Respiratory Medicine (2008) **102**, 1446–1451

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.elsevier.com/locate/rmed

Persistence of asthma medication use in preschool children

Mira G. Zuidgeest [a,b], Henriëtte A. Smit [b,*], Madelon Bracke [a], Alet H. Wijga [b], Bert Brunekreef [c,d], Maarten O. Hoekstra [e], Jorrit Gerritsen [f], Marjan Kerkhof [g], Johan C. de Jongste [h], Hubert G. Leufkens [a], The PIAMA-Study Group

[a] *Division of Pharmacoepidemiology and Pharmacotherapy, Utrecht Institute for Pharmaceutical Sciences (UIPS), Faculty of Science, Utrecht University, P.O. Box 80082, 3508 TB, Utrecht, The Netherlands*
[b] *Centre for Prevention and Health Services Research, National Institute for Public Health and the Environment (RIVM), P.O. Box 1, 3720 BA, Bilthoven, The Netherlands*
[c] *Institute for Risk Assessment Sciences, Utrecht University, P.O. Box 80178, 3508 TD, Utrecht, The Netherlands*
[d] *Julius Centre for Health Sciences and Primary Care, University Medical Centre, P.O. Box 85500, 3508 GA, Utrecht, The Netherlands*
[e] *Centre for Pediatric Allergology, Wilhelmina Children's Hospital, University Medical Centre, P.O. Box 85090, 3508 AB, Utrecht, The Netherlands*
[f] *Beatrix Children's Hospital, University Medical Centre Groningen, University of Groningen, P.O. Box 30001, 9700 RB, Groningen, The Netherlands*
[g] *Department of Epidemiology and Statistics, University of Groningen, P.O. Box 72, 9700 AB, Groningen, The Netherlands*
[h] *Department of Pediatrics, Sophia Children's Hospital, Erasmus University Medical Centre, P.O. Box 2060, 3000 CB, Rotterdam, The Netherlands*

Received 10 January 2008; accepted 15 April 2008
Available online 30 June 2008

KEYWORDS
Adherence;
Asthma;
Asthma medication;
Cohort study;
Pharmacoepidemiology;
Preschool children

Summary
Objective: In young children with asthmatic symptoms diagnostic difficulties lead to use of trials of asthma medication as a diagnostic tool. Our aim is to quantify the persistent use of asthma medication, initiated in the first year of life and identify determinants of this persistent use.
Patients and methods: We identified 165 children within the PIAMA (Prevention and Incidence of Asthma and Mite Allergy) birth cohort who used asthma medication before the age of one. Persistent use was investigated during three years after the first prescription. A Cox regression analysis was performed to identify factors associated with persistent use.
Results: A total of 58.8% of children continued using asthma medication after the first prescription and 10.3% continued during three years. Children with doctor-diagnosed asthma (Hazard

* Corresponding author. Tel.: +31 30 274 3830; fax: +31 30 274 4407.
E-mail address: jet.smit@rivm.nl (H.A. Smit).

0954-6111/$ - see front matter
doi:10.1016/j.rmed.2008.04.003

ratio of discontinuation (HR) = 0.64, 95% CI: 0.45—0.91) or prescribed inhaled corticosteroids in the first year of life (HR of discontinuation = 0.59, 95% CI: 0.40—0.86) were 1.6—1.7 times more likely to continue using asthma medication.
Conclusions: Persistence of asthma medication, prescribed in the first year of life is very low and is positively associated with doctor-diagnosed asthma and use of inhaled corticosteroids. Characterizing persistent users of asthma medication is important to understand prescribing of asthma medication in this age group.

