungskosten, Mortalität

Bibliography
DOI https://doi.org/10.1055/a-0948-5356
Online-Publikation: 2019
Gesundheitswesen
© Georg Thieme Verlag KG Stuttgart · New York
ISSN 0941-3790

Correspondence
Josephine Jacob
InGef – Institut für angewandte Gesundheitsforschung
Berlin GmbH
Spittelmarkt 12
10117 Berlin
josephine.jacob@ingef.de

Supplementary Material Table S1–S3 and Fig. S1 finden Sie online unter https://doi.org/10.1055/a-0948-5356

ABSTRACT

Background
Claims data are a valuable data source to investigate the economic impact of new health care services. While the date of enrollment into the new service is an obvious start of follow-up for participants, the strategy to select potential controls is not straightforward due to a missing start of follow-up to ascertain possible confounders. The aim of this study was to compare different approaches to select controls via Propensity Score Matching (PSM) using the disease management program (DMP) bronchial asthma (BA) as an example.

Methods
We conducted a retrospective cohort study of BA patients between 2013 and 2016 to examine total one-year health care costs and all-cause mortality. We implemented different scenarios regarding the selection of potential controls: I) allotment of a random index date with subsequent PSM, II) calendar year-based PSM (landmark analysis) and III) calendar quarter-based PSM. In scenario I, we applied 2 approaches to assign a random index date: a) assign random index date among all quarters with a BA diagnosis and b) assign random index date and thereafter examine if a BA diagnosis was documented in that quarter.

Results
No significant differences in total one-year health care costs between DMP BA participants and non-participants were observed in any of the scenarios. This could to some extent be explained by the higher mortality in the control groups in all scenarios.

Conclusion
If the loss of potential controls can be compensated, scenario Ib is a pragmatic option to select a control group. If that is not the case, scenario III is the more sophisticated approach, with the limitation that baseline characteristics prior PSM cannot be depicted and computational time or memory size needed to conduct the analysis need to be sufficient.

ZUSAMMENFASSUNG

Hintergrund Routinedaten gesetzlicher Krankenkassen werden häufig zur Evaluation ökonomischer Effekte neuer Ver-
sorgungsformen genutzt. Während als Beginn des Follow Up
für Teilnehmer häufig der Tag der Einschreibung in das Pro-
gramm genutzt werden kann, ist die Selektion von Kontrollen
schwieriger aufgrund des Fehlens eines solchen Ereignisses.
Ziel dieser Studie war es, Vorteile und Limitationen von 3 Meth-
oden zur Selektion von Kontrollen mittels Propensity Score
Matching (PSM) am Fallbeispiel des Disease Management Pro-
gramms (DMP) Asthma bronchiale zu zeigen.

Methods

Eine retrospektive Kohorte bestehend aus Asthma Patienten
zwischen 2013 und 2016 wurde identifiziert um Un-
terschieden in den Gesamtleistungskosten und Gesamt mortalität
tzubetrachten. Wir haben 3 Szenarien zur Auswahl geeigneter
Kontrollen verglichen: I) Zuteilung eines zufälligen Index-
datums mit anschließendem PSM, II) Kalenderjahr basiertes PSM (Land-
mark Analyse) und III) Kalenderquartal basiertes PSM. Im ersten
Szenario wurden 2 Methoden zur Zuteilung eines zufälligen In-
dexdatums umgesetzt: a) Zuteilung eines zufälligen Indexda-
tums zu einem Quartal mit Asthma Diagnose und b) Zuteilung
eines zufälligen Indexdatums und anschließende Überprüfung
ob in dem selektierten Quartal eine Asthmadiagnose vorlag.

Ergebnisse

In keinem der Szenarien wurden signifikante Un-
terschiede in den Gesamtleistungskosten zwischen DMP Teil-
nehmern und Nicht-Teilnehmern beobachtet, was möglicher-
weise durch Mortalitätsunterschiede zwischen den Gruppen
erklärt werden kann.

Fazit

Im Falle einer ausreichend großen Anzahl potentieller
Kontrollen ist Szenario Ib eine pragmatische Option zur Sele-
ktion einer Kontrollgruppe. Andernfalls stellt Szenario III die
ausgereifteste Methode dar, obwohl keine Baseline-Charakte-
ristika vor PSM dargestellt werden können und ausreichend
Rechenkapazität bereitgestellt werden muss.

