

Medicine use and disease control among adolescents with asthma

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Abstract

Purpose Pharmacological treatment is a cornerstone in asthma management, but there is limited evidence on how adolescents use their medication and to what extent their asthma is under control. Therefore, the aim of this study was to compare self-reported and register-based medicine use in asthmatic adolescents. Furthermore, we investigated the association between medicine use, patient characteristics, and degree of asthma control.

Methods Cross-sectional analyses of 331 adolescents with asthma from a population-based birth cohort linked to data from the Swedish Prescribed Drug Register. Adolescents' asthma medicine use was assessed with three approaches: self-reported medicine use, self-reported use of someone else's medicines, and dispensed medicines from pharmacies during an 18-month period. Medicine use in adolescents with and without asthma control were compared.

Results In total, 82 % reported use of asthma medicines, 10 % reported use of someone else's medicines, and 62 % were dispensed asthma medicines from pharmacies. Among adolescents with self-reported medicine use, 22 % ($n = 60$) were neither dispensed medicines nor using someone else's medicines. The majority of those using someone else's medicines had also been dispensed asthma medicine (22 out of 33). Among adolescents with asthma, 176 were fully controlled and 155 were uncontrolled. Also, boys had higher odds of having asthma control than girls.

Conclusion Most adolescents with asthma reported use of asthma medicines, but a considerable proportion were neither dispensed any medicines nor using someone else's medicines. Girls were less likely to achieve asthma control. It is important to combine data sources to understand medicine use among adolescents with asthma.

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Keywords Adolescents · Asthma · Drug utilization · Pharmacoepidemiology · Questionnaire · Register

Background

Asthma is one of the most common chronic diseases in adolescents. The global prevalence has been estimated to 14 % in 13–14-year-old adolescents, ranging from 6 to 27 % in different geographical areas [1]. Theoretically, asthma should be easier to diagnose in adolescents than in younger children, given that phenotypes including allergic and exercise-induced asthma are more distinct and that it is easier to measure lung function. However, in reality, both underdiagnosis and undertreatment are quite common in adolescents [2, 3].

The goal of asthma treatment is to achieve asthma control. The definition of well-controlled asthma in the Global Initiative for Asthma (GINA) guidelines is as follows: daytime asthma symptoms less than twice a week, no nightly awakenings due to asthma, bronchodilators needed for symptoms no more than twice a week, and no limitation of activities due to asthma [4]. In a Brazilian study, Alvim et al. found that frequent asthma symptoms, nighttime symptoms, and activity limitations were all associated with poor quality of life for adolescents with asthma [5]. The impact of asthma on health-related quality of life (HR-QOL) can be measured with a generic or disease-specific instrument [6, 7]. An advantage of the generic instrument is the possibility to measure HR-QOL in both healthy and chronically ill adolescents. Self-perceived health is a generic method frequently used in health-related studies. An overall assessment of health can be obtained by asking a simple question such as “how are you feeling?” [8].

Pharmacological treatment is a cornerstone in asthma management. Asthma medications can be classified as controllers or bronchodilators. The controllers—inhaled corticosteroids (ICS) and leukotriene receptor antagonists (LTRAs)—are usually used regularly on a long-term basis to keep asthma under clinical control [4]. The bronchodilators—beta-2-agonists—are used on an as-needed basis or regularly to reverse bronchoconstriction and relieve symptoms. However, many studies have shown room for improvement in drug prescribing to adolescents with asthma [9–11]. In addition, some patients may have poor adherence to the prescribed regimen [11–13]. A review from England concluded that 55 % of all children underused their ICS [13], and a Dutch study showed that less than 10 % of all children and adolescents were persistent with ICS after 1 year [12]. These findings are worrying, but it is also important to acknowledge that asthma in children and adolescents is an intermittent disease and therefore 100 % persistence cannot be expected. Furthermore, it is a challenge to study medication use among adolescents with asthma.

