

Rhinitis in children: Co-morbidities and phenotypes

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Rhinitis and its co-morbidities affect quality of life; and in children, little is known. We therefore aimed to describe the co-morbidities and phenotypes of current rhinitis in 10-yr-old Norwegian children. We used information on rhinitis, asthma, allergic sensitization, anaphylaxis, and lung function tests from clinical examinations and structured parental interviews of 1019 children included in the birth cohort study, the Environment and Childhood Asthma Study, in Oslo. Current rhinitis was reported in 254 (25.0%) of the children, and 87.4% had at least one allergy-related co-morbidity of rhinitis, with conjunctivitis the most prevalent (75.6%). Overall, 11.8% of the children had conjunctivitis combined with current asthma and atopic eczema. Children with rhinitis were also more likely to have severe bronchial hyperresponsiveness (BHR) ($PD_{20} \leq 1 \mu\text{mol}$ methacholine) than children without rhinitis (17.5% and 5.8%, respectively, $p < 0.001$), as well as BHR ($PD_{20} \leq 8 \mu\text{mol}$). The children with rhinitis and allergic sensitization (72.8%) had more frequently BHR, severe BHR, and conjunctivitis, but did not differ with respect to any other co-morbidity from children with rhinitis without allergic sensitization. Children with symptoms reported by exposure to both pollen and furry pets had more often asthma, wheeze, and BHR compared to the children who reported rhinitis symptoms only when exposed to pollen (91.9% of these had symptoms in spring/summer only). In conclusion, current rhinitis is closely associated with conjunctivitis, asthma, atopic eczema, and BHR in childhood. Conjunctivitis and BHR were most strongly linked to rhinitis with allergic sensitization.

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Chronic rhinitis is a common disease that together with frequent co-morbidities such as asthma, bronchial hyperresponsiveness (BHR) (1, 2), conjunctivitis (3), and otitis media (1) may affect quality of life (1, 2). The co-morbidities have been described by the type of allergens associated with the rhinitis symptoms, and rhinitis related to exposure from perennial allergens has been more closely associated with asthma (2) and BHR (6) than with rhinitis related to pollen exposure. It is, however, unclear whether patients who are sensitized to more than one allergen (polysensitization) have more co-morbidities and more severe phenotypes than those who are monosensitized (7).

Although co-morbidities of allergic rhinitis are well described in adult populations, less is known in childhood (1, 7).

Immunoglobulin E (IgE)-mediated hypersensitivity of the nose often referred to as allergic rhinitis is currently classified into intermittent and persistent, as well as mild or moderate severe (9). Although allergens are common elicitors of rhinitis symptoms, rhinitis may also be precipitated by infections, occupational exposure, drugs, hormones, foods, tobacco smoke, emotions, and physical or chemical triggers (9). For practical purposes and lack of adequate phenotype categories in childhood, the majority of children with rhinitis symptoms outside

respiratory infections have been classified by the presence or absence of IgE or skin-test reactivity to allergens, into allergic or non-allergic rhinitis (3). However, the role of allergens in elicitation of rhinitis in the absence of evidence of systemic IgE sensitization may be underappreciated, as local IgE production may underlie the disease expression (10), and little is known on the phenotypes and co-morbidities of rhinitis in children without detectable systemic IgE sensitization (7, 11).

We therefore aimed to investigate the co-morbidities of current rhinitis in 10-yr-old children and secondly to describe the clinical phenotypes identified and the treatment reported for rhinitis in this age group.

Material and methods

Study design and subjects

The present study is part of the birth cohort study the Environment and Childhood Asthma Study (ECA) initiated in Oslo in 1992 and described in detail elsewhere (12). The study enrolled 3754 healthy full-term babies whose parents were sufficiently skilled in Norwegian language to complete the 6-monthly questionnaire from birth to 2 yr of age.

Within the birth cohort, 802 children, not differing from the entire general birth cohort population with respect to most relevant factors (12), had lung function measured at birth (13). At 2 yr of age, a nested case-control study recruited 612 children from the entire ECA study, including children with recurrent or persistent

bronchial obstruction (rBO) by 2 yr and controls with no bronchial obstruction born closest in time to the cases (14). The children were clinically examined 1–2 times between birth and the age of 2, with at least one investigation in 562 children (Fig. 1).

All the 1215 children with lung function measured at birth and/or a clinical investigation by 2 yr were invited to participate in a 10-yr follow-up. In total, 1019/1215 (84%) (Fig. 1) of the children participated in the 10-yr follow-up study with clinical examinations performed at least 4 wk after any suspicion of respiratory tract infection. The examinations included blood tests, skin prick tests for allergic sensitization, lung function by forced flow-volume measurements, bronchial hyperresponsiveness measures by methacholine challenge test, and a treadmill exercise test, as well as a parental structured interview.

