

Prevalence, incidence and persistence of anti-asthma medication use in 2- to 29-year-olds: a nationwide prescription study

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Abstract

Purpose The purpose of this study was to examine gender- and age-specific prevalence, incidence, and the type of anti-asthma medications used in the Norwegian population aged 2–29 years during 2005–2007 and to estimate the share of individuals who regularly redeemed medications over a 3-year period.

Methods We retrieved data from the nationwide Norwegian Prescription Database for all individuals 2–29 years old ($n=1.7$ million) who received anti-asthma medications during 2005–2007. Medications included inhaled short- and long-acting β_2 -agonists, inhaled corticosteroids, fixed-dose combinations of inhaled β_2 -agonists and corticosteroids, and leukotriene antagonists.

Results In 2007, 5.5% (92,074 individuals) of Norwegians aged 2–29 years received anti-asthma medication, and this figure was stable throughout 2005–2007. Prevalence and

incidence were higher among males than females but shifted to female dominance during adolescence. The share of anti-asthma medication users who received inhaled corticosteroids was high in preschool children but decreased by age. Conversely, use of inhaled β_2 -agonists as monotherapy and of fixed combinations increased with age. Fewer than half the individuals were “persistent” to medication treatment for 3 years by redeeming prescriptions regularly (at least once a year).

Conclusions In this nationwide study, annual prevalence of anti-asthma medication use was stable during 2005–2007. The gender- and age-specific profile of prevalence and incidence correspond well with other studies. Fewer than half the individuals redeemed prescriptions regularly over 3 years.

Keywords Asthma · Norway · Pharmacoepidemiology · Prescription database

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Introduction

Asthma is the most common chronic disease among children and adolescents, and the prevalence of the disease varies greatly within and between countries [1, 2]. The prevalence of asthma has been reported to be increasing for decades, but recent studies suggest a levelling off or even a decrease in prevalence among children and young adults [3–5]. Medications are an integral part in the management of asthma to achieve and maintain symptom control, and inhaled corticosteroids are the mainstay of asthma pharmacotherapy [6, 7]. Prescription data on use of anti-asthma medication may serve as a proxy measure for active and clinically important asthma in the Norwegian population [8]. Furu et al. [8] estimated the prevalence of inhaled anti-asthma medication use in 2004 to be 5.4% in all Norwegian

children and adolescents (0–19 years old). However, there are few longitudinal and population-based studies of anti-asthma medication use in children and young adults. Most studies have had a cross-sectional design and have often been conducted on selected age groups in one or a few geographical regions. Longitudinal data is needed to determine how individuals use medications over time. The aim of this study was to examine the gender- and age-specific annual prevalence and incidence and type of anti-asthma medications used in the Norwegian population aged 2–29 years during 2005–2007. We also estimated the share of individuals who regularly redeemed medications over a 3-year period.

Methods

Norwegian Prescription Database (NorPD)

Data were retrieved from the Norwegian Prescription Database (NorPD). From 1 January 2004, all Norwegian pharmacies were obliged to send electronic data on all dispensed prescriptions to NorPD (irrespective of reimbursement status) [9]. Medications are classified according to the Anatomical Therapeutic Chemical (ATC) classification system [10]. The following data from NorPD were retrieved for this study: Unique encrypted personal identification number (PIN), gender, year of birth, year of death, date of dispensing, ATC code, and reimbursement status. A PIN is assigned to every citizen in Norway, and it was the key to identifying all prescriptions dispensed to one individual. The study was approved by the Norwegian Data Inspectorate and evaluated by the Regional Committee for Medical Research Ethics. All Norwegian citizens have unrestricted access to the national tax-supported public health service. The system for general reimbursement of medications is basically a “positive list” system based on a list of diseases or conditions for which specified medications can be reimbursed. Reimbursement should only be granted if the patient has a chronic condition in which long-term medication treatment is needed (>3 months of regular or intermittent treatment during a year) [11]. The physician writes a specific code on prescriptions deemed eligible for reimbursement due to asthma, which is recorded in NorPD. The ceiling for patient copayment per year for reimbursed medications and physician visits is fairly low. In 2007, it was 1,660 NOK (about 200 euros), but there was no copayment for children <12 years of age.