Introduction

When a preschool child with symptoms suggestive of asthma presents at the physician's office, a diagnosis of asthma cannot be made with confidence. [1—4] It is well known that wheezing at a young age may not only be due to asthma but also to other, more transient, respiratory conditions. [2—6] Only a minority of wheezing children will develop persistent symptoms and will, therefore, be diagnosed as having asthma.[7—10] However, despite this diagnostic uncertainty, asthma medication is often prescribed to wheezing infants. Moreover, the response to asthma medication itself is widely used as a diagnostic tool to strengthen or reject the possible diagnosis of asthma.[3,5,11,12] The GINA guidelines state that 'a trial of asthma medication is probably the most confident way to make a diagnosis on asthma in children'.[11] The rationale behind the trial treatment is that young children with wheezing but no underlying asthmatic disease are expected not to respond to treatment and will, therefore, discontinue treatment after evaluation of the effect. It is not known how often infants initiating such trial treatment benefit from the asthma medication and, therefore, continue medication use.[13] Notwithstanding the fact that asthmatic symptoms over time influence persistence of medication use, some patient characteristics, already known at start of asthma medication therapy, might be predictive of persistent asthma medication use in preschool children. If so, this could aid the decision whether or not to start a trial of asthma medication in a preschool child. The objective of this study is to quantify persistence of use of asthma medication in preschool children and identify possible determinants of persistence of use, which can be assessed at start of therapy.

Methods

Study design and study population

For this study we identified 165 children from the PIAMA (Prevention and Incidence of Asthma and Mite Allergy) study, who received asthma medication before the age of one.

The PIAMA study is a prospective birth cohort study among 4146 children. The design of the PIAMA study has been described in detail elsewhere.[14] In short, the participating children are born between July 1996 and October 1997. They were recruited from the general population through prenatal healthcare clinics in three different regions of the Netherlands. Data on respiratory and allergic symptoms, potential risk factors for asthma and allergy and demographic factors were collected by postal questionnaires. Parents were sent a questionnaire during the last trimester of pregnancy, at the child's age of three months and annually thereafter. Longitudinal data on medication use have been collected at age four through prescription data from community pharmacy records. In the Netherlands, pharmacy records are virtually complete with regard to drugs dispensed to patients.[15]

Asthma medication and persistence of use

Medical drug prescriptions were registered according to the Anatomical Therapeutic Chemical (ATC) Classification system.[16] All medicines with ATC code R03 were considered to be asthma medication: inhaled short acting β2-agonists (SABA), oral short acting β2-agonists, inhaled long acting β2-agonists (LABA), inhaled corticosteroids (ICS), inhaled cromones, anticholinergics and montelukast. Oral corticosteroids (H02AB) were not classified as primary asthma treatment. Persistence of use of asthma medication was investigated during a time-window of three years, using discontinuation rates.[17] The index date was defined as the date of the first prescription for asthma medication. Discontinuation of treatment was defined as the occurrence of a treatment gap of more than 365 days between one dispensing of asthma medication and a subsequent dispensing during the study time-window. Time to discontinuation was calculated as the number of days from the index date to the date of the last dispensing before the gap of more than 365 days + a pre-specified time period of 90 days (which is the maximum duration of a single prescription in the Netherlands).

A wide treatment gap of 365 days is chosen because we want to quantify the amount of children receiving an initial prescription for asthma medication without needing asthma medication regularly over the next couple of years and compare these children with the ones who might still have intermittent or seasonal complaints but do return to use of asthma medication at least once every year. If the aim had been to determine continuing availability of asthma medication the allowed treatment gap would have been much smaller.

Statistical analysis

Persistence of use was examined using survival analysis, the endpoint being discontinuation of asthma medication. The overall persistence of use was determined using Kaplan—Meier analyses. Univariate and multivariate Cox regression

models were used to calculate unadjusted and adjusted hazard ratios and 95% confidence intervals (CI) for discontinuation of asthma medication use. The hazard ratio is the effect of a variable on the hazard or risk of an event. In our study the hazard ratio is the ratio of the rates at which children are discontinuing asthma medication in the two compared groups. In terms of interpretation, a hazard ratio of 0.5 for boys would mean that at any point in time half as many boys are discontinuing asthma medication proportionally compared to girls. One has to keep in mind that a variable with a low hazard ratio gives proportional a low likelihood of discontinuation; such a variable is, therefore, a strong predictor of persistence of treatment.