Comparison of the demographic birth characteristics of the children included in the follow-up and those who were not included have previously been described (15). The included ($n = 1019$) and non-included children ($n = 2735$) were in general comparable, except that the included children had more often parents and/or siblings with rhinoconjunctivitis (31.7%) compared to the non-included children (26.9%), $p = 0.004$ and 17.7% vs. 14.8%, respectively ($p = 0.03$) for asthma.

Written informed consent was obtained from the parents, and the study was approved by the Regional Committee for Ethics in Medical Research and the Norwegian Data Inspectorate and reported to the Norwegian Biobank Registry.

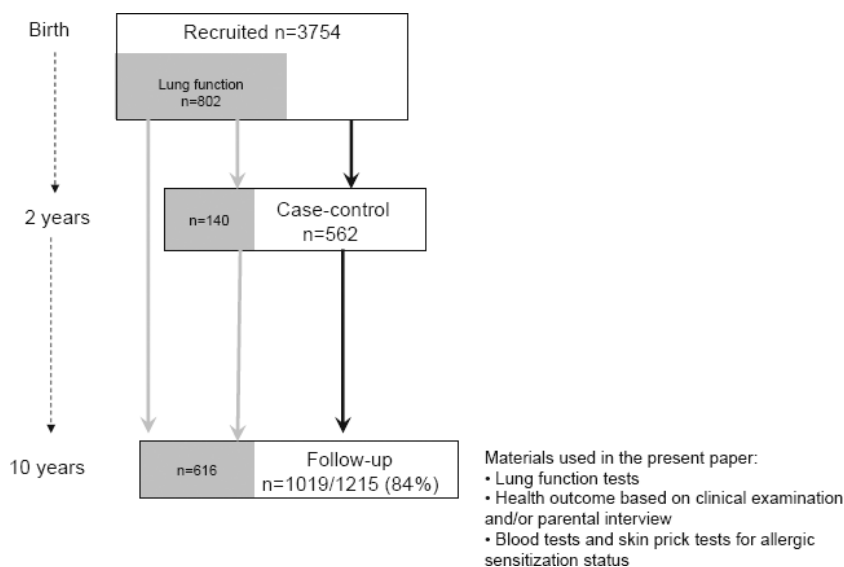


Fig. 1. Illustration of the Environment and Childhood Asthma Study design, with the number of children included in the 10-yr follow-up. The 1215 children who were invited to the follow-up were all traceable children with either lung-function measured at birth ($n = 802$) and/or included in the case-control group at 2 yr ($n = 562$). Of the 1019 children included in the follow-up, 616 children had lung-function measured at birth. Only outcomes from the 10-yr follow-up were used in the present study.

Methods

The 10-yr follow-up. A parental structured interview included central International Study of Asthma and Allergies in Childhood (ISAAC) questions related to allergic and airway symptoms of the child, in addition to detailed questions regarding environmental exposure, life-style, diseases (index child and family), and medication. The questions related to rhinitis focused upon symptoms, medication, triggers, and the impact the symptoms had on daily life activities (Fig 1). Similar specific questions related to asthma, atopic eczema, and anaphylaxis were included, but not reported in detail in the present paper.

Skin prick tests (SPT) were performed according to the European standard (16) with the following standardized allergen extracts from ALK (Soluprick[®], ALK-Abello, Denmark): House dust mites (HDM) (*Dermatophagoides pteronyssinus* and *Dermatophagoides farinae*), German cockroach, dog, cat and rabbit, birch, timothy (grass) and mugwort pollens, molds (*Cladosporium herbarium* and *Alternaria*), egg white, milk, peanut, and codfish. SPT were considered positive with a mean wheal diameter at least 3 mm larger than the negative control (saline).

Total and specific serum IgE (IgE and sIgE, respectively) were analyzed with a radioallergo-sorbent fluorescence immunoassay (ImmunoCAP[®] system, Phadia, Uppsala, Sweden) according to the instructions by the manufacturer. Specific IgE was analyzed with the same

panel of allergens as for SPT and considered positive with sIgE ≥ 0.35 kU/L. The lower detection limit was 0.1 kU_A/L for sIgE and 0.1 PAU/L for total IgE.

Baseline spirometry was measured according to European standards (17) on a Sensor Medics Vmax 20c (SensorMedics Diagnostics, Yorba Linda, CA, USA) prior to and after methacholine and exercise challenge tests on separate days. Lung function was reported as percent predicted of forced expiratory flow at 50% of vital capacity (FEF_{50}) and forced expiratory volume in one-second (FEV_1) [reference values of healthy 10-yr-old children from the ECA study obtained by methods described by Stanojevic et al. (18)].