Study population

The use of anti-asthma medications during 2005–2007 was studied in the Norwegian population aged 2–29 years

(nearly 1.7 million individuals in 2007). All individuals who redeemed prescriptions for anti-asthma medications with the specific reimbursement code for asthma were included in this study. Medications included were (Table 1) inhaled short- and long-acting β_2 -agonists (IBA), inhaled corticosteroids (ICS), fixed-dose combinations of inhaled long-acting β_2 -agonists and corticosteroids (FDC), and leukotriene receptor antagonists (LTRA). Other medications used for obstructive airways diseases (anticholinergics, cromoglicic acid, xanthines, omalizumab, and oral corticosteroids) are mainly used as add-on therapy to the four medications included in this study. In 2007, these medications would only yield 573 additional medication users of all ages to those already included (0.62% of all anti-asthma medication users) and did not influence the age- and gender-specific population measures presented in this study.

There are few studies on anti-asthma medication use in young adults, and in this study, we examined the use of anti-asthma medications in both children from the age of two years and young adults up to 29 years of age. In this age group, one can assume that there is no diagnostic overlap with chronic obstructive pulmonary disease (COPD), and medication use can be a valuable proxy measure of asthma. We excluded 0- and 1-year-olds because of a relatively high share of prescriptions with an invalid PIN for these age groups in 2006 and 2007. Prescriptions with an invalid PIN cannot be linked to individuals, and including them would not give a reliable comparison across years and age groups. The percentage of dispensed prescriptions with an invalid PIN for 2- to 29-year-olds was between 2.6% and 3.7% per year.

Measures

Prevalence

Prevalence was estimated as the number of individuals who redeemed at least one prescription of anti-asthma medications in a calendar year. The denominator was gender- and age-specific figures for the midyear Norwegian population in each year retrieved from Statistics Norway. Annual prevalence was also measured as the number of individuals who redeemed prescriptions on at least two different days in a calendar year (referred to as “two prescriptions” in “Results”).

Incidence

New (incident) users of anti-asthma medications in 2007 were defined as individuals who redeemed at least one prescription in 2007 but who did not redeem any during 2004–2006 (i.e., had a medication-free run-in period of 3 calendar years) [12]. The denominator was the gender- and

Table 1 Medication groups, ATC codes^a, and generic names of anti-asthma medications included in the study

Medication group	Abbreviation	ATC code	Generic names
Inhaled β_2 -agonists	IBA	R03AC02	Salbutamol
		R03AC03	Terbutaline
		R03AC04	Fenoterol
		R03AC12	Salmeterol
		R03AC13	Formoterol
Inhaled glucocorticoids	ICS	R03BA01	Beclomethasone
		R03BA02	Budesonide
		R03BA05	Fluticasone
Fixed-dose combination of inhaled β_2 -agonists and glucocorticoids	FDC	R03AK06	Salmeterol + fluticasone
		R03AK07	Formoterol + budesonide
Leukotriene receptor antagonists	LTRA	R03DC01	Zafirlukast
		R03DC03	Montelukast

IBA inhaled short- and long-acting β_2 -agonists, *ICS* inhaled corticosteroids, *FDC* fixed-dose combinations of inhaled long-acting β_2 -agonists and corticosteroids, *LTRA* leukotriene receptor antagonists

^a Anatomical Therapeutic Chemical classification system [10].

age-specific Norwegian population as of 1 January 2007 retrieved from Norwegian Statistics minus individuals who redeemed prescriptions during 2004–2006. Incidence was also estimated with run-in periods of 1 and 2 calendar years.

Type of medications redeemed

All individuals who redeemed prescriptions during a year were assigned to four mutually exclusive medication groups. The relative share of all individuals in each of the four groups was calculated. Individuals who redeemed medications from more than one medication group during a year were assigned to the group with the higher rank:

- IBA: Individuals did not redeem any other anti-asthma medication during the year.
- ICS: Individuals may also have redeemed IBA but did not redeem FDC or LTRA during the year.
- FDC: Individuals may also have redeemed IBA and/or ICS as single-component inhalers but did not redeem LTRA during the year.
- LTRA: Individuals may also have redeemed any of the other medications during the year.