Studies comparing parental-reported use with dispensed asthma medicines have shown varying results [14–18]. In a previous study, we found that although 90 % of the 12-year-olds with asthma had parental-reported asthma medicine use, 30 % of them had not been dispensed such medicine during the preceding 18 months [14]. A potential explanation could be that the 12-year-olds shared medicines with someone else. This has, to the best of our knowledge, not been addressed in other studies.

Given the limited evidence on how adolescents use asthma medication, the aim of this study was to compare self-reported and register-based assessment of medicine use in adolescents with asthma. A secondary aim was to investigate how medicine use and patient characteristics were associated with having asthma control.

Methods

Study design and study population

This study included families participating in the population-based prospective birth cohort BAMSE (Children Allergy Milieu Stockholm Epidemiology Survey) with 4089 adolescents born between 1994 and 1996 [19]. The families have been followed through questionnaires completed when the adolescents were around 0, 1, 2, 4, 8, 12, and 16 years. We used the 16-year follow-up questionnaire ($n = 3315$, 76 % response rate), which the adolescents responded to between autumn 2010 and spring 2013 (Fig. 1). The questionnaire contained questions on each adolescent's health status, habits, use of medication, and family history of asthma. We used the

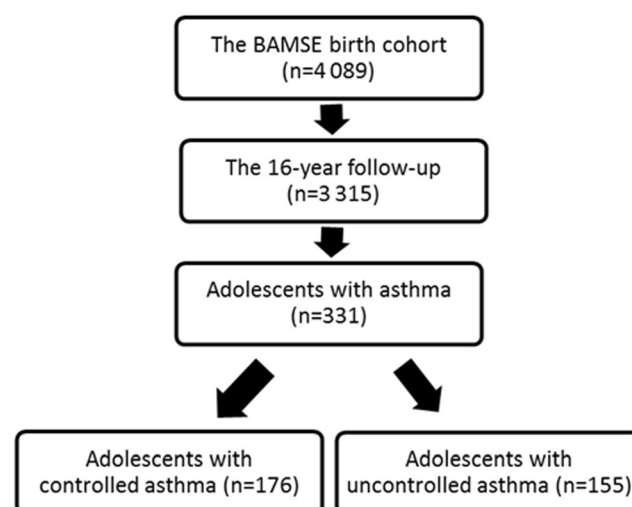


Fig. 1 Flow chart describing patient selection in the current study within the BAMSE birth cohort. Adolescents with partly uncontrolled asthma are included in the uncontrolled group

baseline parental questionnaire for detailed information about patient characteristics. Information about asthma diagnosis was collected from all the previous questionnaires. The final study population consisted of 331 adolescents with asthma, with an asthma prevalence of 10 % in the whole cohort.

This study investigated asthma medicine use in relation to asthma control using cross-sectional analyses. The self-reported medicine use from the 16-year follow-up questionnaire was linked to data on dispensed medicines from the Swedish Prescribed Drug Register (SPDR), using each adolescent's personal identity number (PIN) [20]. The SPDR is kept by the National Board of Health and Welfare and contains information about each adolescent (sex, age, PIN) and all medicines dispensed including Anatomical Therapeutic Chemical (ATC) codes, date of prescribing and dispensing, number of packages, and the dosage texts for each prescription. The register contains complete dispensing data for all inhabitants in the country with PINs included for more than 99.7 % of all prescriptions [21]. All prescriptions dispensed at Swedish pharmacies are included in the SPDR regardless of whether the medicines are subsidized or not. According to Swedish legislation, all prescriptions are valid up to 1 year after they have been prescribed and may be repeatedly dispensed until the total prescribed amount is purchased. A 3-month supply is the maximum amount patients are allowed to be dispensed at each refill to get their medicines subsidized [22].

Asthma and asthma control

Asthma was defined at the time of the 16-year questionnaire as doctor's diagnosis of asthma at any time since birth and at least one episode of wheeze in the last 12 months or asthma medicine use occasionally or regularly in the last 12 months [23]. Severe asthma was defined as having more than 12 episodes of wheeze in the last 12 months and doctor's diagnosis of asthma at any time since birth.