The following possible determinants of continuation of medication use were investigated, representing patient characteristics (gender, educational level of the parents), severity of symptoms (doctor-diagnosed asthma, prescribing of inhaled corticosteroids, antibiotic use), familial predisposition (allergic status of family members, eczema of the child, use of other allergy medication) and environmental influences (smoke exposure, pet exposure, day care). Because doctor-diagnosed asthma and prescribing of inhaled corticosteroids are expected to be related, an interaction term is added for these two variables. Statistical analyses were performed using SAS, version 9.1 (SAS Institute, Cary, NC).

Results

General characteristics of the study population of 165 children who started using asthma medication in their first year of life are shown in Table 1. Male gender was predominant, with 69.7% boys in our study population. More than half (56%) of the study population had at least one parent with reported atopy (not shown in Table 1) and in 13% both parents were atopic. The most commonly used asthma medications were β2-agonists, prescribed to more than 80% of the study population and use of inhaled corticosteroids was seen in 40%. Almost 70% of the study population reported wheezing in the first year of life of which 30% also reported cough. Cough without wheeze was reported by 11% of the study population. The majority (57.6%) did not have parental-reported doctor-diagnosed asthma in the year asthma medication use was initiated.

Overall persistence of asthma medication use was low, falling below 15% after three years of follow-up (Fig. 1). Since 41.2% of the study population received a single prescription for asthma medication, a steep fall in persistence can be observed after approximately three months of treatment. After these three months, a steady decline in persistence was seen, becoming less steep around 16 months of follow-up and reaching the level of 10.3% at the end of follow-up.

Results from the univariate Cox regression analyses are shown in Table 2. Since the hazard ratios are for discontinuation of asthma medication, hazard ratios below 1.0 imply a higher persistence of asthma medication use. Most characteristics, including an allergic father, the use of antibiotics, eczema and pet exposure were not related to continuing use of asthma medication. Doctor-diagnosed asthma, prescribed inhaled corticosteroids and the allergic status of the mother were significantly associated with persistent use of asthma medication. After adjusting for the other significant variables and gender (see Table 3) only doctor-diagnosed asthma and use of inhaled corticosteroids remain significantly associated. Children with doctor-diagnosed asthma within the 1st year of life were 1.6

Table 1 General characteristics of the study population: children receiving asthma medication in the 1st year of life.

Patient characteristics	($n = 165$)
Sex, % boys[b]	69.7
Mean age at end of follow-up, yrs (SD)	3.6 (0.19)
Mother's educational level, %[c,f]	
Low	23.0
Intermediate	44.2
High	32.7
Father's educational level, %[c,f]	
Low	24.7
Intermediate	39.5
High	35.8
Ethnicity, % Dutch[d]	94.6
Any other siblings, %[c]	70.9
Allergic sibling(s), %[c]	33.9
Allergic mother, %[a]	32.1
Allergic father, %[b]	37.5
Parental asthma, %[a,b,g]	20.0
Mother smoking during pregnancy, %[b]	14.1
Smoke exposure in the home, %[c]	20.7
Pet exposure in the home, %[c]	46.7
Day care, %[c]	33.3
Wheeze, %[c]	68.9
Recurrent wheeze, %[c,h]	34.9
Dry cough at night, without cold, %[c]	40.4
Doctor-diagnosed asthma, %[c]	42.4
Doctor-diagnosed bronchitis, %[c]	52.8
Lower respiratory tract infection(s), %[c,i]	56.9
Eczema, %[c]	23.3
Asthma medication, %[e,j]	100
Inhaled/oral β2-agonists	82.4
Inhaled corticosteroids	41.8
Parasympathicolytics	40.0
Oral corticosteroids, %[e]	1.8
Antibiotics, %[e]	58.2
Other allergy medication, %[e,k]	50.9

