Messages from the Aalst Allergy Study

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Background: **The prevalence of sensitization and allergic disease has increased significantly worldwide. The aim of the "Aalst Allergy Study" was to document prevalences of sensitization and allergic symptoms, and to evaluate the effect of personal and environmental influences on these prevalences in an unbiased Belgian pediatric population.**

Methods: **A cross-sectional study was performed in an unbiased population of 2021 Belgian schoolchildren (3.4-14.8 years). Skin prick testing with the most common aeroallergens was performed. Allergic symptoms as well as potential risk factors for sensitization and allergic disease were documented by a parental questionnaire.**

Results: **The prevalence of sensitization to the most common aeroallergens and the prevalence of allergic diseases (eczema, asthma and rhinoconjunctivitis) were in line with the data in the literature. The association of current allergic symptoms with sensitization was only significant in the children aged ≥6 years. Age, gender, body mass index, bedroom environment and exposure to pets were the factors significantly associated with sensitization and allergic symptoms.**

Conclusions: **Our study corroborates the reported prevalences of sensitization and allergic diseases. Moreover the study illustrates the complexity of the search for factors involved in the process of sensitization and allergic disease. The impact of different potential causative factors is not only influenced by mutual interactions of these factors, but also by the existence of distinct subtypes of disease.**

World J Pediatr 2009;5(3):182-190

Key words: **Aalst Allergy Study; allergic symptoms; risk factors; sensitization; skin prick test**

Introduction

The prevalence of allergic sensitization has increased dramatically worldwide during the recent years.[1-3] Recent Australian data suggest that this increase may now be levelling off.[4] Allergen exposure in childhood is a risk factor for sensitization and allergic sensitization is generally agreed to be an important risk factor of allergic diseases.[5-7] On the other hand it has been hypothesized that allergen exposure in early childhood may induce tolerance and may have a protective effect on sensitization.[8,9] Early life events seem to have a major impact on the development of sensitization or tolerance.[9-11] Besides environmental factors, however, personal factors such as genetic predisposition and gender also influence atopy.[12,13]

In order to evaluate the prevalences of sensitization and allergic symptoms and the effect of personal and environmental influences in an unbiased Belgian pediatric population we performed the "Aalst Allergy Study" (AAS).

Methods

The AAS is a cross-sectional study that was performed from January 2004 to June 2005 in an unselected sample of children aged 3.4 to 14.8 years (mean age, 9.3 years) attending randomly selected nursery, primary and secondary schools in the city of Aalst and the surrounding area. Aalst is a Belgian municipality, 19 miles northwest from Brussels. Aalst has a total population of 76 852 for a total area of 78.12 square kilometers, which gives a population density of 983.83 inhabitants per square kilometers.

The parents of all 2674 children of the 2nd grade of nursery school, the 1st, 3rd and 5th grade of primary school and the 1st grade of secondary school were contacted, received a questionnaire (see below) and were invited to participate in this study. The parents of 2021

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doi:10.1007/s12519-009-0035-0

Table 1. Baseline characteristics of the study population

Characteristics	Study population, *n*=2021 (%)
Age (in years)	3.4-14.8 (mean 9.3±0.1)
3.4-<6 y	358 (17.7)
6-<8 y	278 (13.8)
8-<10 y	302 (14.9)
10-<12 y	666 (33.0)
12-14.8 y	417 (20.6)
Gender	
Male	990 (49.0)
Female	1031 (51.0)
Family composition	
No siblings	409 (20.2)
≥1 sibling	1601 (79.2)
Missing	11 (0.5)
Current animals	
No animals	627 (31.0)
Cat	395 (19.5)
Dog	494 (24.4)
Cat and dog	500 (24.7)
Missing	5 (0.2)
Animals at birth	
None	1103 (54.6)
Cat	217 (10.7)
Dog	486 (24.0)
Cat and dog	179 (8.9)
Missing	36 (1.8)
Passive smoke exposure	
No smoking	1160 (57.4)
Smoking mother	211 (10.4)
Smoking father	337 (16.7)
Smoking mother and father	287 (14.2)
Missing	26 (1.3)
Maternal smoking during pregnancy	
No	1657 (82.0)
Yes	307 (15.2)
Missing	57 (2.8)
Prematurity	
No	1867 (92.4)
Yes	122 (6.0)
Missing	32 (1.6)
Breastfeeding	
No	1128 (55.8)
0-3 months	506 (25.0)
3-6 months	222 (11.0)
>6 months	108 (5.3)
Missing	57 (2.8)

