

ORIGINAL ARTICLE

Limited agreement between current and long-term asthma control in children: the PACMAN cohort study

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Abstract

Background: Several studies have shown that predictors of asthma treatment outcomes differ depending on the definition of the outcome chosen. This provides evidence that different outcomes studied may reflect distinct aspects of asthma control. To assess predictors of asthma control, we need firm outcome phenotypes. The aim of this study was to investigate the association between measurements of current and long-term asthma control.

Methods: We included 527 children using inhaled corticosteroids participating in the Pharmacogenetics of Asthma medication in Children: Medication with ANti-inflammatory effects cohort. Current asthma control (previous week) was defined using the Asthma Control Questionnaire. Long-term asthma control was based on Global Initiative for Asthma guidelines. Not well-controlled asthma in a season was defined as ≥ 3 of the following items present in a season: (i) day-time or (ii) night-time symptoms, (iii) limitations in activities, and (iv) rescue medication use. Asthma control during (i) the previous season and (ii) the year preceding the pharmacy visit was used as long-term asthma control definitions. Current and long-term asthma control were compared to investigate agreement.

Results: Long-term uncontrolled asthma rates were highest in autumn and winter (50%) and lowest in summer (32%) ($p < 0.05$). Overall agreement between current and long-term asthma control was limited (66% for previous season and 68% for previous year).

Conclusion: Congruence between current and long-term asthma control was limited. Furthermore, we showed significant seasonal differences. It is therefore important to calculate asthma control over a longer period of time, instead of using current asthma control as indicator.

Several studies have shown that a substantial proportion of patients with asthma do not reach sufficient disease control (1–3). Suboptimal asthma control is associated with a lower

quality of life and an excess in health care use with consequently increased health care costs for society. It is therefore important to obtain in-depth knowledge on determinants of asthma control and to develop interventions to improve this. It is well known that inhaled corticosteroids (ICS) improve asthma control (4). A recent study of Rogers et al. (5) showed that genetic and phenotypic predictors of long-term ICS treatment response differ depending on the definition of the outcome chosen (lung function or exacerbations). In line with these findings, Wu and coworkers also reported different

Abbreviations:

ACQ, asthma control questionnaire; ATC, anatomical therapeutical chemical; CI, confidence interval; ICS, inhaled corticosteroids; GINA, global initiative for asthma; GOAL, gaining optimal asthma control; MARS, medication adherence report scale; SABA, short-acting beta-agonist.

predictors for symptoms and exacerbations (6). This provides evidence that the two outcomes studied reflect distinct aspects of asthma control. Thus, we need firm asthma control phenotypes to assess phenotypic and genetic predictors of asthma control.

Asthma control can be defined in different ways. O'Byrne et al. (7, 8) compared three different asthma control classification systems [the Asthma Control Questionnaire (ACQ), Global Initiative for Asthma (GINA), or Gaining Optimal Asthma Control (GOAL) study criteria] and showed that the two categorical scales used in their study (GINA and GOAL criteria) provided comparable results. The ACQ, an ordinal measurement scale, was more responsive to change over time than the categorical scales used in their study (8).

The aim of this study was to investigate the agreement between definitions of current and long-term asthma control using data from the Pharmacogenetics of Asthma medication in Children: Medication with ANti-inflammatory effects (PACMAN) cohort (9). Both current asthma control, in the last week, and long-term asthma control, during the past season and during the previous year, were determined and compared.