BHR was tested directly and indirectly, respectively by:

- 1 Methacholine challenge test assessed according to international guidelines (19), by doubling the cumulative dose of methacholine and reported as the dose of methacholine causing a fall in FEV_1 of 20% from the (post-saline) baseline value (PD₂₀ methacholine)
- 2 A standardized exercise test (20) performed on the second day by a 6- to 8-minute treadmill run at 95% estimated maximum pulse level, and an incline of 5% of the treadmill. The response was measured as maximum fall in FEV_1 assessed before and 3, 6, 10, and 15 min after running. The exercise test was considered positive for exercise-induced bronchoconstriction (EIB) with a fall in $FEV_1 > 10\%$ of baseline FEV_1

Table 1. Questions related to symptoms, triggers, and medical treatment of rhinitis from the structured parental interview at the 10-yr follow-up (the questions are translated from Norwegian)

Interview questions	Outcomes
Has the child had any of the following symptoms during the last 12 months (without a cold): a) runny nose, b) blocked nose, c) sneezing, d) itchy/runny eyes?	Rhinitis (a, b, and/or c) Conjunctivitis (d)
What is causing the eye/nose symptoms? a) Not known b) Dog c) Cat d) Other furry pets e) Other causes f) Pollen from trees g) Other pollens h) Temperature changes/physical activity	Unknown cause of symptoms (a) Symptoms related to furry pets (b,c, d) Symptoms related to pollens (f, g) Symptoms related to furry pets and pollens (b, c d and b, c) Symptoms related to other causes than allergens (e, h) Time of year when symptoms occur
Does the child have symptoms of rhinitis during a) the whole year, b) spring/summer or c) autumn/winter	
How much impact have these symptoms had on daily-life activities? a) None b) A little c) Moderate d) Severe	Impact on daily activities
Has the child ever been given the diagnosis hayfever/allergic rhinitis?	Doctor diagnosed hayfever ever
What kind of treatment has the child received because of symptoms of rhinitis? a) none b) don't know c) topical antihistamines d) systemic antihistamines e) topical corticosteroids f) systemic corticosteroids g) sodium cromoglycate h) leukotriene antagonist i) immunotherapy j) homeopathy k) other alternative medicine	Received medical treatment because of rhinitis (b–i) Alternative medicine (j–k)

Definitions

Allergy-related co-morbidities of rhinitis were defined as current conjunctivitis, asthma, atopic eczema, otitis media, and reported anaphylaxis (ever).

Current rhinitis was present in a child reporting at least one of the following symptoms during the last 12 months (without a cold): runny nose, blocked nose, or sneezing (Table 1). *Conjunctivitis* required a report of itchy/runny eyes during the last 12 months.

Rhinitis with allergic sensitization was defined in a child with rhinitis combined with at least one positive SPT and/or sIgE to any of the *inhalant* allergens: *seasonal* (pollens or molds) or *perennial* (house dust mites, cat, dog, rabbit, or cockroach). *Mixed sensitization* was defined with SPT/sIgE positive to at least one seasonal and one perennial allergen.

Bronchial hyperresponsiveness was defined as a categorical variable with three groups: PD₂₀ methacholine ≤ 1 μ mol, > 1 to ≤ 8 μ mol, and > 8 μ mol, and as a continuous variable with the methacholine dose-response slope (DRS) calculated from each individual (percent decline in FEV₁ after the final dose of methacholine divided by the cumulative dose of methacholine inhaled) (21).

Asthma was defined by the presence of at least two of the three criteria; asthma symptoms, doctor diagnosis of asthma, and/or use of asthma medication. *Current asthma* was defined in children by asthma plus at least one of the following criteria; asthma symptoms or use of asthma medication within the last 12 months and/or a positive exercise challenge test at the 10-yr follow-up visit (12).

Current wheeze required a positive response to the question 'Has your child experienced heavy breathing, chest tightness and/or wheezing during the last 12 months?'

Otitis media was defined by reported otitis media during the last 12 months.

Atopic eczema was determined as current or ever with a positive response within the last 12 months or ever, respectively, and *anaphylaxis* by a positive response to having ever had anaphylaxis.

Statistical analyses

To adjust for the enrichment of children with bronchial obstruction during the first 2 yr of life, an overall prevalence of rhinitis was calculated by the weighted mean of the prevalence of rhinitis for the following groups: (i) rBO by age 2 (ii) controls, and (iii) the follow-up children

who were not included in the case-control group. The rhinitis prevalence was calculated for girls and boys separately (six groups in total), and the weight was the number of children in each group. The calculated weighted prevalence is reported with confidence intervals. Categorical variables were compared using Pearson's chi-square test. One-way ANOVA analysis was used to compare DRS and total IgE (both log-transformed) and presented as geometric mean with 95% confidence intervals (95% CI). FEV₁ and FEF_{50%} predicted were presented as mean with 95% CI. A logistic regression analysis was used to assess the association between current rhinitis and increasing number of sensitizing allergens. P-values ≤ 0.05 were considered significant. Statistical analyses were performed with Statistical Package for Social Sciences (SPSS version 14.0; SPSS Inc., Chicago, IL, USA).

