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ORIGINAL ARTICLE

Choice of time period to identify confounders for propensity score matching, affected the estimate: a retrospective cohort study of drug effectiveness in asthmatic children

Osemeke U. Osokogu[a,*], Javeed Khan[a,b], Swabra Nakato[a], Daniel Weibel[a], Maria de Ridder[a], Miriam C.J.M. Sturkenboom[a], Katia Verhamme[a,c]

[a]*Department of Medical Informatics, Erasmus University Medical Center, 3015 GE Rotterdam, The Netherlands*
[b]*Department of Statistics, Universiteit Hasselt, BE 3590 Diepenbeek, Belgium*
[c]*Department of Bioanalysis, Faculty of Pharmaceutical Sciences, Universiteit Gent, Gent, Belgium*

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Abstract

Objectives: To control for confounding by indication in comparative (drug) effectiveness studies, propensity score (PS) methods may be used. Since childhood diseases or outcomes often present as acute events, we compared the effect of using different look-back periods in electronic health-care data, to construct PSs. This was applied in our research on the effect of a combination of inhaled corticosteroids/long-acting beta-2 agonists (ICS + LABA), either as fixed combination or used as loose combination (2 separate inhaler devices) in the prevention of severe asthma exacerbations.

Methods: We created a cohort of children (5−17 years) diagnosed with asthma from the Dutch Integrated Primary Care information database. Within this cohort, we identified new users of ICS + LABA, either as fixed combination or loose combination (2 separate inhaler devices). The outcome of interest was severe asthma exacerbations. PSs for type of treatment were created using comorbidity and drug use history in different time windows: 1 week, 1 month, 3 months, 1 year, and full history prior to the start of treatment. PSs were used for matching subjects in both exposure groups. Time to first asthma exacerbation was analyzed with Cox proportional hazard regression. The results were compared with published clinical trials.

Results: Of 39,682 asthmatic children, 3,500 (8.8%) were new users of either ICS + LABA fixed (3,324 [95.0%]) or loose (176 [5.0%]). The crude hazard ratio (HR) for a severe asthma exacerbation, comparing ICS + LABA fixed to loose was 0.37 (95% confidence interval [CI]: 0.20−0.66). PS-matched HRs (1 week, 1 month, 3 month, 1 year, and full history) were 0.48 (95% CI: 0.22−1.04); 0.60 (95% CI: 0.26−1.38), 0.69 (95% CI: 0.31−1.57), 0.56 (CI: 0.25−1.24), and 0.58 (CI: 0.24−1.36), respectively.

Conclusions: PS matching can be used to control for confounding in pediatric comparative (drug) effectiveness studies, the impact of different look-back periods to implement the PS is important. Controlling for confounders occurring in the 3 months preceding drug exposure may yield results comparable to clinical trial results.

Keywords: Propensity scores; Comparative effectiveness; Pediatrics

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Conflict of interest: M.S. is heading a research group that occasionally conducts postauthorization safety studies for pharmaceutical companies (Novartis, GSK, and Servier); none is related to this topic. K.V. works for a research group who in the past received unconditional research grants from Pfizer/Boehringer Ingelheim, Yamanouchi, Novartis, and GSK; none of which are related to the contents of this article.

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* Corresponding author. Department of Content and Innovation, Elsevier BV, Amsterdam, The Netherlands. Tel.: +31645491474; fax: +31107044722.

E-mail address: oosokogu@gmail.com (O.U. Osokogu).

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What is new?

Key findings

- Comparative effectiveness studies are important to provide estimates of real-life drug effects in children, especially for older drugs which often have not been properly investigated in children and are frequently used.
- Confounding by indication is an important issue in comparative effectiveness studies but may be addressed by using propensity scores (PSs).
- No methodological work has yet investigated the effect of different time windows when constructing PSs, especially not in pediatrics.

What this adds to what was known?

- In database studies of comparative drug effectiveness in children, the time window (before drug exposure) during which patient characteristics are extracted for constructing PSs has an impact on the efficiency of the PSs.
- Patient characteristics occurring during the 3 months before drug exposure yielded the most efficient PSs. Applying the 3-month PSs resulted in the largest adjustment of the crude estimates of treatment effects.

What is the implication and what should change now?

- In studies of comparative effectiveness in children, PSs can be used to control confounding by indication.
- Sensitivity analyses may be conducted routinely to assess the impact of different time windows (for including patient characteristics in PSs) on the efficiency of the PSs.

1. Introduction

Historically, children have been underrepresented in randomized clinical trials because of ethical, scientific, and technical issues as well as commercial priorities [1]. Yet, doctors prescribe drugs in children often based on evidence extrapolated from adults. Appropriate pediatric doses and formulations are often lacking. To evaluate the ''real-world'' effectiveness of drug therapies in pediatrics, comparative effectiveness studies can be conducted. In such studies, drug exposure is dependent on prescribers' decisions taking into account the clinical (including disease severity), functional, and/or behavioral characteristics of patients. In addition, the prescribers' preferences may vary over time. Selective prescribing can result in confounding by indication [2], which should be adequately controlled to obtain valid study results.

Asthma is a common and chronic condition in children. Inadequate treatment can result in poor quality of life. The Global Initiative for Asthma (GINA) recommends a stepwise asthma treatment, depending on the underlying asthma severity [3]. Step 3 and step 4 of asthma treatment consist of use of inhaled corticosteroids (ICSs) in combination with long-acting beta-2 agonists (LABA) [4]. Clinical guidelines promote the use of ICS + LABA as fixed compared with loose combination as studies have shown that treatment adherence is higher for the fixed combination. In young children (<6 years), few studies, and to our knowledge none in children only investigated the effectiveness of fixed ICS + LABA combination vs. loose combination in the prevention of asthma exacerbations. To obtain valid results, confounding by indication resulting from varying levels of asthma severity and from other patient characteristics should be adequately controlled.

Methods for confounding control depend on the type of design and treatment pattern (intermittent or chronic), but one of the most recommended strategies to control for confounding by indication in cohort studies is the use of propensity scores (PSs), especially when the number of events is small and the set of measurable risk factors high [5,6]. The PS is an estimated probability of receiving one specific treatment rather than another, given a set of baseline characteristics [7]. It is used to adjust for imbalances between treatment groups. The utility of PS in such situations has been extensively demonstrated [8−14].

The factors that exacerbate asthma and result in treatment step-up are likely to occur shortly before treatment step-up, but the relevant period over which confounding occurs is not clear. Since there is no clear guidance on the impact of, or use of different look-back periods to build the propensity score model, we investigated this using a real-life example: comparing the effectiveness of loose and fixed combinations of ICS + LABA in the prevention of severe asthma exacerbations as a prototype.

2. Methods

2.1. Study design and data source

We conducted a retrospective cohort study utilizing data from the Dutch Integrated Primary Care Information (IPCI) database, a population-based general practice database. IPCI is a longitudinal observational dynamic database containing the complete electronic medical records of approximately 1,500,000 patients from about 450 general practitioners (GPs) in the Netherlands. In the Dutch health-care system, patients register with a single GP who acts as a gatekeeper for secondary care. The IPCI patients' records comprise anonymized data pertaining to demographics, symptoms and diagnoses, referrals, laboratory tests and results, drug