Novel views on endotyping asthma, its remission, and COPD

Carpaij, Orestes

DOI:
10.33612/diss.136744640

Chapter 3

Childhood factors associated with complete and clinical asthma remission at 25 and 49 years

Orestes A. Carpaij #, Maartje A.E. Nieuwenhuis #, Gerard H. Koppelman, Maarten van den Berge, Dirkje S. Postma, Judith M. Vonk

#: shared first author

Eur Respir J. 2017 Jun 8;49(6)

Abstract

While asthma is a chronic respiratory disease without cure, asthma remission is the highest attainable goal for patients. The aim of this study is to assess asthma (remission) persistence till age of 49 and which factors in childhood are associated with clinical and/or complete asthma remission.

In 1972-1976, children diagnosed with clinical asthma were characterized (questionnaires, peripheral blood, bronchial hyperresponsiveness, lung function and skin prick tests (SPT)) and were re-examined in young adulthood and late adulthood. In these latter visits, the subjects were divided in three groups: persistent asthma (PersA), clinical- (ClinR) and complete asthma remission (ComR).

188 subjects were seen at age 25 (±21), while 102 were seen at age 48.9 (±2.1). 66 subjects were completely characterized in all three visits. At 49 years, 75.0% of the ComR subjects did not relapse in asthma. Childhood factors associated with ComR compared to PersA were having a leukaemia positive family history, a higher FEV_1/FVC ratio, a positive mould SPT, less childhood wheeze during a cold and having an atopic mother.

It is possible to have persistent remission after childhood asthma over 39 years of follow-up. Therefore is important to find out which genetic and/or environmental factors drive asthma remission.

Introduction

Asthma can go into remission later in life in approximately 35% of all patients [1]. Asthma remission is associated with childhood onset of asthma [2, 3], the male sex, smoking cessation, initially less severe airway obstruction and, notably, more severe bronchial hyperresponsiveness (BHR) [4, 5]. Unfortunately, patients in asthma remission may show relapse later in life. Data regarding childhood factors that predict clinical asthma remission in adulthood are sparse, and even fewer data on complete asthma remission [6] or the persistence of asthma remission throughout the lifespan are presently available. Therefore, the aim of the current study is to explore whether asthma remission persists in children, followed from childhood up to an average age of 49 years. Furthermore, we determined which factors in childhood are associated with clinical and/or complete asthma remission that persists during adulthood.

Methods

An asthma cohort was created from 1972–1976 (visit 1) and re-investigated from 1987–1989 (visit 2) [7] and 2013–2014 (visit 3). At visit 1, 406 children diagnosed with asthma were referred to the University Medical Center Groningen, and characterised by extensive standardised questionnaires, peripheral blood measurements, BHR, lung function and skin prick tests. At visit 2, 285 children (209 children with BHR at visit 1) were re-examined in young adulthood. At visit 3, 102 subjects with BHR at visit 1 were included and re-examined.

Predicted spirometry values at all visits were those of Quanjer [16]. At visit 1 and 2, the histamine concentration (range 0.5 to 32 mg/ml) with a decrease in FEV_1 >10% from pre-challenge FEV_1 was taken as the threshold for BHR. At visit 3, the BHR-test was discontinued if the FEV1 decreased ≥20% from pre-challenge FEV_1 or if the highest dose of methacholine bromide (range 0.038 – 39.3 mg/ml) had been given. The skin prick test (SPT) was regarded positive if the mean of the perpendicular diameters of the wheal was > 0.7 times the mean diameter of histamine as positive control.