Introduction

Cohort studies are often used to compare participants of a new
service to non-participants. In these studies, participants are typi-
cally followed from the start of the service until the occurrence
of the outcome event or the end of a prespecified follow up period.
These studies must cope with 2 challenges: i) to avoid selection
bias, participants should be followed from start of the service (start
of follow up) and ii) potential controls should be selected from the
population who is comparable with respect to possible confound-
ers. While i) can be easily implemented, ii) is not straightforward due
to a missing start of follow up to ascertain possible confounders.
For the assessment of the economic effectiveness of new health servic-
es it is essential to select appropriate methods for the selection of
controls. The aim of this study was to compare 3 approaches to se-
lect propensity score matched controls in the absence of an obvious
start of follow up for non-participants using the disease manage-
ment program (DMP) DMP bronchial asthma (BA) as an example. As
the primary outcome total one-year health care costs were com-
pared between patients who newly enrolled in DMP bronchial asth-
ma between 2013 and 2016 and patients who did not.

Methods

Data source

Claims data are a valuable data source for health services research to
investigate the economic impact of new health care services [1–4].

The study was based on anonymized claims data from the InGef
(Institut für angewandte Gesundheitsforschung Berlin) research
database1 [5, 6]. At the time of analysis, the database contained
longitudinal data of approximately 8.3 million Germans insured in
one of 61 statutory health insurances (SHI) between 2012 and
2017. In addition to sociodemographic information, the database
contains information about ambulatory services and diagnoses;
hospital data including admission periods, main and secondary dis-
charge diagnoses (coded according to the German modification of
the 10th revision of the International Classification of Diseases (ICD-
10 GM)) and procedures conducted; drug prescription data; infor-
mation on prescribed aids and remedies; and the costs which ac-
crued in these sectors. All patient-level and provider-level data in
the InGef research database are anonymized to comply with Ger-
man data protection regulations and German federal law. Hence,
approval of an Ethics Committee was not required.

Study cohort

We conducted a retrospective cohort study including BA patients
between 2013 and 2016. Data from 2012 to 2017 were used to
assess in- and exclusion criteria, baseline characteristics, total one-
year health care costs and one-year all-cause mortality in follow up.

Patients were eligible to enter the cohort if they were continu-
ously enrolled in 2012. Furthermore, patients had to be continu-
ously enrolled between 2013 and 2017 or between 2013 and their
date of death (cf. » Fig. 1). Patients had to have at least one verified
ambulatory BA diagnosis (ICD-10 GM J45) between 2013 and 2016.
Individuals enrolled in the DMP BA before 2013 were excluded from
the study population. Three different scenarios to determine partic-
ipants and non-participants with corresponding baseline period and
follow up were defined. In each of the scenarios, patients with ex-
treme total health care costs of more than 100,000€ in the baseline
period were excluded. All patients had to be alive on the first day of
follow up.

Analysis scenarios/observation periods

Scenario Ia – random index date among quarters with
BA diagnosis

Enrollment in the DMP BA was assessed between 2013 and 2016.
Participants were followed from the first day of the quarter follow-
ing the index quarter of enrollment for a period of one year or until
death. Non-participants were assigned a random index date based
on the distribution of DMP enrollment dates among participants
and were followed from the first day of the quarter after the random
index date. Random index dates were only assigned to quarters

1 former HRI research database
in which an ambulatory verified BA diagnosis was documented. Covariates were assessed in the baseline period of four quarters before the index quarter.

**Scenario Ib – random index date**
This scenario is similar to scenario Ia with the exception that the assignment of random index dates was not restricted to quarters with a BA diagnosis. Patients without a verified BA diagnosis in the quarter of the assigned index date and patients who had died before the assigned random index date were excluded from the analysis.

**Scenario II – landmark period**
DMP enrollment was assessed in each year between 2013 and 2016. Patients were classified into 2 exposure groups depending on whether they enrolled in the DMP BA between January 1st and December 31st of the respective year (landmark year). Follow up started on January 1st of the following year for both participants and non-participants and ended on the last day of that year or the day of death. Covariates were assessed in the year prior to the landmark year. Participants and non-participants who were matched in one year were excluded from the matching procedure in the subsequent years. Selected participants and non-participants in each year were pooled and analyzed as one cohort.

**Scenario III – calendar quarter based PSM**
In every calendar quarter between 2013 and 2016 individuals who enrolled in the DMP BA were matched to individuals who did not enroll in the DMP BA based on covariates assessed in the 4 quarters prior to that calendar quarter. Participants and non-participants which were matched in one calendar quarter were excluded from the matching procedure in the quarters thereafter. This process was repeated for all calendar quarters between 2013 and 2016. Individuals were followed from the first day following the matching quarter for a period of four quarters or until death.

