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

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

*To the Editor:*


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.

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.

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<sub>10</sub> (provocative concentration causing a 10% fall in FEV<sub>1</sub> (forced expiratory volume in 1 s) histamine  $\leq 16$  mg·mL<sup>-1</sup>; visit 3: PC<sub>20</sub> methacholine  $\leq 39.3$  mg·mL<sup>-1</sup>) and/or normal FEV<sub>1</sub> (>80% predicted pre-bronchodilator). ComR was defined as ClinR, combined with a negative BHR test and a normal FEV<sub>1</sub> (>80% predicted pre-bronchodilator) (supplementary 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.

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 ( $\pm 2$ ) years, of whom 25 only completed questionnaires. At visit 3, 102 subjects with a mean age of 49 ( $\pm 2$ ) years were re-assessed, of whom 34 only completed questionnaires (supplementary figure 2).

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

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**Asthma remission is rare but strictly defined complete asthma remission is persistent in most cases**  
<http://ow.ly/g0ZK30b1ACC>

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TABLE 1 Childhood factors associated with complete and clinical asthma remission

	Complete remission <i>versus</i> persistent asthma		Complete/clinical remission <i>versus</i> persistent asthma	
	Visit 2 <sup>#</sup>	Visit 3 <sup>¶</sup>	Visit 2 <sup>+</sup>	Visit 3 <sup>§</sup>
<b>Characteristics</b>				
Age at first visit per year	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 per year	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 (0.99–7.4)	1.9 (0.8–4.5)
<b>Symptoms</b>				
Sputum	0.6 (0.2–2.0)	0.4 (0.1–1.7)	0.8 (0.4–1.8)	<b>0.4 (0.1–0.8)</b>
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 dyspnoea 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	<b>0.2 (0.1–0.7)</b>	6.3 (0.7–56.4)	<b>0.2 (0.1–0.7)</b>	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)
<b>Peripheral blood measurements</b>				
ln-transformed eosinophil count per 10 <sup>6</sup> per 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 protein <25th percentile <sup>f</sup>	0.2 (0.03–1.8)	1.8 (0.4–8.2)	<b>0.2 (0.1–0.8)</b>	1.4 (0.5–3.8)
<b>Peri- and postnatal factors</b>				
Breastfeeding >6 months	2.4 (0.2–28.1)	1.0	<b>5.5 (1.1–27.1)</b>	0.3 (0.1–2.1)
History of pneumonia	0.2 (0.03–1.8)	0.5 (0.1–4.8)	<b>0.1 (0.01–0.9)</b>	0.7 (0.2–2.2)
<b>Environmental exposures</b>				
Pets in household	1.3 (0.4–4.1)	2.4 (0.4–12.5)	1.1 (0.5–2.5)	<b>3.1 (1.2–8.2)</b>
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)
House dusty/damp/rotten floors/mouldy <sup>##</sup>	2.9 (0.8–11.0)	1.7 (0.3–11.6)	<b>3.1 (1.2–8.2)</b>	1.6 (0.5–4.6)
<b>Family history</b>				
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	<b>0.02</b>	0.18	<b>0.1 (0.01–0.7)</b>	0.3 (0.1–1.1)
Family history of cardiac disease	3.2 (0.9–10.9)	2.0 (0.3–11.5)	<b>2.8 (1.1–6.8)</b>	2.0 (0.6–6.2)
Family history of leukaemia	<b>18.0 (2.6–124)</b>	1.0	<b>7.6 (1.2–49.0)</b>	1.2 (0.2–9.2)
<b>Lung function</b>				
FEV <sub>1</sub> per % 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 <sub>1</sub> <80% predicted	0.4 (0.1–1.1)	0.8 (0.2–3.2)	<b>0.5 (0.2–0.97)</b>	1.4 (0.6–3.2)
FEV <sub>1</sub> %/IVC ratio	<b>1.1 (1.01–1.2)</b>	1.1 (0.97–1.2)	1.0 (0.97–1.1)	1.0 (0.96–1.1)
FEF <sub>25–75%</sub> /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)
<b>Skin prick test</b>				
House dust mite positive <sup>¶¶</sup>	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 <sup>¶¶</sup>	<b>8.8 (1.7–46.1)</b>	9.4 (0.99–89.5)	3.6 (0.9–14.1)	3.1 (0.5–18.7)
Any skin prick test positive <sup>¶¶</sup>	0.8 (0.2–2.3)	2.5 (0.6–11.0)	0.9 (0.4–1.9)	0.8 (0.3–1.8)
<b>Hyperresponsiveness</b>				
log <sub>2</sub> -transformed histamine threshold per mg·mL <sup>-1</sup>	1.1 (0.7–1.6)	1.9 (0.8–4.7)	1.0 (0.8–1.3)	0.9 (0.6–1.2)
Histamine threshold per mg·mL <sup>-1</sup>	0.8 (0.2–2.8)	0.11	1.1 (0.5–2.6)	1.5 (0.6–3.6)

Data are presented as odds ratios of the childhood factor corrected for sex and age at visit 1 (95% CI) or p-values (Fisher's exact test). FEV<sub>1</sub>: forced expiratory volume in 1 s; IVC: inspiratory vital capacity; FEF<sub>25–75%</sub>: forced expiratory flow at 25–75% of forced vital capacity. <sup>#</sup>: 25 years of age; remission, n=14; asthma, n=154. <sup>¶</sup>: 49 years of age; remission, n=10; asthma, n=61. <sup>+</sup>: 25 years of age; remission, n=34; asthma, n=154. <sup>§</sup>: 49 years of age; remission, n=41; asthma, n=61. <sup>f</sup>: <6.8 g·dL<sup>-1</sup>. <sup>##</sup>: characteristics of the house include one or more of dusty/moist *versus* dry house, rotten floor and/or mould. <sup>¶¶</sup>: 0.7 times higher than the diameter of the positive histamine control. Bold represents statistical significance.

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<sub>1</sub> was missing in almost half of the ClinR subjects.

Sixty-three subjects were fully examined during both follow-up visits (supplementary 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.

Table 1 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<sub>1</sub>/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.

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<sub>1</sub> <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].

In 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.

**Orestes A. Carpaij<sup>1,2,5</sup>, Maartje A.E. Nieuwenhuis<sup>1,2,5</sup>, Gerard H. Koppelman<sup>1,3</sup>, Maarten van den Berge<sup>1,2</sup>, Dirkje S. Postma<sup>1,2</sup> and Judith M. Vonk<sup>1,4</sup>**

<sup>1</sup>University of Groningen, University Medical Center Groningen, Groningen Research Institute for Asthma and COPD (GRIAC), Groningen, The Netherlands. <sup>2</sup>University of Groningen, University Medical Center Groningen, Dept of Pulmonology, Groningen, The Netherlands. <sup>3</sup>University of Groningen, University Medical Center Groningen, Dept of Pediatric Pulmonology and Pediatric Allergology, Beatrix Children's Hospital, Groningen, The Netherlands. <sup>4</sup>University of Groningen, University Medical Center Groningen, Dept of Epidemiology, Groningen, The Netherlands. <sup>5</sup>These authors contributed equally.

Correspondence: Judith M. Vonk, Dept of Epidemiology, University Medical Center Groningen, University of Groningen, Hanzplein 1, 9713 GZ Groningen, The Netherlands. E-mail: j.m.vonk@umcg.nl

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