

ENVIRONMENTAL DETERMINANTS

Asthma Symptoms in Pediatric Patients: Differences throughout the Seasons

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Introduction. Seasonal variation in asthma has been widely recognized. The aim of this study was to describe seasonal patterns of asthma symptoms and asthma medication use in a cohort of pediatric asthma medication users and to study determinants of seasonal childhood asthma. **Methods.** For this study, 602 children participating in the Pharmacogenetics of Asthma medication in Children: Medication with Anti-inflammatory effects) cohort were included. Parents were asked about their child's respiratory symptoms and quick-reliever medication use over the past year. Logistic regression analysis was used to study determinants of seasonality in asthma control (the level of disease control based on symptoms, limitations in activities, and rescue medication use). **Results.** There was a decline in asthma symptoms and asthma medication use during the summer period and a peak occurred from autumn to spring. The prevalence of wheeze ranged from 32% in summer to 56% in autumn. The prevalence of respiratory symptoms and medication use was significantly lower during summer ($p < .0001$). Oral steroids and antibiotics use and strong parental necessity beliefs were associated with uncontrolled asthma, regardless of seasonality. Allergic rhinitis was associated with an increased risk of uncontrolled asthma during spring [odds ratio (OR): 1.9; 95% confidence interval (CI): 1.3–2.8] and summer (OR: 1.9; 95% CI: 1.2–3.0). Eczema was associated with a higher risk of uncontrolled asthma during autumn (OR: 1.5; 95% CI: 1.0–2.2) and winter (OR: 1.3; 95% CI: 1.0–1.9). **Conclusion.** We showed seasonal patterns in asthma symptoms and medication use. Associations were shown between allergic rhinitis and asthma control during spring/summer and eczema was associated with uncontrolled asthma during autumn/winter. Seasonality in asthma morbidity and health-care use is most likely associated with atopic constitution and viral infections, which are common during fall, winter, and spring.

Keywords allergic rhinitis, asthma, children, medication use, PACMAN, seasonality

INTRODUCTION

Asthma is the most common chronic disorder in childhood and one of the leading causes for pediatric emergency department visits (1, 2). Seasonal patterns in asthma medication use (3) and pediatric asthma hospital admissions have been described previously (4). A decline in medication use and hospital admissions was found during the summer period (5). A review article of Sears and Johnston (6) described a peak in hospitalization for pediatric asthma patients in Canada in September (during the period 1990–2004).

It has been suggested that variable environmental factors might account for the observed seasonal patterns in asthma symptoms and related health-care utilization. Previous studies have shown associations between climate factors (i.e., temperature, humidity, rainfall, barometric pressure) and asthma exacerbations (4, 7, 8). In contrast, Gergen et al. (9) found no correlation between seasonal

patterns of asthma and atopy, environmental tobacco smoke exposure, and air pollutants.

The purpose of this study was to describe possible seasonal patterns of asthma symptoms in a cohort of pediatric asthma medication users. In addition, we investigated determinants of asthma control and investigated whether there were seasonal differences in predictors of asthma control status. This might be of interest for the treating physician when assessing asthma control and appropriate treatment strategies. Better understanding of seasonal risk factors could be useful for lifestyle changes and prevention of asthma (exacerbations).

METHODS

Study Population and Setting

Recruitment of the Pharmacogenetics of Asthma medication in Children: Medication with Anti-inflammatory effects (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 (10). Briefly, children aged 4–12 years who are regular users (≥ 3 prescriptions within the last 2 years and ≥ 1 prescription

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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. The PACMAN study has been approved by the Medical Ethics Committee of the University Medical Center Utrecht.

During the pharmacy visit, parents filled in a questionnaire to collect information regarding general health, asthma and respiratory symptoms, medication use, adherence, parent's beliefs about medicines, and environmental and socio-demographic factors. Furthermore, the child's inhalation technique was scored with an inhaler-specific inhalation control checklist (10).

Seasonal Differences in Asthma Symptoms and Medication Use

Parents were asked about their child's airway symptoms over the past 12 months. The questionnaire completed during the pharmacy visit contained questions regarding the presence of asthma symptoms, limitations in activities, sleep disturbances, and extra medication use during the different seasons in the past 12 months. (For example: "Has your child had tightness of the chest or shortness of breath during summer (June–August)?") 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.) The prevalence of asthma symptoms (wheeze, cough, and shortness of breath), sleep disturbances, limitations in daily activities, and rescue medication use was compared for the four seasons.

