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ORIGINAL REPORT

Short look-back periods in pharmacoepidemiologic studies of new users of antibiotics and asthma medications introduce severe misclassification†

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ABSTRACT

Purpose The aim of this study was to quantify the effect of the look back period on the misclassification of new users of antibiotics and asthma medications.

Methods We included all children born in Denmark from 1995 through 2006 and all prescriptions of antibiotics and asthma medication from 1995 through 2011. The study period was 2007 through 2011. True new users redeemed their first prescription in the study period whereas prior users redeemed their first prescription before the study period. Look-back periods ranged from 30 days up to 12 years prior to the study period, and we defined new users as those without a prescription in the look-back period. The relative misclassification (RM) was estimated as the number of defined new users divided by the number of true new users.

Results For antibiotics, the RM decreased from 4.75 for look-back periods of 30 days to 2.36 for 2 years and 1.33 for 5 years. For asthma medication, the RM decreased from 2.53 for look-back periods of 30 days to 1.48 for 2 years and 1.20 for 5 years. Older age, male gender, and absence of treatment-related diagnoses were associated with higher RM.

Conclusions Studies applying the new user design are strongly dependent on the available information on prescriptions. For drug classes with intermittent use such as asthma medications, even a 2-year look-back period produced severe misclassification. Excluding children with a prior treatment-related diagnosis can reduce the level of misclassification. Copyright © 2015 John Wiley & Sons, Ltd.

KEY WORDS—pharmacoepidemiology; new users; methods; misclassification; antibiotics; asthma medications

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INTRODUCTION

In a range of pharmacoepidemiological studies the new user design is the preferred design.[1] For example in studies on medication side effects,[2,3] risk estimates will be downward biased if prior users are included, since these typically are a selected group of patients who did not experience earlier adverse events. Another example is studies on choice of medication type, where past experience with particular medications may either favor re-selection or avoidance of a particular drug,[4] e.g. because of anaphylactic reactions.

Yet, in most pharmacoepidemiological studies information on past history of drug exposure is only partially available, either because early data were not available or because individuals were not under observation before they moved into the capture area or switched their medical insurance to become covered. For want of data this aspect has sometimes been ignored,[4] but ordinarily researchers decide on a look-back period to identify subjects without recent prescriptions for the medication of interest. From the perspective of the individual he or she is a new user the first time he or she fills a prescription on a drug. After the first course of treatment has ended the person can reinitiate treatment as a prior user. With limited information on past history it is however impossible to fully construct this from observed data.

Previous research has considered how to select the optimal length of the look-back period[5,6] and how the

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length of the look back period impacts results,[7,8] yet studies continue to use diverse definitions of the look-back period, even for the same medication. For example in studies of statin use various lengths of look-back periods were applied. A study on statin use and fracture risk used 3 months,[9] a study on acute kidney injury in statin initiators used 6 months,[10] a study on cardiovascular drugs used 1 year,[11] and a study on long-term persistence in use of statins applied 18 months.[12] Other studies have used all available prior information to classify individuals, although this may induce time-dependent misclassification[13,14]—individuals with their first observed prescription filling in the beginning of the study period will effectively have a shorter look-back period than those observed late in the period.

While it is known that the use of look-back periods may introduce bias,[15] less is known on how the cohorts created by this approach differ from the corresponding cohorts of true new users and true never users. It is also not known how the composition of patient characteristics (potential confounders) differs between true new users/never users and users/non-users defined based on a finite look-back period.

As the Danish Register of Medicinal Product Statistics (RMPS) was established in 1995 it offers a unique possibility to study the degree of misclassification in the cohort of all children born and living in Denmark since 1995. Apart from a negligible risk for getting medications when abroad or while admitted to a hospital, this cohort can be classified into true new users or prior users at any given time point since 1995. As example medications we chose antibiotics and asthma medications, since these are both commonly used by children[16] and to varying degrees used intermittently, which means that even extended look-back periods may not yield perfect protection against inadvertent inclusion of users in a new user design that are in fact not true new users.