In addition, we conducted pre-specified sensitivity analysis for scenario II and III in which patients could be selected as a control first and later switch into the DMP group. Follow up for individuals who were selected as a control first and later became a case was not censored at the time of switch.
Baseline characteristics

Baseline characteristics were included in the calculation of the Propensity Score (PS) to adjust for possible confounders regarding the investigated outcome between the study groups. (▶ Table S1 in the supplement provides an overview of all baseline characteristics assessed and their definition.

Exposure and endpoints

The exposure DMP BA enrollment was assessed using the DMP information available in the InGef research database.

The sum of all-cause cumulated costs in € for hospitalizations, ambulatory care, drug treatment and remedies and aids within the one-year follow up period was investigated as the primary outcome in this study.

To assess the potential impact of the proportion of deceased individuals on the primary outcome in each study group, the one-year all-cause mortality was investigated.

Statistical analysis

Baseline characteristics are reported for the unmatched (scenarios Ia and Ib only) and matched BA cohorts. Baseline characteristics for the unmatched cohorts of scenarios II and III and the respective sensitivity analyses are not presented because patients could be potential controls in multiple years (scenario II) or quarters (scenario III) and unique baseline periods could not be determined.

A Propensity Score Matching (PSM) was performed to select matched study cohorts in all scenarios [7–9]. PSM is a method which attempts to match DMP BA participants and non-participants based on their probability for participation in the DMP. This probability was calculated using a logistic regression model with the variable DMP BA participation as the dependent variable. The covariates which were included in the calculation of the Propensity Score (PS) are listed in ▶ Table S1 of the supplement. Based on the PS, a 1:1 nearest-neighbor matching with a caliper of 0.2 of the standard deviation of the logit of the propensity score was conducted.

The balance of covariates in the baseline period between the study groups were assessed by calculating the standardized difference in means (SMD), using a threshold of 0.1 to indicate imbalance [10]. The outcome total one-year health care costs and one-year all-cause mortality were compared using a paired t-test and McNemar’s test, respectively, to account for the matched structure of the data [11].

Analyses were performed using R version 3.5.0. The PS matching was performed with the R package MatchIt (version 3.0.2).

Results

A total of 431,120 BA patients were selected from the InGef research database between 2013 and 2016. Approximately 7% of these patients enrolled in the DMP BA in this period (cf. ▶ Fig. 1).

▶ Table 1 displays patient characteristics of the unmatched DMP BA participants and DMP BA non-participants in scenario Ia and Ib.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>DMP n = 27,997</th>
<th>Scenario Ia</th>
<th>Scenairo Ib</th>
<th>Scenairo Ia</th>
<th>Scenairo Ib</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age [mean (SD)]</td>
<td>41.0 (21.0)</td>
<td>42.8 (22.2)</td>
<td>-0.08</td>
<td>45.9 (21.8)</td>
<td>-0.22</td>
</tr>
<tr>
<td>Female (%)</td>
<td>56.5</td>
<td>52.3</td>
<td>-0.08</td>
<td>53.5</td>
<td>-0.06</td>
</tr>
<tr>
<td>Clinical characteristics</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Allergy (%)</td>
<td>37.4</td>
<td>28.0</td>
<td>0.21</td>
<td>32.2</td>
<td>0.11</td>
</tr>
<tr>
<td>Influenza vaccination (%)</td>
<td>22.0</td>
<td>16.6</td>
<td>0.14</td>
<td>20.8</td>
<td>0.03</td>
</tr>
<tr>
<td>Charlson Comorbidity Index [mean (SD)]</td>
<td>1.3 (1.1)</td>
<td>1.4 (1.6)</td>
<td>-0.04</td>
<td>1.7 (1.6)</td>
<td>-0.25</td>
</tr>
<tr>
<td>Status asthmaticus (%)</td>
<td>0.8</td>
<td>0.2</td>
<td>0.12</td>
<td>0.3</td>
<td>0.08</td>
</tr>
<tr>
<td>N prescriptions short acting beta agonists [mean (SD)]</td>
<td>2.6 (3.0)</td>
<td>1.3 (2.6)</td>
<td>0.48</td>
<td>1.9 (3.1)</td>
<td>0.24</td>
</tr>
<tr>
<td>N prescriptions inhaled corticosteroids [mean (SD)]</td>
<td>0.8 (1.5)</td>
<td>0.4 (1.2)</td>
<td>0.27</td>
<td>0.5 (1.4)</td>
<td>0.16</td>
</tr>
<tr>
<td>Enrolled in an additional DMP (%)</td>
<td>2.7</td>
<td>7.4</td>
<td>-0.18</td>
<td>9.2</td>
<td>-0.24</td>
</tr>
<tr>
<td>Health care resource utilization</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>N visits pulmonologist [mean (SD)]</td>
<td>0.7 (1.2)</td>
<td>0.3 (0.87)</td>
<td>0.45</td>
<td>0.4 (1.0)</td>
<td>0.29</td>
</tr>
<tr>
<td>N hospitalizations [mean (SD)]</td>
<td>0.2 (0.6)</td>
<td>0.3 (0.8)</td>
<td>-0.04</td>
<td>0.3 (0.8)</td>
<td>-0.07</td>
</tr>
<tr>
<td>Ambulatory care costs in € [mean (SD)]</td>
<td>774 (738)</td>
<td>650 (739)</td>
<td>0.17</td>
<td>719 (748)</td>
<td>0.07</td>
</tr>
<tr>
<td>Hospital costs in € [mean (SD)]</td>
<td>685 (2600)</td>
<td>858 (3357)</td>
<td>-0.05</td>
<td>949 (3477)</td>
<td>-0.08</td>
</tr>
<tr>
<td>Pharmaceutical costs in € [mean (SD)]</td>
<td>546 (1571)</td>
<td>544 (1870)</td>
<td>0.00</td>
<td>674 (2020)</td>
<td>-0.07</td>
</tr>
<tr>
<td>Costs for aids and remedies in € [mean (SD)]</td>
<td>180 (591)</td>
<td>210 (854)</td>
<td>-0.04</td>
<td>240 (892)</td>
<td>-0.07</td>
</tr>
<tr>
<td>Total treatment costs in € [mean (SD)]</td>
<td>2184 (3645)</td>
<td>2262 (4683)</td>
<td>-0.02</td>
<td>2582 (4880)</td>
<td>-0.08</td>
</tr>
</tbody>
</table>