Methods

Study population and setting

Recruitment of the PACMAN cohort started in April 2009 by means of selecting pediatric asthma medication users from community pharmacies. Details of this study protocol have been described elsewhere (9). Briefly, children aged 4–12 years who are regular users (≥ 3 prescriptions within the last 2 years and ≥ 1 prescription in the last 6 months) of asthma medication (Anatomical Therapeutic Chemical code R03) were selected from pharmacies in the Netherlands. Selected children and their parents were invited for a visit to their own community pharmacy. Recruitment for the PACMAN cohort took place throughout the year. Nevertheless, most children were included in spring (46%) and autumn (30%) as a result of holiday seasons (summer and winter). Only 7% of the population was included during summer, and 17% was included during winter. To assess whether the studied selection was a representative to the general population, information was extracted from the pharmacy information system in four randomly chosen pharmacies participating in the PACMAN cohort study. The following information was extracted: number of children registered to the pharmacy aged 4–12 years (gender and age), number of children aged 4–12 years who filled a prescription for asthma medication in the past 2 years (gender and age), and the number of children who fulfilled the PACMAN inclusion criteria (as described earlier). The PACMAN study has been approved by the Medical Ethics Committee of the University Medical Centre Utrecht.

During the pharmacy visit, parents filled in a questionnaire to collect information regarding general health, asthma and respiratory symptoms, medication use, adherence [the 5-item medication adherence report scale questionnaire (10)],

parent's beliefs about medicines, and environmental and socio-demographic factors. This questionnaire also contained questions regarding the presence of asthma symptoms, limitations in activities, sleep disturbances, and extra medication use during the different seasons (spring, summer, autumn, and winter) in the past 12 months. In addition, a question on the frequency of the described symptoms during the different seasons was added: '*How often did your child experience these symptoms during spring/summer/autumn/winter?*' (Answers: daily, weekly, monthly, or rarely symptoms).

Furthermore, the child's lung function was measured [both before and after use of a short-acting beta-agonist (SABA)] with a hand-held diagnostic spirometer (Microspirometer, Micro Medical, Kent, UK), fractional exhaled nitric oxide levels were measured with a hand-held analyzer (Niox Mino, Aerocrine, Solna, Sweden), and the child's inhalation technique was scored with an inhaler-specific inhalation control checklist (9). The children and parents were asked to withhold bronchodilating agents such as short-acting β -agonists and anti-cholinergic agents 4 h before the pharmacy visit and long-acting β -agonists 36 h before testing. For this study, we only selected children who used ICS in the past year.

Definitions

We defined both current asthma control (control of symptoms during the last week) and long-term asthma control [asthma control during the previous season (3 months) and asthma control during the previous year (12 months)].

Current asthma control

Current asthma control outcome (well-controlled, partially, or not well-controlled asthma) was defined using the 6-item ACQ. This questionnaire can be used to differentiate between well-controlled and not well-controlled asthma, an ACQ score < 0.75 indicating good asthma control, a score between 0.75 and 1.50 indicating partially controlled asthma, and an ACQ score of ≥ 1.50 indicating not well-controlled asthma (11). This questionnaire is validated in patients with asthma aged ≥ 18 years, but has also been successfully used in pediatric populations (12).

Long-term asthma control

Long-term asthma control was based on the definitions from the GINA guidelines (13). First, asthma control was defined based on the presence of symptoms in a specific season. Not well-controlled asthma was defined as ≥ 3 of the following items present in a specific season: (i) day-time asthma symptoms, (ii) night-time asthma symptoms, (iii) limitations in daily activities, and (iv) rescue medication use. Partially controlled asthma was defined as the presence of one or two of the above-described items, and well-controlled asthma was defined if none of the above-described items were present. Second, we used a definition for asthma control that was adjusted for the frequency of symptoms during a season (as is also proposed according to the GINA criteria). Children

with three or more features of frequent symptoms (daily or weekly symptoms during a season) were classified as not well controlled, children with one or two features of monthly symptoms were classified as partially controlled, and children who only experienced rarely symptoms (less than once a month) during a season were classified as well controlled.

Long-term asthma control was defined as: (i) asthma control during the previous season (3 months) and (ii) asthma control during the previous year (12 months). Overall long-term asthma control during the past year was defined as at least three seasons in which the symptoms were controlled, and not well-controlled asthma was defined as at least three seasons with uncontrolled asthma. These two definitions of long-term asthma control were compared with current asthma control (based on the ACQ).