The aim of this paper is to identify two cohorts of true new users of antibiotics and asthma medications, respectively, and compare them to cohorts of alternatively defined new users according to various lengths of the look-back periods. The level of misclassification of new users will be quantified as a function of the length of the look-back period, and we will examine the differences in patient characteristics in the defined cohorts.

METHODS

The study population in this nationwide register-based cohort study included all children born in Denmark from 1 January 1995 to 31 December 2006. Data on birth, death, and migration was obtained from the Danish Civil Registration System (CRS) which provides complete information on all individuals officially residing in Denmark.[17] Individuals were followed from date of birth until date of emigration, date of death, or end of study 31 December 2011, whichever came first.

From the RMPS all prescriptions of antibiotics and asthma medication from 1 January 1995 to 31 December 2011 were retrieved. Data were available from 1 January 1995 and RMPS contains information on date of prescription fill, amount, and type of drug according to the Anatomic Therapeutic Chemical (ATC) classification system. Prescriptions for antibiotics were defined as ATC code J01. These were subdivided into narrow-spectrum antibiotics (ATC codes: J01BA, J01CE, J01CF, J01DE, J01DF, J01EA, J01EB, J01FA, J01FF, J01XA, J01XC, J01XD, J01XE, J01XX) and broad-spectrum antibiotics (ATC codes: J01AA, J01CA, J01CR, J01DB, J01DC, J01DD, J01DH, J01EE, J01GB, J01MA, J01XB). Asthma medications were defined as ATC code R03, which was subdivided into β-agonists (R03AC) and inhaled glucocorticoids (R03BA).

We used the 5-year period from 1 January 2007 to 31 December 2011 as the study period. Individuals redeeming at least one prescription in the study period were categorised as either true new users or true prior users according to the date of their first prescription: *True new users* in the study period were individuals redeeming their first prescription in the study period without any prior redemption since initiation of the database. True prior users were individuals who were observed to have redeemed at least one prescription before the study period.

To mimic the typical approach used in pharmacoepidemiological studies we compared the true new users to cohorts obtained by use of look-back periods of varying lengths—the latter are termed *defined new users*. Users were considered to be defined new users if they did not have a prescription during the look-back period, and prior users if they had at least one prescription in the look-back period. We used look-back periods ranging from 30 days to 12 years. In this cohort, a look-back period of 12 years in effect implies the complete prescription history which is the actual definition used for discriminating true new users and true prior users.

To investigate whether information on previous diseases could be used to supplement a short look-back period for improved classification, we used the Danish National Patient Registry (DNPR) to identify hospital admissions using the International Classification of

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Diseases (ICD) 10th edition. The registry was established in 1977 recording information on all patients discharged from Danish hospitals. Since 1995 outpatient and emergency room visits have been recorded. In relation to use of antibiotics, a hospital contact with a diagnosis of infection was identified as ICD-10 codes A00-B99. With respect to asthma medication, a diagnosis of asthma was defined as an ICD-10 code for asthma (J45) or status asthmaticus (J46).

We assessed covariates at start of the study period including age, gender, diagnoses of infection, asthma, or status asthmaticus. Age at start of the study period was divided into three groups; less than 3 years, 3 to less than 6 years, and 6 to 12 years. For follow-up time and the number of prescriptions for antibiotics and asthma medications during the study period we calculated median, 10th, and 90th percentile.

To assess the degree of misclassification of new users, we estimated the relative misclassification (RM) as the number of defined new users divided by the number of true new users. RM was calculated for each look-back period. Confidence intervals (CI) were calculated using bootstrap methods. All estimates are accompanied by 95% CIs.

Analyses were stratified on age and gender. In order to investigate the effect of varying the look-back periods for children of a specific age we did a sensitivity analysis for the oldest age groups. For all ages from 7 to 12 years we studied differences in misclassification for different lengths of the look-back period, between the two genders.