A modified version of GINA's definition of asthma control was used with information assessed from the questionnaires the last 12 months instead of the last 4 weeks as stated in the guidelines. Adolescents who fulfilled at least one of GINA's criteria, daytime asthma symptoms more than twice a week, nightly awakenings due to asthma, need for symptom reliever more than twice a week, and activity limitation due to asthma in the last 12 months were classified as uncontrolled [4]. Controlled asthma was defined as having none of GINA's criteria.

Asthma medication

The adolescent's asthma medication was assessed using three approaches: self-reported asthma medicine use in the 16-year follow-up questionnaire, self-reported use of someone else's asthma medication in the same questionnaire, and dispensed

asthma medicines recorded in the SPDR in the preceding 18 months. This time window has previously been found to give the best overall agreement between reported medicine use and dispensed medicine among adolescents with asthma [14].

The dispensed asthma medicines included in the analyses were (with ATC-codes [24]):

Short-acting β_2 -agonists, SABA (ATC R03AC02 + R03AC03)

Inhaled corticosteroids, ICS (R03BA)

Fixed combinations of ICS and LABA, fixed comb. (R03AK)

Leukotriene receptor antagonists, LTRAs (R03DC)

Long-acting β_2 -agonists, LABA (R03AC12 + R03AC13)

Any asthma medication: at least one of SABA, ICS, fixed comb., LTRAs, or LABA

Statistical analysis

A proportion test was used to assess differences in patient characteristics between adolescents with controlled and uncontrolled asthma, respectively. A 5 % significance level was used in all statistical tests.

To illustrate the quantities dispensed of the different medicines, box-plot graphs were used presenting median and range in the number of defined daily doses (DDD) dispensed to each patient during 18 months before the questionnaire was completed [24]. Stratified analyses were made by pharmacological group and degree of asthma control, using Wilcoxon's rank sum test to assess any differences in medians.

Logistic regression was performed to analyze the association between different patient characteristics and odds ratios of having asthma control. These characteristics, potentially acting as confounders, were chosen based on knowledge from literature and clinical experience [26, 27]. Patient characteristics included in the full model were sex, mother's age at birth <25 years, university education of at least one parent, living in more than one home, family history of allergic disease, smoking status, patient education about asthma medicines from a healthcare professional, and feeling completely healthy.

Medicine use was included both in the asthma definition and as one of the outcomes. Therefore, a sensitivity analysis was conducted to see if a change in asthma definition affected the adolescent's proportion of asthma medicine use (self-reported, using someone else's medicines and dispensed medicines). The three alternative asthma definitions were the following: having a doctor's diagnosis at any time since birth in combination with any wheeze in the last 12 months; doctor's diagnosis at any time since birth in combination with three episodes of wheeze in the last 12 months; and at least two of the following criteria: doctor's diagnosis at any time since birth, at least one

episode of wheeze in the last 12 months, and asthma medicine use occasionally or regularly in the last 12 months.

All analyses were conducted using the statistical software STATA SE 12.1.

Results

Among adolescents with asthma ($n = 331$), 53 % ($n = 176$) had fully controlled asthma and 47 % ($n = 155$) had uncontrolled asthma (Table 1, Fig. 1). In the group with controlled asthma, the proportion of boys was higher compared to the group of adolescents with uncontrolled asthma. One out of ten adolescents with asthma ($n = 38$) met the criteria for severe asthma, all of them with uncontrolled asthma. The adolescents with severe asthma had similar sex distribution (47 % boys vs. 50 % boys for all adolescents with asthma), but they had more often younger mothers (18 vs. 8 % for all adolescents with asthma) and parents with lower education (42 % of the parents with higher education compared with 50 % for all adolescents with asthma) and reported that they used medicines to a higher extent compared with all adolescents with asthma (92 vs. 82 %).