Statistical analysis

Chi-square testing was used to compare frequency data, and Kruskal–Wallis testing was used for comparison of means. The proportion of overall agreement and kappa statistics with their 95% corresponding confidence (CI) intervals were calculated to quantitate agreement between current and long-term asthma control. Kappa statistics were interpreted using the classification system developed by Landis and Koch (14): $\kappa \leq 0$ poor agreement; $\kappa = 0\text{--}0.2$ indicating slight agreement, $\kappa = 0.21\text{--}0.4$ indicating fair agreement, $\kappa = 0.41\text{--}0.60$ indicating moderate agreement, $0.61\text{--}0.80$ substantial agreement, and κ values $0.81\text{--}1.00$ indicating almost perfect to perfect agreement. All analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC, USA).

Results

Selected subjects vs. general population

Figure 1 shows the characteristics of a random sample of the PACMAN study population compared to the complete population (children aged 4–12 years) out of four randomly chosen pharmacies (data were pooled, because there were no significant differences between the pharmacies). Almost 8% of the children (aged 4–12 years) registered to these pharmacies filled a prescription for asthma medication in the past 2 years. Around one-third of these asthma medication users met the PACMAN inclusion criteria.

Response rate

Until February 2011, 2114 children were selected from 67 Dutch pharmacies. For 595 (28.1%) parents and their children, the telephone number was unknown in the pharmacy and could not be traced through Internet or a national telephone number service. Furthermore, 393 (18.6%) parents, whose telephone numbers were known, could not be reached after at least five phone calls during office hours. Therefore, in total, 1126 parents could be invited by telephone, and of these, 684 parents (60.7%) agreed to participate. No data were obtained in 82 (12.0%) children because of various

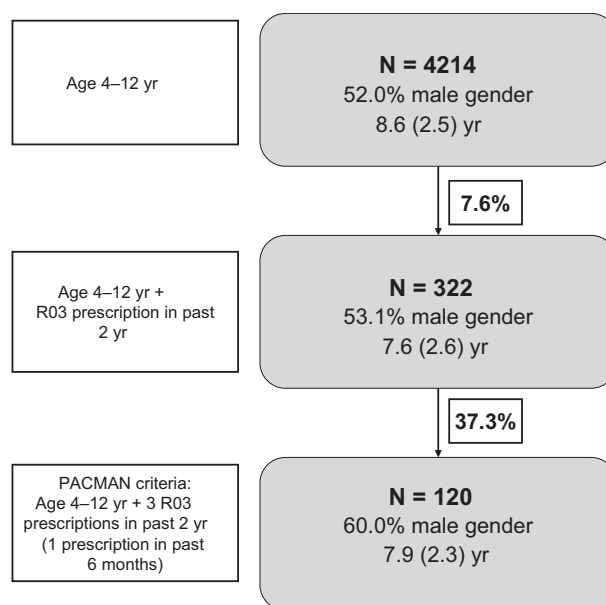


Figure 1 Selection of Pharmacogenetics of Asthma medication in Children: Medication with ANti-inflammatory effects (PACMAN) study subjects in four randomly selected pharmacies. This flow scheme shows the selection of study participants for the PACMAN study from the complete population of children registered in one of the four randomly chosen community pharmacies.

reasons (e.g., child was unwilling to participate, parents/children did not show up at the scheduled appointment, or the parent/children were willing to participate, although unable to come to the pharmacy in the period of patient inclusion). As a result, 602 children were included in the study, indicating a response rate of 53.5%. For this study, we only included children using ICS in the past year ($n = 527$). The general characteristics of this population are shown in Table 1: 61% of the participants were men and the mean age was 8.4 years.

Current asthma control during the past week

Figure 2 shows current asthma control as defined by the ACQ scores. Most patients are classified as well controlled (54.5%). A quarter (24.3%) is classified as partially controlled, and 21.2% of the children had not well-controlled asthma.