Persistence to medication

Regular redemption of prescriptions over a 3-year period (persistence) was measured among individuals who redeemed at least one prescription during 2005 according to the minimum refill model [13]. The criteria for being categorized as “persistent” was redeeming at least one prescription in 2006 (1-year persistence) and at least one

prescription in both 2006 and 2007 (2-year persistence). One hundred and fifteen individuals who died during 2005–2007 were excluded. Among the individuals who redeemed prescriptions during 2005, we also measured the share that did not redeem prescriptions in 2006 but did redeem in 2007 (i.e., individuals who had a refill gap of at least 1 year). Prescriptions are valid for 1 year from the day of prescribing, but the Norwegian reimbursement regulations restrict the maximum number of days supplied per redemption to 3 months use. Hence, individuals in need of daily treatment of their asthma generally redeem prescriptions several times during a year and were classified as persistent. In addition, individuals with intermittent or seasonal complaints who redeemed prescriptions regularly (at least once a year) but who do not necessarily have a supply of medication covering every day of a year, were also classified as persistent. Furthermore, as the aim of this analysis was to estimate the share of individuals that regularly received anti-asthma treatment over a 3-year period, individuals were deemed persistent even if they changed medication group during follow-up.

Results

In 2007, 5.5% (92,074 individuals) of the Norwegian population aged 2–29 years redeemed at least one reimbursed prescription for anti-asthma medications.

Prevalence

The annual prevalence (redeemed at least one prescription) was fairly stable from 2005 to 2007, changing from 5.6% to

5.9% in males and 4.9% to 5.0% in females (Table 2). An increase was more pronounced in children aged 12 years or younger and was highest in 2- to 5-year-old males (1.0 percentage point increase). The shape of the gender- and age-specific prevalence curve was unchanged during 2005–2007, and the curve for 2007 is presented in Fig. 1 (lines). The prevalence was highest among 2-year-olds, 13% for males and 9% for females, but was nearly halved by the age of 10. In males, the prevalence decreased further during adolescence and stabilized above 3% from 20 years onward. In contrast, females had an increasing prevalence during adolescence and had higher prevalence than males from 16 years onward.

Annual prevalence of redeeming prescriptions at least twice a year (two prescriptions) was 3.4% for males and 2.7% for females (2007). Although the prevalence levels were lower for two prescriptions, the shape of the gender- and age-specific curve (not shown) did not change from that observed for one prescription (Fig. 1).

Incidence

The incidence in 2007 (3 calendar years medication-free run-in period) was 1.5% in both males and females. As can be seen from the incidence curve in Fig. 1 (*bars*), females have a higher incidence than males from the age of 14. The

incidence was highest in the youngest age groups and was relatively stable after 20 years of age. Applying shorter run-in periods increased the incidence to 2.3% and 1.7% for, respectively, 1- and 2-year run-in periods. The incidence levels increased in all age groups and the shape of the incidence curve (figure not shown) was similar to the curve for a 3-year run-in period (Fig. 1).

Type of medications redeemed

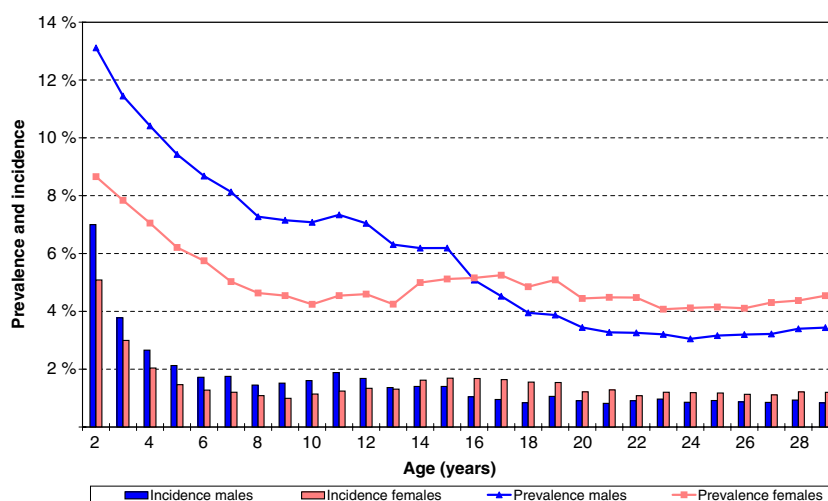
The type of medications redeemed was relatively stable from 2005 to 2007. Age-specific figures for 2007 (Fig. 2) reveal that the use of IBA as monotherapy was least frequent in preschool children at 14% and increased to 35% of all users aged 20–29 years. In the youngest age group, 69% of individuals were in the ICS group, but this share decreased with age. Conversely, FDC use was low in the youngest but increased by age and comprised 42% of all users >20 years of age. Taken together, the share of all medication users on corticosteroids (either as a single-component inhaler or as fixed-dose combination inhaler) was 75% in 2-year-olds but the share decreased with age. The only gender difference of note was that 27% of 13- to 15-year-old males used IBA monotherapy compared with 35% of females.