Definition of Asthma Control

Asthma control was defined based on the international Global Initiative for Asthma guidelines (11). First, asthma control was defined based on the presence of symptoms in a specific season. Uncontrolled asthma was defined as ≥ 3 of the following items present in a specific season: (1) daytime asthma symptoms, (2) nighttime asthma symptoms, (3) limitations in daily activities, and (4) rescue medication use. Subsequently, this initial definition of asthma control was adjusted for the frequency of symptoms during a season. Children with frequent symptoms (daily or weekly symptoms during a season) were classified as uncontrolled; children with monthly symptoms were classified as partially controlled; and children who experienced symptoms rarely (less than once a month) during a season were classified as well controlled.

Determinants of Uncontrolled Asthma throughout the Seasons

We studied the influence of child characteristics [gender (male vs. female), ethnicity (Dutch (non-immigrant) vs. non-Dutch (immigrant)), presence of eczema and allergic rhinitis (yes/no)], medication use [adherence (good vs. poor), inhalation technique (good vs. poor), parental perception toward medication use, course of antibiotics and oral steroids during past year (yes/no)], and environmental factors [environmental tobacco smoke exposure (yes/no), pet exposure (yes/no), and living environment (urban vs. rural environment)] on asthma control.

Parent-reported adherence was assessed by using the Medication Adherence Report Scale (MARS) comprising five questions on medication use behavior (12). The MARS was dichotomized using a cut-off point for the sum score: a score of <21 was considered as poor adherence (13, 14). Inhalation technique was scored using a validated questionnaire developed by van der Palen et al. (15). Parental perception toward medication use include beliefs about medication (both parental necessity beliefs and concerns about their child's medication use) and knowledge about asthma medication. Beliefs about medicines were assessed using the validated *Beliefs about Medicines Questionnaire* (BMQ). This questionnaire comprises two scales with each five questions: the necessity scale and the concerns scale. All items are measured on a 5-point Likert scale (16). The questions on necessity beliefs focus on the need for medication use to maintain present and future health. The questions on concerns focus on concerns about potential adverse consequences of medication use. Higher scores on the specific scales indicate stronger need beliefs or concerns. BMQ scores greater than scale midpoint (>15) were considered as stronger beliefs (14).

Statistical Analysis

Chi-square test was used to compare frequency data. Logistic regression analysis was used to study determinants of uncontrolled asthma. Odds ratios (ORs) and their corresponding 95% confidence intervals (CIs) were calculated. Univariate analyses were performed to study individual determinants of uncontrolled asthma and multivariate analysis was performed to assess independence of the associated factors. The only variables associated with uncontrolled asthma ($p < .10$) in the univariate analyses were included in the multivariate analysis. The inclusion of potential confounders in the logistic regression model was based on the assessment of the influence of each potential confounder on the OR for the association between the univariate-associated factors and uncontrolled asthma. The child's gender, ethnicity, parental beliefs about medicines, exposure to pets, environmental tobacco smoke, and living environment were all considered potential confounding factors. Age was included as covariate in the model. Potential confounding factors were included in the multivariate model if they induced a 10% change or more in the crude

regression coefficient for the determinant of interest (17). All analyses were performed using SAS Version 9.1 (SAS Institute, Cary, NC, USA).

RESULTS

Study Population

Until February 2011, 2114 children were selected from 67 Dutch pharmacies. For 595 (28.1%) of these children there was no contact telephone number registered in the pharmacy nor could a telephone number be traced through Internet or a national telephone number service. Another 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 from 82 (12.0%) children due to various reasons (e.g., child was unwilling to participate, parents/children did not show up at the scheduled appointment, or the parents/children were willing to participate, though 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%. The general characteristics of this population are shown in Table 1: 62% of the participants were male and the mean age was 8.3 years. Almost 75% of the children had a doctor's diagnosis of asthma.

