Pharmacology & Therapeutics 201 (2019) 8–24

Contents lists available at ScienceDirect

Pharmacology & Therapeutics

journal homepage: www.elsevier.com/locate/pharmthera

A review on the pathophysiology of asthma remission

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ARTICLE INFO

Available online 8 May 2019

Keywords:
Clinical asthma remission
Complete asthma remission
Predictors
Prevalence
Biomarkers
Airway remodeling

ABSTRACT

Asthma is a chronic respiratory condition, which is highly prevalent worldwide. Although no cure is currently available, it is well recognized that some asthma patients can spontaneously enter remission of the disease later in life. Asthma remission is characterized by absence of symptoms and lack of asthma-medication use. Subjects in asthma remission can be divided into two groups: those in clinical remission and those in complete remission. In clinical asthma remission, subjects still have a degree of lung functional impairment or bronchial hyperresponsiveness, while in complete asthma remission, these features are no longer present. Over longer periods, the latter group is less likely to relapse. This remission group is of great scientific interest due to the higher potential to find biomarkers or biological pathways that elicit or are associated with asthma remission.
Despite the fact that the definition of asthma remission varies between studies, some factors are reproducibly observed to be associated with remitted asthma. Among these are lower levels of inflammatory markers, which are lowest in complete remission. Additionally, in both groups some degree of airway remodeling is present. Still, the pathological disease state of asthma remission has been poorly investigated. Future research should focus on at least two aspects: further characterisation of the small airways and airway walls in order to determine histologically true remission, and more thorough biological pathway analyses to explore triggers that elicit this phenomenon. Ultimately, this will result in pharmacological targets that provide the potential to steer the course of asthma towards remission.

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Abbreviations: ALL, Acute lymphocytic leukaemia; BHR, Bronchial hyperresponsiveness; BMI, Body mass index; $FEF_{25-75\%}$, Forced expiratory flow at 25-75% of the expired forced expiratory volume; FEV_1, Forced expiratory volume in one second; ICS, Inhaled corticosteroids; LRTI, Lower respiratory infection; PC_{20}, Provocative concentration (e.g. histamine, methacholine, adeno-'5-monophosphate) causing 20% a drop of FEV_1; SABA, Short-acting beta-agonist; SNP, Single nucleotide polymorphism; SPT, Skin prick test.

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https://doi.org/10.1016/j.pharmthera.2019.05.002
0163-7258/

1. Introduction

Asthma is a usually chronic respiratory disease with an estimated 300 million individuals affected worldwide. It is characterized by variable airflow obstruction associated with symptoms of dyspnea, cough and bronchial hyperresponsiveness as outlined in the GINA guidelines (Bateman et al., 2018). Current treatments fail to cure the disease. Nevertheless, it has been reported that asthma can go into spontaneous remission (Carpaij et al., 2017; Vonk et al., 2004), meaning that asthmatics at some point are no longer burdened by the disease, and do no longer require any asthma medication. These "ex-asthmatics" are labelled to be in clinical asthma remission, but might still have (asymptomatic) bronchial hyperresponsiveness or a low lung function (Broekema et al., 2011). In fewer cases, subjects go into complete asthma remission, additionally having no pulmonary function impairment or bronchial hyperresponsiveness (Carpaij et al., 2017; Vonk et al., 2004). To date, most discussion of asthma treatment goals revolves around disease control (Bateman et al., 2008; Taylor, Cowan, Greene, Willan, & Sears, 2005; Upham & James, 2011), whereas exploring the induction of asthma remission as a therapeutic goal has so far attracted little interest. In this review, we highlight the definition, prevalence and characteristics of asthma remission. Next, we describe factors associated with the induction of asthma remission, inflammatory markers, histological signs and genotypes linked to this phenomenon. Finally, we discuss current research on identifying biological pathways that could trigger asthma remission, which may be used for therapeutics in the future.

2. Definition of asthma remission

Defining asthma remission seems straightforward, but is not an easy task. Asthma is a usually chronic disease characterized by variable airflow obstruction, bronchial hyperresponsiveness and inflammation, and disease severity fluctuates over time. As such, episodes with little or no disease activity can alternate with periods of more disease symptoms and renewed dependence on medication use. Consequently, patients in remission of the disease have a certain risk of relapse (Bronnimann & Burrows, 1986; Butland & Strachan, 2007; Carpaij et al., 2017; Vonk et al., 2004). This resembles "remission" of cancer (National Cancer Institute, 2018), in which the disappearance of signs and symptoms does not ensure that the disease is cured. Yet, it is thought that remission of cancer is the closest to cure and has smaller chance of relapse, especially in "complete remission" of cancer, certainly for many non-operable lung cancers (National Cancer Institute, 2018). The risk of relapse also pertains to other inflammatory diseases, such as rheumatoid arthritis (Tiippana-Kinnunen, Paimela, Laasonen, & Leirisalo-Repo, 2010;Upham & James, 2011), inflammatory bowel disease (Vidal et al., 2006) and multiple sclerosis (Steinman, 2014). In principle, the relapse risk depends on how strict remission is defined and what features must be absent. Thus to apply similar reasoning to asthma where the label of remission needs to be associated with minimal occurrence of relapse, the definition of asthma remission should be strict including an absence of symptoms, its period, no medication use, as well as absence of lung function impairment and bronchial hyperresponsiveness.The complexities of and guidelines for defining asthma remission are discussed below.

2.1. Symptom perception

The asthmatic's perception of the severity of symptoms has a dominant important role in the effective management of asthma (Banzett, Dempsey, O'Donnel, & Wamboldt, 2000). In line with this, individuals with asthma remission might also have poor perception of symptoms and feel no need for treatment. Yet, the mechanisms underlying poor perception are not well understood (Still & Dolen, 2016). One concept explaining poor perception is that of temporal adaptation; the diminished perception of symptoms is caused by psychological modification due to chronic obstruction and dyspnea (Still & Dolen, 2016). In other words, individuals with remitted asthma could experience symptoms differently than family and associates would judge them.

2.2. The symptom-free period

According to most definitions, individuals in asthma remission should not have experienced any degree of asthma-related symptoms during a reasonable period of time. In the many studies carried out so far, a broad range of symptom-free periods is used to define asthma remission (Upham & James, 2011). Table 1 shows that the duration of absence of symptoms was on average one year, with a range of 6 months to 5 years. Studies are limited in their accuracy to determine the symptom-free period for several reasons. First, in retrospective cohorts, asthma remission should not be defined as having "no medical records for current asthma" since these individuals could have been treated somewhere else. Second, questions such as "did you experience asthma symptoms in the previous year?" are dichotomous and do not allow for reporting subtle symptoms, resulting in an overestimation of remission prevalence in large survey studies. We think it is highly probable that standardized questioning with several lines (e.g. wheeze, dyspnea on exertion, several triggers) will identify more subjects who still have some symptoms. And last, determining the symptom-free period is affected by selection bias; asthma symptoms might be underestimated by the clinical researcher and the participant who wants to enroll, when investigating the relatively rare occurrence of asthma remission (Upham & James, 2011). Since individuals with remitted asthma are difficult to find, researchers might underrate wheezing in order to fill the cohort. In addition, it can be debated whether patients who re-experience symptoms during methacholine and adeno-'5-monophosphate provocation tests should be labelled as symptom free (van den Toorn, Overbeek, Prins, Hoogsteden, & De Jongste, 2002), while healthy non-asthmatic individuals would not experience dyspnea (Basoglu et al., 2005). In principle, true asthma remission should be defined as having no asthma symptoms (i.e. wheezing, asthma attacks, including dyspnea during provocation) for at least one year.

2.3. Medication use

A key factor that should be assessed in order to ascertain asthma remission is absence of medication use. In contrast to fully controlled asthma, patients are usually considered to be in asthma remission when they did not take any asthma-related medication for at least one year. Thus in order to define true asthma remission, individuals should not take any symptom-relievers and anti-inflammatory agents, including immunosuppressant medication used for other diseases.

2.4. Lung function and bronchial hyperresponsiveness

In order to make the definition of asthma remission less dependent on symptom perception, Vonk *et al.* suggested dividing remission into clinical and complete asthma remission. Both definitions share the absence of wheeze, asthma attacks and use of asthma medication for more than one year. Yet in clinical asthma remission, individuals still have a positive bronchial hyperresponsiveness (BHR) test and/or lung function impairment, while in subjects with complete asthma remission, these features are absent (Vonk et al., 2004). Defining complete asthma remission results in fewer subjects who meet these criteria (Carpaij et al., 2017; Panhuysen et al., 1997; Sears et al., 2003; Vonk et al., 2004; Wang, Datta, Weiss, & Tantisira, 2018). Despite the scarcity of subjects, studying complete asthma remission has two advantages. First, it is of scientific interest; this strict phenotype has higher potential to elucidate biological biomarkers and pathways that are associated with asthma remission (Broekema et al., 2011; Vonk et al., 2018). Second, the risk of asthma relapse is lower in complete remission subjects:

Table 1
Various definitions, prevalence rates and factors associated with asthma remission.