Characteristics	Study population, *n*=2021 (%)
Place of residence at birth	
Urban versus rural	
Urban	685 (33.9)
Rural	1089 (53.9)
No data	247 (12.2)
Age of building	
<50 y	905 (44.8)
≥50 y	686 (33.9)
No data	430 (21.3)
Current place of residence	
Urban versus rural	
Urban	607 (30.0)
Rural	1373 (67.9)
No data	41 (2.1)
Age of building	
<50 y	1134 (56.1)
≥50 y	587 (29.0)
No data	300 (14.8)
Bedroom conditions	
Stuffed toys	
No	139 (6.9)
1-5	830 (41.1)
>5	954 (47.2)
No data	98 (4.8)
Bedding material	
Synthetic	1324 (65.5)
Duvet or non-synthetic	531 (26.3)
No data	166 (8.2)
Floor	
Wood or fitted carpet	239 (11.8)
Rest	1715 (84.9)
No data	67 (3.3)
Family history of allergy	
No allergy	433 (21.4)
Parental allergy only	312 (15.4)
Sibling allergy only	171 (8.5)
Parental and sibling allergy	315 (15.6)
Missing	790 (39.1)
Day-care center attendance	
No	1190 (58.9)
Yes	773 (38.2)
Missing	58 (2.9)

children (75%) returned a completed questionnaire and gave permission by written consent to perform skin prick testing in their children. The baseline characteristics of the study population are summarized in Table 1.

The questionnaire included questions on rhinoconjunctivitis and asthma, that were adapted and translated from the International Study of Asthma and Allergies in Childhood (ISAAC) questionnaire.[1] The presence of eczema, as well as the time of occurrence, was documented by parentally reported eczema. We defined current allergic symptoms as the presence of wheezing, dyspnea, airway hyperreactivity, rhinitis, conjunctivitis or eczema in the last 12 months. A positive family history of allergy was defined as the presence of one of the allergic symptoms in one of the parents or siblings.

The questionnaire further included questions about demographic characteristics (age, gender, nationality, maternal and paternal profession) and potential risk factors for sensitization, such as prematurity, feeding practices in the neonatal period, family history of allergy, number of siblings, frequency of childhood infections, vaccinations, place of residence (urban or rural), housing characteristics (age of building, heating, dampness, bedroom conditions, etc), animal contacts and tobacco smoke exposure (pre- and postnatal).

The allergen panel (Stallergenes, Waterloo, Belgium) consisted of the most common aeroallergens—*Dermatophagoides pteronyssinus, Alternaria tenuis*, cat, *dog*, mixed grass pollens [*Dactylis glomerata* (orchardgrass), *Poa pratensis* (Kentucky bluegrass), *Lolium perenne* (perennial ryegrass), *Anthoxanthum odoratum* (Gramineae) and *Phleum pratense* (Timothy)], tree pollens [*Alnus glutinosa* (Common Alder), *Betula alba* (Common Birch), *Corylus avellana* (Hazel) and *Carpinus betulus* (European hornbeam)], and *Blatella germanica* (cockroach). Atopy was defined as at least one positive skin test to any of the seven allergens tested.[14]

The Chi-square test or Fisher's exact test was used to study the differences in prevalence according to age and gender. Differences in mean BMI for the different age categories were tested by ANOVA. Logistic regression analysis was used to study the association between co-variates and the different outcomes of interest. In a univariate analysis, the association between each covariate and the outcome of interest was studied. We then added one by one all risk factors for the outcome into the model. If any of these factors changed the estimate with more than 5%, these risk factors were entered into the final model. A P value <0.05 was considered statistically significant. All statistical analyses were done using SPSS 13.0 (SPSS Inc., Chicago, IL, USA).[15-22]

Results

Prevalence of sensitization and allergic symptoms

A total of 483 children (23.9%, 95% CI 22.1-25.8%) had evidence of allergic sensitization.[15] The age standardized prevalence rate was 20.5% (95% CI 17.9-23.2%).