Results

Prevalence of symptoms of current rhinitis

Information on current rhinitis was available for 1015/1019 children from the 10-yr follow-up, and 254 (25.0%) of these children had symptoms of current rhinitis. More than one symptom was reported by 72%. The crude prevalence was similar to the calculated prevalence adjusting for the enrichment of children with rBO during the first 2 yr of life: 25.0%, 95% CI: (22.3, 27.7).

Rhinitis co-morbidities

At least one allergy-related co-morbidity was reported in 87.4%, and 43.4% had at least two co-morbidities (Fig. 2). Combined rhinoconjunc-

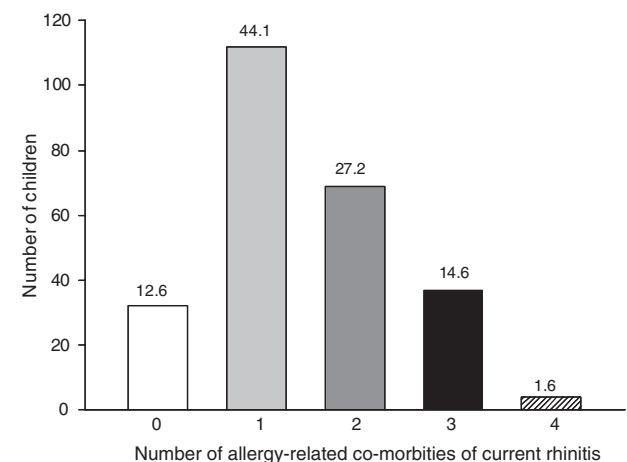


Fig. 2. Bars referring to number of children with none, 1, 2, 3, or 4 allergy-related co-morbidities of current rhinitis: conjunctivitis, current asthma, current atopic eczema, otitis media, and anaphylaxis (percent given above each bar).

tivitis, current asthma, and atopic eczema were found in 11.8%. The most common co-morbidity to rhinitis was conjunctivitis symptoms (itchy or runny eyes) reported in 192/254 (75.6%) whereas the latter was reported as the only symptom in 28 children. Compared to those without rhinitis, children with current rhinitis had a higher prevalence of current asthma (31.7%), wheeze (32.1%), current atopic eczema (30.3%), and more frequently BHR ($PD_{20} \leq 8 \mu\text{mol}$), severe BHR ($PD_{20} \leq 1 \mu\text{mol}$) as well as higher DRS (all $p < 0.001$, Table 2), but similar frequency of anaphylaxis ($n = 8$ and 6 , respectively). Children with combined rhinoconjunctivitis symptoms did not differ in other co-morbidities compared to children with rhinitis symptoms only. Children with rhinitis had similar rates of allergic sensitization whether they had asthma or not (78.5% and 70.0% respectively, $p = 0.16$). The children with rhinitis, but no asthma, had more frequently BHR ($PD_{20} \leq 8 \mu\text{mol}$) than children with neither asthma nor rhinitis (29.2% and 21.7%, respectively) and similar for severe BHR ($PD_{20} \leq 1 \mu\text{mol}$) (10.1% and 4.7%, respectively), $p = 0.001$.

Allergic sensitization and rhinitis phenotypes

Timothy grass, birch, dog, cat, and mugwort were the most prevalent sensitizing inhalant

allergens in the present study (Fig. 3a). In addition to the male preponderance for current rhinitis (59.4% boys) (Table 2), boys had also more often rhinitis combined with sensitization to inhalant allergens (65.9%) (Table 3). Girls were more likely to report symptoms of rhinitis without being sensitized to any inhalant allergens (58.0%). Among children with rhinitis, 185 (72.8%) were sensitized to at least one inhalant allergen and the majority had mixed sensitization (64.9%), whereas 25.9% were sensitized to seasonal allergens only. Rhinitis children *with* compared to children *without* sensitization to inhalant allergens had significantly more often conjunctivitis (85.9% vs. 47.8%, respectively, $p < 0.001$), BHR and severe BHR and a positive EIB test (Table 3). They were similar in relation to current asthma, wheeze, otitis media, and atopic eczema (Table 3).

