

ORIGINAL ARTICLE

Asthma symptoms and medication in the PIAMA birth cohort: Evidence for under and overtreatment

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Abstract

Objective: Under and overtreatment of asthma may be a serious problem especially in young children, but the evidence is scarce and no longitudinal data are available. Our aim was to investigate whether inhaled medication use in young children was in agreement with asthma symptoms at the age of 2–8 yr.

Methods: Data were used from the 'Prevention and Incidence of Asthma and Mite Allergy' birth cohort, consisting of 3963 children born in the Netherlands. Between age 2 and 8 yr, children were followed up using annual postal questionnaires. Age-specific prevalences of asthma symptoms were assessed and compared with reported use of inhaled bronchodilators and/or corticosteroids.

Results: The proportion of current wheeze decreased with age. About a third of 'current wheezers' did not use any inhaled medication during the years in which symptoms were reported. At 8 yr, 30% of children with reported 'severe current asthma symptoms' were not using inhaled corticosteroids. On the other hand, up to 50% of children with inhaled corticosteroids for at least 2 yr did not report any wheezing during those 2 yr.

Conclusion: The proportion of symptomatic children without appropriate treatment was substantial throughout childhood, even when parents reported prolonged or severe symptoms. Treatment of asymptomatic children with inhaled corticosteroids increased with age and accounted for up to a third of all inhaled steroid use at 8 yr. These findings suggest that under and overtreatment of asthma in children was common.

Asthma symptoms are highly prevalent in children, but an asthma diagnosis is difficult at young age when symptoms are non-specific. Nonetheless, it is important that asthmatic children are adequately treated with bronchodilators (BD) and inhaled corticosteroids (ICS) or leukotriene receptor antagonists, as these reduce symptoms and improve quality of life (1–2). On the other hand, the majority of symptomatic preschool children will outgrow their symptoms during childhood (3).

Long-term prescription of ICS in children, without regular evaluation, may lead to overtreatment.

Indeed some previous studies have shown evidence that considerable undertreatment as well as overtreatment of asthma exists in children (4–8). Only few studies have addressed under and overtreatment in preschool children, in whom it is particularly difficult to make an accurate asthma diagnosis (5–7). Importantly, previous studies were all cross-sectional in design and could not follow symptoms and medication use over multiple years (4–12).

Using the longitudinal data from the 'Prevention and Incidence of Asthma and Mite Allergy' (PIAMA) birth cohort, we investigated whether medication use corresponded with

Abbreviations:

BD, bronchodilators; ICS, inhaled corticosteroids; PIAMA Study, 'Prevention and Incidence of Asthma and Mite Allergy' Study.

parental report of asthma symptoms in children aged 2–8 yr. By inspecting medication use among children with asthma symptoms of different severity, type and duration, we estimated the rate of undertreatment. Reports of asthma symptoms among long-term ICS users were assessed to evaluate possible overtreatment.

Patients and methods

Study population

Recruitment of the PIAMA cohort took place in 1996–97 by means of a screening questionnaire distributed to 10232 pregnant women visiting one of the 52 prenatal clinics in The Netherlands (13). Based on this screening, 7862 women were invited and 4146 (53%) agreed and gave informed consent. Their children were followed up annually for 8 yr, using postal questionnaires for parental completion, based on the International Study of Asthma and Allergies in Childhood (ISAAC) core questionnaires (14). A detailed description of the study has been published elsewhere (15).

Definitions

Parents were asked about their child's airway symptoms every year. Data on shortness of breath and prescription of specific types of inhaled medication were collected only after the age of 2 yr. Several symptom outcomes were defined at the ages of 3–8 yr, each pertaining to the past 12 months. 'Current wheeze' was assessed with the question: 'Has your child had wheezing or whistling in the chest in the last 12 months?' And 'Current shortness of breath' with: 'Has your child had tightness of the chest or shortness of breath in the last 12 months?' These symptoms were considered 'frequent' if parents reported four or more episodes in the past year. A range of asthma symptoms was inspected in relation to medication use. A child was considered to have 'Severe current asthma symptoms' when the parents reported wheezing in the past year, AND an episode of wheeze or shortness of breath severe enough to limit speech to two words at the time and/or four or more episodes of wheeze/shortness of breath severe enough to keep the child awake at night. All national and international guidelines used during the study period advise maintenance therapy with ICS in children with severe asthma symptoms (1, 16). 'Doctors diagnosed current asthma' was assessed using the question: 'Did a doctor ever diagnose asthma in your child AND has your child had asthma in the last 12 months?'