The presence of persistent asthma (PersA), clinical asthma remission (ClinR) and complete asthma remission (ComR) was determined at visits 2 and 3. ClinR was defined

as the absence of symptoms (dyspnoea attacks and/or wheezing), without asthma medication over the last year, irrespective of the presence or absence of a positive BHR test (visit 2: PC_{10} (provocative concentration causing a 10% fall in FEV_1 (forced expiratory volume in 1 second) histamine ≤16 mg/ml; visit 3: PC_{20} methacholin ≤39.3 mg/ml) and/or normal FEV_1 (>80% predicted pre-bronchodilator). ComR was defined as ClinR, combined with a negative BHR test and a normal FEV_1 (>80% predicted pre-bronchodilator) (figure 1). Subjects with PersA still had symptoms and/or used asthma medication. Associations between childhood factors and asthma outcome (ComR versus PersA and ComR/ClinR versus PersA) at visits 2 and 3 were studied, by performing multivariate logistic regression with adjustments for sex and age at visit 1 using the SPSS 22 software (SPSS Inc, Chicago, IL, USA). A P-value <0.05 was considered statistically significant.

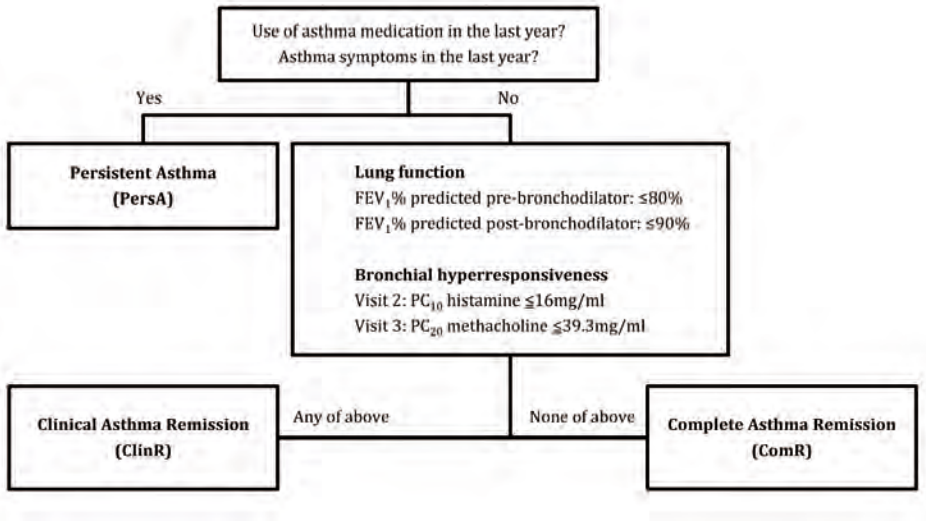

Figure 1: flowchart to define persistent asthma, clinical asthma remission and complete asthma remission.

Results and discussion

Of the initial cohort of 406 children, 209 had BHR at visit 1. At visit 2, 188 subjects were re-assessed at a mean age of 25 (±2) years, of whom 25 only completed questionnaires. At visit 3, 102 subjects with a mean age of 49 (±2) years were re-assessed, of whom 34 only completed questionnaires (figure 2).

	Visit 1 (1972–76) 406 subjects	Visit 2 (1987-89) 209 subjects	Visit 3 (2013-14) 209 subjects
Excluded	187 No BHR 10 Incomplete childhood data	21 Lost to follow-up	65 No response 31 Untraceable 6 Not cooperative 5 Deceased
Included	209 subjects	188 subjects	102 subjects
Asthma outcome	-	154 PersA (81.9%) 20 ClinR (10.6%) 14 ComR (7.5%)	61 PersA (59.8%) 31 ClinR (30.4%) 10 ComR (9.8%)

Figure 2: subject recruitment during al visits.

Subjects who completed questionnaires only at visits 2 or 3 could only be classified as ClinR or PersA, as indications of BHR and FEV_1 were missing. Subjects with questionnaire data at visit 2 only, had significantly lower FEV_1/IVC (inspiratory vital capacity) values at baseline, compared to subjects with both questionnaire and spirometry data, without any other statistically significant demographic differences (table 1).

The prevalence of complete remission was 7% at age 25 and 10% at age 49, indicating that ComR is a rare phenomenon. To our knowledge, only one other study using the same definition reported that 22% of children with asthma were in ComR after a follow-up of 30 years [6]. The prevalence of ComR in our study is probably an underestimation, because information on BHR and FEV_1 was missing in almost half of the ClinR subjects.