[a] Data collected from questionnaires at the time of pregnancy.
[b] Data collected from questionnaires at the age of 3 months.
[c] Data collected from questionnaires at the age of 1 year.
[d] Data collected from questionnaires at the age of 2 years.
[e] Data collected from the community pharmacy at the age of 4 years.
[f] Educational level: low = primary, lower vocational and lower general; intermediate = senior high school and intermediate vocational; and high = higher vocational an university.
[g] Father or mother or both reported to have (had) asthma.
[h] Recurrent wheeze: ≥4 episodes wheeze.
[i] Lower respiratory tract infections: bronchitis, pneumonia and pertussis.
[j] Due to our selection criteria the use of asthma medication within the study population is 100%.
[k] Nasal antiallergics, systemic antihistamines, topical corticosteroids and antiallergic eye preparations.

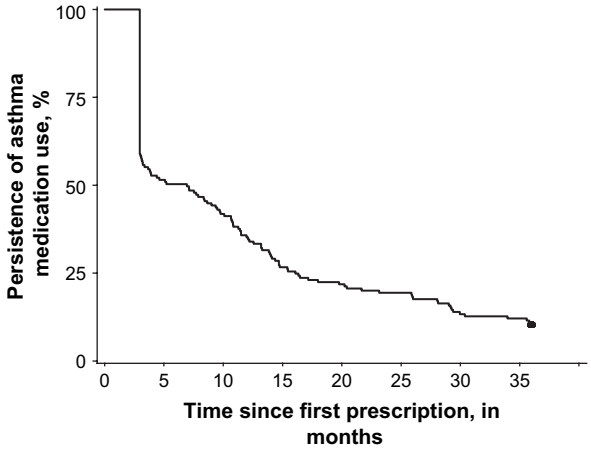

Figure 1 Persistence of asthma medication use within the study population: children receiving asthma medication in the 1st year of life.

times more likely (hazard ratio of discontinuation = 0.64) to continue asthma medication than children without such a diagnosis. The strongest determinant of persistence of use was a prescription for inhaled corticosteroids in the first year of life, with a highly significant hazard ratio of discontinuation of 0.59, rendering children using inhaled corticosteroids almost two times more likely to continue treatment than children not using these drugs. No interaction was found between the variables doctor-diagnosed asthma and inhaled corticosteroid use.

Repeating the multivariate Cox regression, including three dummy variables for the possible combinations of the variables doctor-diagnosed asthma and inhaled corticosteroid use, rendered a significant adjusted hazard ratio of discontinuation of 0.34 (95% CI: 0.25—0.63) for the group of children with both a diagnosis of asthma and use of inhaled corticosteroids. The difference in persistence between children with both doctor-diagnosed asthma and a prescription for inhaled corticosteroids and children without both, is visualized by a Kaplan—Meier curve in Fig. 2. The main difference in persistence between the groups was due to a difference in discontinuation after the first prescription. After this steep fall, the declining trend runs parallel between the compared groups.

Table 2 Univariate analyses of discontinuation of asthma medication use in relation to patient characteristics.

		95% CI for the HR_{crude}	
	HR_{crude}	Lower	Upper
Sex, boys	0.74	0.52	1.04
Mother's educational level	1.03	0.83	1.27
Father's educational level	0.94	0.76	1.16
Doctor-diagnosed asthma	0.56[a]	0.38	0.76
Prescribed ICS	0.52[a]	0.37	0.73
Antibiotics	0.87	0.62	1.20
Allergic mother	0.67[a]	0.47	0.96
Allergic father	1.12	0.80	1.57
Allergic sibling(s)	0.82	0.58	1.16
Parental asthma	0.71	0.47	1.08
Eczema	1.08	0.96	1.23
Allergy medication	0.87	0.63	1.20
Smoke exposure in the home	1.17	0.99	1.38
Pet exposure in the home	0.99	0.72	1.37
Day care	1.16	0.83	1.63

Definition of abbreviations: CI = confidence interval; HR = hazard ratio; and ICS = inhaled corticosteroids.
[a] Significant values $p < 0.05$.