Asthma medicine use among adolescents with asthma

A total of 82 % ($n = 272$) of all adolescents with asthma reported that they had used asthma medicines in the last 12 months, 10 % ($n = 33$) reported that they had used another person's asthma medicines at least once during the last 12 months, and 62 % ($n = 204$) had been dispensed asthma medicines from pharmacies during the last 18 months. The overlap between these groups is illustrated in a proportional Venn diagram (Fig. 2). Seven out of ten adolescents with self-reported medicine use were also dispensed medicines

($n = 201$). Among adolescents with self-reported medicine use, 18 % were neither dispensed any medicines nor did they report using someone else's medicines. Two out of three of those who claimed that they had used someone else's medicines were dispensed asthma medicines (22 out of 33). Also, 56 adolescents (17 %) had no medicine use, i.e., did not report any use, did not use someone else's medicines, and were not dispensed any medicines at pharmacies. Among adolescents with severe asthma ($n = 38$), 92 % had self-reported medicine use, 13 % reported they used someone else's medicine, and 74 % were dispensed medicines at a pharmacy. However, 8 % of them had no asthma medicine use at all.

The sensitivity analysis, conducted to see if a change in asthma definition affected the overall use of asthma medicines, showed no differences regarding the proportion using asthma medicines assessed through the different methods. Details are presented in the [online supplement](#).

Comparing asthma medicine use among adolescents with and without asthma control

Self-reported use of asthma medications was more common among adolescents with uncontrolled asthma (89 vs. 76 %) (Table 2). Both groups were using someone else's asthma medicines: 6 % among those with controlled asthma and 14 % among those with uncontrolled asthma. Half of the adolescents with controlled asthma were dispensed asthma drugs compared with 7 out of 10 for the uncontrolled group. Also, 40 of the adolescents with controlled asthma and 16 of the adolescents with uncontrolled asthma had no medicine use. SABA, fixed combination, and ICS/fixed combination were used more often among adolescents with uncontrolled asthma (Table 2). There was no statistical difference in the use of ICS, LTRAs, and LABA.

Table 1 Patient characteristics in the study population ($n = 331$)

Patient characteristics	Fully controlled asthma, C ($n = 176$)	Uncontrolled asthma, U ($n = 155$)	Proportion test C vs. U
Male	101 (57 %)	64 (41 %)	<0.01
Mother's age at birth <25 years	11 (6 %)	17 (11 %)	0.12
At least 1 parent with university education	92 (52 %)	75 (48 %)	0.48
Living in more than 1 home	55 (31 %)	53 (34 %)	0.54
Family history of allergic disease ^a	80 (0.47 %)	69 (0.45 %)	0.76
Severe asthma ^b	0	38 (0.25 %)	N/A
Asthma education	92 (56 %)	91 (59 %)	0.63
Smoking	16 (9 %)	15 (10 %)	0.87
Feeling completely healthy	125 (71 %)	99 (64 %)	0.17

N/A not applicable

^a Mother and/or father with a doctor's diagnosis of asthma and asthma medication and/or doctor's diagnosis of hay fever in combination with allergy to furred pets and/or pollen

^b Twelve episodes of wheeze in the last 12 months and doctor's diagnosis of asthma at any time since birth

Fig. 2 Proportional Venn diagram illustrating medicine use among adolescents with asthma recorded with different methods. Among adolescents with asthma ($n = 331$), 83 % ($n = 275$) had either self-reported use, were using someone's medicine, or had dispensed medicine



In general, the number of DDDs dispensed to the adolescents was low for all medicines (Fig. 3). The median number of DDDs for ICS was 50, for both adolescents with controlled and uncontrolled asthma. For fixed combinations of ICS and LABA, the median was 180 for adolescents with asthma control and 90 for adolescents with uncontrolled asthma (p value = 0.03). The difference in medians when comparing adolescents with controlled and uncontrolled asthma was significant also for SABA (30 vs. 50 DDDs, $p < 0.01$). Also, the number of DDDs dispensed for SABA varied a lot, in particular for adolescents with uncontrolled asthma with a range between 14 and 1425 DDDs during the 18-month period.