The IBA group contained both short- (SABA) and long- (LABA) acting β_2 -agonists. Further analysis of this group

Table 2 Annual number of individuals (*n*) and prevalence (%) of redeeming at least one prescription for anti-asthma medication in 2- to 29-year-olds during 2005–2007

Age group (years)	2005		2006		2007	
	<i>n</i>	%	<i>n</i>	%	<i>n</i>	%
Males						
2–5	11,951	10.1	12,383	10.5	13,146	11.1
6–12	15,043	6.8	16,015	7.2	16,559	7.5
13–15	5,820	6.0	6,061	6.2	6,027	6.2
16–19	5,059	4.2	5,378	4.3	5,632	4.4
20–29	9,486	3.3	9,430	3.3	9,518	3.3
2–29	47,359	5.6	49,267	5.8	50,882	5.9
Females						
2–5	7,878	6.9	8,182	7.2	8,460	7.4
6–12	8,885	4.2	9,623	4.6	9,948	4.8
13–15	4,308	4.7	4,447	4.8	4,380	4.8
16–19	5,771	5.0	6,052	5.1	6,229	5.1
20–29	12,782	4.6	12,437	4.5	12,175	4.3
2–29	39,624	4.9	40,741	5.0	41,192	5.0
Total						
2–5	19,829	8.5	20,565	8.9	21,606	9.3
6–12	23,928	5.5	25,638	5.9	26,507	6.2
13–15	10,128	5.3	10,508	5.6	10,407	5.5
16–19	10,830	4.6	11,430	4.7	11,861	4.7
20–29	22,268	4.0	21,867	3.9	21,693	3.8
2–29	86,983	5.3	90,008	5.4	92,074	5.5

Fig. 1 Annual prevalence (*lines*) and incidence (*bars*) of redeeming at least one prescription for anti-asthma medication in 2- to 29-year-olds in 2007



revealed that 3,402 individuals received LABA in 2007. Among these, 1,337 (39%) did not receive any type of inhaled corticosteroids (ICS or FDC) during 2005–2007. These figures were lower in children <11 years of age.

Persistence to medication

Persistence was measured among 86,868 individuals aged 2–29 years who redeemed prescriptions in 2005. Sixty-one percent of these individuals redeemed prescriptions in 2006 (1-year persistence), whereas 45% redeemed prescriptions in both 2006 and 2007 (2-year persistence). Both 1- and 2-year persistence was fairly similar in males and females and was quite stable throughout the age groups (Fig. 3). Ten percent of individuals who redeemed prescriptions in 2005 did not redeem prescriptions in 2006 but did redeem in 2007.

Discussion

In this nationwide study, 5.5% of all 2- to 29-year-olds in Norway received anti-asthma medications during 2007, and this figure was fairly stable throughout 2005–2007. The prevalence and incidence was higher in males than in females, but there was a shift to female dominance during adolescence. There were substantial differences in the type of medication used by different age groups. The use of ICS decreased with age, whereas use of FDC and IBA monotherapy increased with age. Fewer than half of the individuals who redeemed prescriptions in 2005 also redeemed prescriptions in the two subsequent years.

We found that most users were in the inhaled corticosteroid groups (ICS or FDC), which corresponded well with current guidelines for managing asthma [6, 7]. A Finnish study reported a higher share of 0- to 15-year-olds using FDC than in our study, especially in 0- to 3-year-olds [14]. According to guidelines, FDC is to be used in more

advanced steps of asthma treatment [(step 3, Global Initiative for Asthma (GINA) [7]] but a relatively high share of medication users were on this treatment (36–42% of 13- to 29-year-olds). This could be due to overprescribing of these medications instead of single-component inhalers. Regular follow-up in view of stepping down treatment for some of these individuals could be warranted.

The use of inhaled corticosteroids is displaced by use of IBA monotherapy (mainly SABA) in older age groups, and in 20- to 29-year-olds, one out of three individuals used IBA monotherapy. Although some corticosteroid users are classified in the LTRA group, this alone can not explain the fall in corticosteroid use by age and our results may reflect underuse of corticosteroids in the oldest age groups.