Table 3 Multivariate analyses of discontinuation of asthma medication use in relation to patient characteristics.

		95% CI for the HR_{adj}	
	HR_{adj}	Lower	Upper
Sex, boys	0.75	0.52	1.08
Doctor-diagnosed asthma	0.64[a]	0.45	0.91
Prescribed ICS	0.59[a]	0.40	0.86
Allergic mother	0.82	0.56	1.20

Definition of abbreviations: CI = confidence interval; HR_{adj} = the hazard ratio of the variable adjusted for all other variables in the model; and ICS = inhaled corticosteroids.
[a] Significant values $p < 0.05$.

Discussion

The study described here shows that 58.8% of children initiating asthma treatment before the age of one, continue medication use after the first prescription and only 10.3% is persistent after three years of follow-up. Children with doctor-diagnosed asthma and users of inhaled corticosteroids in the first year of life were 1.6—1.7 times more likely to continue using asthma medication. When both diagnosed with asthma and receiving inhaled corticosteroids, children were three times more likely to continue until the age of 3. No other measures were significantly associated with persistence of asthma medication use.

Our results show that most of the time a trial of asthma medication in very young children does not lead

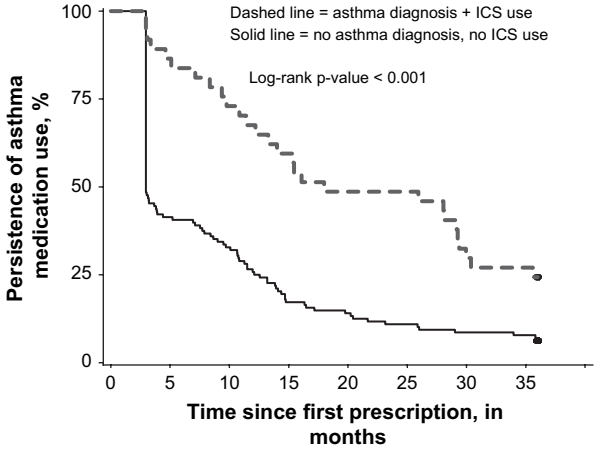

Figure 2 Difference in persistence between children with both an asthma diagnosis and a prescription for inhaled corticosteroids (ICS) and children without both diagnosis and ICS in the first year of life.

to regular asthma medication use. Children who do become persistent asthma medication users could not be identified by objective measures that can be determined at start of therapy. Only the 'physician-decided' measures, doctor-diagnosed asthma and prescribing of inhaled corticosteroids are associated with persistent asthma medication use.

The low persistence found in our study is consistent with the findings from previous studies that no valid criteria exist to prospectively identify children who will develop asthma within a group of wheezing children.[1,2,18–20] Moreover, a great proportion of those who wheezed in their first years of life did so for other reasons than asthma.[2–6]

However, other studies did find certain factors to be associated with persistent wheeze and asthma later in life, including early allergic sensitization,[1,9,18,21,22] atopic disease (such as rhinitis, eczema), eosinophilia,[19,22,23] female sex,[21] tobacco smoke exposure,[21,22] a family history of asthma,[1,9,19,22–25]early and/or severe wheezing.[18,19,25] Other characteristics, including pet or farm animal exposure,[18] day care attendance or having older siblings[18,26] and house-dust endotoxine[18] might reduce the risk of asthma. This association is not reflected in an association with persistent asthma medication use. Our results show that demographic characteristics, familial predisposition and environmental influences were not significantly associated with persistence of asthma medication use.