Ordered in quality of design, age of enrollment and follow-up

Study *36 cohorts*	Cohort design *Asthma diagnosis and quality of the study*	N	*Age* *Enrollment*	Definition of asthma remission	Classification of remission	Proportion	Associated with remission
The Childhood Asthma Management Program (CAMP), USA (Covar et al., 2010; Wang et al., 2018)	Prospective cohort with 15-year clinical FU. Asthma: enrolled asthmatic children in CAMP trial, mild-to-moderate persistent asthma with positive methacholine test. High quality: large cohort, well-defined and clinically assessed asthma and asthma remission diagnosis.	909	5-12Y	No signs of: asthma reported symptoms Medication use: no asthma-medication Period: 1 year	Remission	6% (18Y)	- No positive SPT's - Fewer positive SPT's - Less sensitive to allergens - Mild symptoms in childhood - Higher baseline FEV_1
					Remission	-	- Not defined
					Clinical remission, i.e. FEV_1/FVC ratio >80%	26% (23Y)	- Female sex - Less BHR at baseline - Higher baseline FEV_1 - Higher baseline FEV_1/FVC - Lower blood IgE - Lower blood eosinophils - Wheezes during colds
					Complete remission, i.e. FEV_1/FVC ratio >80%, PC_{20} methacholine >25mg/ml	15% (23Y)	- Female sex - Less BHR at baseline - Higher baseline FEV_1 - Higher baseline FEV_1/FVC - Lower blood IgE - Lower blood eosinophils - Wheezes during colds
Outpatient cohort of Pediatric clinic of Golestan University Hospital In Ahvaz, Iran (Assar, Idani, Monajemzadeh, Ganai, & Rahim, 2013)	Prospective cohort with **5**-year clinical FU. Asthma: registered in outpatient pediatric clinic with ≥2 asthma attacks in past. High quality: well-defined and clinically assessed asthma and asthma remission diagnosis.	197	6-10Y	No signs of: asthma symptoms Medication use: no ICS or SABA Period: 1 year	Remission FEV_1/FVC >80%, exercise challenge test <15% decline after 6-8 minutes of running	**33**% (15Y)	- No family history of asthma - No passive smoking - No eczema
Outpatient cohort of Hacettepe University Pediatric Allergy and Asthma Unit, Turkey (Sekerel et al., 2006)	Prospective cohort with 11-year clinical FU. Asthma: registered at outpatient clinic with ≥1 visit every 2 year for 6 years, reversible airway obstruction with spirometry. High quality: well-defined and clinically assessed asthma and asthma remission diagnosis.	115	5Y	No signs of: asthma symptoms Medication use: no controller medication Period: 1 year	Remission	**53**% (17Y)	- Male sex - No blood eosinophilia
					Clinical remission, i.e. % pred. ≤80%, PC_{20} methacholine ≤8mg/ml	26% (17Y)	- Male sex
					Complete remission, i.e. FEV_1 % pred. >80%, PC_{20} methacholine >8mg/ml	27% (17Y)	- Not described
Isle of Wight Birth Cohort, United Kingdom(Arshad et al., 2014; Soto-Ramírez et al., 2013; Zhang et al., 2018)	Prospective cohort with 18-year clinical FU. Asthma: physician diagnosed <10 year, asthma treatment in the last year. High quality: reasonably defined asthma diagnosis, well-defined and clinically assessed asthma remission diagnosis.	181	1Y	No signs of: asthma symptoms Medication use: no asthma-medication Period: 1 year	Remission	**31**% (18Y)	- Male sex
					Clinical remission, i.e. PC_{20} methacholine <8mg/ml	11% (18Y)	- Less BHR at baseline - Less atopy
					Complete remission, i.e. PC_{20} methacholine ≥8mg/ml	10% (18Y)	
Outpatient cohort of Marmara University Pediatric Allergy and Immunology Department, Turkey (Aydogan et al., 2013)	Retrospective cohort with 10-year clinical FU. Asthma: diagnosis based on GINA and ARIA guidelines. High quality: reasonably defined asthma diagnosis, well-defined and clinically assessed asthma remission diagnosis.	62	2-8Y	No signs of: asthma symptoms Medication use: no asthma-medication Period: 1 year	Remission	**50**% (16Y)	- Negative family history
					Clinical remission, i.e. PC_{20} methacholine <8mg/ml, negative SPT	16% (16Y)	- Less BHR at baseline - Absence of rhinitis - Higher childhood FEV_1
					Complete remission, i.e. PC_{20} methacholine ≥8mg/ml, negative SPT	34% (16Y)	- Higher childhood $FEF_{25-75\%}$
Obstructive Lung Disease in Northern Sweden Studies (OLIN), Sweden (Andersson et al., 2013; Bjerg & Rönmark, 2008)	Prospective cohort with **12**- year clinical FU. Asthma: physician diagnosed by pediatricians. High quality: reasonably defined asthma diagnosis, well-defined and clinically assessed asthma remission diagnosis.	248	7-8Y	No signs of: wheeze Medication use: no asthma-medication Period: 3 years	Remission, mean FEV_1 % pred. 90%, median PC_{20} methacholine: 3.4mg/ml	**21**% (19Y)	- Male sex - No SPT positivity to animals
Outpatient cohort of Pediatric Allergy Outpatient Unit at the Central Hospital of Skövde, Sweden	Prospective cohort with **21**-year clinical FU. Asthma: registered at outpatient clinic, ≥3 episodes of wheezing.	55	5-14Y	No signs of: asthma symptoms Medication use: no	Remission	**16**% (30Y)	- Male sex

(Kjellman & Gustafsson, 2000)	High quality: reasonably defined asthma diagnosis, well-defined and clinically assessed asthma remission diagnosis.			asthma-medication Period: 1 year			
Outpatient cohort of Pediatric pulmonology department of the University Medical Center Groningen, The Netherlands (Vonk et al., 2004)	Prospective cohort with 30-year clinical FU. Asthma: registered at outpatient clinic, physician diagnosed, positive histamine test. High quality: well-defined and clinically assessed asthma and asthma remission diagnosis.	119	5-14Y	No signs of: wheeze or asthma attacks Medication use: no ICS Period: 1 year	Remission Clinical remission, i.e. PC_{20} methacholine ≤16mg/ml or FEV_1 % pred. ≤90% Complete remission, i.e. PC_{20} methacholine and >16mg/ml, FEV_1 % pred. >90%	**52**% (32-42Y) 30% (32-42Y) 22% (32-42Y)	- Higher baseline FEV_1 - Higher increase in FEV_1 - Less pack years in adulthood
Outpatient cohort of Pediatric pulmonology department of the University Medical Center Groningen, The Netherlands (Carpaij et al., 2017)	Prospective cohort with **39**-year clinical FU. Asthma: registered at outpatient clinic, physician diagnosed, positive histamine test. High quality: well-defined and clinically assessed asthma and asthma remission diagnosis.	63	7-12Y	No signs of: asthma symptoms Medication use: no asthma-medication Period: 1 year	Remission Clinical remission, i.e. FEV_1 % pred. ≤90% or PC_{20} methacholine ≤9.8mg/ml Complete remission, i.e. FEV_1 % pred. >90% and PC_{20} methacholine >9.8mg/ml	**18**% (25Y) **40**% (49Y) 11% (25Y) 30% (49Y) 7% (25Y) 10% (49Y)	- Not wheezing during cold - No pneumonia in childhood - Dusty house in childhood - Leukemia in family history - No FEV_1 <80% in childhood - Having pets in childhood - Not described - Not described - Not wheezing during cold - No maternal atopy - Leukemia in family history - Having a higher FEV_1/FVC - SPT positivity to mould - Not found
Adult-Onset Asthma and Inflammatory Subphenotypes (ADONIS), The Netherlands (Westerhof et al., 2018)	Prospective cohort with **5**-year clinical FU. Asthma: physician diagnosed, reversibility ≥12% or positive methacholine test, excluded if asthma in childhood. High quality: well-defined and clinically assessed asthma and asthma remission diagnosis, yet wide age-range of enrollment.	194	18-75Y	No signs of: asthma symptoms Medication use: no asthma-medication Period: 1 year	Remission Clinical remission, i.e. PC_{20} methacholine <4mg/ml Complete remission, i.e. FEV_1 % pred. >80% and PC_{20} methacholine >4mg/ml	**16**% (+5Y) 6% (+5Y) 10% (+5Y)	- Lower ICS dosage at onset - Less BHR at baseline - No nasal polyps - Less blood neutrophils
Outpatient cohort of *Department of Chest Diseases, Ankara University School of Medicine, Turkey* (Sözener, Aydın, Mungan, & Mısırlıgil, 2015)	Retrospective cohort with **7**-year clinical FU. Asthma: registered at outpatient clinic, diagnosed according to the GINA guidelines. High quality: reasonably defined asthma diagnosis, well-defined and clinically assessed asthma and asthma remission diagnosis.	200	<47Y	No signs of: asthma symptoms Medication use: no asthma-medication Period: 2 years	Remission Clinical remission, i.e. positive methacholine test Complete remission, i.e. negative methacholine test	**11**% (53Y) 4% (53Y) 2% (53Y)	- Younger age of onset - Not described - Not described
Dunedin Multi-disciplinary Health and Development Study (DMHDS), New Zealand (Sears et al., 2003)	Prospective cohort with **26**-year clinical FU. Asthma: questionnaire-based, wheezing reported. Moderate quality: debatable definition of asthma diagnosis, clinically assessed asthma remission diagnosis, yet no medication use described.	613	3Y	No signs of: wheeze Medication use: not defined Period: 2 years	Remission Clinical remission, i.e. PC_{20} methacholine ≤8mg/ml or reversibility ≥10% at any assessment from 9-21 Y Complete remission, i.e. PC_{20} methacholine >8mg/ml and reversibility <10% at any assessment from 9-21 Y	**15**% (26Y) 10% (26Y) 5% (26Y)	- Not described
Childhood Asthma Study (CAS), USA (Limb et al., 2005)	Prospective cohort with **11**-year clinical FU. Asthma: physician diagnosed and treated for ≥1 year. Moderate quality: reasonably defined asthma diagnosis, well-defined and clinically assessed asthma remission diagnosis, immunotherapy use in asthma remission group.	85	5-12Y	No signs of: asthma symptoms Medication use: no asthma-medication Period: 1 year	Remission* FEV_1 % pred. >80%, FEV_1/FVC ratio >80%, mean PC_{20} methacholine: 0.2mg/ml **46% used active immuno-therapy*	**15**% (23Y)	- Lower blood IgE - Fewer positive SPT's
Melbourne Asthma Study (MAS), Australia (Horak et al., 2003; Martin, McLennan, Landau, & Phelan, 1980; Tai et al., 2014; Williams & McNicol, 1969)	Prospective cohort with **42**-year clinical FU. Asthma: reports of wheezing by self-report by the parent at recruitment. Severe asthma: ≥10 attacks in 2 years before age or persistent symptoms at age 10, according to GINA guidelines.	269	7-10Y	No signs of: wheeze Medication use: no asthma-medication Period: 3 years	Remission	20% (14 Y) 33% (21 Y) **40**% (42 Y) 52% (50 Y)	- Mild symptoms in childhood - Male sex - Mild symptoms in childhood - No childhood hayfever