Use of antibiotics was stratified by individuals having a previous hospital discharge diagnosis of infection and use of asthma medications was stratified by individuals having a previous hospital discharge diagnosis of asthma or status asthmaticus. Furthermore analyses of use of antibiotics were stratified on narrow-spectrum and broad-spectrum antibiotics. Asthma medication was stratified on β-agonists and inhaled glucocorticoids. Within each stratum the RM was estimated.

SAS software V.9.2 (SAS Inc, Cary, North Carolina, USA) and Stata Release 13 (StataCorp LP, College Station, TX, USA) were used to analyse the data. In Denmark, register-based studies do not require ethics committee approval. The study was approved by the Danish Data Protection Agency (record number 2012-41-0696).

RESULTS

We identified 792 198 children born from 1 January 1995 to 31 December 2006. Of these children 25 151 (3.2%) emigrated and 3690 (0.5%) were dead or lost. Characteristics of the final study population of 763 357 are presented in Tables 1A and 1B. The proportion of females was 48.7%, and this was constant for all age groups.

For antibiotics (Table 1A), we found 502 792 (65.9%) children in the RMPS with a prescription in the study period. Of the children 41.5% (37.7% of the females and 45.1% of the males) filled their first prescription on antibiotics before the age of 1 year; 77.4% of the true new users, 20.2% of the prior users, and 12.4% of the non-users were younger than 3 years; and 3.6% of the true new users, 12.1% of the prior users, and 8.4% of the non-users had an infection diagnosis prior to the study period. True new users and prior users filled a median number of 3 and 2 prescriptions of antibiotics during the study period, respectively.

For asthma medication (Table 1B), we found 156 869 (20.5%) children in the RMPS with a prescription during the study period. Among them, 26.3% (22.4% of the females and 30.1% of the males) were younger than 1 year when filling their first prescription

Table 1A. Characteristics of antibiotics users in the study period among 763 357 children born in Denmark 1995–2006

Number of users during the study period	True new users ($n = 99\,211$)		Prior users ($n = 403\,581$)		Non-users ($n = 260\,565$)	
Age*	1.1	(0.2; 5.6)	6.1	(1.9; 10.9)	7.5	(2.5; 11.1)
0– < 3 years	76 831	(77.4)	81 531	(20.2)	32 412	(12.4)
3– < 6 years	13 443	(13.6)	116 358	(28.8)	57 973	(22.2)
6–12 years	8937	(9.0)	205 692	(51.0)	170 180	(65.3)
Gender						
Females	51 582	(52.0)	198 778	(49.3)	121 362	(46.6)
Males	47 629	(48.0)	204 803	(50.7)	139 203	(53.4)
Prior diagnosis of infection	3533	(3.6)	48 639	(12.1)	21 942	(8.4)
Number of prescriptions during the accrual period*	3	(1; 8)	2	(1; 6)	0	(0; 0)
Follow-up time, years*	6	(5.2; 10.6)	11.1	(6.9; 15.9)	12.5	(7.5; 16.1)

Data are given as number (percentage) of patients, unless otherwise specified.
*Median, 10% and 90% percentiles in parenthesis.

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Table 1B. Characteristics of asthma medication users in the study period among 763 357 children born in Denmark 1995–2006

Number of users during the study period	True new users ($n = 55\,151$)		Prior users ($n = 101\,718$)		Non-users ($n = 606\,488$)	
Age*	1.1	(0.2; 8.4)	5.3	(1.5; 10.7)	3.6	(1.6; 10.9)
0– < 3 years	39 547	(71.7)	29 123	(28.6)	122 104	(20.1)
3– < 6 years	6533	(11.8)	27 728	(27.3)	153 513	(25.3)
6–12 years	9071	(16.4)	44 867	(44.1)	330 871	(54.6)
Gender						
Females	26 632	(48.3)	42 335	(41.6)	302 755	(49.9)
Males	28 519	(51.7)	59 383	(58.4)	303 733	(50.1)
Prior diagnosis of asthma	260	(0.5)	18 176	(17.9)	17 193	(2.8)
Number of prescriptions during the accrual period*	2	(1; 11)	3	(1; 20)	0	(0; 0)
Follow-up time, years*	6.1	(5.2; 13.4)	10.2	(6.5; 15.7)	11.5	(6.6; 15.9)