In contrast, we found that doctor-diagnosed asthma and prescribing of inhaled corticosteroids were significantly associated with persistence of asthma medication use. As both these measures and the outcome, persistence of asthma medication use, are not objective measures but physician-based, care should be taken in interpreting these results. It is not unlikely that physicians are more inclined to continue medication use after diagnosing a child with asthma or prescribing inhaled corticosteroids. Therefore, it is important that physicians check the necessity of continuing medication on a regular basis. In addition, restricting treatment to the group of children with doctor-diagnosed asthma and use of inhaled corticosteroids does not necessarily lead to better targeting of asthma medication, since a diagnosis of asthma is very difficult to make before the age of 5 and, if given, should be considered a working diagnosis.[11,27,28]

However, the low percentage of persistence in our study and the finding that one-third of the children in our study population does not report wheezing in the year that asthma medication is initiated raises the question whether overtreatment occurs, as has been reported in previous studies.[1,2,13,23,29,30] Especially since recent evidence suggests that early inhaled corticosteroid treatment has no effect on the natural history of asthma or wheeze later in childhood and that the beneficial effect during episodes of wheezing in preschool children is small to none existent.[20,31,32] Another study found no relation between responses to inhaled bronchodilators in infancy and asthma later in life, concluding that the presence or absence of a response to bronchodilators in early life cannot be used as a predictor of asthma.[33]

The current study has some limitations. First, we only have information on medication use for the first four years of life, hence the maximum follow-up of three years after start of asthma therapy. We do realize that the diagnostic and treatment problems do not disappear at the age of 4. However, since already very few children remain persistent user after these three years we do not feel that the insight into persistent asthma medication use in this population would be much greater if we were able to add more years of follow-up. Second, in this study we cannot determine whether the persistence or discontinuation of medication is a just action. About one-third of all children discontinuing medication reported asthmatic symptoms in the year after their medication was discontinued (data not shown). This could imply undertreatment, especially since a quarter of non-persistent children resumes medication use in year 4. Third, parental-reported doctor-diagnosed asthma might not be the true reflection of asthmatics. This has been shown to differ substantially from a diagnosis of asthma derived from the GPs clinical records in the sense that self-reported asthma renders many more 'asthmatics' than do the GP's records.[34]

In conclusion, we show that a treatment trial in most cases does not lead to regular use of asthma medication. Only 58.8% of children continue medication use after the initial prescription. With a three-year persistence of only 10.3% and the conflicting evidence on the benefit and diagnostic value of not only trials of inhaled corticosteroids,[20,31,32,35,36] but also β2-agonists[37] and anticholinergics[38] in children suffering from (transient) wheeze, there might be room for improvement in prescribing practice. It is important to identify which children should or should not be receiving asthma medication. However, our data showed that no objective measures, including a family history of asthma, eczema and smoke exposure, are associated with persistence of asthma medication use. These findings stress the need for objective tools to diagnose asthma at a young age.

Conflict of interest statement

All authors have declared no conflict of interest except for dhr. Johan C. de Jongste: JCDJ participated in a scientific advisory board for GlaxoSmithKline in 2006 and received euro 1500 payment. Speakers fees for JCDJ were paid to the Erasmus MC (AstraZeneca: euro 3100, GlaxoSmithKline: euro 1100, in 2005 and 2006). The Department of Pediatric Respiratory Medicine, Erasmus MC—Sophia Children's Hospital received project funding in the past three years from Roche (2004: 153.585; 2005: 221.850); Chiron (2005: euro 15.200), Transave (2005: euro 31.700), Pfizer (2005: euro 61.200).

Ethics statement

The PIAMA study has been approved by the appropriate ethical committees. All subjects gave informed consent to the study.

Acknowledgements

The authors thank the study members and their parents for their cooperation and dedication. They also thank all field workers of the PIAMA study for collecting the data and the

participating community pharmacies for supplying the prescription data.