DMP Disease Management Program; SMD standardized mean difference; SD standard deviation; BA bronchial asthma; NOTE: DMP participants for scenario Ia and Ib agree
not enrolled in the DMP BA. The share of patients enrolled in an additional DMP was higher in BA non-participants. Total treatment costs (€) in the baseline period were comparable between DMP BA participants and DMP BA non-participants.

Following the PSM, baseline demographics and clinical characteristics were balanced with all standardized differences smaller than 0.1 in all scenarios (cf. Table 2). The proportion of DMP BA participants for whom an adequate matching partner could be found was above 95\% in all scenarios except scenario III (88\%, cf. Fig. 1). Due to the different base cohorts of whom the participants and non-participants are selected, the total number of matched pairs differed substantially between the scenarios: In the sensitivity analysis for scenario II, the largest number of matched pairs (n = 29,607) could be analyzed. Scenario III lead to the least matched pairs (n = 26,490) after matching.

No significant differences in total health care costs between DMP BA participants and DMP BA non-participants were observed in any one of the scenarios (cf. Table 3). Total health care costs varied, depending on the scenario, between 2636€ and 2659€ in DMP BA participants and between 2563€ and 2634€ in DMP BA non-participants. The largest difference between the two patient groups of approximately 90€ was observed in the calendar quarter based PSM.

In all scenarios, DMP BA non-participants had a higher mortality than participants (cf. Table 3). The magnitude of the difference varied greatly between the scenarios. The mortality was more than 3 times higher in scenario Ia in DMP BA non-participants than in DMP BA participants (0.99 vs. 0.31\%; p < 0.001). In the landmark approach in scenario II the mortality was still twice as high in DMP BA non-participants than in DMP BA participants. The smallest difference in mortality was found in scenario III.

### Discussion

We investigated 3 different scenarios to select a propensity score matched control group in the absence of an obvious start of follow up in the control group. In summary, total health care costs in the first year after enrollment were similar between BA patients participating in the DMP BA and BA patients who do not in all scenarios. We observed differences regarding the one-year mortality between the 2 patient groups and between the different scenarios.

The similar health care costs between DMP BA participants and non-participants are contradictory to studies evaluating other DMPs, which partly observed significantly reduced costs for participants of the DMP [12]. We attribute this to the fact that DMPs are mostly evaluated regarding inpatient cost or investigated for longer follow up periods [12, 13]. In our study, in line with other studies investigating the effects of the DMP diabetes mellitus type II, we also observed lower costs in the inpatient setting for DMP BA participants (cf. Table S2 in the supplement) [12, 13]. This was compensated by higher costs in the ambulatory setting (prescriptions and physician visits).