In our regression model, we found that boys had higher odds of having asthma control compared with girls. The findings stayed true also after adjusting for patient characteristics (OR-adjusted = 1.90, CI 1.19–3.04; Table 3).

Discussion

In this study, the majority of adolescents with asthma reported that they used asthma medicines, but one third of them had not been dispensed any medicines during the 18 months prior to responding to the questionnaire. We found, among adolescents with self-reported medicine use, that 22 % were neither dispensed any medicines nor using someone else's medicines. Also, 10 % had used someone else's asthma medicines and 17 % of the adolescents had no medicine use. Furthermore, girls with asthma were less likely to have asthma control than boys.

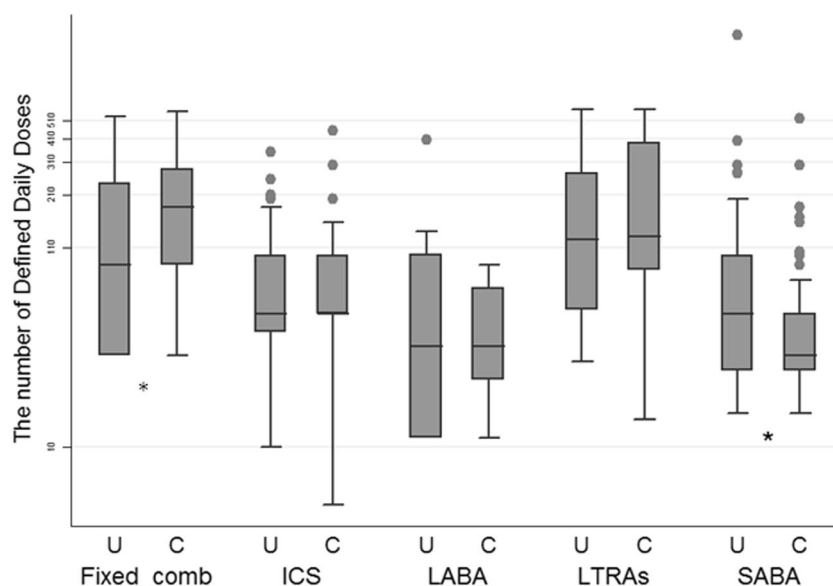
The utilization of medicines among adolescents with asthma has been studied in a large number of studies from different countries using different methods. Some studies show a good concordance between questionnaires and registers [15–18]. However, our previous study showed that 30 % of

Table 2 The use of asthma medication among adolescents with controlled and uncontrolled asthma

Use of asthma medication	Fully controlled asthma, C ($n = 176$)	Uncontrolled asthma, U ($n = 155$)	Proportion test C vs. U
Self-reported use	134 (76 %)	138 (89 %)	<0.01
Using someone else's medicine	11 (6 %)	22 (14 %)	0.02
Dispersed medicine ^a	95 (54 %)	109 (70 %)	<0.01
SABA	68 (39 %)	89 (57 %)	<0.01
ICS	41 (23 %)	37 (24 %)	0.90
LTRAs	23 (13 %)	20 (13 %)	0.96
LABA	6 (3 %)	11 (7 %)	0.13
Fixed comb.	40 (23 %)	51 (33 %)	0.04
SABA only	15 (16 %)	20 (18 %)	0.63
ICS or fixed comb.	75 (43 %)	84 (54 %)	0.04
LTRAs but not ICS/fixed comb.	4 (8 %)	2 (3 %)	0.32

^a Assessed through dispensing data from the Swedish Prescribed Drug Register. Any of the asthma medicines (SABA, ICS, LABA, fixed comb.) dispensed during the preceding 18 months