Sixty-three subjects were fully examined during both follow-up visits (figure 3). Of all subjects with PersA at visit 2, 15 developed ClinR (29%) and four developed ComR (8%) at visit 3. Seven out of the 63 subjects (11%) had ComR/ClinR between the ages 25 to 49. The prevalence of asthma-relapse at visit 3 was 36%, i.e. clinical asthma after ComR/ClinR at visit 2. Notably, using the strict definition of remission, 75% of the subjects with ComR at age 25 had no relapse of asthma by the age of 49.

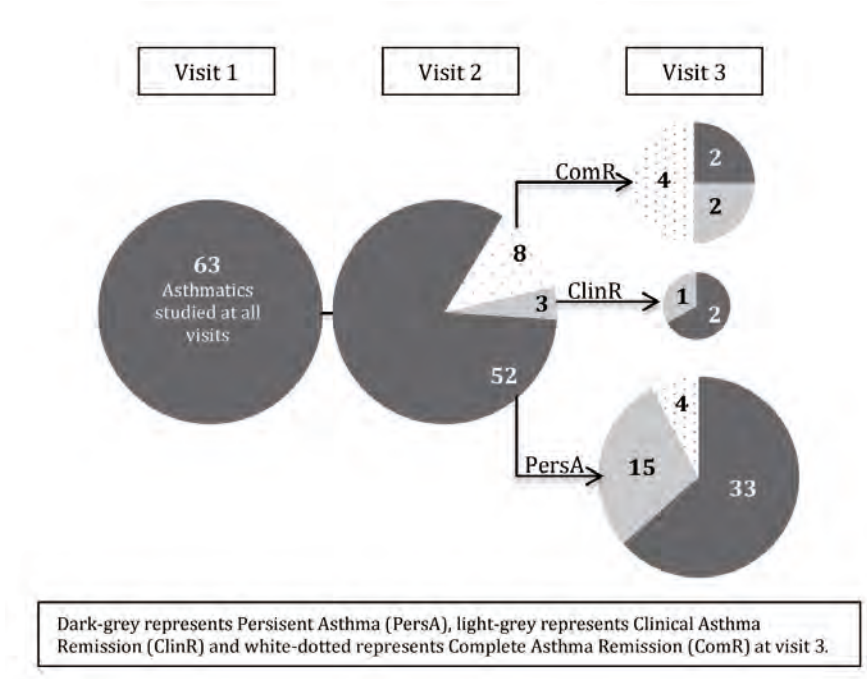

Figure 3: timeline of asthma remission persistence and relapse. Dark-grey represents persistent asthmatics (PersA), light-grey represents clinical asthma remission (ClinR), and the white-dotted pie piece represents complete asthma remission (ComR).

Table 2 shows results of the analyses of childhood factors associated with ComR versus PersA and ComR/ClinR versus PersA. The variables presented are childhood factors associated with asthma remission in previous studies [2, 4, 5, 7–9] and statistically significant factors in the present study (supplementary tables 3–6 for complete results). Three childhood factors were positively associated with ComR at visit 2, i.e. a family history of leukaemia, a higher FEV_1/IVC ratio and a positive skin prick test to mould. Acute lymphocytic leukaemia has been previously associated with a lower prevalence of atopic diseases [10, 11]. This inverse relationship might be caused by an imbalance between TH1 and TH2 cells, predisposing the patient to either autoimmune or atopic disease [12]. Although only five children had a family history of leukaemia in our cohort, results suggest that this phenomenon might also play a role in asthma remission.