The small difference in health care costs between participants and non-participants is to some extent influenced by the higher mortality in the control groups in all scenarios, because costs are about 6 to 8 times higher in the deceased than in the non-deceased (cf. Table S3 in the supplement). Since the proportion of de-
participants. Two large statutory health insurances published mortality was compared between DMP BA participants and non-

tially between the study groups, the influence of mortality on costs compared to non-deceased patients further do not vary substan-

tively in general and the ratio of costs in deceased

In patient populations in whom the mortality is higher, e. g. in heart failure patients, the impact of the chosen method to select a control on total health care costs might be more pronounced. Studies investigating mortality in participants and non-participants

ceased patients is low in general and the ratio of costs in deceased compared to non-deceased patients further do not vary substan-

tially between the study groups, the influence of mortality on costs is quite moderate.

To our knowledge, no other studies were published in which mortality was compared between DMP BA participants and non-

The especially large difference between DMP BA participants and DMP BA non-participants in scenario Ia could be caused by the used most efficiently since an index date is assigned first and covari-

Parts of the differences in mortality can probably be explained by selection effects which claims data do not offer enough information about. Patients who are more likely to have beneficial outcomes of the DMP might be more likely to participate. Previous studies have shown that DMP participants differ with regard to socio-demographic and clinical characteristics from patients not participating [16, 17]. Covariates were selected to adjust for fac-

tors with an impact on total one-year health care costs. Since these covariates might not be sufficient to adjust for factors with an impact on all-cause mortality, a different set of covariates might lead to an improved control of confounding and thus might be considered in future analyses on these or related study questions.

The highest mortality rates were observed in scenario Ia and II. The especially large difference between DMP BA participants and DMP BA non-participants in scenario Ia could be caused by the used method to assign an index date to the non-participants. Patients were only assigned index dates in quarters in which they were still alive. In scenario Ib, on the other hand, the random index date was assigned randomly among all possible quarters and patients who died before their assigned random index date in this scenario were excluded thereafter. In detail, from the 401,154 non-DMP participants, 15,137 died between 2013 and 2016. From these patients, 1,482 are excluded in scenario Ia (index dates which are assigned to quarter of death) while 4,364 are excluded in scenario Ib (index dates which are assigned to quarter of death or later). The average time to death for deceased patients is also lower in this group than in scenario Ib (704 vs. 766 days after matching).

An advantage of scenario I is the possibility to compare baseline characteristics prior and post matching. For the other scenarios, the cohort of potential controls may contain the same individuals across the index years (scenario II) or index quarters (scenario III) and thus, a unique baseline could not be determined.

A further drawback of the landmark approach (scenario II) is that covariates were assessed in the baseline period prior to the landmark year and the outcomes were assessed in the year following the landmark year. Changes in clinical characteristics within the landmark year are not factored in the calculation of the PS for the risk adjustment. In a post-hoc comparison of characteristics in the baseline period and in the landmark year it became apparent that an adequate balance of these variables cannot necessarily be expected (cf. ▶ Fig. S1 in the supplement).

The largest number of matched pairs could be analyzed in the sensitivity analysis of scenario II. Scenario III lead to the lowest num-

ber of matched pairs, possibly caused by the fact that individuals who enroll in the DMP BA later in the follow up are selected as controls first and can thus not be considered as DMP BA participants anymore. In the sensitivity analysis of scenario III, in which patients could switch from the control status to become a DMP BA partici-

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of new health services should adequately consider different options to select controls in the absence of an obvious start of follow up. Studies reporting large differences in mortality between DMP participants and non-participants should be interpreted with some caution, as these differences might in part be caused by the underlying method to select controls and their start of follow up which is often insufficiently described [13].

Conclusion

No significant differences in total one-year health care costs between DMP BA participants and non-participants were observed in any of the scenarios. This could to some extent be explained by the higher mortality in the control groups in all scenarios.

If the loss of potential controls can be compensated, scenario lb is a pragmatic option to select an adequate control group. If that is not the case, scenario III is the more sophisticated approach, with the limitation that baseline characteristics prior to matching cannot be depicted and computational time or memory size needed to conduct the analysis need to be sufficient.

To confirm the performance of the presented methods, it would be worthwhile to implement this study design using a health care service or intervention for which large differences in health care costs have been found.

Conflict of Interest

None.

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