(continued on next page)

Table 1 (*continued*)

Ordered in quality of design, age of enrollment and follow-up

Study *36 cohorts*	Cohort design *Asthma diagnosis and quality of the study*	N	*Age* *Enrollment*	Definition of asthma remission	Classification of remission	Proportion	Associated with remission
	Moderate quality: debateable asthma definition, well-defined and clinically assessed asthma remission diagnosis, multiple follow-up visits.						- No childhood eczema - - No SPT positivity
Outpatient cohort Asthma clinic at Beatrix-oord hospital Haren, The Netherlands (Panhuysen et al., 1997)	Prospective cohort with **25**-year clinical FU. Asthma: registered at outpatient clinic, physician diagnosed, positive histamine test. Moderate quality: well-defined asthma diagnosis, clinically assessed asthma remission, yet pulmonary medication was used within the remission-group.	181	13-44Y	No signs of: cough, sputum, dyspnea, wheeze and asthma attacks Medication use: not defined Period: 3 years	Remission* Clinical remission, i.e. PC_{20} histamine ≤4mg/ml or FEV_1 % pred. ≤90% Complete remission, i.e. PC_{20} histamine >4mg/ml and FEV_1 % pred. >90% **5% used pulmonary medication*	**40**% (48Y) 25% (48Y) 11% (48Y)	- Male sex - Younger age of onset - Higher baseline FEV_1 - Less BHR at baseline
Military service men in 1987–1990 referred to the Central Military Hospital, Finland (Lindström et al., 2012)	Prospective cohort with **20**-year clinical FU. Asthma: based on medical records; asthma symptoms, medication use, lung function and allergy tests. Moderate quality: reasonably defined asthma diagnosis, well-defined and clinically assessed asthma remission diagnosis, yet predominantly men.	119	19-21Y	No signs of: asthma symptoms Medication use: no asthma-medication Period: 3 years	Remission	**12**% (41Y)	- Not described
European Community Respiratory Health Survey II (ECRHSII), Europe, North America, Oceania (de Marco et al., 2006)	Prospective cohort with **9**-year of clinical FU. Asthma: physician diagnosed, asthma-like symptoms and/or medication in the last year. Moderate quality: debatable definition of asthma, clinically assessed asthma remission diagnosis, yet ICS use in subset of asthma remission subjects.	856	20-44Y	No signs of: asthma-like symptoms or asthma attacks Medication use: no asthma-medication Period: 1 year	Remission* **16% used ICS in the last 12 months*	**12**% (35Y)	- Higher baseline FEV_1 - Lowest increase of BMI
Risk Factors for Asthma in Adults Study (RAV), Denmark (Traulsen, Halling, Bælum, Davidsen, & Miller, 2018)	Prospective cohort with **9**-year clinical FU. Asthma: questionnaire based, 'have you ever had asthma?', combined with asthma-like symptoms, use of medication in the last year or airflow obstruction. Moderate quality: questionnaire based asthma diagnosis, well-defined and clinically assessed asthma remission diagnosis.	239	20-44Y	No signs of: asthma symptoms Medication use: no asthma-medication Period: 1 year	Remission	**28**% (+9Y)	- Not described
Seinäjoki Adult-onset Asthma Study (SAAS), Finland (Tuomisto et al., 2016)	Prospective cohort with **12**-year clinical FU. Asthma: physician diagnosed, objective lung function measurements showing reversible obstruction, symptoms of asthma. High quality: reasonably defined asthma diagnosis, asthma remission definition 6 months and still could have a degree of symptoms.	203	46Y	No signs of: asthma symptoms, Asthma Control Test score of 25 Medication use: no asthma-medication Period: 6 months	Remission Clinically assessed, i.e. FEV_1 % pred. >80%, FEV_1/FVC >70%, reversibility <12%, FeNO ≤20ppb	**6**% (58Y) 3% (58Y)	- Higher baseline FEV_1/FVC - Lower blood IgE - Not described
Lung Disease in Northern Sweden study (OLIN), Sweden (Rönmark et al., 1999)	Prospective cohort with **10**-year clinical FU. Asthma: ≥2 asthma attacks during last year, reversibility >15% or PC_{20} methacholine <4mg/ml, including ≥3 following: 1. Recurrent wheeze, 2. Attacks of shortness of breath, 3. ≥2 asthma provoking factors, 4. Normal breathing between asthma attacks or periods of asthma. Moderate quality: debatable definition of asthma, well-defined asthma remission, yet including subjects with persistent wheeze and medicine use.	267	35-66Y	No signs of: recurrent wheeze or attacks of shortness of breath Medication use: no asthma-medication Period: 1 year	Remission* Clinically assessed, i.e. FEV_1 % pred. ≥80%* **Including few subjects with persistent wheeze and medicine use*	**6**% (+10Y) 4% (+10Y)	- Younger age of onset - Mild asthma in adulthood - Cessation of smoking
Environment and Childhood Asthma (ECA) Study in Oslo, Norway (Carlsen et al., 2006)	Prospective cohort with **10**-year questionnaire FU. Asthma: 2 of 3 criteria: 1. Symptoms 0-10 years, 2. Doctor's diagnosis, 3. Use of asthma medication 0-10 years. Lower quality: debatable definition of asthma, asthma remission defined by no current record of asthma, including children with doctor's diagnosis <6 years.	616	0Y	No signs of: dyspnea, chest tightness and/or wheezing (no record of current asthma) Medication use: no asthma-medication Period: 1 year	Remission* **including children with doctor's diagnosis <6 years.*	**55**% (10Y)	- Female sex
Tucson Children's Respiratory Study, USA (Guerra et al., 2004)	Prospective cohort with **16**-year clinical FU. Asthma: reporting presence of wheezing >3 episodes in	166	2Y	No signs of: wheeze Medication use: not	Remission	**42**% (13-16Y)	- No obesity - No early onset of puberty