The children who were sensitized to more than one allergen (polysensitization) ($n = 266$) were twice as likely to have current rhinitis compared to the children who were monosensitized ($n = 83$) (59.8% vs. 31.1%, respectively, $p < 0.001$). The 26 rhinitis children who were monosensitized were mostly sensitized to pollens; timothy grass ($n = 11$), birch ($n = 10$), and mugwort ($n = 2$). More severe BHR ($PD_{20} \leq 1$) was common for children with polysensitization compared to children who were monosensitized

Table 2. Co-morbidities and clinical characteristics for children with and without current rhinitis at 10 yr of age (percent unless otherwise stated)

	No rhinitis $n = 761(75\%)$	Current rhinitis $n = 254 (25\%)$	p-Value
Gender (boys)	52.3	59.4	0.048
Conjunctivitis	3.7	75.6	<0.001
Current asthma	10.3	31.7	<0.001
Current wheeze	7.6	32.1	<0.001
Otitis media last year	7.1	9.1	0.3
Atopic eczema			
Previous	12.8	20.1	0.004
Current	18.2	30.3	<0.001
Anaphylaxis (ever)	1.1	2.4	0.1
FEV ₁ % predicted [mean (95% CI)]	99.6 (98.9, 100.3)	99.4 (98.1, 100.6)	0.8
FEF ₅₀ % predicted [mean (95% CI)]	98.8 (97.3, 100.4)	96.8 (94.3, 99.4)	0.2
PD ₂₀ methacholine			
$\leq 1 \mu\text{mol}$	5.8	17.5	
>1 to $\leq 8 \mu\text{mol}$	21.5	30.6	<0.001
$>8 \mu\text{mol}$	72.7	52.0	
DRS [GM (95%CI)]	1.07 (0.96, 1.20)	2.63 (2.09, 3.31)	<0.001
Exercise-induced bronchoconstriction	16.5	22.0	0.069
Sensitization to inhalant allergens			
None	78.4	27.2	
Seasonal	7.4	18.9	<0.001
Perennial	6.2	6.7	
Seasonal and perennial (mixed)	8.0	47.2	
Sensitization to food allergens	8.8	37.3	<0.001
Total IgE [GM (95%CI)]	35.7 (32.0, 39.7)	128.8 (105.4, 157.4)	<0.001

Significant P-values ($P < 0.05$) are highlighted in bold.

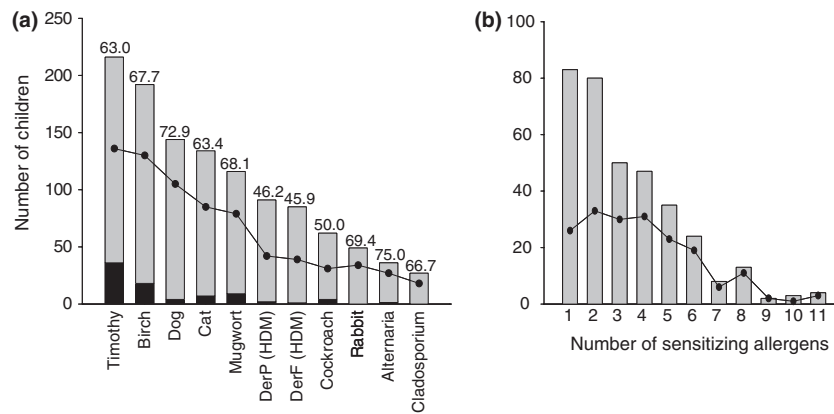


Fig. 3. (a) Grey bars represent the number of children with sensitization to each of the specific inhalant allergens tested with increasing order from the most common (timothy grass) to the least common (Cladosporium), and the black fields of the bars represent the number of children with monosensitization. The dots represent the number of children for each specific sensitizing allergen who also had current rhinitis (percent with current rhinitis is given above each bar). (b) Grey bars represent the number of children with monosensitization (sensitized to only one allergen) and the number of children sensitized from 2 and up to 11 inhalant allergens tested (polysensitization). The dots represent the number of children with current rhinitis.

Table 3. Co-morbidities and phenotypes of rhinitis for children without and with sensitization to inhalant allergens (percent unless otherwise stated)

	Rhinitis without sensitization to inhalant allergens, n = 69	Rhinitis with sensitization to inhalant allergens, n = 185	p-Value
Gender (boys)	42.0	65.9	0.001
Conjunctivitis	47.8	85.9	<0.001
Current asthma	25.0	34.3	0.2
Current wheeze	23.5	35.3	0.08
Otitis media last year	5.8	10.3	0.3
Atopic eczema			
Previous	18.8	20.5	0.8
Current	27.5	31.4	0.6
Anaphylaxis (ever)	1.4	2.7	0.6
FEV ₁ % predicted [mean (95% CI)]	99.1 (96.8, 101.5)	99.5 (98.1, 100.6)	0.8
FEF ₅₀ % predicted [mean (95% CI)]	97.2 (92.8, 101.5)	96.7 (93.6, 99.8)	0.9
PD ₂₀ methacholine			<0.001
≤ 1 μmol	4.3	22.4	
>1 to ≤ 8 μmol	24.6	32.8	
>8 μmol	71.0	44.8	
DRS [GM (95%CI)]	1.25 (0.89, 1.76)	3.44 (2.60, 4.54)	<0.001
Exercise-induced bronchoconstriction	11.3	25.6	0.030

Significant P-values ($P < 0.05$) are highlighted in bold.