Information on asthma medication was collected by the question: 'Has your child had medication for lung problems prescribed by a doctor in the last 12 months?' Parents were asked to specify the medication from a list that included generic and brand names of all medication registered for asthma treatment in the Netherlands. Inhaled asthma medication use was categorized annually in four groups: (i) no inhaled medication; (ii) only BD; (iii) only ICS; and (iv) BD and ICS. Cromones were not advised by national asthma guidelines and rarely prescribed during the study (<0.2%).

Leukotriene receptor antagonists were introduced in Dutch guidelines in 2003 (16) and only seven children used montelukast at 8 yr. Therefore, only BD and ICS were considered in our analyses.

Statistical analyses

Proportions of children with inhaled medication and different types of asthma symptoms were compared at every year of age using SAS software version 9.1 (SAS Institute, Inc., Cary, NC, USA). Longitudinal data allowed us to differentiate children with incidental wheezing, from those with wheezing in two consecutive years. Inhaled medication in asymptomatic children may imply either overtreatment or a good treatment response. During the study period, guidelines recommended to reduce and eventually withdraw ICS in children that have become completely free of wheeze using 3-monthly intervals (17, 18). Therefore, we considered ICS use in at least two consecutive years without a single-reported episode of symptoms as suggestive for overtreatment. We performed complete case analyses for every time point, excluding children with missing data at a certain age from the analysis only at that specific age.

Results

Study population

From the 4146 included mothers, 183 (4.5%) dropped out before returning any postnatal questionnaires because of various reasons (e.g. stillbirth, language barrier, not interested, moved). General characteristics of the study population at baseline (n = 3963) are given in Table 1. Of the baseline

Table 1 Population characteristics at baseline and annual response rate

Characteristic	n (%)
Baseline population	3963 (100)
Gender (boy)	2056 (52)
Preterm birth	190 (5)
Caesarean section	332 (9)
Older siblings (present)	1994 (51)
Allergic mother	1237 (31)
Allergic father	1217 (31)
Breastfeeding ever given	3200 (82)
Education mother (low)	894 (23)
Smoking in pregnancy	556 (14)
Questionnaire returned at age: (% from baseline)	
3 yr	3693 (92)
4 yr	3561 (90)
5 yr	3518 (89)
6 yr	3472 (88)
7 yr	3373 (85)
8 yr	3314 (84)
Every age (3–8 yr)	3033 (77)

population, 199 children (5.0%) were lost to follow-up before the age of 3 yr. The remaining 3764 returned at least 1 questionnaire between the age of 3–8 yr and were included in the analyses. The age-specific response rates are given in Table 1: 3033 children (77% of baseline) completed a questionnaire every single year from age 3–8. Children that were lost to follow-up before age 3 ($n = 199$) or missed at least 1 questionnaire, thereafter, ($n = 731$) were similar to children with complete data ($n = 3033$) with respect to gender, pregnancy duration, delivery by caesarean section, proportion with older siblings and allergy of the father. However, children with complete data had a higher level of parental education, were more likely to be ever breastfed, and less likely to be exposed to cigarette smoke during pregnancy (data not shown). The average response rate between 3 and 8 yr was 88% from baseline, and at 8 yr, 3314 children (84%) returned a completed questionnaire.