Table 1: characteristics of subjects who were fully examined versus only filled in a questionnaire

Baseline characteristics	Visit 2 (n = 188)		P	Visit 3 (n = 102)		P
	Fully examined (n = 163)	Only questionnaires (n = 25)		Fully examined (n = 68)	Only questionnaires (n = 34)	
Age at visit 1 (years)	9.7 (1.4)	9.2 (1.4)	.16	9.6 (1.6)	9.8 (1.4)	.64
Male seks (%)	69.9	80.0	.35	76.5	63.2	.26
Height (cm)	143 (10)	140 (9)	.15	143 (10)	144 (10)	.47
FEV_1 % predicted (%)	77 (68-85)	73 (63-83)	.18	77 (65-84)	76 (68-80)	.60
FEV_1/IVC ratio (%)	74 (67-78)	67 (60-77)	.02	74 (66-79)	71 (67-77)	.30
Histamine threshold (mg/ml)	8 (4-16)	8 (4-16)	.18	12 (8-16)	8 (4-16)	.27
Eosinophil count x 10^6/L *	451 (231-715)	440 (336-605)	.53	462 (264-710)	402 (237-677)	.55

*Data are presented as mean (standard deviation), median [interquartile range], or percentage, P: p-value calculated with Fisher's exact test, Independent T-test and Mann-Whitney U test, *: for visits 1 and 2 eosinophils from a counting chamber.*

Table 2: Childhood factors associated with complete and clinical asthma remission

	Complete remission *versus* Persistent Asthma		Complete and clinical remission *versus* Persistent asthma	
	Visit 2: 25 years Remission (n = 14) Asthma (n = 154) OR (95% CI)	**Visit 3: 49 years Remission (n = 10) Asthma (n = 61) OR (95% CI)**	**Visit 2: 25 years Remission (n = 34) Asthma (n = 154) OR (95% CI)**	**Visit 3: 49 years Remission (n = 41) Asthma (n = 61) OR (95% CI)**
Age at 1st visit, years	1.3 (0.9-1.9)	1.0 (0.6-1.5)	1.0 (0.8-1.3)	1.0 (0.7-1.3)
Period between visits, years	1.3 (0.9-1.9)	1.0 (0.9-1.1)	1.1 (0.9-1.4)	1.0 (0.9-1.1)
Male sex	1.7 (0.4-6.3)	1.4 (0.3-6.0)	2.7 (.99-7.4)	1.9 (0.8-4.5)
Symptoms				
Sputum	0.6 (0.2-2.0)	0.4 (0.1-1.7)	0.8 (0.4-1.8)	**0.4 (0.1-0.8)**
Shortness of breath at rest	0.7 (0.2-2.5)	0.4 (0.1-2.3)	1.1 (0.5-2.6)	0.3 (0.1-0.9)
Attack of dyspnea at rest with wheezing	0.5 (0.2-1.8)	0.4 (0.1-2.0)	1.0 (0.4-2.6)	0.5 (0.2-1.2)
Wheeze during a cold	**0.2 (0.1-0.7)**	6.3 (0.7-56.4)	**0.2 (0.1-0.7)**	2.0 (0.8-5.0)
Cough	1.8 (0.4-8.6)	0.9 (0.2-4.7)	0.8 (0.3-1.8)	0.8 (0.3-2.4)
Peripheral blood				
Ln eosinophil count, x 10^6/L	0.9 (0.5-1.5)	1.0 (0.6-1.9)	0.8 (0.6-1.2)	1.2 (0.8-1.9)
Total proteins (<6.8 g/dL)	0.2 (0.03-1.8)	1.8 (0.4-8.2)	**0.2 (0.1-0.8)**	1.4 (0.5-3.8)
Peri- and postnatal factors				
Breastfeeding > 6 months	2.4 (0.2-28.1)	1.0*	**5.5 (1.1-27.1)**	0.3 (0.1-2.1)
History of pneumonia	0.2 (0.03-1.8)	0.5 (0.1-4.8)	**0.1 (0.01-0.9)**	0.7 (0.2-2.2)
Environmental exposures				
Pets in household	1.3 (0.4-4.1)	2.4 (0.4-12.5)	1.1 (0.5-2.5)	**3.1 (1.2-8.2)**
Firstborn child	1.5 (0.4-4.4)	0.5 (0.1-2.7)	0.7 (0.3-1.6)	0.9 (0.3-2.1)

Table 2: (continued)