(20.5% and 9.8%, respectively, $p = 0.005$), and polysensitized children had also more often current asthma (29.0%) than the children with monosensitization (13.4%), $p = 0.005$. Moreover, the likelihood of rhinitis increased with increasing number of allergic sensitizations (Fig. 3b), with odds ratio 1.45, 95% CI: (1.25, 1.68), $p < 0.001$.

Specific triggers of rhinitis symptoms were not identified in 55 children, and only five reported symptoms triggered by temperature alterations or physical activity. The remaining 194 children reported rhinitis symptoms triggered by aller-

gens. They were more likely to be allergic sensitized (85.1%) and to suffer from conjunctivitis (88.7%) than those with unknown or non-allergen triggers (33.3%), (both $p < 0.001$). There was also a tendency towards more wheeze in the children with allergen-triggered rhinitis ($p = 0.057$), but they were otherwise comparable in relation to current asthma, atopic eczema, otitis media, anaphylaxis, BHR, and EiB (all $p > 0.2$).

Overall, 178/254 (70.1%) reported rhinitis symptoms after exposure to pollen (125 to pollen only and 53 to pollen and furry pets), whereas 15

children reported symptoms only when exposed to furry pets. Children with both pollen and furry pets as perceived triggers had more frequently co-morbidities of BHR, asthma, and wheeze compared to the children with symptoms only related to pollen (Table 4). The majority of the children with pollen-triggered rhinitis had a mixed sensitization status (50.4%), whereas 28.8% were sensitized to seasonal allergens only and 18.4% were not sensitized to any inhalant allergens (Table 4). As expected, most of the children with rhinitis related to pollen exposure only reported symptoms in spring/summer season (91.9%). In spite of less co-morbidities, they were more likely to have symptoms with moderate/severe impact on daily life activities (52.0%) compared to children with pollen and furry pets as perceived triggers (35.8%, $p = 0.048$).

Regardless of rhinitis symptoms, the children with mixed sensitization had more frequently severe BHR ($PD_{20} \leq 1$) (23.5%) than the children with a seasonal allergen sensitization only (7.8%), $p = 0.001$ and similar for DRS [GM: 3.15, (95% CI: 2.3, 4.24) for mixed vs. 1.45 (1.02, 2.05) for seasonal sensitization, $p = 0.001$]. However, the children with sensitization to perennial allergens *only* did not differ in BHR

(PD_{20} methacholine and DRS) from the children with a mixed sensitization (both $p > 0.1$).

Medical treatment of rhinitis

Medical treatment was reported in 177 (69.7%) children with current rhinitis, most often systemic ($n = 149$, 58.7%) or topical (38.6%) antihistamines. The 75 children treated with one mode of medication only most often had systemic (31%) followed by topical (8%) antihistamines or intra-nasal corticosteroids (3%). The majority of medically treated patients (57%) reported more than one medication, most often systemic as well as topical antihistamines ($n = 39$, 22%), followed by systemic antihistamines combined with topical corticosteroids (5%) or sodium cromoglycate (3%). In addition, 56 children reported three or more types of medications, mostly systemic and topical antihistamines combined with local corticosteroids (8%) or sodium cromoglycate (7%), or a combination of all four (4%). Only six of the children received leukotriene antagonists combined with antihistamines and corticosteroids medication.

Treatment with alternative or complementary medicine was reported in 18 children (7.0%), 14

Table 4. Co-morbidities and clinical characteristics for children with symptoms of rhinitis triggered by pollen only or by pollen *and* furry pets (percent unless otherwise stated)

	Symptoms related to pollen only (n = 125)	Symptoms related to pollen <i>and</i> furry pets (n = 53)	p
Gender (boys)	57.6	64.2	0.4
Conjunctivitis	89.6	88.7	0.9
Current asthma	28.5	47.1	0.018
Current wheeze	29.6	49.1	0.013
Otitis media last year	8.8	15.1	0.2
Atopic eczema			
Previous	17.6	22.6	0.8
Current	32.8	39.6	0.4
FEV ₁ % predicted [mean (95% CI)]	99.8 (98.1, 101.4)	98.5(95.4, 101.6)	0.5
FEF ₅₀ % predicted [mean (95% CI)]	98.6(94.8, 102.4)	91.4 (86.1, 97.8)	0.06
PD ₂₀ methacholine			
$\leq 1 \mu\text{mol}$	12.2	32.1	
>1 to $\leq 8 \mu\text{mol}$	27.6	32.1	0.002
$>8 \mu\text{mol}$	60.2	35.8	
DRS [GM (95%CI)]	2.2(1.6, 3.0)	5.0(2.9, 8.6)	0.008
Exercise-induced bronchoconstriction	17.2	25.0	0.3
Sensitization to inhalant allergens			<0.001
None	18.4	7.5	
Perennial	2.4	7.5	
Seasonal	28.8	7.5	
Seasonal and perennial (mixed)	50.4	77.4	
Total IgE [GM(95%CI)]	142.5(109.8, 184.9)	283.9(172.8, 466.2)	0.008
Symptoms in spring/summer only*	91.9	49.1	<0.001
Moderate/severe impact on daily life activities	52.0	35.8	0.048
Doctor-diagnosed hayfever	54.8	84.6	<0.001
Any rhinitis treatment	84.0	90.6	0.3