Data are given as number (percentage) of patients, unless otherwise specified.
*Median, 10% and 90% percentiles in parenthesis.

on asthma medication. True new users of asthma medications were younger than prior and non-users. Gender was evenly distributed among true new users and non-users, whereas prior users were predominantly males (58.4%). Two hundred sixty (0.5%) of the true new users, 17.9% of the prior users, and 2.8% of the non-users had a diagnosis of asthma before the study period. There was substantial variation in the number of prescriptions during the study period. True new users filled a median number of 2 prescriptions, while prior users filled a median number of 3 prescriptions.

Tables 2A and 2B show the RM of defined new use and patient characteristics for look-back periods of lengths 30 days, 180 days, 2 years, 5 years, and 12 years. For antibiotics the RM decreased from 4.75 for a look-back period of 30 days to 1.33 for a 5-year look-back period (Table 2A). For asthma medication the RM decreased from 2.53 for a look-back period of 30 days to 1.20 for a 5-year look-back period (Table 2B). For both cohorts median age and the proportion of patients with a prior diagnosis of interest decreased with longer look-back periods.

The RM of antibiotics and asthma medication is stratified on age and gender in Figures 1 and 2, respectively. The degree of RM was associated with higher age of the child for both antibiotics and asthma medications. This was most pronounced for antibiotics. Males had a higher RM than females in all age groups for both antibiotics and asthma medications. For children less than 3 years the RM was only slightly higher among males. This difference increased with age and was most distinct for children aged 6 to 12 years.

The breakdown of antibiotic use into narrow-spectrum and broad-spectrum antibiotics revealed 444 395 (58.2%) users of narrow-spectrum antibiotics and 226 205 (29.6%) users of broad-spectrum antibiotics (Table 3A). The relationship between length of the look-back period and RM showed the same pattern as overall use although the degree of misclassification was smaller. For narrow-spectrum antibiotics the RM decreased from 3.40 for a 30-day look-back period to 1.26 for a 5-year look-back period. For broad-spectrum antibiotics the RM decreased from 2.34 for a look-back period of 30 days to 1.20 for a 5-year

Table 2A. Relative misclassification of defined new users compared to true new users of antibiotics among 763 357 children born in Denmark 1995–2006

Number of users during the study period	($n = 502\,792$)	
Length of the look-back period	Number of defined new users	Relative misclassification (95% CI)
30 days	470 819	4.746 (4.722, 4.769)
Age*	5.3 (0.9; 10.7)	
Females	235 204 (50.0)	
Prior diagnosis of infection	48 189 (10.2)	
180 days	396 489	4.000 (3.976, 4.017)
Age*	5.5 (0.8; 10.8)	
Females	198 898 (50.2)	
Prior diagnosis of infection	38 656 (9.7)	
2 years	233 667	2.355 (2.345, 2.366)
Age*	5.8 (0.4; 11.0)	
Females	118 581 (50.7)	
Prior diagnosis of infection	18 372 (7.9)	
5 years	131 848	1.329 (1.325, 1.333)
Age*	1.9 (0.3; 10.8)	
Females	67 899 (51.5)	
Prior diagnosis of infection	6839 (5.2)	
12 years (i.e. true new users)	99 211	1.00 (reference)

Data are given as number (percentage) of patients, unless otherwise specified.
*Median, 10% and 90% percentiles in parenthesis. Relative misclassification is calculated with 95% CI.