References

1. Kurukulaaratchy RJ, Matthews S, Holgate ST, Arshad SH. Predicting persistent disease among children who wheeze during early life. *Eur Respir J* 2003;**22**(5):767—71.
2. Helms PJ. Issues in pediatric asthma. *Pediatr Pulmonol* 2001; **21**(Suppl.):49—56.
3. Grigg J. Management of paediatric asthma. *Postgrad Med J* 2004;**80**(947):535—40.
4. Silverman M, Pedersen S. Early intervention in childhood asthma. Summary. *Eur Respir J Suppl* 1998;**27**:66s—8s.
5. Bush A. Phenotype specific treatment of asthma in childhood. *Paediatr Respir Rev* 2004;**5**(Suppl. A):S93—101.
6. Martinez FD. What have we learned from the Tucson children's respiratory study? *Paediatr Respir Rev* 2002;**3**(3):193—7.
7. Kurukulaaratchy RJ, Fenn MH, Waterhouse LM, Matthews SM, Holgate ST, Arshad SH. Characterization of wheezing phenotypes in the first 10 years of life. *Clin Exp Allergy* 2003; **33**(5):573—8.
8. Brooke AM, Lambert PC, Burton PR, Clarke C, Luyt DK, Simpson H. The natural history of respiratory symptoms in preschool children. *Am J Respir Crit Care Med* 1995;**152**(6 Pt. 1): 1872—8.
9. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med* 1995;**332**(3):133—8.
10. Morgan WJ, Stern DA, Sherrill DL, Guerra S, Holberg CJ, Guilbert TW, et al. Outcome of asthma and wheezing in the first 6 years of life: follow-up through adolescence. *Am J Respir Crit Care Med* 2005;**172**(10):1253—8.
11. Global strategy for asthma management and prevention: global initiative for asthma (GINA). Available at: http://www.ginasthma.org; 2006.
12. *British Guideline on the Management of Asthma: a national clinical guideline*. Revised edition July 2007. British Thoracic Society, Scottish Intercollegiate Guidelines Network; 2007.
13. Chauliac ES, Silverman M, Zwahlen M, Strippoli MP, Brooke AM, Kuehni AC. The therapy of pre-school wheeze: appropriate and fair? *Pediatr Pulmonol* 2006;**41**(9):829—38.
14. Brunekreef B, Smit HA, de Jongste JC, Neijens HJ, Gerritsen J, Postma D, et al. The prevention and incidence of asthma and mite allergy (PIAMA) birth cohort study: design and first results. *Pediatr Allergy Immunol* 2002;**13**(Suppl. 15):55—60.
15. Mantel-Teeuwisse AK, Klungel OH, Verschuren WM, Porsius A, de Boer A. Comparison of different methods to estimate prevalence of drug use by using pharmacy records. *J Clin Epidemiol* 2001;**54**(11):1181—6.
16. Anonymous. Anatomical therapeutic chemical (ATC) classification index. In: WHO Collaborating Centre for Drug Statistics Methodology. Available at: http://www.whocc.no/atcddd/.
17. Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol Drug Saf* 2006;**15**(8):565—74 [discussion 575—7].
18. Martinez FD. Development of wheezing disorders and asthma in preschool children. *Pediatrics* 2002;**109**(2 Suppl.):362—7.
19. Castro-Rodriguez JA, Holberg CJ, Wright AL, Martinez FD. A clinical index to define risk of asthma in young children with recurrent wheezing. *Am J Respir Crit Care Med* 2000;**162**(4 Pt. 1):1403—6.
20. Bisgaard H, Hermansen MN, Loland L, Halkjaer LB, Buchvald F. Intermittent inhaled corticosteroids in infants with episodic wheezing. *N Engl J Med* 2006;**354**(19):1998—2005.
21. Shapiro GG. Among young children who wheeze, which children will have persistent asthma? *J Allergy Clin Immunol* 2006;**118**(3):562—4.