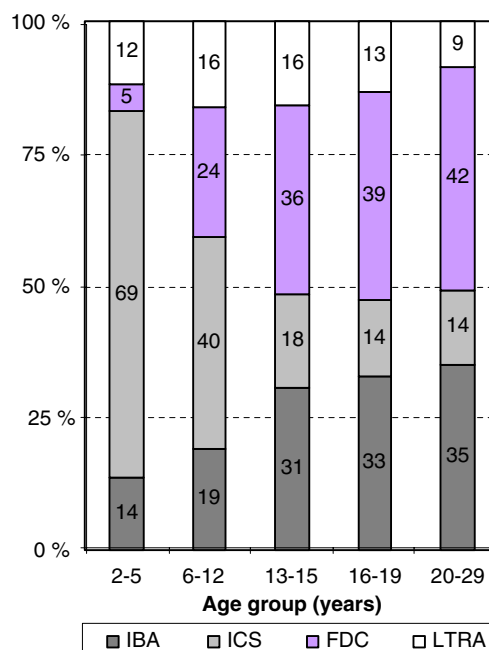
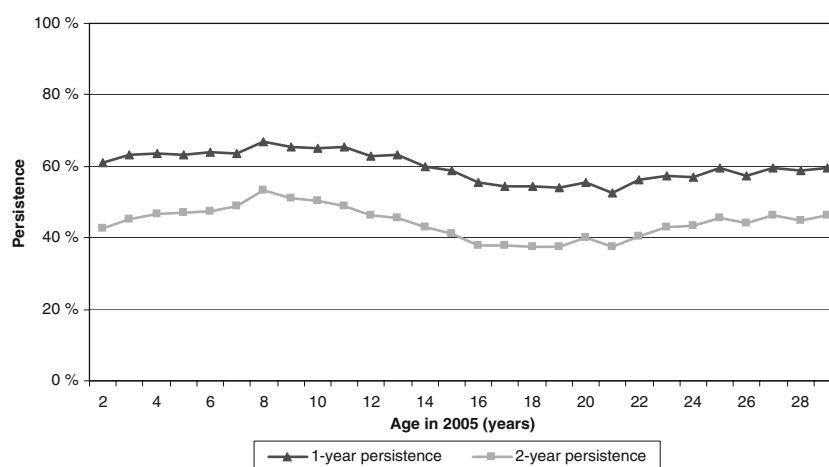


Fig. 2 Relative share of all users of anti-asthma medications in different medication groups in 2007

Fig. 3 Persistence to anti-asthma medication for 1 and 2 years in individuals 2–29 years old who redeemed at least one prescription in 2005



However, according to guidelines, SABA may be used as monotherapy in mild, intermittent asthma [6, 7]. We found that 39% of individuals receiving LABA may be using it as monotherapy (did not receive any type of inhaled corticosteroids during study period). There is widespread agreement that LABA should not be used as monotherapy [15], and guidelines discourage such practice [6, 7].

Studies of prevalence and incidence of asthma and of anti-asthma medication use have mainly been based on questionnaires and have often been conducted on selected age groups in a few regions. Some studies in Norway have indicated prevalence of asthma of similar magnitude to prevalence of use of anti-asthma medication found in our study [16, 17], whereas others have higher estimates [1, 18–20]. Prescription studies from other countries mainly focus on the use of one medication group (e.g., ICS) rather than grouping all anti-asthma medications together to reflect the share of the population in anti-asthma treatment. A prescription study from The Netherlands with a comparable method found similar figures to ours in 0- to 14-year-olds [21]. The higher prevalence of childhood asthma in males and the diverging trend observed for males and females during adolescence is in agreement with results from other studies on the occurrence of asthma at different ages [22–24].

Few studies have measured the incidence of anti-asthma medication use. A small Swedish study based on parent-reported anti-asthma medication use in 3 consecutive years reported a slightly lower incidence than our study [25]. However, comparing our results to questionnaire-based studies is difficult, because we do not have a washout period that extends back to birth. The incidence decreased when longer run-in periods were applied, but the difference between 2- and 3-year run-in periods was small. However, even with a 3-year run-in period, there could still be incident cases who are transiently free of symptoms with long treatment gaps and thus are not true incident cases. All age groups had the same medication-free run-in period, but

only 2- and 3-year-olds had run-in periods starting at birth. As more years are accumulated in the database, incidence analysis from birth is possible also for older children and adolescents. This will allow us to separate the truly incident cases (never treated before) from individuals transiently free of symptoms and medication treatment.