Fig. 3 Range in number of defined daily doses dispensed for each patient during 18 months in relation to asthma control, assessed with data from the Swedish Prescribed Drug Register. *Asterisks* indicate statistical difference. *U* uncontrolled asthma, *C* controlled asthma



the adolescents with parental-reported medicine use had not purchased any asthma medicine in the preceding 18 months [14]. In this study, we had the opportunity to assess medicine use in three different ways to get a deeper understanding about how adolescents with asthma use their medicines and to use the adolescents' own answers, while in the previous study, we used parental-reported use of medicines. Our findings, that one eighth of all adolescents with asthma use someone else's medicines and that half of them are not identified in a prescription register have, to the best of our knowledge, not been shown before. It is, however, known from other therapeutic areas (i.e., pain medication and allergy medication) that adolescents borrow medicines from others [28, 29]. In a study from the USA, one out of five adolescents shared medicines, and in an Irish study, 26 % of adolescents reported they borrowed

someone else's medicines. The best source of information on adolescent medicine use can still be debated. It is likely that dispensed medicines recorded in pharmacy dispensing databases provide an underestimation of the medicine use. On the other hand, self-reported medicine use can provide an overestimation. The choice of source for describing adolescents' medicine use will depend on the research question, i.e., whether it is interesting to study the concomitant use or any use of medicines in a specific period of time.

Among adolescents with asthma, 17 % had no medicine use at all, and among adolescents with severe asthma, 8 % had no medicine use, which is a rather high proportion. Since the group with severe asthma was small, this finding should be interpreted with caution. Örtqvist and colleagues, however, showed that dispensed asthma medication is a suitable proxy

Table 3 Factors associated with having asthma control among adolescents with asthma

Factors associated with asthma control	OR-unadjusted (95 % CI)	OR-adjusted ^a (95 % CI)
Male	1.91 (1.24–2.97)	1.90 (1.19–3.04)
Mother's age at birth <25 years	0.54 (0.25–1.19)	0.51 (0.21–1.26)
At least 1 parent with university education	1.17 (0.76–1.80)	1.13 (0.71–1.81)
Living in more than 1 home	0.87 (0.55–1.37)	0.81 (0.48–1.35)
Family history of allergic disease ^b	1.07 (0.69–1.66)	1.01 (0.63–1.60)
Asthma education	0.90 (0.57–1.40)	0.80 (0.50–1.28)
Smoking	0.94 (0.45–1.97)	1.00 (0.42–2.38)
Feeling completely healthy	1.39 (0.87–2.20)	1.31 (0.79–2.18)

^a Or adjusted for sex, mother's age at birth <25 years, higher parental education, adolescents living in more than one home, family history of allergic disease, adolescents having received asthma education, adolescents smoking, and feeling completely healthy

^b Mother and/or father with a doctor's diagnosis of asthma and asthma medication and/or diagnosis of hay fever in combination with allergy to furred pets and/or pollen

for asthma in adolescents [30]. Thus, even though some of the adolescents in our study might have outgrown their asthma, underuse of medications is likely.

We found that half of the adolescents had controlled asthma. This is in line with other findings. In a Danish study on young adults with asthma, 41 % had asthma control [31]. Klok and colleagues found that 60 % of preschool children had controlled asthma [32]. Appropriate use of asthma medicines is important for asthma control, but there are also other contributing factors including exposure to tobacco smoke, confirmed food allergy, and obesity [4]. In our study, smoking was not a risk factor for poor asthma control, which could be explained by the low numbers of adolescents smoking in our study. Also, we found that adolescents with uncontrolled asthma used medicines to a higher degree. This might be surprising, knowing that pharmacological treatment may improve asthma control. However, this finding illustrates the difficulties analyzing cause-effect in a cross-sectional study design, since higher medicine use may simply indicate a more severe disease. Also, one of the criteria for uncontrolled asthma is using SABA more than twice a week. This was illustrated by the fact that all adolescents with severe asthma were in the uncontrolled group. Still, it is important to acknowledge that there may be problems with adolescents not having the appropriate knowledge of how to handle their inhalers, thus leading to poor association between purchased volumes and uncontrolled asthma. This is beyond what we could study with this material but would warrant further research.