*The children who did not have symptoms in spring/summer season only had symptoms throughout the year (none had symptoms exclusively during winter season). Significant P-values ($P < 0.05$) are highlighted in bold.

with homeopathic medicine. The alternative medicine was mostly ($n = 16$) used as complementary to traditional medicine.

Discussion

Current rhinitis was reported in 25.0% of 10-yr-old children and was associated with at least one allergy-related co-morbidity in 87.4%, and 43.4% had at least two co-morbidities. Most common were conjunctivitis, current asthma, and atopic eczema, but the children with rhinitis were also likely to have current wheeze and BHR. Seventy-three percent of the children with rhinitis were sensitized to at least one inhalant allergen and these children had more frequently conjunctivitis and BHR, but did not differ in other co-morbidities compared to the rhinitis children with no allergic sensitization.

As many as 11.8% of the children with current rhinitis (3.0% of all children in the present study) had all three co-morbidities of conjunctivitis, asthma, and atopic eczema present, which are much higher than the reports from the ISAAC study (0.6–1.1% of 13- to 14-yr-old children from Europe) (22). For the rhinitis children in the present study, conjunctivitis was the most commonly reported co-morbidity by 75.5%. Thus, rhinoconjunctivitis is likely to be one disease entity for the majority of children in this age group with allergic sensitization and rhinitis. The 25.0% prevalence of current rhinitis in the present study is in line with the findings of the ISAAC study, phase three (22) that reported symptoms of rhinitis in 23.4–31.2% of the 13- to 14-yr old European children. Current nose and eye symptoms were reported for 9.8–15.2% (22) compared to 18.9% in the present study.

The link between asthma and allergic rhinitis is well established (9) and confirmed in the present study as almost one in three children (31.7%) with rhinitis had asthma. We also found that BHR was associated with rhinitis, as has previously been confirmed by others (23), but not different between children with rhinitis *with* and *without* conjunctivitis, as in line with the Manchester Asthma and Allergy Study (MAAS) study (24). Although BHR is a feature of asthma, it is non-specific, and in the present study, BHR was associated with rhinitis also in children *without* current asthma. Moreover, because rhinitis and asthma often co-exist, co-morbidities and symptoms of chronic rhinitis may be attributed to a common airway disease starting at the nose and including asthma (1, 2). However, allergic sensitization in children with rhinitis was similar in children without (70.0%) and with asthma (78.5%) supporting

the notion that the co-existence of asthma and rhinitis is not solely because of atopic predisposition in these two diseases (2).

Children in the present study with rhinitis were much more likely to suffer from conjunctivitis symptoms if they had allergic sensitization (85.9% vs. 47.8%) most commonly to both seasonal and perennial allergens. This is in line with another report (80% mixed sensitization) although including only subjects that suffered from allergic rhinitis alone (25). In that study, conjunctivitis was reported to be more common among subjects with seasonal (64.9%), than with perennial (46.4%) or mixed sensitization (47.9%) (25). In phase two of the ISAAC study (3), associations of rhinoconjunctivitis were more common with sensitization to seasonal allergens [population attributable fraction in affluent countries (36%)] than with perennial allergens (25%). However, mixed sensitization status was not assessed in the ISAAC study. Also, the present children with rhinitis symptoms reported to be triggered by exposure to both pollen and furry pets had more asthma, wheeze, and frequently BHR than children with symptoms reported to be triggered exclusively by pollen. Also, in regard to sensitization status, children with a mixed sensitization had more severe BHR than children sensitized to seasonal allergens only. Others have also reported that the risk of asthma was higher for young adults with rhinitis when exposed to pollens or to animals compared to those with rhinitis related to only one of these triggers (2). Moreover, sensitization with concomitant exposure to perennial allergens is shown to enhance the development of BHR in children with asthma or wheeze (26). However, in the present cohort, home allergen exposure was measured by dust sampling from the children's mattresses, and children with current rhinitis and/or allergic sensitization to any allergen or to cat or dog allergens, had in general lower concentrations of allergens than children without rhinitis. Increasing dog allergen levels were associated with less BHR (reduced DRS) (manuscript submitted). Thus, because of the confounding effect of pet avoidance in these families with children with rhinitis (15), it is difficult to know whether sensitization combined with exposure to the sensitizing allergen would result in more co-morbidities than for sensitization alone.