	Complete remission *versus* Persistent Asthma		Complete and clinical remission *versus* Persistent asthma	
	Visit 2: 25 years Remission (n = 14) Asthma (n = 154) OR (95% CI)	**Visit 3: 49 years Remission (n = 10) Asthma (n = 61) OR (95% CI)**	**Visit 2: 25 years Remission (n = 34) Asthma (n = 154) OR (95% CI)**	**Visit 3: 49 years Remission (n = 41) Asthma (n = 61) OR (95% CI)**
Dusty/mouldy house[a]	2.9 (0.8-11.0)	1.7 (0.3-11.6)	**3.1 (1.2-8.2)**	1.6 (0.5-4.6)
Family history				
Atopic father	0.9 (0.2-3.6)	0.5 (0.1-3.0)	1.4 (0.6-3.5)	0.6 (0.2-1.5)
Atopic mother	**0.02***	0.18*	**0.1 (0.01-0.7)**	0.3 (0.1-1.1)
Cardiac disease in the family	3.2 (0.9-10.9)	2.0 (0.3-11.5)	**2.8 (1.1-6.8)**	2.0 (0.6-6.2)
Leukaemia in the family	**18.0 (2.6-124)**	1.0 *	**7.6 (1.2-49.0)**	1.2 (0.2-9.2)
Lung function				
FEV_1 % predicted	1.0 (0.99-1.1)	1.0 (0.96-1.1)	1.0 (0.99-1.1)	1.0 (0.97-1.1)
FEV_1 % predicted <80%	0.4 (0.1-1.1)	0.8 (0.2-3.2)	**0.5 (0.2-0.97)**	1.4 (0.6-3.2)
FEV_1 % IVC ratio	**1.1 (1.01-1.2)**	1.1 (0.97-1.2)	1.0 (0.97-1.1)	1.0 (0.96-1.1)
$FEF_{25-75\%}$ IVC ratio	1.0 (0.99-1.05)	1.0 (0.99-1.1)	1.0 (0.99-1.03)	1.0 (0.99-1.03)
Skin prick test				
House dust mite positive#	0.7 (0.2-2.4)	3.3 (0.8-14.2)	0.7 (0.3-1.6)	1.0 (0.4-2.2)
Mould positive#	**8.8 (1.7-46.1)**	9.4 (0.99-89.5)	3.6 (0.9-14.1)	3.1 (0.5-18.7)
Any skin prick test positive#	0.8 (0.2-2.3)	2.5 (0.6-11.0)	0.9 (0.4-1.9)	0.8 (0.3-1.8)
Hyperresponsiveness				
Histamine threshold, mg/ml	0.8 (0.2-2.8)	0.11*	1.1 (0.5-2.6)	1.5 (0.6-3.6)

*Data are presented as mean (SD), median (25th-75th percentile), or n (%). OR: odd ratio of the childhood factor, corrected for sex and age at visit 1 with 95% Confidence Interval, a: characteristics of house include ≥1 of the following: dusty/moisty vs. dry house, rotten floor and/or mould in house , *: p-value Fisher's exact test, #: times higher than the diameter of the positive histamine control.*

Two childhood factors that reduced the chance of ComR at visit 2 were symptoms of wheezing and an atopic mother. The finding of a lower frequency of ComR or ClinR at 25 years in the offspring of an atopic mother is consistent with the report of Burgess *et al.*, who found less frequent ClinR in similar subjects [3].

Four childhood factors increased the chances of ComR/ClinR at visit 2: being breastfed for more than 6 months; living in a dusty/damp house, with rotten floors and/or mould; and having a family member with cardiac disease, or with leukaemia. At visit 3, having pets during childhood was positively associated with ComR/ClinR. In addition, being breastfed for more than 6 months was associated with ComR/ClinR. A systematic review reported a reduced risk of asthma in breastfed children [13]. Furthermore, breastfed children are less susceptible to respiratory infections in early life, which are associated with the development and persistence of asthma [14]. Further studies are needed to assess whether prolonged breastfeeding also facilitates asthma remission when asthma has developed.