Guidelines state that, apart from the use of inhaled short-acting β_2 -agonists “as needed” by individuals with mild, intermittent asthma, medications should be used on a daily basis also during periods with no symptoms [6, 7]. The prescription pattern in these 3 years indicates that a substantial number of individuals did not use medications regularly. Even with the loose criterion for persistence applied in this study, less than half were deemed as being in persistent treatment for 3 years. This is consistent with results from a Canadian study of persisting asthma based on health care administrative data [26]. Some of the nonpersistent individuals may have asthma remission, whereas others may relapse later on. This is supported by other results of this analysis indicating that 10% were without prescriptions in 2006 but resumed treatment in 2007. Furthermore, the number of incident cases was lowered when we increased the run-in period, which indicates that many individuals had longer treatment gaps (>1year).

These findings support the belief that asthma is a heterogeneous condition of several phenotypes, with great variability within and between individuals in terms of clinical expression, age at onset, and persistence of symptoms over time [27, 28]. The heterogeneity of asthma over time in the same individual illustrates the challenges encountered when studying risk factors for asthma, as the same individual may switch from being regarded as asthmatic to nonasthmatic depending on when the information is collected [29]. Also, the phenotype could have implications for the type of medications that should be predominantly used by different age groups. For example, a large share of infants and small children with respiratory

symptoms are expected to be nonatopic children with frequent respiratory infections where use of ICS has no established value [30]. However, separating atopic and nonatopic children of this age may not be feasible.

We have no information about the diagnosis that led to the prescription for anti-asthma medication, and some disease misclassification could occur. Similar medications are also used for COPD, but COPD is uncommon in people <30 years and such diagnostic overlap should not affect this study. Diagnosis of asthma in infants and young children is difficult, and a large percentage of wheezers at this age have transient conditions that do not progress to asthma [27, 28]. Therefore, in the lowest age groups, one can expect that respiratory medications are also used by individuals who do not develop asthma. However, exclusion of mixtures with β_2 -agonists or ephedrine will reduce such misclassification, as these are mainly used for incidental, unspecific, respiratory tract symptoms and infections in preschool children. Furthermore, including only prescriptions specifically reimbursed for asthma should exclude some of the individuals who do not have a chronic condition, e.g., who only received nonreimbursed medication once as part of the diagnosis of asthma-like symptoms. However, patients with mild asthma are more difficult for physicians to detect and diagnose. Our estimates do not include these mild, undiagnosed patients who have not been prescribed medications. The population measures in this study should reflect active and clinically important asthma where pharmacotherapy is deemed necessary.

The strengths of this study are that it provides gender- and age-specific information on use of anti-asthma medications for the entire Norwegian population of this age. Follow-up of individuals over time enables us to measure incidence and persistence of treatment. Several factors should ensure a low threshold for seeking medical advice and receiving medical treatment for asthmatic symptoms in Norway: generally high level of education, a well-developed government-financed health-care system, a high rate of practising physicians per 1,000 inhabitants, and low patient copayment fee for medications and physician visits. The receipt of anti-asthma medication should therefore be a common event for most individuals with asthma in Norway.

A data capture period of 1 year attenuates effects of seasonal variation in asthma, whereas the use of electronic prescription data eliminates recall and information bias. All anti-asthma medications in Norway are prescription-only, and all redeemed prescriptions are included in NorPD, regardless of reimbursement status and the physician's speciality or occupation. Furthermore, we measure medications redeemed from the pharmacy rather than medications prescribed by physicians, thus avoiding primary noncompliance [31].

A longer follow-up period could give stronger evidence on whether the incident cases identified in this analysis are actually new individuals on anti-asthma medication. It would be interesting to see the extent to which the persistent individuals identified in this study used medications beyond 3 years and whether nonpersistent individuals resumed medication treatment later on. Furthermore, a large share of infants with respiratory symptoms have early, transient wheeze, and these infants do not develop persistent asthma. If the first prescription for anti-asthma medication marks the onset of asthma symptoms in an individual, one would expect to see lower persistence in the group of individuals that starts medication use as infants compared with those starting at an older age. NorPD is continuously updated with data on redeemed prescription medications, which makes such follow-up studies possible.

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