The prevalence rates of sensitization to the most common allergens were as follows: *Dermatophagoides pteronyssinus* 291 (14.4%), mixed grass pollens 205 (10.1%), tree pollens 67 (3.3%), cat 97 (4.8%), dog 54 (2.7%) and *Alternaria tenuis* 58 (2.9%). Sensitization to *Blatella germanica* was present in only 11 (0.5%) children.[15,18] The AAS prevalence rates of eczema, respiratory symptoms and rhinoconjunctivitis for the whole study population are shown in Table 2.

Table 2. Prevalences of eczema, respiratory symptoms and rhinoconjunctivitis for the whole study population

	Study population, n=2021 (%)
Eczema ever	
No	1529 (75.7)
Yes	464 (23.0)
Missing	28 (1.4)
Respiratory symptoms	
Wheezing ever	
No	1551 (76.7)
Yes	410 (20.3)
Missing	60 (3.0)
Dyspnea ever	
No	1713 (84.8)
Yes	252 (12.5)
Missing	56 (2.8)
Chronic cough ever	
No	1439 (71.2)
Yes	551 (27.3)
Missing	31 (1.5)
Doctor's diagnosed asthma	
No	1891 (93.6)
Yes	100 (4.9)
Missing	30 (1.5)
Airway hyperreactivity	
Exercise-induced	
No	1798 (89.0)
Yes	181 (9.0)
Missing	42 (2.1)
Laughing-induced	
No	1899 (94.0)
Yes	66 (3.3)
Missing	56 (2.8)
Weather-induced	
No	1793 (88.7)
Yes	174 (8.6)
Missing	54 (2.7)
Rhinoconjunctivitis ever	
No rhinoconjunctivitis	1492 (73.8)
Conjunctivitis only	52 (2.6)
Rhinitis only	262 (13.0)
Rhinoconjunctivitis	153 (7.6)
Missing	62 (3.1)

In our study, all investigated current allergic symptoms were positively associated with sensitization.[17] The association was strongest for rhinoconjunctivitis and stronger for respiratory allergic symptoms than for eczema. After stratification of the whole study population into children younger than or older than 6 years, we found that the associations of any of the investigated allergy symptoms with overall sensitization were limited to the children older than 6 years. No significant association could be documented in the group of children younger than 6 years.

Association of personal and environmental factors with the prevalence of sensitization and allergic symptoms

Age and gender[15]

Overall sensitization to at least one allergen increased significantly with age from 15.9% (95%CI: 12.4-20.0%) for the younger age group up to 30.5% (95%CI: 26.2-35.0%) for the older age group (Fig. A). The increase with age was gradual, but a marked increase was observed at the age of 8 to10 years.

A significant association with increasing age was also seen for the individual allergens *D. pteronyssinus*, mixed grass pollens, and tree pollens. For cat, dog, *Alternaria tenuis* and *Blatella germanica*, no statistically significant increase of sensitization with age could be documented (Fig. A and B).

When studying sensitization in relation to gender, we observed that the prevalence of sensitization was much higher in boys than in girls; 293 (29.6%) of the 990 boys were sensitized compared to 190 (18.4%) of the 1031 girls. The male predominance was present in all age categories, but was more obvious in the categories of children under 8 years. In the categories of children older than 8 years, the male predominance remained, but the ratio of male to female decreased.

When stratifying into boys and girls, it was observed that sensitization increased with age for both boys and girls with a steep increase after the age of 8 years for girls (OR_{adj} 4.0) and after the age of 10 years for boys (OR_{adj} 3.3).

Body mass index (BMI)[22]

Our study showed an increased prevalence of sensitization in underweight girls only, not in underweight boys, nor in overweight or obese children. We also found a strong positive association between obesity and exercise induced respiratory symptoms in both boys and girls.

Indoor allergen exposure[19]

Allergen exposure in childhood is a risk factor for sensitization. On the other hand it has been