Prevalence of asthma symptoms and inhaled medication

Current wheezing at least once was reported by 15.8% at 3 yr and showed a gradual decline to 5.9% at age 7 (Table 2). The prevalence of shortness of breath and markers for symptom severity such as speech limiting, nightly or frequent symptoms all decreased with age. The prevalence of 'doctors diagnosed current asthma' did not decrease and had the highest prevalence at 8 yr. BD use decreased with age, and ICS use varied between 7 and 8% between ages 2 and 8 yr. When ICS were prescribed after the age of 2, they were often continued for multiple years. Figure 1 shows that at

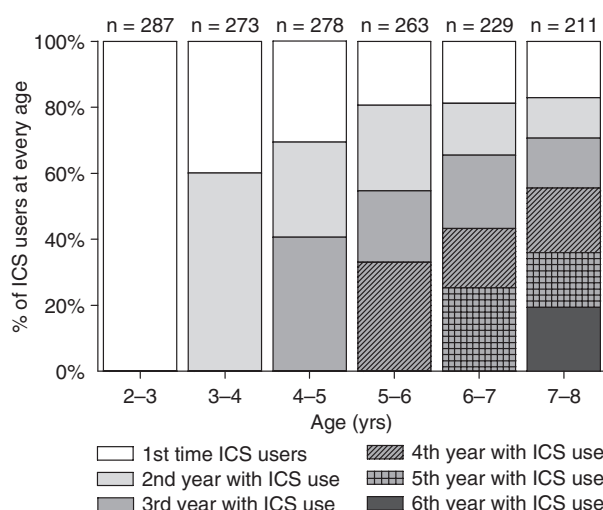


Figure 1 Number of years that inhaled corticosteroids was used after the age of 2 yr. ICS, Inhaled corticosteroids. Numbers above bars represent the absolute number of children that used inhaled corticosteroids that year. Example: At age 3–4 yr, $n = 273$, children were using ICS; 60% of those children were using ICS for the 2nd year in a row, 40% started using ICS at age 3–4 yr for the 1st time. Note that only inhaled corticosteroid use after the age of 2 yr was taken into account.

the age of 5, only 20% of children using ICS started ICS in that year. At 8 yr, over 70% of ICS users had been using ICS for at least 3 yr.

Table 2 Age-specific prevalence of symptoms and medication use

	Asthma symptoms (%)					
	Age 2–3 yr	Age 3–4 yr	Age 4–5 yr	Age 5–6 yr	Age 6–7 yr	Age 7–8 yr
Wheezing						
Current wheezing	15.8	11.9	9.6	7.8	5.9	6.7
Frequency						
1–3 times per year	12.0	8.7	6.6	5.6	4.5	5.3
≥4 times per year	3.8	3.2	3.0	2.2	1.4	1.4
Shortness of breath						
Current shortness of breath	15.0	12.9	12.1	10.4	7.5	8.9
Frequency						
1–3 times per year	11.2	9.1	8.1	7.5	5.5	6.6
≥4 times per year	3.8	3.8	4.0	2.9	2.0	2.3
Speech limiting symptoms	3.3	2.5	1.9	1.5	1.1	0.9
Awake at night because of symptoms	13.0	11.4	10.1	7.6	5.5	5.1
Doctors diagnosed current asthma	4.2	4.2	4.0	3.9	2.8	4.6
Inhaled medication (%)						
	Age 2–3 yr	Age 3–4 yr	Age 4–5 yr	Age 5–6 yr	Age 6–7 yr	Age 7–8 yr
Bronchodilators	12.9	10.5	10.7	9.3	7.8	7.5
Inhaled corticosteroids	8.0	7.8	8.1	7.7	6.8	6.5
Bronchodilators and inhaled corticosteroids	6.3	6.3	6.7	6.1	5.4	4.7