Five factors were found to reduce the chances of ComR/ClinR at visit 2, i.e. symptoms of wheezing during a cold; a total protein level <25th percentile; pneumonia during childhood; an atopic mother; and FEV_1 <80% predicted. At visit 3, sputum production in childhood was negatively associated with ComR/ClinR (table 1). Children of an atopic mother had less frequent ComR/ClinR and ComR at 25 years, whereas no association with atopy in the father was observed. This finding is consistent with those of another study that found less frequent ComR/ClinR in children of a mother with asthma [3].

Conclusion

Our study shows that over 39 years of follow-up, it is indeed possible to have persistent asthma remission after having childhood asthma, even though this was evident in only 11% of the subjects under investigation. Specifically, using the strict definition of complete asthma remission, we showed that when complete remission is present at age 25, 75% of this group have persistent remission to age 49. Several factors during childhood were found to be associated with a higher chance of asthma remission during adulthood, e.g. breastfeeding >6 months and a family history of leukaemia; and a lower chance of asthma remission, e.g. wheezing during a cold in childhood and an atopic mother. However, more research is needed to confirm our observations, using larger cohorts with a standard definition of asthma remission.

References

1 Upham JW, James AL. Remission of asthma: The next therapeutic frontier? *Pharmacol Ther*. 2011;130(1):38-45.

2 De Marco R, Locatelli F, Cerveri I, *et al.* Incidence and remission of asthma: A retrospective study on the natural history of asthma in italy. *J Allergy Clin Immunol*. 2002;110(2):228-235.

3 Burgess JA, Matheson MC, Gurrin LC, *et al.* Factors influencing asthma remission: A longitudinal study from childhood to middle age. *Thorax*. 2011;66(6):508-513.

4 Holm M, Omenaas E, Gislason T, *et al.* Remission of asthma: A prospective longitudinal study from northern europe (RHINE study). *Eur Respir J*. 2007;30(1):62-65.

5 Ronmark E, Jonsson E, Platts-Mills T, Lundback B. Incidence and remission of asthma in schoolchildren: Report from the obstructive lung disease in northern sweden studies. *Pediatrics*. 2001;107(3):E37.

6 Vonk JM, Postma DS, Boezen HM, *et al.* Childhood factors associated with asthma remission after 30 year follow up. *Thorax*. 2004;59(11):925-929.

7 Roorda RJ, Gerritsen J, van Aalderen WM, *et al.* Follow-up of asthma from childhood to adulthood: Influence of potential childhood risk factors on the outcome of pulmonary function and bronchial responsiveness in adulthood. *J Allergy Clin Immunol*. 1994;93(3):575-584.

8 Vonk JM, Postma DS, Boezen HM, *et al.* Childhood factors associated with asthma remission after 30 year follow up. *Thorax*. 2004;59(11):925-929.

9 Andersson M, Hedman L, Bjerg A, Forsberg B, Lundback B, Ronmark E. Remission and persistence of asthma followed from 7 to 19 years of age. *Pediatrics*. 2013;132(2):e435-42.

10 Limb SL, Brown KC, Wood RA, *et al.* Adult asthma severity in individuals with a history of childhood asthma. *J Allergy Clin Immunol*. 2005;115(1):61-66.

11 Schuz J, Morgan G, Bohler E, Kaatsch P, Michaelis J. Atopic disease and childhood acute lymphoblastic leukemia. *Int J Cancer*. 2003;105(2):255-260.

12 Wen W, Shu XO, Linet MS, *et al.* Allergic disorders and the risk of childhood acute lymphoblastic leukemia (united states). *Cancer Causes Control*. 2000;11(4):303-307.

13 Liblau RS, Singer SM, McDevitt HO. TH1 and TH2 CD4+ T cells in the pathogenesis of organ-specific autoimmune diseases. *Immunol Today*. 1995;16(1):34-38.

14 Lodge CJ, Tan DJ, Lau MX, *et al.* Breastfeeding and asthma and allergies: A systematic review and meta-analysis. *Acta Paediatr*. 2015;104(467):38-53.

15 Rossi GA, Colin AA. Infantile respiratory syncytial virus and human rhinovirus infections: Respective role in inception and persistence of wheezing. *Eur Respir J*. 2015;45(3):774-789.