	previous year in at least on survey or physician diagnosed. Lower quality: debatable definition of asthma, undefined medication use in asthma remission.			defined Period: 1 year			- No childhood sinusitis - No positive SPT
Comprehensive medical record database of the Olmsted Medical Center, USA (Javed et al., 2013)	Retrospective cohort with **10**-year of database FU. Asthma: extensive criteria list in publication. Lower quality: reasonably defined asthma diagnosis using a database, debatable definition of asthma remission.	117	8Y	No signs of: no medical records indicating asthma symptoms, visits or admissions Medication use: no asthma-medication Period: 3 years	Remission	**24**% (18Y)	- Caucasian ethnicity
Population-based sample of 11.048 neonates, Greece (Bacopoulou et al., 2009)	Prospective cohort with **18**-year questionnaire FU. Asthma: physician diagnosed and treated at some point in life. Lower quality: debatable definition of asthma, asthma remission defined by no current record of asthma, including children with doctor's diagnosis <6 years.	562	0Y	No signs of: asthma symptoms (no record of current asthma Medication use: not defined Period: 1 year	Remission* **including children with doctor's diagnosis <6 years.*	**69**% (18Y)	- Female sex - No family history of atopy - Smoking cessation - No maternal smoking during pregnancy.
Dunedin Multi-disciplinary Health and Development Study (DMHDS), New Zealand (Taylor et al., 2005)	Prospective cohort with **23**- year clinical FU. Asthma: questionnaire-based: 'do you have asthma?' Lower quality: questionnaire-based definition of asthma diagnosis, undefined medication use in asthma remission .	176	3Y	No signs of: wheeze Medication use: not defined Period: 1 year	Remission	**39**% (18Y) 25% (26Y)	- Older age of onset - Higher baseline FEV_1 - Higher baseline FEV_1/FVC - Less BHR at baseline - Less reversibility - Not described
Comprehensive medical evaluation for eligibility for national service between 1999 and 2008, Israel (Cohen et al., 2015)	Cross-sectional cohort with **3**-year of database FU. Asthma: medical records indicating asthma symptoms, requiring medication, FEV_1 <80% and/or positive exercise challenge test. Lower quality: cross-sectional design, database record defined asthma and asthma remission diagnosis.	26.400	17Y	No signs of: asthma symptoms Medication use: no asthma-medication Period: 3 years	Complete remission, i.e. FEV_1 and FEV_1/FVC >80%, no decline of <10% in FEV_1 exercise challenge test, methacholine challenge PC_{20} >8mg/ml	22% (17Y)	- Not described
Random stratified cluster sample of non-Mexican white American households in Tucson, USA (Bronnimann & Burrows, 1986)	Prospective cohort with **9**-year of clinical FU. Asthma: questionnaire-based 'have you ever had asthma?', 'how many asthma attacks have you had in the past year?', 'how often are you bothered by attacks of shortness of breath and wheezing?' Lower quality: questionnaire based asthma diagnosis, wide age-range at enrollment, debatable asthma remission definition, limited assessment of asthma remission at follow-up.	136	6-80Y	No signs of: asthma attacks, <2 attacks of shortness of breath with wheezing Medication use: no asthma-medication Period: 1 year	Remission	**22**% (overall) 35% (<10Y) 65% (10-19Y) 28% (20-29Y) 15% (30-39Y) 6% (40-49Y) 18% (50-59Y) 27% (60-69Y) 25% (70-79Y)	- Mild asthma in adulthood - Younger age of onset - Higher baseline FEV_1 - Co-existing emphysema
Outpatient cohort of Prince of Wales's General Hospital Department of Pediatrics and Allergy, London (Blair, 1977)	Retrospective cohort with **20**-year questionnaire FU. Asthma: recurrent ≥3 attacks of paroxysmal dyspnea with wheezing. Lower quality: debateable definition of asthma, undefined medication use in asthma remission.	267	<12Y	No signs of: asthma symptoms Medication use: not defined Period: 2 years	Remission	**28**% (<32Y)	- Not described
European Community Respiratory Health Survey I (ECRHSI), Europe, North America, Oceania (de Marco et al., 2004)	Cross-sectional cohort, survey-based. Asthma: questionnaire-based : 'have you ever had asthma ?' and 'how old were you when you had your first asthma attack?' Lower quality: cross-sectional design, questionnaire based asthma diagnosis, asthma remission defined by no current	1.558	0-44Y	No signs of: asthma attacks (no record of current asthma) Medication use: no asthma-medication Period: 2 years	Remission	**43**% (<10Y) 34% (10-20Y) 16% (20-44Y)	- Younger age of onset - Negative family history - Less acute resp. infections - Contact with older children - Pets in childhood household

(continued on next page)

Table 1 (*continued*)

Ordered in quality of design, age of enrollment and follow-up

Study *36 cohorts*	Cohort design *Asthma diagnosis and quality of the study*	N	*Age* *Enrollment*	Definition of asthma remission	Classification of remission	Proportion	Associated with remission
	record of asthma.						
Tasmanian Longitudinal Health Study (TAHS, Australia (Burgess et al., 2011)	Prospective cohort with **36**-year questionnaire FU. Asthma: questionnaire-based, 'have you ever had asthma? Lower quality: questionnaire based asthma- and asthma remission diagnosis.	1.620	7-13Y	No signs of: asthma attacks (no record of current asthma) Medication use: no asthma-medication Period: 2 years	Remission	**65**% (46Y)	- Male sex - Younger age of onset - No maternal asthma - No pneumonia in childhood
Alumnae address database of the Brown University School of Medicine, USA (Settipane, Greisner, & Settipane, 2000)	Prospective cohort with **23**-year questionnaire FU. Asthma: physician diagnosed, history of ≥3 clinically recurrent, reversible episodes of wheezing and dyspnea. Lower quality: debatable definition of asthma, undefined medication use in asthma remission.	84	16-20Y	No signs of: asthma symptoms Medication use: not defined Period: 5 years	Remission	**40**% (40Y)	- Younger age of onset
Three population-based multicentre studies: ECRHS-Italy, ISAYA and GEIRD performed in Italy (Pesce et al., 2015)	Cross-sectional cohort, survey-based. Asthma: questionnaire based, 'have you ever had asthma?', 'how old were you when you have your first attack of asthma?' Lower quality: cross-sectional design, questionnaire based asthma diagnosis, asthma remission defined by no current record of asthma, wide age-range of enrollment.	3.087	20-84Y	No signs of: asthma attacks (no record of current asthma) Medication use: inhalers, aerosols or tablets Period: 2 years	Remission	**65**% (0-14Y) 36% (15-29Y) 21% (>30Y)	- Male sex - Younger age of onset
Italian Study on Asthma in Young Adults (ISAYA), Italy (Cazzoletti et al., 2014)	Prospective cohort with **9**-year questionnaire FU. Asthma: self-reported physician's diagnosis of asthma and ≥1 asthma attack in last year and/or current use of medication. Lower quality: questionnaire based asthma- and asthma remission diagnosis.	214	21-47Y	No signs of: wheeze, tightness of the chest, shortness of breath, asthma attacks Medication use: no asthma-medication Period: 1 year	Remission	**30**% (+9Y)	- Older age of onset
Respiratory Health in Northern Europe (RHINE), Iceland, Norway, Sweden, Denmark and Estonia (Holm et al., 2007)	Prospective cohort with 12-year questionnaire FU. Asthma: questionnaire based, 'have you ever had asthma?', 'how old were you when you have your first attack of asthma?' Lower quality: questionnaire based asthma- and asthma remission diagnosis.	1.153	28-56Y	No signs of: asthma symptoms, i.e. "which was the latest year you experienced asthma symptoms?" Medication use: no asthma-medication Period: 2 years	Remission	**19**% (+12Y)	- Cessation of smoking
Hiroshima COPD Cohort Study, Japan (Omori et al., 2017)	Cross-sectional cohort, survey-based. Asthma: questionnaire based, 'Were you ever diagnosed with asthma by a physician?', 'Have you been awakened in the last 12 months by an attack of shortness of breath or wheezing when you did not have a cold?' Lower quality: cross-sectional design, questionnaire based asthma diagnosis, asthma remission defined by no current record of asthma.	388	35-60Y	No signs of: asthma symptoms (no record of current asthma) Medication use: not defined Period: 1 year	Remission* **Remitted childhood asthma divided by total childhood asthma.*	**74%**	- Not described

Legend: BHR: bronchial hyperresponsiveness, BMI: body mass index, FU: follow-up, ICS: inhaled corticosteroids, SABA: short-acting beta-agonist, SPT: skin prick test.

one quarter compared to two-third in clinical asthma remission subjects (Carpaij et al., 2017).