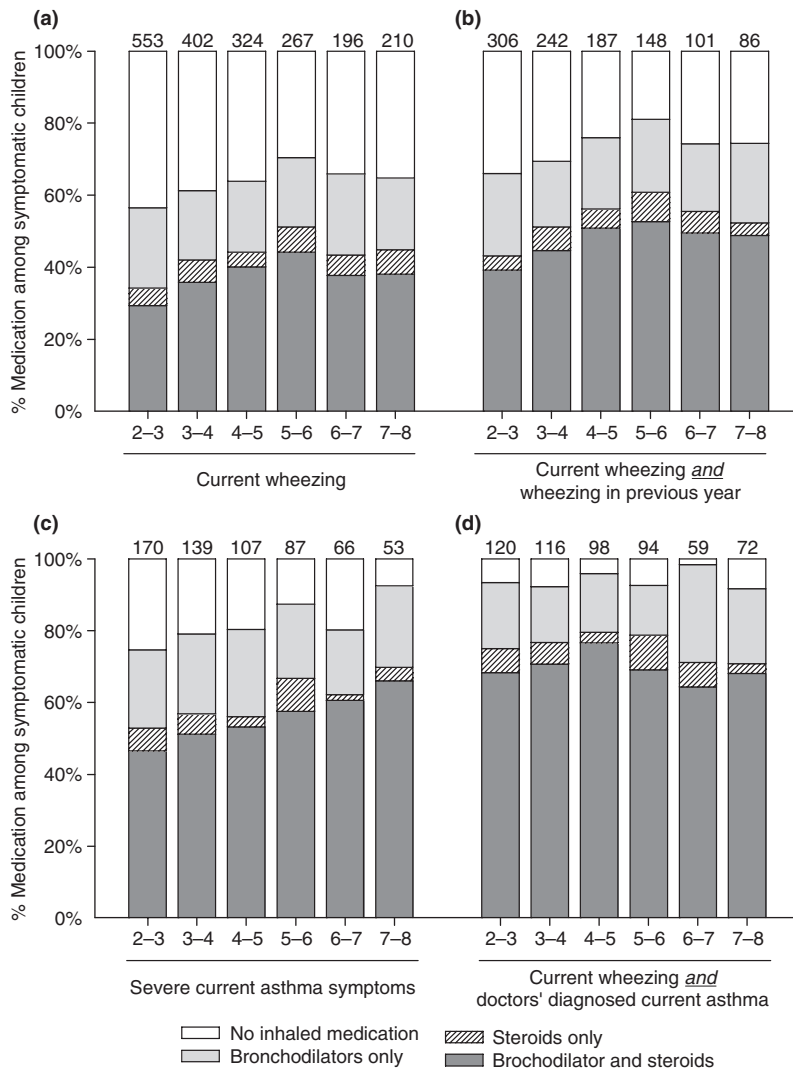


Figure 2 Proportion of inhaled medication among children with symptoms of different duration and severity. (a) Current wheezing; (b) Current wheezing and wheezing in previous year; (c) Severe current asthma symptoms; (d) Current wheezing and doctors' diagnosed current asthma. Numbers above bars represent the absolute number of children that reported symptoms that year.

Undertreatment

Which proportion of symptomatic children indeed received asthma medication? Figure 2 depicts the age-specific proportions of inhaled medication among children with different definitions of asthma symptoms. Among current wheezers at 3 yr, 29% used both ICS and BD and 43% did not use any inhaled medication that year (Fig. 2a). Medication use increased until 5 yr. At 7 and 8 yr, over 30% of current wheezers did not use inhaled medication. Medication use among children who reported current wheezing in two consecutive years is given in Fig. 2b. The proportion receiving medication was only slightly higher in this subgroup, and at 8 yr, 30% was still not using any inhaled medication. The number of children with severe current asthma symptoms was smaller, $n = 53$ at 8 yr. The proportion that used ICS in this group increased with age, but at 8 yr, 30% did not use ICS (Fig. 2c). Our data further indicate that over 90% of the untreated children with severe asthma symptoms consulted a medical doctor in the year of symptoms. Consequently, it is likely that

parents indeed took their symptomatic child to the doctor and that the majority of the undertreatment might have occurred because doctors did not adequately recognize or treat asthma symptoms. Among children with severe asthma symptoms at the age of 3 yr, 41% reported a current doctors' diagnosis of asthma at that age, this increased to 65% at the age of 8. In children with a current doctors' diagnosis of asthma, there appeared to be less undertreatment. Among children with doctors' diagnosed current asthma, more than 90% of the current wheezers was using inhaled medication and 70–80% used ICS, irrespective of age (Fig. 2d).