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Table 2B. Relative misclassification of defined new users compared to true new users of asthma medications among 763 357 children born in Denmark 1995–2006

Number of users during the study period	(n = 156 869)	
Length of the look-back period	Number of defined new users	Relative misclassification (95% CI)
30 days	139 652	2.532 (2.517, 2.548)
Age*	3.7 (0.5; 10.4)	
Females	62 269 (44.6)	
Prior diagnosis of asthma	13 957 (10.0)	
180 days	111 640	2.024 (2.012, 2.036)
Age*	3.7 (0.4; 10.3)	
Females	51 307 (46.0)	
Prior diagnosis of asthma	7640 (6.8)	
2 years	81 494	1.478 (1.471, 1.485)
Age*	3.2 (0.3; 10.4)	
Females	38 512 (47.3)	
Prior diagnosis of asthma	2955 (3.6)	
5 years	66 083	1.198 (1.194, 1.202)
Age*	1.7 (0.2; 10.3)	
Females	31 887 (48.3)	
Prior diagnosis of asthma	1087 (1.6)	
12 years (i.e. true new users)	55 151	1.00 (reference)

Data are given as number (percentage) of patients, unless otherwise specified.
*Median, 10% and 90% percentiles in parenthesis. Relative misclassification is calculated with 95% CI.

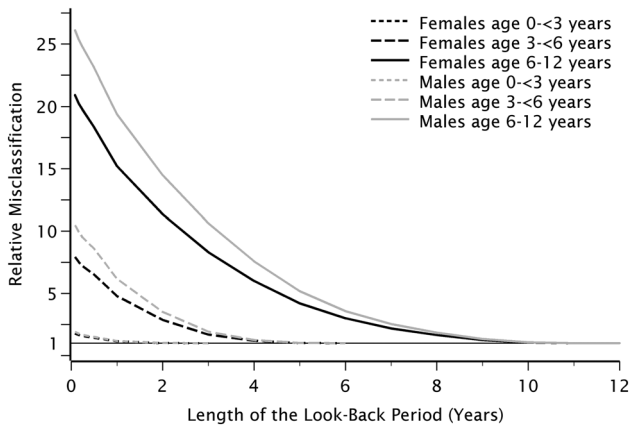

Figure 1. Relative misclassification of new use of antibiotics among 763 357 children born in Denmark 1995–2006, stratified by age and gender

look-back period. Full details for these and the subsequent analyses of the relationship between the RM and length of the look-back period can be seen in supporting figures A1 to A6. Stratification of antibiotics use on children with or without a prior diagnosis of infection showed that RM was greatest among children with infection. For children with a diagnosis of

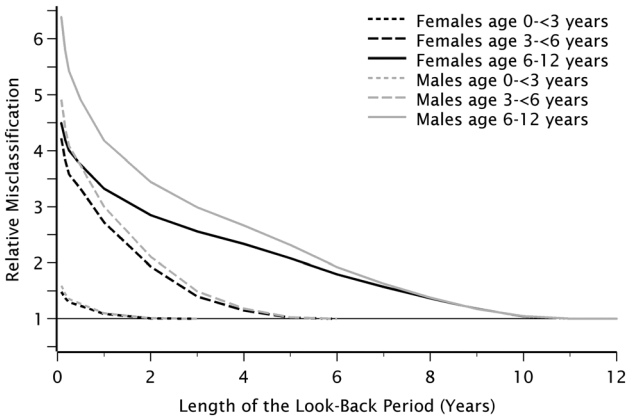

Figure 2. Relative misclassification of new use of asthma medication among 763 357 children born in Denmark 1995–2006, stratified by age and gender

infection the RM decreased from 13.64 for a 30-day look-back period to 1.94 for 5 years look-back. For children without a diagnosis, the RM decreased from 4.42 for a 30-day look-back period to 1.31 for 5 years look-back.