Long-term asthma control during the previous season

Figure 3a shows the level of asthma control during the different seasons (prevalence based, not adjusted for symptom frequency). Uncontrolled asthma rates were highest in autumn (62.2%) and lowest in summer (36.7%) ($p < 0.05$). Well-controlled asthma rates ranged from 8.4% (autumn) to 33.3% (summer). The prevalence of partially controlled asthma varied between 29.4% (autumn) and 33.7% (spring) for the different seasons.

Table 1 Characteristics of study population

	Study population (n = 527)
General	
Male gender, %	61.0
Age, mean $\pm$ s.d.	8.4 $\pm$ 2.5
Caucasian ethnicity, %	89.6
Clinical characteristics	
Hay fever, %	47.1
Eczema, %	66.2
Food allergy, %	52.5
Doctor-diagnosed asthma, %	76.2

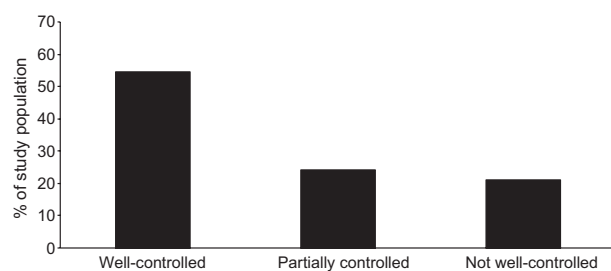
**Figure 2** Definition of current asthma control status by ACQ. ACQ, asthma control questionnaire.

Figure 3b shows asthma control, taking the symptom frequency into account. Uncontrolled asthma rates were highest in autumn and winter (49.8% and 49.9%, respectively) and lowest in summer (31.6%) ($p < 0.05$). The prevalence of well-controlled asthma was highest in summer (28.7%) and lowest in autumn and winter (16.7% and 18.5%, respectively). Asthma symptoms were not well controlled during the previous season (Fig. 3b) in 46.8% of the patients. Symptoms were well controlled in 22.6% and partially controlled in 30.6% of the patients.

Long-term asthma control during the previous year

Asthma symptoms were not well controlled during the past year in 40.9% of the patients (symptoms in at least three seasons). Symptoms were well controlled in 25.4% and partially controlled in 33.7% of the patients (Fig. 3b).

Agreement between current and long-term asthma control

Overall agreement between current asthma control and asthma control during the previous season was 66%. Kappa statistics indicated 'fair agreement' (Table 2). A large proportion of the children with current well-controlled asthma did not meet our definition of long-term asthma control (specificity 52.4% and sensitivity 95.9%). Overall agreement between current control and long-term control over the past year was also fair (overall agreement 68%, $\kappa = 0.40$).

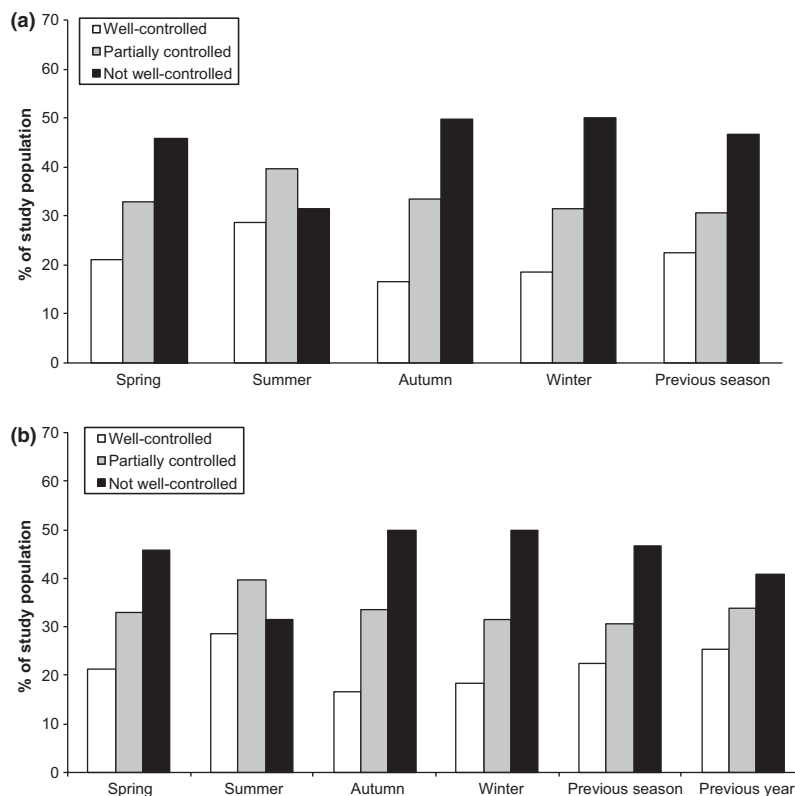
**Figure 3** Definition of long-term asthma control status. (a) Prevalence-based asthma control. Asthma control status (well controlled, partly controlled, or uncontrolled) during a specific season. (b) Asthma control adjusted for symptom frequency. Asthma control status (well controlled, partly controlled, or uncontrolled), adjusted for frequency of symptoms during a season.