Overtreatment

Of all children who received ICS at the age of 3 yr, 67% reported current wheezing, the majority less than four episodes per year (Fig. 3a). Among ICS users, the proportion of children that did not wheeze increased over time to well over 50% at age 7 and 8 yr. Less than half of children with current ICS use reported 'doctors diagnosed current asthma'. This

Figure 3 Proportion of wheezing symptoms among children currently using inhaled corticosteroids. (a) Current wheezing, with frequency; (b) Doctors' diagnosed asthma symptoms. ICS, Inhaled corticosteroids. Numbers above bars represent the absolute number of children that reported current inhaled corticosteroid use that year.

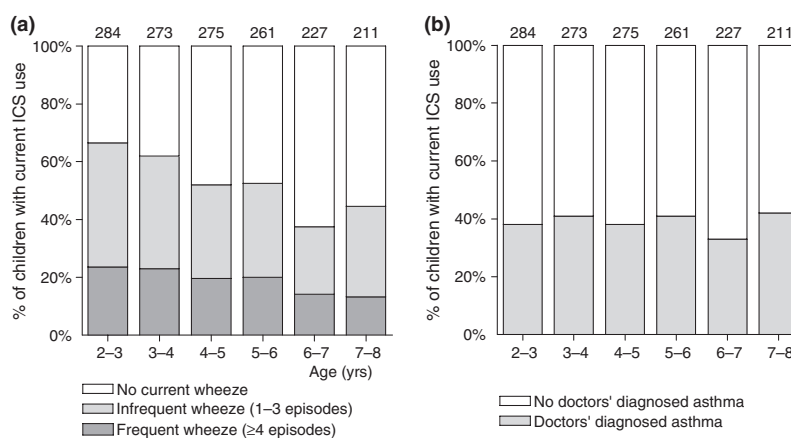
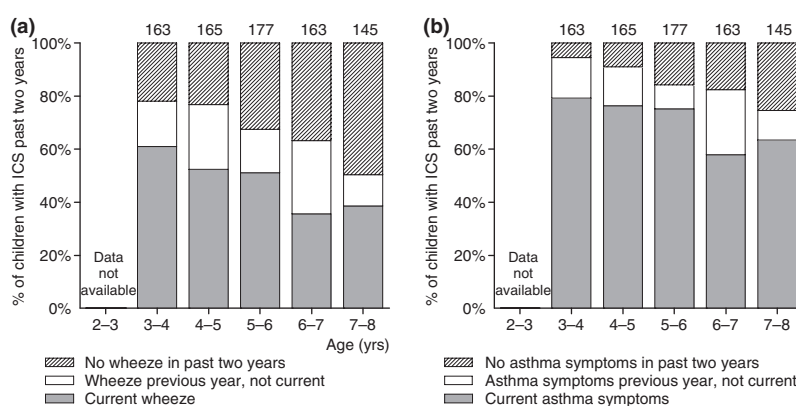


Figure 4 Reported symptoms among children using inhaled corticosteroids for at least two consecutive years. (a) Wheezing symptoms; (b) Asthma symptoms (wheezing and/or shortness of breath). ICS, Inhaled corticosteroids. Numbers above bars represent the absolute number of children that were using inhaled corticosteroids for at least two consecutive years.



was still the case at 8 yr, at which point the majority of ICS users had been using ICS for several years (Fig. 3b). Considering that ICS may not have been used for the entire year, e.g., as part of a medication trial to confirm an asthma diagnosis (17, 18), we inspected symptoms in children with ICS over multiple years. Figure 4a depicts wheezing symptoms in the past 2 yr among children that were using ICS in two consecutive years. At the age of 3-4 yr, 22% of these children did not report a single episode of wheezing for the entire 2-yr period. At the age of 8 yr, this percentage had increased to 50% ($n = 72$). This group represented 36% of all children using ICS and 2.3% of the entire study population at 8 yr. Wheezing is not the only symptom for which ICS are prescribed, and therefore, we also considered 'current shortness of breath'. Among children who reported ICS use at the age of 7 and 8, 26% did not report a single episode of wheezing or shortness of breath during that 2-yr period (Fig. 4b). At least 80% of children with ICS but no symptoms had reported wheezing prior to ICS initiation (data not shown).