Seasonal Differences in Asthma Symptoms and Medication Use

Figure 1 shows the prevalence of reported asthma symptoms and reliever medication use for the entire population over the past year (during the 12 months preceding the pharmacy visit). There was a decline in asthma symptoms (cough, shortness of breath, and wheeze) and rescue medication use during the summer period and a peak occurred from autumn to spring. The prevalence of respiratory symptoms and rescue medication use was significantly lower during the summer

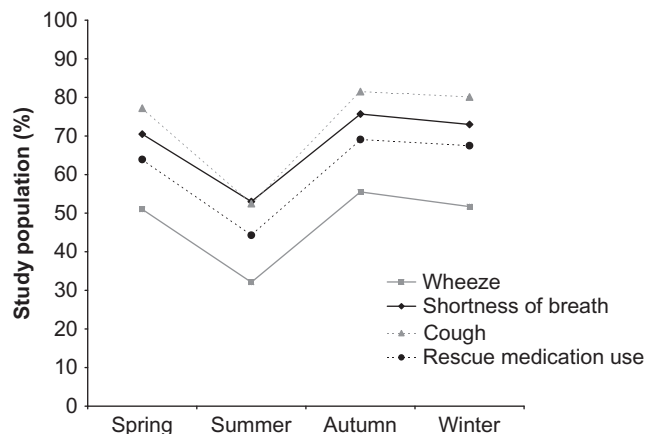


FIGURE 1.—Overall seasonality of asthma symptoms and medication use.

period compared with the other seasons ($p < .0001$). Cough was the most frequently reported respiratory symptom with a prevalence ranging from 53% in summer to 82% during autumn. Wheeze, more specific for asthma, was reported for 32% in summer and ranged to 56% during autumn.

Seasonal variation in wheeze and asthma medication use was evident across both age groups (children aged under 6 years and children aged 6 years and older) (Figure 2A). Figure 2B shows that seasonal variation in both genders is evident and nearly identical. For atopic children, wheeze and rescue medication use were significantly higher ($p < .05$) during spring and summer (Figure 2C).

Determinants of Uncontrolled Asthma

Figure 3 shows asthma control during different seasons. Well-controlled asthma rates ranged from 19% in autumn and winter, 21% in spring to 29% in summer. Uncontrolled asthma rates are lowest in summer (31%) and highest in spring (45%), autumn (48%), and winter (48%). The univariate and multivariate associations between potential determinants and uncontrolled asthma in the different seasons are shown in Tables 2 and 3. Both oral steroids use and antibiotics use during the past year were associated with increased risk of uncontrolled asthma in all seasons. The same was true for parental necessity beliefs toward their child's medication use. Allergic rhinitis was associated with an increased risk of uncontrolled asthma during spring (OR: 1.9; 95% CI: 1.3–2.8) and summer (OR: 1.9; 95% CI: 1.2–3.0). Eczema was associated with a higher risk of uncontrolled asthma during autumn (OR: 1.5; 95% CI: 1.0–2.2) and winter (OR: 1.3; 95% CI: 1.0–1.9).

DISCUSSION

We showed the existence of seasonal variation in respiratory symptoms and medication use in a cohort of pediatric asthma medication users. The prevalence of asthma symptoms (wheeze, shortness of breath, and cough) and rescue medication use was lowest in summer.

TABLE 1.—Characteristics of study population.

Study population (n = 602)	
General	
Male gender (%)	61.6
Age, mean (SD)	8.3 ± 2.5
Caucasian ethnicity (%)	87.4
Clinical characteristics	
Allergic rhinitis ^a (%)	46.1
Eczema ^a (%)	64.9
Food allergy ^a (%)	51.2
Doctor-diagnosed asthma (%)	74.4
Medication use in the past 12 months	
SABA	82.7
ICS	87.5
Antibiotics	36.0
Oral steroids	7.0

Notes: SABA, short-acting beta-agonist; ICS, inhaled corticosteroids.

^aBased on parental reporting in the questionnaire.