22. NAEPP. National Asthma Education and Prevention Program. Expert panel report: guidelines for the diagnosis and management of asthma update on selected topics—2002. *J Allergy Clin Immunol* 2002;**110**(Suppl. 5):S141—219.
23. Schonberger H, van Schayck O, Muris J, Bor H, van den Hoogen H, Knottnerus A, et al. Towards improving the accuracy of diagnosing asthma in early childhood. *Eur J Gen Pract* 2004; **10**(4):138—45, 151.
24. Lowe LA, Simpson A, Woodcock A, Morris J, Murray CS, Custovic A. Wheeze phenotypes and lung function in preschool children. *Am J Respir Crit Care Med* 2005;**171**(3):231—7.
25. Taussig LM, Wright AL, Holberg CJ, Halonen M, Morgan WJ, Martinez FD. Tucson children's respiratory study: 1980 to present. *J Allergy Clin Immunol* 2003;**111**(4):661—75 [quiz 676].
26. Ball TM, Castro-Rodriguez JA, Griffith KA, Holberg CJ, Martinez FD, Wright AL. Siblings, day care attendance, and the risk of asthma and wheezing during childhood. *N Engl J Med* 2000;**343**(8):538—43.
27. *Expert Panel Report 3: guidelines for the diagnosis and management of asthma, National Asthma Education and Prevention Program*. National Heart, Lung, and Blood Institute; 2007.
28. Bush A. Diagnosis of asthma in children under five. *Prim Care Respir J* 2007;**16**(1):7—15.
29. Goodman DC, Lozano P, Stukel TA, Chang C, Hecht J. Has asthma medication use in children become more frequent, more appropriate, or both? *Pediatrics* 1999;**104**(2 Pt. 1):187—94.
30. Clavenna A, Rossi E, Berti A, Pedrazzi G, De Rosa M, Bonati M. Inappropriate use of anti-asthmatic drugs in the Italian paediatric population. *Eur J Clin Pharmacol* 2003;**59**(7):565—9.
31. Guilbert TW, Morgan WJ, Zeiger RS, Mauger DT, Boehmer SJ, Szefler SJ, et al. Long-term inhaled corticosteroids in preschool children at high risk for asthma. *N Engl J Med* 2006; **354**(19):1985—97.
32. Murray CS, Woodcock A, Langley SJ, Morris J, Custovic A. Secondary prevention of asthma by the use of Inhaled Fluticasone propionate in Wheezy INfants (IFWIN): double-blind, randomised, controlled study. *Lancet* 2006;**368**(9537):754—62.
33. Hyvarinen MK, Kotaniemi-Syrjanen A, Reijonen TM, Korhonen K, Kiviniemi V, Korppi M. Responses to inhaled bronchodilators in infancy are not linked with asthma in later childhood. *Pediatr Pulmonol* 2006;**41**(5):420—7.
34. Mohangoo AD, van der Linden MW, Schellevis FG, Raat H. Prevalence estimates of asthma or COPD from a health interview survey and from general practitioner registration: what's the difference? *Eur J Public Health* 2006;**16**(1):101—5.
35. McKean M, Ducharme F. Inhaled steroids for episodic viral wheeze of childhood. *Cochrane Database Syst Rev* 2000;**2**: CD001107.
36. Bisgaard H, Allen D, Milanowski J, Kalev I, Willits L, Davies P. Twelve-month safety and efficacy of inhaled fluticasone propionate in children aged 1 to 3 years with recurrent wheezing. *Pediatrics* 2004;**113**(2):e87—94.
37. Chavasse R, Seddon P, Bara A, McKean M. Short acting beta agonists for recurrent wheeze in children under 2 years of age. *Cochrane Database Syst Rev* 2002;**3**:CD002873.
38. Everard ML, Bara A, Kurian M, Elliott TM, Ducharme F. Anticholinergic drugs for wheeze in children under the age of two years. *Cochrane Database Syst Rev* 2004;**1**:CD001279.