3. Prevalence of asthma remission

3.1. The prevalence of clinical and complete asthma remission

The prevalence of the asthma remission has a very broad range in studies so far, for three main reasons. First, the age at baseline varies with the type of cohort (e.g. birth cohorts, outpatient clinic cohorts, retrospective national service databases, cross-sectional international surveys, and follow-up on finished clinical trials). Second, some research groups clinically assessed subjects at baseline and at follow-up, while others defined asthma and its remission solely on a questionnaire-based answer. Questionnaire-based studies generally had higher prevalence rates and did not always specify medication use. And last, the years of follow-up ranged from five years to four decades, increasing the difficulty in comparing the results per study. For these reasons and for estimation of prevalence rates, in this manuscript we only included studies meeting the following criteria: clinically assessed asthma diagnosis or medical record diagnosis based on GINA guidelines (Bateman et al., 2018), clinically assessed asthma remission status, and specifically defined asthma remission criteria (i.e. no asthma symptoms such as wheeze or asthma attacks, no asthma-related medication, for at least 1 year). Table 1 lists an overview of 36 cohorts assessing the prevalence of asthma remission ordered by age at baseline and years of follow-up (figure 1 for PubMed search term). Eleven of the cohorts (white colored rows) were used to estimate the prevalence. We excluded cohorts only enrolling children with a doctor's diagnosis of asthma before the age of six, due to the fact that the diagnosis in this age group is mixed with transient wheezers, who are not the same as asthmatics (Martinez, 2002).

The proportions of asthma remission per age group at follow-up were 33 – 53% in adolescence (<18 years), 6 – 33% in young adulthood (≥18 and ≤30 years), 11 – 52% in adulthood (>30 years). The majority of the studies focused on asthmatic children and their chance of going into asthma remission. This focus is likely due to the following reasons: asthma is the most common non-communicable disease among children (World Health Organization, 2017), the remission proportion is highest in this age sub-group (Bronnimann & Burrows, 1986; de Marco, Pattaro, Locatelli, & Svanes, 2004; Pesce et al., 2015), and elucidating this phenomenon within this population is of highest prognostic value (Wang et al., 2018). Studies determining the adult-onset asthma remission proportion on the other hand, are limited. This is because cohorts usually include individuals with child- and adulthood-onset of asthma, consequently mixing both groups when determining asthma remission. A recent prospective study only assessed adult-onset asthma, and found a remission prevalence of 16% within five years (Westerhof, Coumou, de Nijs, Weersink, & Bel, 2018). Based on these data, it is premature to state that childhood-onset phenotype of asthma has a higher chance of going into remission compared to the adult-onset phenotype of the disease.

A few studies included lung function and histamine or methacholine provocation tests, thus allowing estimations for complete versus clinical asthma remission rates. The majority of the studies found a higher proportion of clinical asthma remission (ranging 10-30%) than the complete asthma remission status (ranging 5-22%). Two studies however, found higher prevalence proportions of complete compared to clinical remission (Aydogan et al., 2013; Westerhof et al., 2018) . An explanation for this difference could be that Westerhof *et al.* used a >4mg/ml methacholine threshold cut-off, classifying clinical remission subjects with mild bronchial hyperresponsiveness in the complete remission group.

4. Predictors of asthma remission

Despite the previously described differences between studies, there appears to be a degree of consistency in the factors that were associated with asthma remission later in life. The following baseline characteristics were positively associated with a higher asthma remission prevalence (last column in table 1younger age of onset, mild asthma at onset, male sex, higher baseline lung function, less bronchial hyperresponsiveness at baseline, lower blood eosinophils and IgE at baseline, lower skin prick test scores (SPT), no comorbidities (i.e. nasal polyps, eczema, atopy or rhinitis), no pneumonia in the past, a negative family history of asthma and atopy, cessation of smoking and environmental factors (e.g. pets in household). The majority of the listed factors are well established due to the fact that these are also inversely related to uncontrolled asthma (Bateman et al., 2018). In the following section, some of these factors are further discussed.

4.1. Male sex

One of the acknowledged factors associated with asthma remission is male sex (Andersson et al., 2013; Arshad et al., 2014; Burgess et al., 2011; Kjellman & Gustafsson, 2000; Panhuysen et al., 1997; Tai et al., 2014). Before puberty, the prevalence of asthma is higher in boys than in girls. However, in adulthood, the prevalence of asthma reverses to be higher in females (Postma, 2007). Female sex hormones have been linked to asthma and its morbidity; the risk of developing asthma is increased for those with a higher cumulative female sex hormone concentration seen in pregnancy (Jenkins et al., 2006) and early-onset menarche (McCleary, Nwaru, Nurmatov, Critchley, & Sheikh, 2018; Postma, 2007; Salam, Wenten, & Gilliland, 2006). Additionally, 30–40% of female asthmatics experience perimenstrual asthma worsening (Melgert, Ray, Hylkema, Timens, & Postma, 2007; Vrieze, Postma, & Kerstjens, 2003). The TRIALS study assessed associations of transition though puberty with asthma remission in 2,230 male and female subjects (Vink, Postma, Schouten, Rosmalen, & Boezen, 2010). The authors found a higher prevalence of asthma in girls aged 16 compared to boys, which was related to a higher incidence and lower remission rate of asthma in females compared to their male peers. From these studies, the hypothesis is that a lower level of female sex hormones might result in a higher chance of asthma remission.

There are three other potential mechanisms to explain why females have a less chance of asthma remission. First, there is a difference in physical growth of the lungs from birth into adulthood between boys and girls (Melgert et al., 2007); boys tend to have a later growth spurt than girls, which makes them more prone to wheezing due to smaller diameters of the airways. Second, the TRIALS study identified obesity as an additional/independent risk factor for asthma in female subjects both in cross-sectional and longitudinal analyses. Obesity is accompanied by an increased production of estrogens, with – next to the effect on puberty - potential effects on asthma as well (Castro-Rodríguez, Holberg, Morgan, Wright, & Martinez, 2001). And last, methacholine hyperresponsiveness is more severe in the post-pubertal female asthmatics compared to their male peers (Tantisira et al., 2008). With these associations, targetting sex hormones - such as oral contraceptives - might work as therapy. Unfortunately, studies investigating the effect of oral contraceptive pills on asthma published contradicting results; one survey found a reduced prevalence of current wheeze in women with a history of asthma while on contraceptives (Salam et al., 2006), while another found no association (Jenkins et al., 2006). In contrast, oral contraceptive pills have also been associated with an increased risk for asthma (Macsali et al., 2009; Salam et al., 2006), and shown to have DNA methylating effects on polymorphisms of the GATA3 gene, a master regulator of Th2 cell differentiation, which is related to a higher risk of developing asthma (Guthikonda et al., 2014).

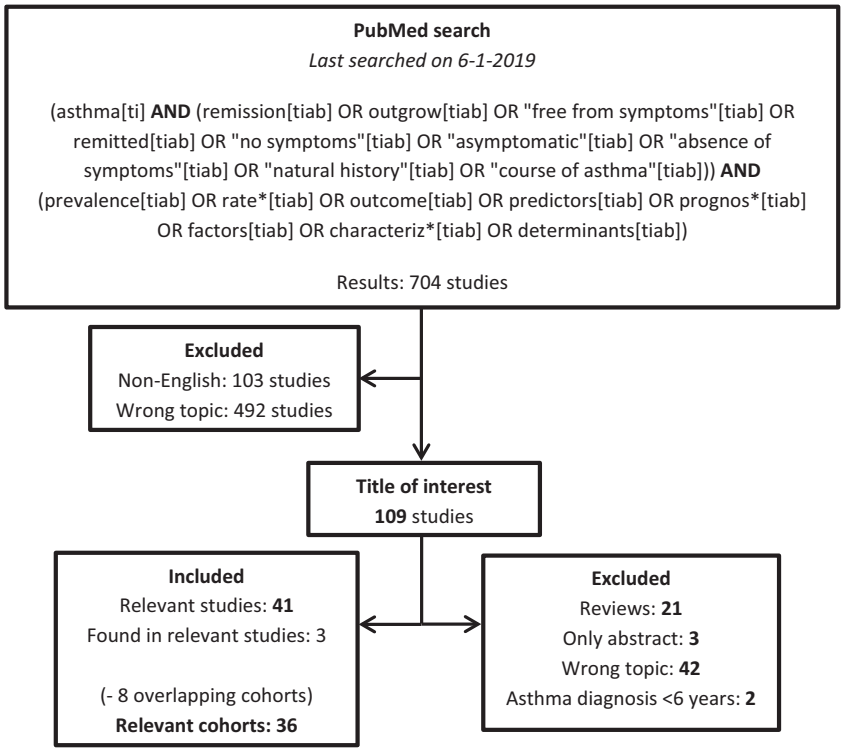

Fig. 1. PubMed search algorithm.