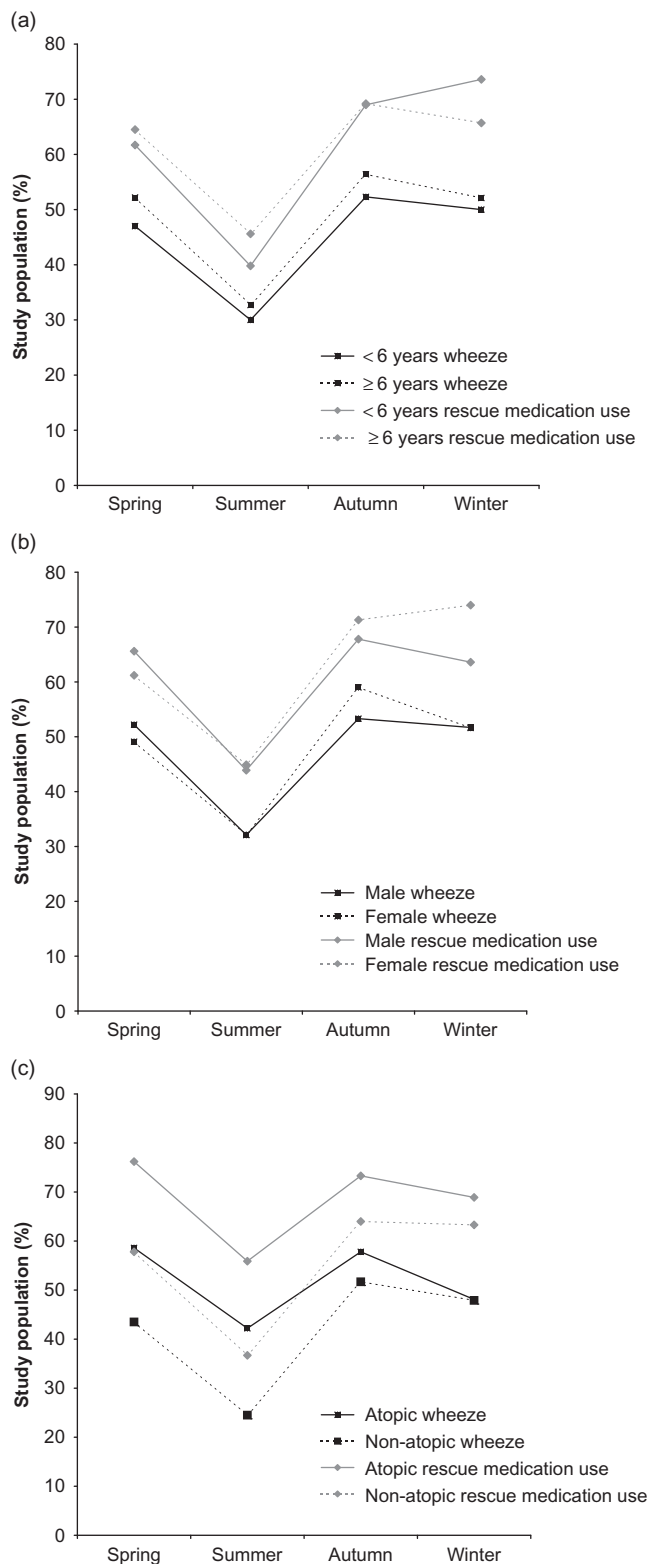


FIGURE 2.—Seasonality of asthma symptoms and medication use by (A) age, (B) gender, and (C) atopic status (a child was considered atopic if one of the following conditions was present: eczema or allergic rhinitis).

Uncontrolled asthma was present in approximately one-third of the children during summer (31%) compared with up to half of the population in spring (46%), autumn (48%), and winter (48%) periods. This is in line with other studies reporting a summer improvement

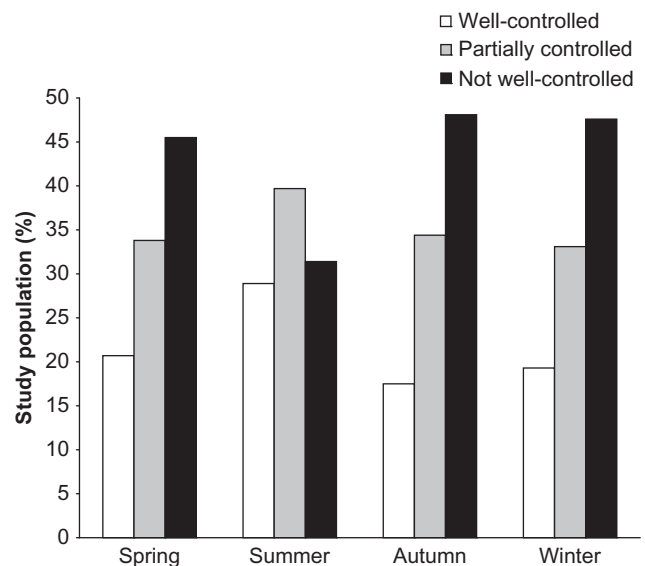


FIGURE 3.—Seasonality of asthma control.

and a clear pattern of fall–winter worsening for asthma symptoms and related health-care utilization (3, 6, 9). Strong parental beliefs toward the need for medication use were associated with a higher risk of uncontrolled asthma in all seasons except summer. Antibiotics use and oral steroids use were also associated with uncontrolled asthma symptoms, regardless of seasonality. During spring and summer, allergic rhinitis was associated with uncontrolled asthma and during autumn and winter eczema was associated with a higher risk of uncontrolled asthma, suggesting that atopic constitution plays an important role in asthma control in these children.