The use of β-agonists and inhaled glucocorticoids unveiled similar results as the overall use of asthma medications (Table 3B). We identified 102 037 (13.4%) users of β-agonists and 73 856 (9.7%) users of inhaled glucocorticoids. The RM decreased from 1.91 for a 30-day look-back period to 1.06 for use of β-agonists. For inhaled glucocorticoids the RM decreased from 1.86 for a look-back period of 30 days to 1.04 for a look-back period of 5 years. For asthma medication the RM decreased from 53.68 for a look-back period of 30 days to 4.18 for 5 years look-back for children with a prior diagnosis of asthma, whereas the RM decreased from 2.29 for a look-back period of 30 days to 1.18 for 5 years look-back for children without a diagnosis of asthma.

The sensitivity analysis showed the same pattern for both antibiotics and asthma medications. The misclassification was consistently highest among males for all age groups (data not shown), which may be explained by males being more likely to fill their first prescription of antibiotics and asthma medication before the age of 1 year.

DISCUSSION

This nationwide cohort study of children found that varying lengths of the look-back period had substantial influence on the relative misclassification of children as new users for both antibiotics and asthma medications. Using short look-back periods of 30 days resulted in identifying more than 4.5 times more new

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Table 3A. Relative misclassification of defined new users compared to true new users of antibiotics stratified on drug types and diagnoses prior to the study period among 763 357 children born in Denmark 1995–2006

	Narrow spectrum	Broad spectrum	No prior diagnosis of infection	Prior diagnosis of infection
Number of users during the study period	(n = 444 395)	(n = 226 205)	(n = 450 620)	(n = 52 172)
Length of the look-back period				
30 days	3.402 (3.386, 3.418)	2.342 (2.330, 2.354)	4.417 (4.392, 4.442)	13.640 (13.233, 14.047)
180 days	3.009 (2.995, 3.022)	2.080 (2.070, 2.089)	3.740 (3.721, 3.759)	10.941 (10.605, 11.278)
2 years	2.011 (2.003, 2.018)	1.535 (1.529, 1.541)	2.250 (2.240, 2.260)	5.200 (5.045, 5.355)
5 years	1.258 (1.255, 1.262)	1.199 (1.196, 1.203)	1.307 (1.302, 1.311)	1.936 (1.894, 1.978)

Relative misclassification is calculated with 95% CI.

Table 3B. Relative misclassification of defined new users compared to true new users of asthma medications stratified on drug types and diagnoses prior to the study period among 763 357 children born in Denmark 1995–2006

	β-Agonists	Inhaled glucocorticoids	No prior diagnosis of asthma	Prior diagnosis of asthma
Number of users during the study period	(n = 102 037)	(n = 73 856)	(n = 138 433)	(n = 18 436)
Length of the look-back period				
30 days	1.910 (1.898, 1.922)	1.863 (1.849, 1.876)	2.290 (2.274, 2.305)	53.681 (47.580, 59.781)
180 days	1.619 (1.610, 1.628)	1.463 (1.454, 1.472)	1.895 (1.884, 1.906)	29.385 (25.823, 32.946)
2 years	1.230 (1.225, 1.234)	1.153 (1.149, 1.158)	1.431 (1.424, 1.437)	11.365 (10.115, 12.616)
5 years	1.063 (1.061, 1.065)	1.043 (1.041, 1.045)	1.184 (1.180, 1.188)	4.181 (3.712, 4.650)

Relative misclassification is calculated with 95% CI.

users of antibiotics and up to 2.5 times more new users of asthma medications. As expected the misclassification was substantially higher in the older age groups. Even a 2-year look-back period produced severe misclassification (136% for antibiotics, 48% for asthma medications), and yet look-back periods of this length are infeasible in most applied studies, either because the observation period is too short, or because a look-back period longer than two years would introduce selection for example in a claims database with substantial turnover, e.g. for patients under age 65 in the US. The level of misclassification can be reduced considerably by excluding children with a prior treatment-related diagnosis.