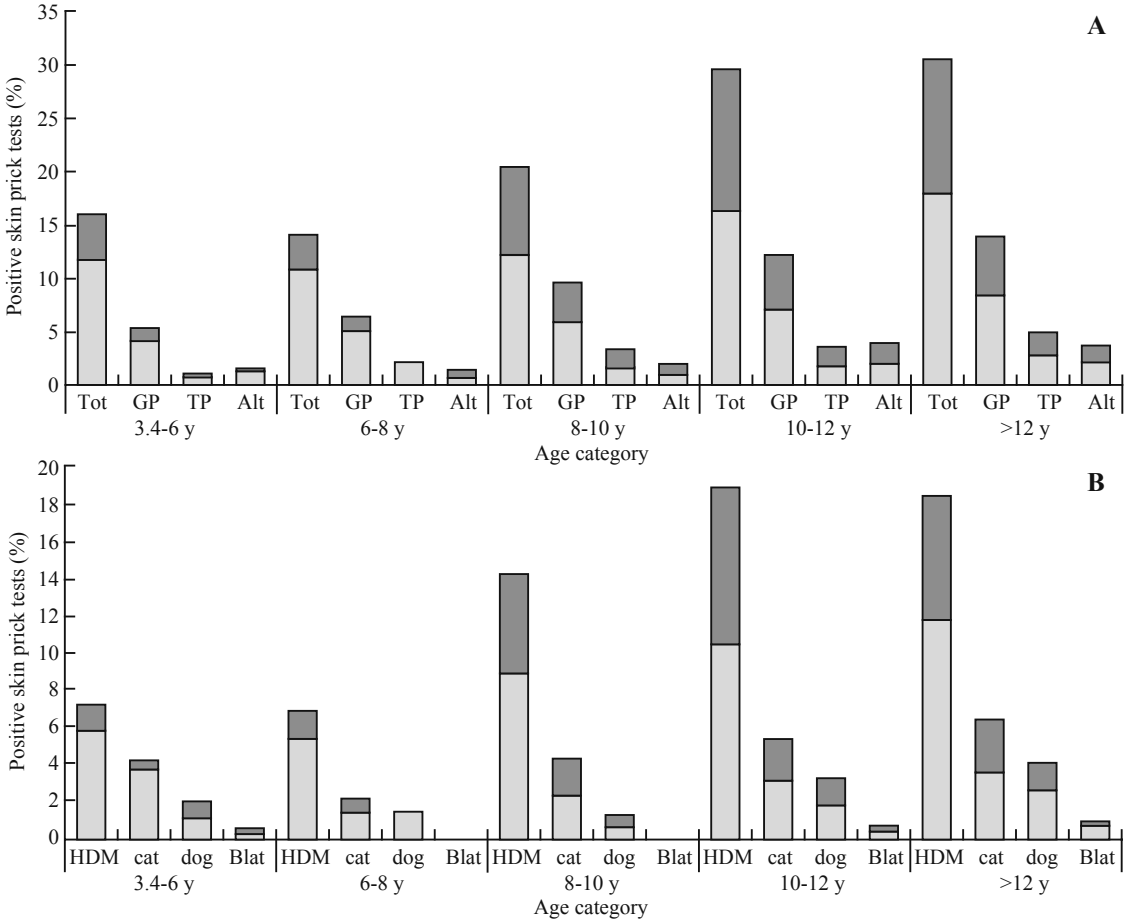

Fig. Overall sensitization (**A**) and sensitization for the different tested indoor and outdoor aeroallergens (**A** and **B**), according to the different age group and expressed as male/female ratios (light color: boys; dark color: girls). Tot: overall; GP: mixed grass pollens; TP: tree pollens; Alt: *Alternaria tenuis*; HDM: house dust mite; Blat: *Blatella germanica* (adapted from Govaere et al[15]).

hypothesised that allergen exposure in early childhood may induce tolerance and may have a protective effect on sensitization. In the AAS we focused on the influence of bedroom conditions on sensitization and allergic symptoms.

The presence of stuffed toys in the bedroom correlated with a lower prevalence of overall sensitization and a lower prevalence of conjunctivitis and allergic respiratory symptoms. This effect was almost exclusively present in children with a positive family history of allergy and was more pronounced as the number of stuffed toys increased.

A significantly lower prevalence of overall sensitization, sensitization to house dust mite and wheezing was documented in children with non-synthetic bedding materials. That effect was exclusive to children with a positive family history of allergy.

The type of flooring was not associated with sensitization or allergic symptoms.

Pets[21]

Dog ownership at birth and dog ownership at present were not associated with sensitization whereas the presence of a domestic dog both at birth and at present seemed to protect against overall sensitization (OR_{adj} 0.6 [95%CI: 0.5-0.9]). None of the categories of cat ownership (at birth and/or at the time of the study) were associated with overall sensitization.

No significant association was found in pet ownership with sensitization for one of the individual allergens or with current allergic symptoms.