4.2. Severity of asthma

The severity of asthma-onset is a recognized factor influencing the outcome of asthma remission (Bronnimann & Burrows, 1986; Rönmark, Jönsson, & Lundbäck, 1999; Tai et al., 2014). In moderate and severe cases of asthma, the disease activity stays much the same over long periods of time (Chen, FitzGerald, Lynd, Sin, & Sadatsafavi, 2018; Sears et al., 2003; Tai et al., 2014), while subjects with mild and intermittent symptoms are likely to experience asthma remission. The Melbourne Asthma Study followed clinical and lung function features of childhood asthmatics aged 7–10 until the age of 50 (Tai et al., 2014). Within this cohort, the children who solely wheezed during bronchitis and respiratory infections had the highest chance of remitted symptoms through all years ranging from 40–65%. Strikingly, severe asthmatic children had the lowest remission rates; around 10%. Even though we have to keep in mind that the wheeze bronchitis- is not the same as the asthma-phenotype, figure 2 illustrates that an increase in asthma severity is negatively correlated with the remission rate.

Very recently, authors of the CAMP-trial assessed whether clinical features in childhood asthmatics could predict asthma outcome later in life (Wang et al., 2018). A model based on childhood clinical features was made to predict asthma remission in young adulthood. With a baseline FEV_1/FVC ratio ≥85%, a PC_{20} methacholine ≥1mg/ml and blood eosinophil count of <500 cells/μl, the probability of asthma remission at age 23 was 82.6%. In other words, this study demonstrated that subjects with milder asthma in childhood (i.e. no pulmonary obstruction, relatively mild bronchial hyperresponsiveness and low blood eosinophils) have a higher chance of going into remission. We applied this model on our own cohorts and found that children with these features had the highest chance of remission as well (Carpaij et al., 2019).

4.3. Pneumonia

Several studies found that the occurrence of pneumonia during childhood was associated with a reduced likelihood to go into asthma remission later in life (Burgess et al., 2011; Carpaij et al., 2017; Strachan, Butland, & Anderson, 1996). This is in agreement with the hypothesis that childhood lower respiratory tract infections (LRTI), such as pneumonia, could influence asthma persistence (Burgess et al., 2012; Castro-Rodríguez et al., 1999) or trigger its inception (Thomas, Lemanske, & Jackson, 2014). The incidence of pneumonia is estimated to be 7.4% in the first three years of life with Respiratory Syncytial Virus (RSV) as the most common infectious agent in children (Castro-Rodríguez et al., 1999). The Tasmanian Longitudinal Health Study (TAHS) found that a higher frequency of infectious diseases in childhood protected against asthma later in life, but pneumonia was positively associated with self- or parent-reported asthma until adolescence (Burgess et al., 2012). These findings suggest a balance between infections and asthma persistence in children.

Other pediatric studies relied on radiologically diagnosed infiltrations (Backman, Piippo-Savolainen, Ollikainen, Koskela, & Korppi, 2014; Castro-Rodríguez et al., 1999; Clark, Coote, Silver, & Halpin, 2000), and saw an increase of asthma diagnoses after admissions due to childhood pneumonia and also bronchiolitis . The authors of the Tucson Children's Respiratory Study included children in the first years of life with radiologically confirmed pneumonia, and re-examined them up until eleven years of age (Castro-Rodríguez et al., 1999). Here, children with pneumonia had lower levels of FEV_1 and $FEF_{25-75\%}$ compared to the unaffected children. More interesting, but unfortunately with insufficient subjects to draw a strong conclusion, a negative trend was seen in the maximal expiratory flow in neonates two months after birth, prior to these infections. This implies that these children might already have diminished lung function since birth, making them more susceptible for LRTIs later on. Thus, in accordance to the susceptibility-theory, individuals who go into asthma remission might be born with a better lung function than asthmatics with persistent disease activity.

Only one study was found that investigated pneumonia in adulthood and asthma remission. The ADONIS project enrolled 194 adult-onset asthmatics diagnosed in the previous year, assessed the patient reported trigger of asthma-onset and followed the five year course of asthma (Coumou, Westerhof, de Nijs, Amelink, & Bel, 2018). While the

majority of patients could not recall any triggers (38%), 8% of the subjects thought that a pneumonia was the trigger. Adult-onset asthmatics that were thought to have been elicited by pneumonia, had a significantly higher chance of clinically verified asthma remission over the next five years.

Although the exact role of pneumonia on the course of asthma remains vague, it is clear that individuals affected by these infections are not burdened by asthma persistence per se. What triggers asthma persistence or remission may depend on peri- and postnatal factors, the severity of the infection, the ensuing local damage, microbe type and exposure duration (Gern & Busse, 2002; Matricardi et al., 2000). Still, it is difficult to disentangle subjects developing asthma due to LRTIs from subjects that were already susceptible for asthma, subsequently having a higher risk of respiratory infections (Clark et al., 2000). It is highly probable that LTRIs are merely a sign of underlying asthma susceptibility (Backman et al., 2014). Abnormal lung function, altered airway structure and immune responses to viral infections all predispose infants to lower respiratory infections, which could further damage the airways leading to respiratory morbidity later in life (Martinez, 2005; Openshaw, Dean, & Culley, 2003). Accordingly, individuals with asthma remission might be less susceptible (e.g. normal lung function, unaltered airway structure and immune response), enabling them to recover faster from respiratory infections.

4.4. Leukemia

We have previously shown that another factor associated with asthma remission is having a positive family history for leukemia (Carpaij et al., 2017). In this study, children who had a first or second degree family member were associated with both clinical and complete asthma remission at 25 years. Our results are in agreement with previously published findings as there have several links between leukemia and allergic diseases. In contrast, children with atopic first degree relatives seemed to have a lower risk for acute lymphocytic leukemia (ALL) (Schüz, Morgan, Böhler, Kaatsch, & Michaelis, 2003; Wen et al., 2000). Various studies found a reduced chance to develop childhood asthma while affected by ALL (Jourdan-Da Silva et al., 2004; Rudant et al., 2010; Wen et al., 2000). Children born by caesarean delivery – causing a deviant immune-maturation - developed more asthma and ALL than children delivered via the vaginal route (Sevelsted, Stokholm, Bønnelykke, & Bisgaard, 2015). A meta-analysis found a significant pooled odds-ratio of ALL in atopy (0.69 ,95% CI 0.54 – 0.89) (Linabery, Jurek, Duval, & Ross, 2010), while a more current meta-analysis updated a negative trend between ALL and asthma by Linabery *et al.* (OR 0.79, 95% CI 0.61-1.02) to a non-significant odds-ratio ($P = 0.45$) (Zhou & Yang, 2015). These findings suggest that a subset of allergic diseases and ALL have a protective effect on each other. Both conditions are linked to the hygiene hypothesis (Wiemels, 2012), proposed by Strachan to explain the rising prevalence of allergy in the western population (Strachan, 1989). However, this would imply similar incidence patterns. The asthma-leukemia relation may also be false due to several reasons. One, the mentioned pooled case-control studies that assess allergy do so by parental recall of allergies (Wiemels, 2012). The parents of children affected by ALL may be more likely to imagine factors that may have caused their child's condition, leading to false positive associations. A second reason is that treatment for leukemia might alleviate asthma symptoms, thereby mimicking remission while extreme immunosuppression was given. A case report described asthma remission after high-dose chemotherapy and autologous stem transplantation for breast cancer (Palmieri et al., 2003) , suggesting a beneficial effect of this therapy. On the other hand, chemotherapy for ALL in children was able to suppress asthma, but did not lead to long-term relief (Weigel et al., 2000). To date, no studies elucidated the biological connection to asthma and leukemia, leaving the inverse relationship of asthma remission and leukemia as a mere signal.

5. Interventions to induce asthma remission

The majority of factors that are associated with asthma remission cannot be altered or treated. Some treatments such as ICS and biological treatments can induce full control of symptoms but have not been associated with real remission. A few factors however, can be influenced and are thought to have an effect on asthma remission; weight loss and immunotherapy. It is noteworthy that bilateral lung transplantation has