We have shown that parental perception toward medication use is a very important factor in pediatric asthma control. Within the Prevention and Incidence of Asthma and Mite Allergy (PIAMA) cohort we have also studied the determinants of uncontrolled asthma and showed parental necessity beliefs to be associated with uncontrolled asthma (18). This finding was against our expectation, as previous research has shown an association between strong necessity beliefs and higher adherence rates for asthma medication (19) which, in turn, is expected to lead to improved asthma control. However, also in this study, regardless of seasonality, strong parental beliefs toward the necessity of their child's medication use were associated with higher risk of uncontrolled asthma. Therefore, we believe that these strong need beliefs may reflect a population with more severe asthma.

Children with reported oral steroids use and antibiotics use were at an increased risk of uncontrolled asthma. Oral steroids use has been associated with inadequate asthma control (20). Oral steroids are prescribed for treatment of severe exacerbations (11, 21, 22), and antibiotics are used in the treatment of respiratory symptoms such as acute coughing (22). Use of these drugs may reflect more severe, uncontrolled disease.

We found allergic rhinitis to be associated with a higher risk of uncontrolled asthma during spring and

TABLE 2.—Determinants of uncontrolled asthma (uncontrolled vs. controlled): univariate analysis.

	Spring OR (95% CI)	Summer OR (95% CI)	Autumn OR (95% CI)	Winter OR (95% CI)
Child characteristics				
Male gender	1.1 (0.7–1.5)	1.1 (0.7–1.7)	0.7 (0.5–1.0)	0.7 (0.5–1.0)
Dutch ethnicity (non-immigrant)	0.5 (0.3–1.0)	0.5 (0.3–1.1)	0.9 (0.5–1.6)	0.6 (0.3–1.1)
Eczema ^a	1.5 (1.1–2.2)	1.4 (1.0–2.3)	1.7 (1.1–2.4)	1.4 (1.0–2.0)
Allergic rhinitis ^a	2.0 (1.4–2.8)	2.0 (1.3–3.1)	1.1 (0.8–1.6)	1.3 (0.9–1.9)
Medication use				
Good adherence	1.0 (0.7–1.4)	1.2 (0.8–1.8)	1.4 (1.0–2.0)	1.2 (0.8–1.7)
Poor inhalation technique	0.8 (0.5–1.2)	1.0 (0.6–1.8)	1.1 (0.7–1.7)	0.9 (0.6–1.4)
Strong need beliefs ^a	1.9 (1.3–2.7)	1.5 (1.0–2.3)	2.0 (1.4–2.8)	2.0 (1.4–2.9)
Strong concern beliefs ^a	1.5 (1.0–2.3)	1.3 (0.8–2.2)	1.5 (1.0–2.3)	1.8 (1.2–2.8)
Antibiotics	2.0 (1.4–2.9)	1.8 (1.2–2.9)	1.9 (1.3–2.7)	2.7 (1.9–3.9)
Oral steroids	3.7 (1.8–7.7)	3.6 (1.7–7.5)	4.5 (2.0–9.9)	2.2 (1.1–4.5)
Environmental factors				
Environmental tobacco smoke exposure	1.0 (0.6–2.0)	1.5 (0.7–3.2)	0.5 (0.3–1.0)	0.8 (0.4–1.6)
Pets	1.0 (0.7–1.4)	1.0 (0.7–1.6)	1.2 (0.9–1.7)	1.3 (0.9–1.9)
Urban environment	0.9 (0.6–1.2)	1.5 (0.7–3.2)	1.0 (0.7–1.4)	1.5 (1.0–2.1)

Notes: OR, odds ratio; CI, confidence interval. Values in bold indicate significance at $p < 0.05$.