Table 2 Congruence between current and long-term asthma control

Current asthma control (ACQ) – Long-term asthma control	Overall agreement, % (n)	Kappa (95% CI)
Previous season (3 months)	65.8	0.38 (0.29; 0.47)
Previous year (12 months)	67.8	0.40 (0.31; 0.49)

ACQ, asthma control questionnaire.

The characteristics of the study population when using the definition for long-term asthma control (previous season) are shown in Table 3. As a confirmation of this finding, children with long-term not well-controlled asthma used more often oral steroids, short-acting beta agonists, leukotriene receptor antagonist, and antibiotics compared to children with partially or well-controlled asthma ($p < 0.05$). Current asthma control rates (based on ACQ scores) were significantly lower for children with asthma that was not well controlled or par-

Table 3 Description of study population (long-term asthma control previous season)

	Controlled N = 105	Partly controlled N = 142	Uncontrolled N = 217
General characteristics			
Gender, male	64.8	63.4	59.0
Age, mean (s.d.)	8.5 (2.4)	8.4 (2.4)	8.4 (2.5)
Dutch ethnicity	90.4	90.6	86.3
Doctor-diagnosed asthma	81.3	74.2	73.2
Medication use			
OCS	1.9	5.6	12.4*
SABA	76.2	87.3	88.0*
LABA	29.5	24.7	25.8
LTRA	5.7	6.3	12.4**
AB	29.8	34.8	43.7*
Good adherence	59.1	54.2	58.5*
Good inhalation technique	86.7	83.8	81.2
Environmental factors			
Smoke exposure	10.5	8.5	7.0
Pet exposure	44.8	32.4	38.6
Urban environment	63.8	58.5	63.1
Current asthma control, ACQ			
Well controlled	69.6	59.7	36.6*
Partially controlled	27.5	27.3	23.2*
Not well controlled	2.9	13.0	40.3*
Mean (s.d.)	1.4 (0.5)	1.6 (0.7)	2.1 (0.9)*

For the definition of long-term asthma control phenotypes (asthma control in previous 3 months), data were available for 88.0% of our study population ($n = 464$).

OCS, oral corticosteroids; SABA, short-acting beta-agonist; LABA, long-acting beta-agonist; LTRA, leukotriene antagonist; AB, antibiotics; ACQ, asthma control questionnaire.

* $p < 0.05$.

** $p < 0.10$.

tially controlled in the previous season compared to children with well-controlled asthma. Therapy adherence and inhalation technique were not associated with asthma control. The characteristics of the study population when using the definition for overall asthma control in the past year did not change our results (Appendix 1).

Discussion

Our data show that there exists a relatively low prevalence of currently uncontrolled asthma (21%) in a cohort of pediatric asthma medication users. At the same time, long-term uncontrolled asthma rates were higher, and agreement between current and long-term asthma control was limited. Of interest, we additionally showed significant seasonal variation in asthma control.