Other risk factors

Preterm birth seemed to be protective in the development of eczema, whereas birthweight did not.[16]

The other analyzed risk factors such as month of birth, vaccinations, breastfeeding, day-care attendance, frequency of childhood infections, pre- and/or postnatal passive smoke exposure, housing conditions, growing up in a farming environment, number of siblings and birth order showed no association with the prevalence of sensitization and allergic symptoms in children.

Discussion

The prevalences of skin sensitization for the most common aeroallergens in the AAS are in line with the data in the literature from neighbouring European countries.[3,23-31] As for cockroach only two European studies described cockroach sensitization in a non-selected pediatric population. A study of German school children aged 5-11 years living in Dresden showed a prevalence of 4.2%;[32] a study of Italian preschool children showed 0.45% sensitization.[33] The sensitization rate in our study group was much lower than that in the German study,[32] and comparable with the findings in Italian preschool children.[33] Differences may be explained by differences in age range of the study population and by differences in cockroach allergen exposure,[34] due to differences in socio-economic conditions and indoor environments.

The prevalence rates of allergic symptoms in the AAS are in line with the data of the ISAAC.[1,35] However, comparison of prevalence data remains difficult due to differences in definitions, study population, and others.

When sensitization is presumed to be the cause of allergic diseases in the vast majority of children, similar "allergic" symptoms occur in non-atopic individuals. On the other hand, we know from daily practice that many subjects sensitized to aeroallergens do not always experience allergic symptoms.[36,37] In our study, all investigated current allergic symptoms were positively associated with sensitization.[17] After stratification of the whole study population into children younger than or older than 6 years, we found that the associations of any of the investigated allergic symptoms with overall sensitization were limited to the children older than 6 years. No significant association could be documented in the group of children younger than 6 years. This might be due to the overlap of the "allergic" symptoms (such as sneezing, runny or blocked nose, cough and wheezing) with viral induced symptoms, which have a high prevalence in the younger age group. On the other hand, our data also illustrate that many children without sensitization still had identifiable "allergic" symptoms, confirming the observation that the development of allergic symptoms is not solely attributable to allergic sensitization and highlighting the need to further investigate the role of allergic sensitization in "allergic" symptoms.[30,38-41]

The personal and environmental factors significantly associated with the prevalence of sensitization and allergic symptoms in the AAS were age, gender, BMI, bedroom environment and exposure to pets.

Overall sensitization is significantly associated with increasing age. The significant association of sensitization with increasing age for individual allergens such as *D. pteronyssinus*, mixed grass pollens and tree pollens does correlate with the hypothesis that allergen exposure in childhood is a risk factor for sensitization.[1,5] For cat, dog, *Alternaria tenuis* and *Blatella germanica*, no statistically significant increase of sensitization with age could be documented. This might be due to the small numbers of subjects in the different age groups rather than a real lack of effect, or might be suggestive for induction of tolerance, as has been hypothesized previously by others for cat and

dog.[4,8,9,11]

Gender, especially male sex, is a known risk factor for sensitization and allergy.[42] Boys suffer more often from asthma than girls, while in adults the gender ratio is reversed.[43,44] The exact timing and underlying mechanism of this change in gender ratio and disease severity is not clear. Some studies suggest that an increase in sensitization alone can not explain this observation.[45] Data from our study show that children under the age of 8 years have a significantly higher male/female ratio of sensitization than children older than 8. This is prominent for all tested allergens. After the age of 8 years, male predominance persists, but a significant increase in percentage of sensitized females occurs. Our data showed, for the first time ever, the age of 8 to 10 years to be a pivotal time for the atopic child with a significant increase in prevalence of sensitization and a significant decrease in the male/female ratio. The observed gender differences and age-related changes may be related to differences in the hormonal environment.[15,46]

In the literature there are conflicting reports about the influence of BMI on the allergic status. A review confined to studies in children and adolescents on the possible association between obesity and asthma or asthma-like symptoms concluded that no study in a Western society has found objective evidence for the association, and results of some studies suggesting a possible association might be due to increased reporting of symptoms in obese children or to diagnostic bias.[47] Similar contradictory results were found for BMI and sensitization.[48-55] Our study showed an increased prevalence of sensitization in underweight girls only, not in underweight boys, nor in overweight or obese children. Reasons for the association of underweight and sensitization in girls are not clear. Nutritional status with nutritional deficiencies in certain nutrients or undernourishment might explain the higher degree of sensitization in underweight children, as a recent study by Chatzi et al[56] showed a potential protective effect of fruity vegetables and fish intake on childhood atopy. However this does not explain the gender difference in the relation between underweight and sensitization.