To our knowledge no other studies have investigated the degree of misclassification in a large population cohort with complete follow-up, although studies with related aims have been conducted. Most notably, Gardarsdottir *et al.* investigated how the incidence of antidepressant drug use depended on varying the length of the look-back period.[7] As here, they found that the estimated incidence varied substantially with length of look-back period, although they used a nine year look-back period as their maximum. Hallas *et al* developed the "Waiting Time Distribution" approach to aid with selecting the optimal look back period.[5] This approach does however not allow selecting the minimum length of the look-back period, to ensure that all identified new users are true new users, but is instead conceived to separate those initiating use of a medication from those already in treatment. In a related approach Mantel-Teeuwisse *et al.* considered how estimation of prevalence depended on varying the length of the period covered by medication following the redemption of a prescription,[18] not unlike Gardarsdottir *et al.*'s investigation of duration of treatment episodes[8]. Stovring *et al.* found that while estimates of incidence and prevalence of use of antidiabetic medications were highly influenced by the length of the look-back period, this did not extend to trends in these over time.[19] Similarly in the study by Benner *et al.* the risk factors for poor statin adherence were found to be robust against varying lengths of the look-back period—although it could not be extended further than 18 months due to data limitations.[12]

This study is based on a nationwide prescription registry covering all prescriptions among children born in Denmark since 1995. Our study could not include antibiotics and asthma medication dispensed at hospitals or from pharmacies outside of Denmark. The impact of this is likely highest for antibiotics which are often used for acute infections, but since the first use of antibiotics occurs during their first year of life for 41.5% of all children, this problem is negligible. Regardless of the problem's magnitude this will not affect the applicability of our results as this

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information is also lacking from most other pharmacoepidemiological studies whether conducted in Denmark or elsewhere.

Our study focused on the misclassification of the exposure of antibiotics and asthma medication. Similar analyses may become feasible for other medications in the future, as may studies on how exposure misclassification affects effect estimates. If patients are only at increased risk of experiencing an adverse event, when given a drug for the first time in their life, application of short look-back periods will bias the association towards the null, since prior users are considered at increased risk, although they are not. Studies with only limited prescription history will therefore tend to be unable to observe an (adverse) drug effect in such settings.

The highest misclassification was seen among the oldest children, and likely this level of misclassification will be close to the typical level present in common pharmacoepidemiological studies applying the new user design to an adult study population. Whether our finding of a consistently higher misclassification among males will also be present among adults is less clear, and should possibly be the subject of future research.

When applying the new user design, we recommend the use of sensitivity analyses to investigate the importance of length of the look-back period. The choice of length of the look-back period depends on the type of drug and outcome that is being studied. Therefore no gold standard can be given. Excluding individuals with certain treatment-related diagnoses can reduce the level of misclassification.

CONFLICT OF INTERESTS

The authors declare no conflict of interest. Henrik Støvring has personally received fees for teaching or consulting from the Danish Association of Pharmaceutical Manufacturers, Astra Zeneca, UCB, and AbbVie. M. Alan Brookhart has received research support from Amgen for unrelated projects and has served as an unpaid scientific advisor for Amgen, Merck, GSK. He received consulting fees from RxAnte and World Health Information Consultants. Til Stürmer receives investigator-initiated research funding and support as Principal Investigator (R01 AG023178) and Co-Investigator (R01 AG042845) from the National Institute on Aging (NIA), and as Co-Investigator (R01 CA174453) from the National Cancer Institute (NCI) at the National Institutes of Health (NIH), and as Principal Investigator of a Pilot Project from the Patient Centered Outcomes Research Institute (PCORI). He does not accept personal compensation of any kind from any pharmaceutical company, though he receives salary support from the Center for Pharmacoepidemiology (current members: GlaxoSmithKline, UCB BioSciences, Merck) and research support from pharmaceutical companies (Amgen, Merck) to the Department of Epidemiology, University of North Carolina at Chapel Hill.

KEY POINTS

- Studies applying the new user design are strongly dependent on the available information on prescriptions.
- Even a 2-year look-back period produces severe misclassification.
- The degree of misclassification can be minimized using data on treatment-related diagnoses.

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