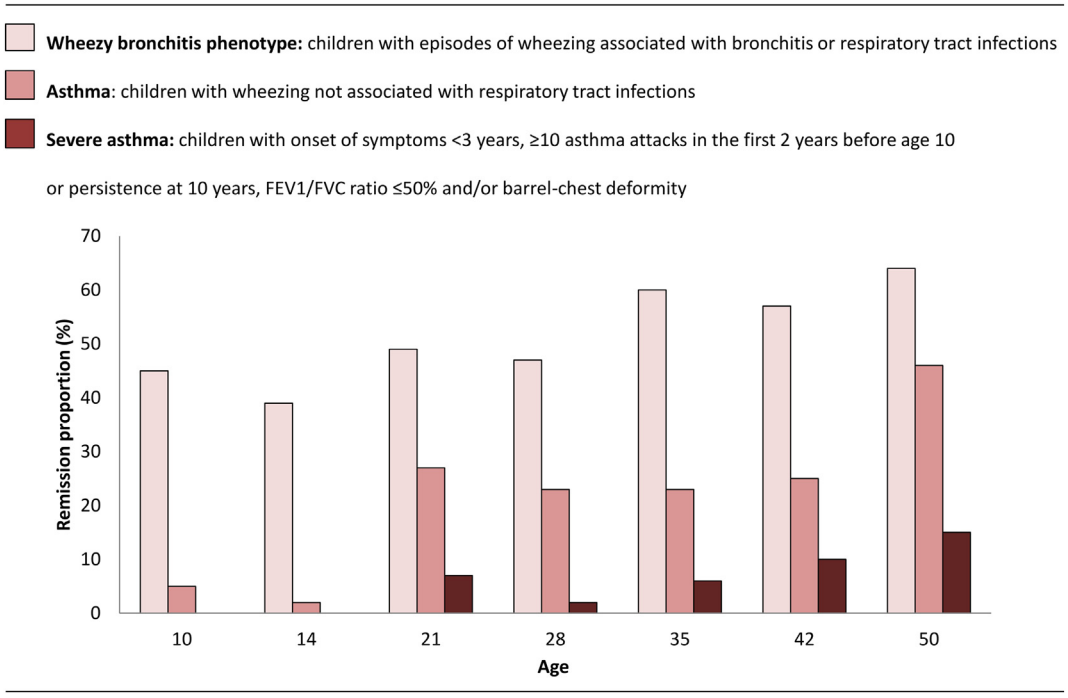

Fig. 2. Remission percentages at age 10 to 50 in children, enrolled at age 7 and divided in three asthma severity levels. This figure shows that less severe asthma is associated with a higher chance of remission later in life. Reproduced, with permission, from Tai et al., 2014.

been linked to asthma remission as well (Schwerk, Ballmann, & Hansen, 2008; Wirtz, Kroegel, Caffier, & Bittner, 2005), still this controversial intervention followed by immunosuppression is not discussed in this review.

5.1. Weight loss

The asthma-obesity relationship is well described, although the mechanisms underlying it are not well understood (Ulrik, 2016). It is hypothesized that this relation is affected by a different type of inflammation (Telenga et al., 2012) and by other comorbidities such as gastro-esophageal reflux and diabetes mellitus type 2 (Carpaij & van den Berge, 2018; Bateman et al., 2018). Weight loss has shown positive effects on several measures of asthma-control (Juel, Ali, Nilas, & Ulrik, 2012). (Scott et al., 2013; Stenius-Aarniala et al., 2000)(Scott et al., 2013) (Schatz et al., 2015), but it is unclear whether weight loss could lead to clinical asthma remission. De Marco *et al.* saw that asthma remission was negatively associated with an increase in BMI over 10 years follow-up (de Marco et al., 2006). Taking this into account, it is possible that non-surgical weight loss can induce asthma remission. Yet, due to the number of subjects needed to be followed up to assess asthma remission, non-surgical weight loss interventions are laborious to carry out and are at risk for confounding.

The other option is surgical weight loss, such as bariatric surgery, which has also been associated with improved asthma control (Boulet, Turcotte, Martin, & Poirier, 2012a)(van Huisstede et al., 2015)(Baltieri et al., 2018; van Huisstede et al., 2015)(Guerron et al., 2018; van Huisstede et al., 2015), but again not necessarily to remission. Macgregor and Greenberg studied 40 morbidly obese patients with severe (i.e. >10 asthma attacks) or moderately severe (i.e. 6–10 attacks) asthma, and saw that after 4 years 49% of the subjects reported asthma remission, while the rest all experienced less symptoms and medication usage (Macgregor & Greenberg, 1993). The United Kingdom National Bariatric Surgery Registry analyzed the prevalence of comorbidities after this surgical intervention over five years (Miras et al., 2018). Of the 50,782 entries, 19% had asthma and were all treated with either inhalers or additional medication. After one year, the prevalence of clinician verified asthma significantly decreased to 14%. Intriguingly, the prevalence of asthma remained somewhat the same after the additional four years of follow-up, indicating that the effect of bariatric surgery on asthma is predominantly within the first year after treatment. The pathophysiology for this might be that in some cases the sudden weight loss improves lung mechanics or alleviates the chronic inflammation due to obesity, decreasing the symptoms to an extent that subjects are not burdened anymore, while in others, the asthmatic inflammation remained the main component of the chronic inflammation.

5.2. Immunotherapy

Various studies found that negativity of skin prick tests (SPTs) was associated with asthma remission (Andersson et al., 2013; Covar et al., 2010; Limb et al., 2005; Tai et al., 2014). Allergen avoidance is also related to asthma remission (Froidure, Vandenplas, D'Alpaos, Evrard, & Pilette, 2015), although it is debateable whether avoiding these triggers is similar to true remission.

Lee *et al.* performed a retrospective cohort study of 627 adults with allergic asthma who were sensitized to house dust mite and/or pollens and underwent subcutaneous immunotherapy (Lee et al., 2017). All participants had documented symptoms, were either bronchial hyperresponsive to methacholine (PC_{20} ≤25 mg/ml) or reversible to salbutamol (≥12% and ≥200 ml), and had a positivity to at least one inhalant allergen during a SPT. In this study, the cumulative incidence of asthma remission continuously increased up to 87% until the 12th year, with an average maintenance period of 5.1 years. Similar results were found in a smaller retrospective study, including 39 mild-moderate asthmatic children treated with a three year sublingual immunotherapy with a mixture of Dermatophagoides (Nuhoglu et al., 2007). Again, high remission rates of 95% were reported. However, both studies were flawed in design: individuals with asthma remission could still use bronchodilators in these cohorts, or could have symptoms if they did not respond to methacholine. Second, both studies did not investigate if asthma relapsed after subjects were withdrawn from immunotherapy. Last and most important, no asthma-control groups were assessed to take into account the natural course of asthma.

Possibly due to these shortcomings, other studies did not see an effect of allergen immunotherapy on the remission rate (Bağ et al., 2013). A double-blind placebo controlled trial was conducted two decades ago, enrolling moderate-to-severe asthmatic children and administering subcutaneous injections of either seven aeroallergen extracts or placebo for ≥18 months (Adkinson et al., 1997). Here, asthma remission (i.e. no medication after 30 months) was achieved in 8% of the immunotherapy- and 9% in the placebo-group, indicating that the injections did not seem to be beneficial for inducing the remission of asthma. Since the latter study has the most scientific credibility, it is not likely that immunotherapy induces asthma remission.

6. Airway inflammation in asthma remission

It has been previously described in other reviews that the level of airway inflammation has a relationship with the development of asthma remission over time (Fuchs, Bahmer, Rabe, & von Mutius, 2017; Upham & James, 2011). Figure 3 illustrates a theory in which asthma severity is correlated to whether a subject experiences symptoms or experiences lung function impairment.

In accordance with figure 3, individuals with remitted asthma might still have ongoing airway inflammation (Broekema et al., 2011). A variety of studies assessed the inflammatory markers in different compartments (e.g. blood, sputum, biopsy), subsequently comparing their presence in asthma remission subjects with either asthmatics, healthy controls, or both (see table 2). In general, the majority of findings were consistent (i.e. markers were higher in asthma remission compared to healthy control and lower compared to persistent asthma), although some studies found no significant differences between the groups. Eosinophils, either in blood, sputum, bronchial alveolar lavage (BAL), or endobronchial biopsy, were the most studied. Of interest, eosinophil cationic protein and eosinophilic peroxidase levels were significantly lower in complete asthma remission subjects compared to persistent asthmatics, but no significant difference was found when comparing the latter with clinical asthma remission. This suggests some eosinophilic activity in the clinical asthma remission group (Broekema et al., 2011), which might have clinical consequences; this same cohort was followed for five years to show that asthmatics with fast FEV_1 decline (i.e. >30ml/year) were linked to higher levels of eosinophils in sputum and biopsies, which was not seen in the complete asthma remission subjects and asthmatics with slow FEV_1 decline (Broekema et al., 2011). Other biomarkers that were significantly different between the groups were blood IgE, blood and subepithelial IL-5, exhaled fractional and (sub-)epithelial inducible nitric oxide, sputum Tumour Necrosis Factor α and (sub-)epithelial tryptase and chymase. The majority of these inflammatory markers are recognised for their link to the Th2 pathway (Tomiita et al., 2015; van Den Toorn et al., 2001; van Den Toorn, Prins, Overbeek, Hoogsteden, & de Jongste, 2000).