^aBased on parental reporting in the questionnaire.

TABLE 3.—Determinants of uncontrolled asthma (uncontrolled vs. controlled): multivariate analysis.

	Spring OR (95% CI)	Summer OR (95% CI)	Autumn OR (95% CI)	Winter OR (95% CI)
Child characteristics				
Male gender	—	—	0.7 (0.5–1.1)	0.7 (0.5–1.0)
Dutch ethnicity (non-immigrant)	0.7 (0.4–1.3)	—	—	—
Eczema ^a	1.2 (0.8–1.8)	1.1 (0.7–1.9)	1.5 (1.0–2.1)	1.3 (1.0–1.9)
Allergic rhinitis ^a	1.9 (1.3–2.8)	1.9 (1.2–3.0)	—	—
Medication use				
Good adherence	—	—	—	—
Poor inhalation technique	—	—	—	—
Strong need beliefs ^a	1.7 (1.1–2.5)	1.1 (0.7–1.9)	1.8 (1.3–2.6)	1.8 (1.2–2.6)
Strong concern beliefs ^a	1.1 (0.7–1.7)	—	1.4 (0.9–2.1)	1.4 (0.9–2.2)
Antibiotics	2.2 (1.4–3.3)	1.8 (1.1–3.1)	1.8 (1.2–2.6)	2.8 (1.9–4.0)
Oral steroids	2.8 (1.3–6.1)	3.4 (1.5–7.9)	4.4 (2.0–9.9)	1.6 (0.8–3.3)
Environmental factors				
Passive smoking	—	—	0.4 (0.2–1.1)	—
Pets	—	—	—	—
Urban environment	—	—	—	1.5 (1.0–2.1)

Notes: OR, odds ratio; CI, confidence interval. Values in bold indicate significance at $p < 0.05$.

^aBased on parental reporting in the questionnaire.

summer periods. During these months, exposure to grass pollen is highest which may trigger the allergic reaction observed in allergic rhinitis. The majority of children with asthma also have allergic rhinitis (23). Both conditions are characterized by inflammation of the respiratory mucosa, and due to their mechanistic intertwine one condition can exacerbate the other (24). It has been shown that asthmatic children with allergic rhinitis have more hospitalizations and more frequent emergency department visits compared with children without allergic rhinitis (25). Allergic rhinitis might therefore be a marker for more difficult-to-control asthma and poorer asthma outcomes. Therefore, treating allergic rhinitis may result in better asthma outcomes (26). Furthermore, Erbas et al. (27) showed that high levels of airborne grass pollen, which may cause the allergic reaction observed in patients

with allergic rhinitis, influenced hospital admissions for asthma. Eczema, also an allergic disorder, was associated with uncontrolled asthma during autumn and winter. Rhinitis is more common in spring, while eczema exacerbations are more common in fall and winter. This finding, together with allergic rhinitis associations with uncontrolled asthma during spring/summer, suggests that an atopic constitution plays an important role in asthma control.

Besides the importance of atopy, the seasonal pattern of respiratory symptoms and asthma medication use found in this study may also be attributed to viral infections caused by influenza as an additional factor. Olenec et al. (28) showed that most asthmatic children in their study were infected with viruses during the peak common cold seasons (spring and fall). These viral infections

were associated with loss of asthma control. It is known that primary care visits for respiratory disorders are driven primarily by viral circulations. Winter visits were threefold higher than summer visits as shown in the study of Moineddin et al. (29). Increased severity of asthma morbidity may be driven primarily by respiratory viruses (rhinovirus in late summer/early fall) and factors related to holiday season such as undertreatment of symptoms during periods with lack of daily routine. Furthermore, school return may be an important reason for a peak after summer: school return may induce stress which can lead to more severe symptoms, and re-exposure to viral infections in the school environment may contribute to this peak (6).

One of the strengths of our study was the availability of information on asthma symptoms for the different seasons over the past year. Many observational studies only have data on respiratory symptoms concerning the past month or the past week. In contrast to these studies, we were able to study the presence of asthma symptoms over the past year and were able to stratify for the different seasons. Another strength of the PACMAN cohort study is that we included pediatric patients in the primary care setting. This has the advantage that we have a cohort which includes a very broad range of asthmatics and not only focuses on children in a specialized care group (lung physician/pediatrician) as most children are also treated within the primary care setting. Furthermore, the response rate in our study was high and comparable with other Dutch cohort studies including a physical examination in pediatric patients (30, 31).