Strengths and limitations

We had the opportunity to use data from a population-based birth cohort with a large number of adolescents and a high response rate (76 % for the 16-year follow-up) ensuring high internal validity. The questionnaires gave us valuable information about the adolescents which was not possible to collect through other methods, such as if they were using someone else's asthma medicine. The record linkage with the register on dispensed medicines provided further information on the purchase of asthma medicines. The SPDR includes all prescribed medicines dispensed at Swedish pharmacies regardless of whether the medicine is subsidized or not. In Sweden, the prescription regulations state that all medicines should be prescribed with the identity of the intended user [33]. However, all children up to the age of 18 living in the same household share a joint reimbursement threshold for co-payment. Consequently, there are no real incentives for parents to separate their children's medicines if they are using exactly the same medication. To what extent siblings share medicines has not been studied, and dispensing data from other family members would have been helpful to assess the validity of the data from SPDR.

Our study had a cross-sectional study design with the limitation of studying the outcome and the characteristics associated with it at any one specific time, as this does not give any indication of the sequence of the events, i.e., whether the exposure occurred before, after, or during the onset of the outcome.

Even though the study population of 331 adolescents with asthma is relatively large, some of the examined factors such as smoking were relatively uncommon. Thus, we cannot entirely rule out an association between these factors and asthma control. The questionnaires in the BAMSE study ask the participants to remember details about their medicine use, wheezing history, and other factors during the preceding 12 months. Despite the fact that the adolescents will see photos of different asthma medicines when answering the questions about asthma medicine use, it can still be hard to remember medicine use in the last year. Therefore, a non-differential recall bias could be expected. A lot of information about the adolescents and their families has been collected over the years, but some information about them is still unknown. We did not have access to medical records to confirm doctors' diagnosis of asthma. However, since the sensitivity analysis with different asthma definitions gave us similar proportions using medicines, the results of this study did not depend on the definition of asthma. The definition of asthma control was assessed using information from the questionnaires the last 12 months instead of the last 4 weeks as stated in the guidelines. That could lead to an overestimation of the proportion of adolescents with uncontrolled asthma.

Conclusions

Most adolescents with asthma reported use of asthma medicines, but a considerable proportion were neither dispensed any medicines nor using someone else's medicines. Girls were less likely to achieve asthma control. It is important to combine data sources to understand medicine use among adolescents with asthma.

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Author's contributions All authors jointly designed the current study. I.K. supervised the data collection. E.D. and I.K. analyzed the data. All authors participated in the interpretation of the findings.

E.D. wrote the initial draft. All authors participated in the critical revision of the manuscript, provided important intellectual input, and approved the final version.

Compliance with ethical standards This study was approved by the Ethics Committee of Karolinska Institutet, Stockholm, Sweden. Informed consent was obtained from all individual participants included in the study.

Conflict of interest The authors declare that they have no competing interests.

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Sensitivity analysis of medicine use among adolescents with different asthma definitions.

Medicine use	Asthma 1 ¹	Asthma 2 ²	Asthma 3 ³	Asthma 4 ⁴
Self-reported use	272 (81%)	174 (87%)	98 (88%)	363 (86%)
Using someone else's medicine	33 (10%)	25 (13%)	19 (17%)	56 (13%)
Dispensed medicine	204 (62%)	134 (67%)	72 (65%)	252 (62%)

¹ The study definition of asthma; doctor's diagnosis of asthma at any time since birth and at least one episode of wheeze in the last 12 months or asthma medicine use occasionally or regularly in the last 12 months.

² At least one episode of wheeze in the last 12 months and doctor's diagnosis of asthma at any time since birth.

³ More than three episodes of wheeze in the last 12 months and a doctors diagnosis of asthma at any time since birth.

⁴ At least two of the following criteria; doctor's diagnosis of asthma at any time since birth, at least one episode of wheeze in the last 12 months or asthma medicine use occasionally or regularly in the last 12 months.