Currently uncontrolled asthma rates (asthma control during the week previous to the pharmacy visit) were low in our study. Less than a quarter of the population experienced symptoms in the past week. Previous cross-sectional studies in pediatric patients with asthma showed much higher rates of uncontrolled asthma in the week previous to the survey with rates ranging from 37% to 76% (15–18). A possible explanation for this discrepancy might be that parents who participated in the PACMAN cohort study may not have scheduled a study visit in the pharmacy while their child experienced a period of uncontrolled asthma. This may be the case because one of the conditions for participation in the PACMAN cohort study was that asthma medication should be withheld the day before the pharmacy visit to allow accurate lung function measurements. When a child experiences a period with severe symptoms and thus uncontrolled asthma, parents may not be willing to stop medication and therefore reschedule the pharmacy appointment. This may have resulted in overestimation of current asthma control in our study population. This limitation is probably shared with other observational studies.

Almost half of the population experienced uncontrolled asthma during the previous season. When defining asthma control over the past year (12 months), this did not change our results. This is in line with other studies on long-term asthma control, showing uncontrolled asthma rates between 44% and 59% in asthmatic children (1, 19–21). Our study showed significant seasonal differences in asthma control, controlled asthma rates being highest in summer and lowest in autumn. Other studies also reported a low prevalence of asthma symptoms in summer and a peak in symptom frequency and severity beginning in autumn (22, 23). This seasonality in asthma may result from an increase in exposure to respiratory viruses, house dust mite, air pollution, and pollen in autumn and spring (24, 25). Because of the variability in asthma control over time, it is very important to stratify for seasonality in asthma control instead of only evaluating current asthma control.

As described earlier, we observed limited agreement between current and long-term asthma control, agreement being especially low for not well-controlled asthma (low specificity). By using data concerning current asthma control

(symptoms during the past week), a patient's asthma control might therefore be easily overestimated.

Based on our findings, we will use long-term asthma control based on the GINA criteria for the previous season as definition for future studies in the PACMAN cohort. We did not show differences in agreement when using long-term asthma control over the past year or long-term asthma control defined as control during the previous season (3 months). For both definitions, agreement with current control measured by means of the ACQ was limited. To decrease the risk of recall bias, because parents were asked retrospectively about their child's respiratory symptoms, asthma control during the season preceding the pharmacy visit was used as definition for long-term asthma control in stead of control over the past year. As older children may better describe to their parents the symptoms that occur, one might expect better agreement between current and long-term asthma control for older children. However, we did not observe improved agreement between these two definitions for older children (data not shown).

We have described the characteristics of the study population using this definition of long-term asthma control (previous season) and show that children with not well-controlled asthma were more often from non-Dutch descent. This is in line with the study from Urbanus-van Laar et al. (26) who showed that ethnic minorities experience poorer asthma health outcomes in the Netherlands. This might be due to the presence of a cultural difference and language barrier in consultations between the physicians and patients. Children with uncontrolled asthma used more frequent additional respiratory medication, such as antibiotics, leukotriene receptor antagonists, and oral steroids in our study. Furthermore, long-term uncontrolled children also experienced more often poor current asthma control, which may reflect the severity of disease and the persistence of respiratory symptoms. Our study suggests that this was not because of poor treatment adherence, because therapy adherence and inhalation technique were not associated with asthma control.

This is one of the first studies reporting on the comparison between current and long-term asthma control defined in an observational epidemiological study. Many other observational studies only have data on respiratory symptoms concerning the past 1 or 2 weeks. In contrast to these studies, we were able to define long-term control of asthma symptoms, which may differ from current asthma control because of factors such as seasonality. Furthermore, the response rate in our study was high and comparable with other cohort studies including a physical examination in pediatric patients (27–29).