A higher prevalence of current rhinitis and in particular, current rhinitis combined with sensitization to inhalant allergens was observed among boys compared to girls. Although rhinitis prevalence have not usually been reported for boys and girls separately (3, 22), the difference

observed among boys and girls in the present study was expected as a male preponderance to allergic disease is often observed in pre-puberty as reported by others (7) and for the children in the present study (manuscript submitted).

Pollen particles may be quite large and are thus more easily trapped in the nose, inducing a local allergic response, without necessarily inducing symptoms in the lower respiratory system (30). This could explain why children with pollen-triggered rhinitis had less often co-morbidities of current asthma, wheeze, and BHR compared to children with symptoms triggered by pollen and furry pets. In addition, continued exposure from perennial allergens may be more relevant to the risk of developing asthma, when compared to exposure to pollens that occurs only during a limited time period of the year. Nevertheless, severe symptoms on daily life activities were mostly reported by children who had pollen-triggered rhinitis, which may be explained by these patients being less well adapted to bouts of sneezing and runny nose during the pollen season, in comparison with the patients with more chronic nasal obstruction because of exposure to perennial allergens. Furthermore, the majority of children without detectable allergic sensitization still reported symptoms of rhinitis related to allergens (most often pollen). This is in line with reports on patients with non-allergic rhinitis who most frequently reported exposure to pollen (and house dust) as the cause of their rhinitis symptoms (31).

In the present study, more children were sensitized to cat and dog allergens (also in regard to monosensitization) than to house dust mite allergens as can be seen in Fig. 3. Twenty-five children with rhinitis were sensitized to both pollen and HDM allergens; however, 18 of these children were *also* sensitized to pet allergens, which illustrate the importance of pet (cat and dog) allergen exposure in this and other areas with similar climate and culture. Reports from Norway and from Sweden have confirmed our finding with mite sensitization being less common than cat and dog sensitization, and HDM allergens are less often detected in dust samples when compared to cat and dog allergens (32–34). In particular, only 12% of 797 mattress dust samples collected from the beds of children included in the present study had detectable concentrations of Der p1 allergens (manuscript submitted). However, HDM as a trigger of symptoms is often difficult to ascertain during an interview apart from persistency of rhinitis. But based on the low number of dust samples with detectable HDM allergens and no difference observed between

children with and without rhinitis with regard to the geometric mean concentrations of Der p1 ($p = 0.9$, ANOVA), we do not think that HDM exposure is an important rhinitis trigger for the children in the present study.

In the present study, 7.0% of the children with rhinitis had used alternative medicine, and most often homeopathic medicine. In a large study from Germany and Switzerland, allergic rhinitis was one of the most common diagnoses among patient using homeopathic medicine (35). The frequent use of alternative and complementary medicine in children with rhinitis and asthma is most often because of dissatisfaction with conventional therapies and concerns about steroid side effects (36).

Strengths and limitations of the study

The present 10-yr follow-up study is asthma enriched because of the inclusion of the nested case-control group (at 2 yr of age), but no difference was seen between the weighted and the crude prevalence of current rhinitis for the included children. However, a strength of the current study is the careful characterization of the population, whereas cohort effects in prospective studies limit the generalization of the prevalence figures to random population samples. The latter was however not a major point whereas the main aim was to describe the co-morbidity and phenotypes associated with rhinitis. The phrasing of the questions regarding rhinitis in the parental interview does not allow us to categorize the children according to the Allergic Rhinitis and its Impact on Asthma (ARIA) document (9) that recommends that the old terms 'seasonal' and 'perennial' should be replaced by the terms intermittent allergic rhinitis and persistent allergic rhinitis, respectively. Many of the children in Oslo with symptoms related to pollen would be in the category of persistent allergic rhinitis, due a long pollen season [several months (including 6–8 wk for grass pollen)]. Patients with pollen-triggered rhinitis may have a greater bronchial hyperresponsiveness during spring/summer seasons (25), but in the present study, we aimed to avoid clinical examinations and methacholine challenge testing during the pollen season. We cannot exclude the presence of rhinosinusitis (infectious rhinitis) (9) in the children with unknown triggers of rhinitis, but the majority reported nevertheless their symptoms to be triggered by allergen exposure. Furthermore, the lack of statistically significant differences in anaphylaxis related to rhinitis co-morbidities may be related to small

numbers of children with this life-threatening condition.

In conclusion, current rhinitis was reported in 25.0% of the 10-yr-old children and was associated with at least one allergy-related co-morbidity in 87.0%, as well as more often severe BHR and wheeze. Conjunctivitis and BHR were associated with rhinitis with allergic sensitization. The majority of the children had a mixed sensitization status, but symptoms triggered by pollen exposure only had the greatest impact on daily life activities.

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