Discussion

Our data on 6 yr longitudinal follow-up showed a substantial proportion of asthma undertreatment, even in children with

prolonged or severe symptoms, which decreased only little with age. At the same time, a considerable proportion of all children with long-term ICS use had not reported any asthma symptoms for the past 2 yr, which is suggestive for overtreatment. This possible overtreatment increased with age and accounted for one-third of all prescriptions at the age of 8 yr.

Undertreatment

Evidence that inadequate treatment of asthma symptoms may be a serious problem has been shown in population surveys in Europe as well as the United States (5, 6). Most previous studies on the adequacy of asthma treatment in children included school children of 8 yr and older (4, 9-12). Given the occurrence of different wheezing phenotypes at preschool age, findings from those studies cannot be generalized to younger children. In preschoolers, undertreatment may be more common than in older children (5, 7). A limitation in all previous studies was the cross-sectional design. Our longitudinal data allowed us to investigate the course of symptoms and medication use over multiple years. Considering that an asthma diagnosis becomes more reliable in older children, we expected that the rate of undertreatment would decrease with age. Indeed, the proportion of current wheezers without any medication decreased slightly until the age of 5,

but remained stable thereafter around 35%. We found that the dissociation between symptoms and treatment was not limited to short-time periods. Among children that wheezed in two consecutive years, a third did not use any inhaled medication. In children with severe asthma symptoms, the use of ICS has been strongly recommended by national and international asthma guidelines throughout the study period (1, 17–19). We found that ICS use increased gradually with age in children with severe symptoms, but that still more than one-third of children with severe asthma symptoms did not use ICS at 8 yr.

Undertreatment may be because of problems in diagnosing asthma in children, and this is supported by our finding that 40% of all current wheezers did not use any inhaled medication compared to only <10% in those with a doctor's diagnosis of asthma. Even in children with severe asthma symptoms less than half reported a doctors' diagnosis at the age of 3 and only 65% at the age of 8 yr. Therefore, it seems important that guidelines not only focus on medical treatment but also on the ability of doctors to recognize and correctly diagnose asthma in children.

Overtreatment

Little is known about the rates of overtreatment, as most surveys included only patients with documented asthma (6, 9, 11, 12). Treatment without apparent indication was documented in up to 23% of preschool children (4, 7). An Italian study suggested that asthma medication was frequently prescribed for respiratory infections, even in the absence of bronchoconstriction (8). We found rates of ICS use in children without symptoms increasing to 50% at 8 yr. Evidently, the absence of symptoms may be a desired effect of the medication indicating good treatment rather than overtreatment, and this can only be assessed using longitudinal data. According to guidelines at the time of the study period, treatment with ICS should be evaluated with 3-month intervals and stepped down and eventually stopped in asymptomatic patients, especially young children (17, 18). Hence, we reasoned that children with ICS during two consecutive years without a single episode of wheeze were probably overtreated. The proportion of children with ICS but no wheezing in the past 2 yr gradually increased and most of these children had reported asthma symptoms prior to ICS initiation. This suggests that overtreatment resulted from failure to withdraw ICS while symptoms disappear.

A novel finding was the high proportion of children using ICS without 'doctors diagnosed current asthma', often for 2 yr or more. Recent guidelines indeed promote ICS before an asthma diagnosis is made, but only as a short trial to support the diagnosis (19, 20). The prolonged mismatch between diagnosis and treatment even in children with severe symptoms confirms that doctors regularly prescribe ICS without the parents being aware of an asthma diagnosis (21). This is unfortunate, as good asthma education improves management of childhood asthma, and effective communication about the diagnosis and treatment helps to prevent both under and overtreatment (22, 23).