Using two different methods (ACQ vs. categorical scale such as GINA criteria) to assess the same outcome could have affected the presented results. The ACQ is an ordinal measurement scale, which is based on intensity and impact of asthma symptoms, while categorical scales such as GOAL or GINA criteria are mainly based on symptom frequency. However, previous studies have shown that both methods of assessing asthma control can be used to differentiate between patients with controlled and uncontrolled asthma symptoms

(30, 31). Therefore, we do not think that the use of different instruments has affected our study results. O'Byrne and colleagues (7) showed that the ACQ was more sensitive to changes in asthma control over time, which may make this tool more valuable in a clinical setting or clinical trials to evaluate medication efficacy or improvement after treatment.

A possible limitation of our study is that symptoms were based on parental reporting. Parents may not always be able to give an accurate estimate of their child's health status. However, this limitation is shared with previous studies and resembles daily clinical practice, where asthma management in young children is also based on parental reporting. Another potential limitation of the study is the large number of missing phone numbers in the pharmacies: more than a quarter of the patients selected from the pharmacies could not be invited for participation because of missing phone numbers. Floor-Schreudering et al. (32) also reported this poor documentation of contact information in pharmacies. We do not anticipate that selection bias was a problem, as a previous pilot study within the PACMAN cohort showed that mean age and gender did not differ between children from families that agreed or refused to participate in the PACMAN cohort study (9). In addition, we compared the PACMAN study population with the general population (children aged 4–12 years) and found that approximately 8% of the children characterized in four randomly selected pharmacies filled a prescription for asthma medication in the past 2 years. The latter is in line with the prevalence of asthma and the prevalence of asthma medication use in childhood (33, 34). Approximately one-third of the children who filled asthma medication prescriptions in the past 2 years were current users and selected for participation in the PACMAN cohort study. This is also in line with previous studies, which showed that discontinuation of asthma medication use in childhood is high (35, 36).

In conclusion, we showed substantial seasonal variation in asthma control. Furthermore, we have demonstrated that the congruence between current and long-term asthma control is limited. This leads us to conclude that a patient's asthma control may be easily overestimated when using data concerning current asthma control (symptoms during the past week). Therefore, to properly define asthma control and treatment response in observational studies, it is important to assess asthma control over a longer period of time, or at least to stratify or adjust for the different seasons as we have shown in this study. Our findings may also be of relevance for daily clinical practice.

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Appendix 1. Description of study population (long-term asthma control previous year)

	Controlled N = 130	Partly controlled N = 172	Uncontrolled N = 209
General characteristics			
Gender, male	63.9	58.7	59.8
Age, mean (s.d.)	8.4 (2.5)	8.4 (2.6)	8.3 (2.4)
Dutch ethnicity	90.3	94.4	85.1
Doctor-diagnosed asthma	85.0	73.9	72.4
Medication use			
OCS	3.1	6.4	12.9*
SABA	76.9	85.5	89.5*
LABA	22.3	29.7	24.9
LTRA	2.3	8.1	12.4**
AB	27.1	33.9	47.8*
Good adherence	61.5	48.7	59.8*
Good inhalation technique	86.9	82.0	82.3
Environmental factors			
Smoke exposure	11.5	7.0	6.7
Pet exposure	38.8	43.6	37.5
Urban environment	64.3	59.7	62.5
Current asthma control, ACQ			
Well controlled	75.6	57.2	36.7*
Partially controlled	19.7	27.1	26.1*
Not well controlled	4.7	15.7	37.2*
Mean (s.d.)	1.3 (0.6)	1.6 (0.8)	2.1 (0.8)*

For the definition of long-term asthma control phenotypes (asthma control in previous year), data were available for 97.0% of our study population (n = 511).

OCS, oral corticosteroids; SABA, short-acting beta-agonist; LABA, long-acting beta-agonist; LTRA, leukotriene antagonist; AB, antibiotics; ACQ, Asthma Control Questionnaire.

*p < 0.05.

**p < 0.10.