The strong positive association between obesity and exercise induced respiratory symptoms in both boys and girls is unlikely to be related to atopy, because neither association of obesity with sensitization nor association with other allergic respiratory symptoms, eczema or rhinoconjunctivitis could be found. Mechanical properties of the respiratory system[57,58] and poor physical fitness[51,57-60] may account for this result.

The protective effect of bedroom exposure to stuffed toys and non-synthetic bedding material could encompass several factors. Stuffed toys and non-synthetic bedding materials can be considered not only as reservoirs of house dust mites (HDM), but also as a reservoir of microbes and endotoxins. Several studies demonstrated a higher degree of sensitization (especially with exposure in infancy and early childhood)[61,62] and/or more allergic symptoms in persons who are more often exposed to allergens such as HDM.[63-65] On the other hand, the presence of microbes and endotoxins may be responsible for a lower prevalence of sensitization and allergic symptoms, as stated in the "hygiene hypothesis"[66] and as reported before.[67,68]

The reported data on the effect of pet ownership on the development of sensitization and allergic disease in children are conflicting.[69-71] The data on the effect of cat ownership are equivocal, with some studies suggesting an increase and others a decrease in risk of sensitization or allergic disease. For dogs, results are more consistent, generally suggesting that owning a dog has no effect or may be protective against the development of specific sensitization to dog and overall sensitization. Our results suggest that domestic cat exposure neither at birth nor at present has any effect on the subsequent development of sensitization and allergic disease. For dogs, the inverse association of sustained dog ownership (both at birth and at present) with overall sensitization, but not with allergic disease, suggests that only prolonged domestic dog allergen exposure, from birth on, may protect against sensitization. A number of interesting hypotheses to explain the relationship between dogs, immune development and atopic outcomes in childhood have been developed, but prove difficult to test.[72] It seems likely that the effect is mediated through stimulation of innate immune responses, although endotoxin levels by themselves do not always explain the relationship between dog ownership and atopic outcomes.[71,73-75]

As for all observational research, our data need to be interpreted with caution. First of all, we conducted a cross-sectional study implicating that we only measured sensitization, allergic symptoms and covariates at a single moment in time. Secondly, there might have been the potential of selection bias, recall bias and confounding. This has been discussed earlier.[15-22]

In conclusion, we studied the prevalence of sensitization to aeroallergens and allergic symptoms in a community population of schoolchildren, aged 3.4 to 14.8 years and found that 23.9% had evidence of allergic sensitization to aeroallergens. Our sensitization data are the first published data ever in unselected Belgian schoolchildren. The personal and environmental factors significantly associated with the prevalence of sensitization and allergic symptoms in the AAS were age, gender, BMI, the bedroom environment and exposure to pets.

The results of our study illustrate the complexity of the search for factors involved in the process of sensitization and allergic disease. Further large, prospective, population-based studies with accurate documentation of the coexisting genetic and environmental subtext and identification of the temporal "windows" are required to further elucidate any individual effect on sensitization and development of allergic disorders, in order to propose a strategy for the primary or secondary prevention of allergic diseases.

Acknowledgements

We thank the collaborators of the AAS (Patrick De Weert, Anne-Marie Van Heesvelde, Trees Evenepoel, Hedwige Creus, their colleagues and the nurses of the participating medical school centers, the colleagues and medical school students of the Department of Pediatrics of the O.L.Vrouw Hospital Aalst) for their support in realizing this project.

Funding: The Aalst Allergy Study was supported by an unrestricted grant from Numico, Stallergènes and UCB.
Ethical approval: This study was approved by the Ethical Committee of the University of Ghent. Informed consent was obtained from the parents of all participants.
Competing interest: None.
Contributors: Van Gysel D and Govaere E equally contributed to this paper. Van Gysel D, Govaere E and De Baets F wrote the protocol. Van Gysel D, Govaere E and Doli E performed the study. Van Gysel D and Govaere E analyzed the data and Verhamme KMC supervised the statistical analysis. Van Gysel D and Govaere E wrote the first draft of the paper and all contributors participated in the revision and final approval of the paper.

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Received December 22, 2008
Accepted after revision February 26, 2009