One of the limitations of our study was that symptoms were based on parental report. Parents may not always be able to give an accurate estimate of their child's asthma symptoms and medication use as described by Dell et al. (32). Recall bias might have been a problem as parents were asked retrospectively about their child's respiratory symptoms. However, this resembles daily clinical practice, where asthma management in young children is also based on parental reporting of symptoms. Furthermore, most children were included during spring or autumn. This is probably due to the holiday seasons in both summer and winter.

CONCLUSION

The current study showed seasonal patterns in both the prevalence of asthma symptoms and the rescue medication use. We have found uncontrolled asthma to be associated with parental perception toward medication use and use of oral steroids and antibiotics, regardless of seasonality. Furthermore, we showed associations between allergic rhinitis and asthma control during spring and summer and between eczema and asthma control during autumn and winter. Thus, atopic constitution is associated with control of asthma symptoms. Atopic children might be more sensitive to seasonal influences, such as increased allergen exposure during spring. Seasonality in asthma morbidity and health-care use

is most likely associated with exacerbations caused by allergic rhinitis and viral infections, which are common during fall, winter, and spring.

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DECLARATION OF INTEREST

The authors declare no conflicts of interest. The authors alone are responsible for the content and writing of this article.

REFERENCES

1. O'Connell EJ. The burden of atopy and asthma in children. *Allergy* 2004; 59(Suppl. 78):7–11.
2. Masoli M, Fabian D, Holt S, Beasley R. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 2004; 59(5):469–478.
3. Butz AM, Thompson RE, Tsoukleris MG, Donithan M, Hsu VD, Mudd K, Zuckerman IH, Bollinger ME. Seasonal patterns of controller and rescue medication dispensed in underserved children with asthma. *J Asthma* 2008; 45(9):800–806.
4. Xirasagar S, Lin HC, Liu TC. Seasonality in pediatric asthma admissions: the role of climate and environmental factors. *Eur J Pediatr* 2006; 165(11):747–752.
5. Han YY, Lee YL, Guo YL. Indoor environmental risk factors and seasonal variation of childhood asthma. *Pediatr Allergy Immunol* 2009; 20(8):748–756.
6. Sears MR, Johnston NW. Understanding the September asthma epidemic. *J Allergy Clin Immunol* 2007; 120(3):526–529.
7. Hashimoto M, Fukuda T, Shimizu T, Watanabe S, Watanuki S, Eto Y, Urashima M. Influence of climate factors on emergency visits for childhood asthma attack. *Pediatr Int* 2004; 46(1):48–52.
8. Mireku N, Wang Y, Ager J, Reddy RC, Baptist AP. Changes in weather and the effects on pediatric asthma exacerbations. *Ann Allergy Asthma Immunol* 2009; 103(3):220–224.