Strengths and limitations

This is the first longitudinal study to report on possible under or overtreatment of asthma in children. Previous cross-sectional studies may have classified any mismatch between symptoms and medication use as incorrect treatment. Our longitudinal data allowed us to quantify the extent of avoidable under or overtreatment during multiple years, taking into account reported symptoms and medication use in previous years. Secondly, considering the large sample size, high follow-up and annual response rates, our results may be extrapolated to the general Dutch population and, perhaps, other Western European countries (6). If any bias resulted from the relatively few missing questionnaires, it most likely led to an underestimation of the mismatch between symptoms and treatment. Missing data occurred more frequently in children whose mother had a low level of education, which is a risk factor for incorrect treatment (24).

An important limitation of our study is that symptoms were based on parental report. This limitation is shared with all previous surveys and resembles clinical practice, where asthma management in children is also based on parental report. Likewise, medication use was recorded using parental report. To estimate the reliability of these data, we compared our findings with those in a subgroup of 777 children, for whom medication data were retrieved directly from the child's pharmacy. This comparison showed very high agreement (>97%) between parental reported medication use and pharmacy prescription data, suggesting that parental self-report of medication use is an appropriate source of data to assess ICS use in children (25). Thirdly, we are not informed about medication dosage and frequency. Therefore, we cannot exclude that some children received either insufficient or too high ICS doses (4, 6). Several studies among asthma patients have shown high rates of poor asthma control (up to 55%), despite the use of inhaled medication (6, 26). Physicians may prescribe or continue inhaled medication on the basis of their clinical experience, which is not reflected in questionnaire data on wheezing and shortness of breath. This could have resulted in overestimation of the percentage of overtreatment. Finally, we performed an observational study comparing asthma symptoms and prescription behaviour with international guidelines. It should be noted that we cannot address any causal relationships between asthma symptoms and medication prescriptions. Future follow-up studies with information on asthma symptoms and medication dosage at weekly or monthly intervals could give further insights into how changes in symptom presentation are related to changes in prescription behaviour.

Implications

To avoid undertreatment, it may be worthwhile to actively screen children for asthma symptoms in primary and secondary care. Easy-to-use clinical scores to predict the likelihood of persistent asthma symptoms in preschool

children may be helpful for this purpose (27). An improvement in symptoms could be caused by a treatment effect, but also by the natural course of asthma, especially if the improvement is prolonged (28). If symptoms disappear completely, ICS should be gradually withdrawn to avoid overtreatment (18). More recent guidelines emphasized the importance of this advice for preschool children (29). The high percentage of ICS users without symptoms during multiple years implies that a regular, critical reappraisal of ICS treatment may be worthwhile, especially in school-aged children. Indeed, a recent study suggested that better asthma control and less frequent use of combination therapy may be achieved by regular visits to the general practitioner (30).

Conclusion

We found evidence for under and overtreatment in children with asthma. Undertreatment decreased with age, and at 8 yr, one-third of children with asthma symptoms did not receive appropriate medication, even if symptoms were prolonged or severe. At the same time, up to one-third of children chronically using ICS did not report any asthma symptoms for the past 2 yr. These findings suggest that over and undertreatment of asthma in children is common.

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Ethical approval

The study protocol was approved by the medical ethics committees of the participating university hospitals.

What is known on this subject

Asthma is difficult to diagnose in preschool children, and this increases the risk of under and overtreatment. Previous studies showed considerable mismatch between reported asthma symptoms and prescribed medication, but longitudinal data are not available for young children.

What this study adds to the field

Under and overtreatment of asthma may be common in young children: 30% of children with asthma symptoms were not using inhaled medication. At 8 yr, a third of the children using inhaled corticosteroids reported no wheezing in the past 2 yr.

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