9. Gergen PJ, Mitchell H, Lynn H. Understanding the seasonal pattern of childhood asthma: results from the National Cooperative Inner-City Asthma Study (NCICAS). *J Pediatr* 2002; 141(5):631–636.
10. Koster ES, Raaijmakers JA, Koppelman GH, Postma DS, van der Ent CK, Koenderman L, Bracke M, Maitland-van der Zee AH. Pharmacogenetics of anti-inflammatory treatment in children with asthma: rationale and design of the PACMAN cohort. *Pharmacogenomics* 2009; 10(8):1351–1361.
11. Global Initiative for Asthma: global strategy for asthma management and prevention report, 2009. Available from <http://www.ginasthma.org/>
12. Horne R, Weinman J. Self-regulation and self-management in asthma: exploring the role of illness perceptions and treatment beliefs in explaining non-adherence to preventer medication. *Psychol Health* 2002; 17(1):17–32.
13. Menckeberg TT (Thesis). Adherence to Inhaled Corticosteroids and Patient Perception: Towards a Better Understanding and Individualised Care. Utrecht: Utrecht University, 2008.
14. Menckeberg TT, Bouvy ML, Bracke M, Kaptein AA, Leufkens HG, Raaijmakers JA, Horne R. Beliefs about medicines predict refill adherence to inhaled corticosteroids. *J Psychosom Res* 2008; 64(1):47–54.
15. van der Palen J, Klein JJ, Kerkhoff AH, van Herwaarden CL, Seydel ER. Evaluation of the long-term effectiveness of three instruction modes for inhaling medicines. *Patient Educ Couns* 1997; 32(1 Suppl.):S87–S95.
16. Horne R, Weinman J. Patients' beliefs about prescribed medicines and their role in adherence to treatment in chronic physical illness. *J Psychosom Res* 1999; 47(6):555–567.
17. Greenland S. Modeling and variable selection in epidemiologic analysis. *Am J Public Health* 1989; 79(3):340–349.
18. Koster ES, Wijga A, Koppelman GH, Postma DS, Brunekreef B, de Jongste JC, Smit HA, Hoekstra MO, Raaijmakers JA, Maitland-van der Zee AH. Uncontrolled asthma at age 8: the importance of parental perception towards medication. *Pediatr Allergy Immunol* 2011; 22:462–468.
19. Conn KM, Halterman JS, Lynch K, Cabana MD. The impact of parents' medication beliefs on asthma management. *Pediatrics* 2007; 120(3):e521–e526.
20. Turktaş H, Mungan D, Uysal MA, Oguzulgen K. Determinants of asthma control in tertiary level in Turkey: a cross-sectional multicenter survey. *J Asthma* 2010; 47(5):557–562.
21. Bacharier LB, Boner A, Carlsen KH, Eigenmann PA, Frischer T, Gotz M, Helms PJ, Hunt J, Liu A, Papadopoulos N, Platts-Mills T, Pohunek P, Simons FE, Valovirta E, Wahn U, Wildhaber J; European Pediatric Asthma Group. Diagnosis and treatment of asthma in childhood: a PRACTALL consensus report. *Allergy* 2008; 63(1): 5–34.
22. Bindels PJE, van der Wouden JC, Ponsioen BP, Brand PL, Salome PL, van Hensbergen W, Van Hasselt PA, Steenkamer TA, Grol MH. NHG-Standaard Astma bij kinderen. *Huisarts Wetenschap* 2006; 49(11): 557–572.
23. Hamouda S, Karila C, Connault T, Scheinmann P, de Blic J. Allergic rhinitis in children with asthma: a questionnaire-based study. *Clin Exp Allergy* 2008; 38(5):761–766.
24. Nathan RA. Management of patients with allergic rhinitis and asthma: literature review. *South Med J* 2009; 102(9):935–941.
25. Kang HY, Park CS, Bang HR, Sazonov V, Kim CJ. Effect of allergic rhinitis on the use and cost of health services by children with asthma. *Yonsei Med J* 2008; 49(4):521–529.
26. Thomas M. Allergic rhinitis: evidence for impact on asthma. *BMC Pulm Med* 2006; 6(Suppl. 1):S4.
27. Erbas B, Chang JH, Dharmage S, Ong EK, Hyndman R, Newbiggin E, Abramson M. Do levels of airborne grass pollen influence asthma hospital admissions? *Clin Exp Allergy* 2007; 37(11): 1641–1647.
28. Olenec JP, Kim WK, Lee WM, Vang F, Pappas TE, Salazar LE, Evans MD, Bork J, Roberg K, Lemanske RF Jr, Gern JE. Weekly monitoring of children with asthma for infections and illness during common cold seasons. *J Allergy Clin Immunol* 2010; 125(5):1001–1006. e1.
29. Moineddin R, Nie JX, Domb G, Leong AM, Upshur RE. Seasonality of primary care utilization for respiratory diseases in Ontario: a time-series analysis. *BMC Health Serv Res* 2008; 8:160.
30. Eijkemans M, Mommers M, de Vries SI, van Buuren S, Stafleu A, Bakker I, Thijs C. Asthmatic symptoms, physical activity, and overweight in young children: a cohort study. *Pediatrics* 2008; 121(3): e666–e672.
31. Scholtens S, Brunekreef B, Visscher TL, Smit HA, Kerkhof M, de Jongste JC, Gerritsen J, Wijga AH. Reported versus measured body weight and height of 4-year-old children and the prevalence of overweight. *Eur J Public Health* 2007; 17(4):369–374.
32. Dell SD, Foty R, Becker A, Franssen E, Chapman KR. Parent-reported symptoms may not be adequate to define asthma control in children. *Pediatr Pulmonol* 2007; 42(12):1117–1124.

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