7. Airway remodeling in asthma remission

Chronic inflammation of the airways may lead to altered structure in the airway wall, referred to as remodeling (Bousquet, Jeffery, Busse, Johnson, & Vignola, 2000). Airway remodeling, such as increased basement membrane thickness, can occur early in childhood and is associated with an increased risk of developing clinical asthma (Bonato et al., 2018). Studies investigating airway remodeling in asthma

remission are scarce (Broekema et al., 2011; van Den Toorn et al., 2001). A cross-sectional study assessing remodeling enrolled 54 never-smoking adolescents aged 18–25 in three groups; asthmatics, asthma remission subjects and healthy controls (van Den Toorn et al., 2001). Endobronchial biopsies were obtained from the segmental divisions of the main bronchi. While the reticular basement membrane thickness in asthma and asthma remission subjects was similar (11.5 μm ±1.5 versus 10.9 μm ±1.3 respectively), both were significantly thicker than those in the healthy controls (7.9 μ ±1.0, both $P < 0.001$). Additionally, the reticular basement membrane to total membrane ratio of the remission subjects differed significantly from the values obtained from the asthmatics and in controls, falling between these two ranges. The collagen III density in the biopsies – a component of airway remodeling – was not significantly different between the groups. Another group investigated the phenomenon of airway remodeling in a comparable design, including 129 adults of all ages and dividing remission subjects in either clinical- or complete remission (Broekema et al., 2011). The authors found that asthmatics and individuals with clinical remission had a higher degree of inflammatory markers in blood and biopsies than asthmatics had, but basement membrane thickness was not significantly different. Of interest, asthmatics who used ICS had a significantly lower basement membrane thickness compared to ICS-naïve asthmatics and clinical remission subjects (5.3 μm [2.8-8.2] versus 5.7 μm [2.8-12.6] and 6.5 μm [3.8-11.7, $P = 0.04$ and $P < 0.001$ respectively). Again, no difference in collagen III stained submucosae was found between the groups.

These studies suggest that basement membrane thickening is still present in clinical and complete remission. The authors questioned if basement membrane thickening by itself could be a risk factor for asthma relapse, or if it is just an end-stage of disease with histological "scarring"(Broekema et al., 2011). To answer this question, asthma remission subjects need to be followed at different and longer time points, undergoing bronchoscopies for such histological assessments. Unfortunately, these longitudinal studies are hard to perform and as such the question still remains to be addressed.

8. Genotyping asthma remission

Only three genetic studies have been performed on asthma remission subjects. To explore if SERPINE1 polymorphism is linked to asthma remission, Dijkstra *et al.* re-evaluated a longitudinal cohort of 281 asthmatics and asthma remission subjects (Dijkstra et al., 2011; Panhuysen et al., 1997), with an independent population-based cohort as a control group. Asthmatics with the 5G allele had significantly higher serum total IgE levels, a lower FEV_1, and a faster annual FEV_1 decline compared to the control cohort. More interestingly, complete asthma remission was significantly more prevalent in subjects with the 4G/4G genotype (20%), compared to the 4G/5G (11%) or 5G/5G genotype (4%). The SERPINE1 -675 4G/5G promotor polymorphism regulates plasminogen activator inhibitor (PAI)-1 levels, a key regulator of the plasminogen activator system, and has been associated with elevated serum IgE levels (Bucková, Izakovicová Hollá, & Vácha, 2002; Pampuch et al., 2006), and both the development and the severity of asthma (Cho et al., 2001; Cho, Ryu, & Oh, 2004; Pampuch et al., 2006). The authors concluded that these findings could reflect differences in chronic airway inflammation and remodeling between the genotypes.

Genome-wide association studies (GWAS) have provided insights into the origins of asthma and identified multiple genes associated with its development (Portelli, Hodge, & Sayers, 2015), but GWAS studies examining remission are more scarce. In a recent GWAS study, Vonk et al investigated 612 persistent asthmatics, 178 clinical remission subjects and 55 complete remission subjects as an identification cohort and replicated the results in two smaller independent cohorts (Vonk et al., 2018). Only one single nucleotide polymorphism (SNP) could be replicated in clinical remission, while in complete asthma remission, two SNPs were replicated: the top SNP, *rs6581895*, almost reached genome-wide significance and was an expression quantitative locus (eQTL) for fibroblast growth factor receptor substrate 2 (FRS2) and chaperonin containing TCP1 subunit 2 (CCT2). FRS2 is a critical regulator of VEGF receptor signalling in lung tissue, which may affect angiogenesis (Chen et al., 2014), potentially contributing to the resolution of inflammation (Chen et al., 2014). CCT2 has been associated with cell growth (Amit et al., 2010) and maintenance of cell proliferation (Izawa, Goto, Kasahara, & Inagaki, 2015). The second SNP, *rs1420101*, is a cis-eQTL for IL1RL1 and IL18R1 a trans-eQTL for IL13 in lung tissue. Intriguingly, the expression of IL1RL1, IL18R and IL13 are associated with a risk for asthma (Akhabir et al., 2014; Akhabir & Sandford, 2011). This could imply that these variants play a role in regulating type 2 inflammation (Vonk et al., 2018).

Finally, there is increasing interest in the role of the airway microbiome in respiratory diseases. The microbiome may play a significant role in airway remodeling through the stimulation of various immune and inflammatory pathways, subsequently affecting the course

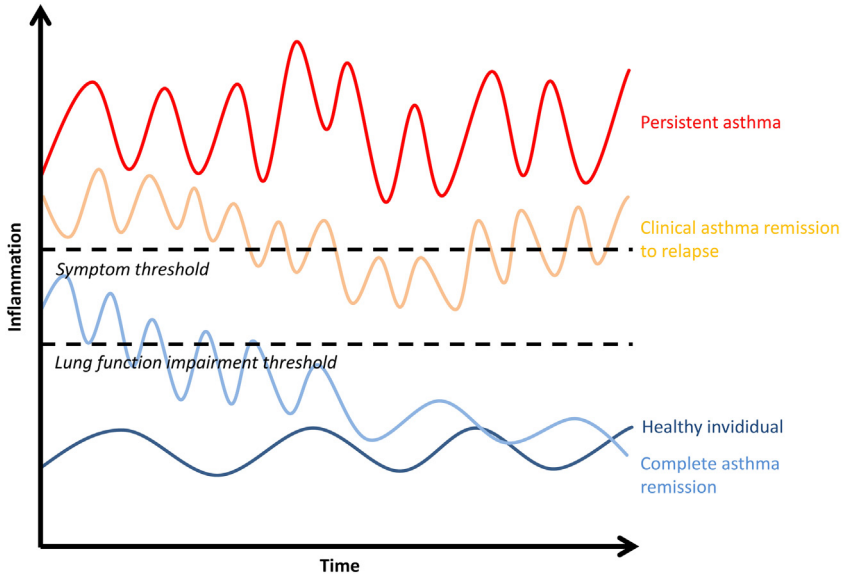

Fig. 3. Theoretical trajectory of persistent asthma, asthma remission and relapse over time. Adapted, with permission, from Upham & James, 2011.

Table 2
Biomarkers associated with clinical and complete asthma remission in cross-sectional studies.

Markers in asthma remission	Significantly higher/lower than in healthy controls (P < 0.05)			Significantly higher/lower than in persistent asthmatics (P < 0.05)		
	Higher (+)	Lower (-)	Non-significance	Higher (+)	Lower (-)	Non-significance
Blood eosinophils	Kim et al., 2018 Boulet, Turcotte, Plante, & Chakir, 2012b[ComR]		Xu et al., 2000 Waserman et al., 2012 Volbeda et al., 2010		Broekema et al., 2011 Kim et al., 2018 Noma et al., 1999 Waserman et al., 2012	Boulet, Turcotte, Plante, et al., 2012
Blood IgE	Kim et al., 2018 Noma et al., 1999 van Den Toorn et al., 2001		Waserman et al., 2012 Boulet, Turcotte, Plante, et al., 2012[ComR] Volbeda et al., 2010		Xu et al., 2000 van Den Toorn et al., 2001 Broekema et al., 2011	Kim et al., 2018 Waserman et al., 2012 Andersson et al., 2013 Panhuysen et al., 1997 Boulet, Turcotte, Plante, et al., 2012[ComR]
Blood IL-5 activity	Noma et al., 1999 Tomiita et al., 2015				Noma et al., 1999	Tomiita et al., 2015
Blood IL-10 activity			Tomiita et al., 2015			Tomiita et al., 2015
Blood regulating T-cells [B]			Boulet, Turcotte, Plante, et al., 2012[ComR]		Boulet, Turcotte, Plante, et al., 2012[ComR]	
Exhaled air FeNO	van Den Toorn et al., 2000		-		Arshad et al., 2014	van Den Toorn et al., 2000
Sputum eosinophils	Obase et al., 2001		Boulet, Turcotte, Plante, et al., 2012[ComR]		Waserman et al., 2012 Volbeda et al., 2010[A]	Boulet, Turcotte, Plante, et al., 2012[ComR] Broekema et al., 2011 Arshad et al., 2014 Obase et al., 2001
Sputum ECP	Obase et al., 2001		Waserman et al., 2012 Broekema et al., 2011		Waserman et al., 2012 Broekema et al., 2011[ComR]	Broekema et al., 2011 Arshad et al., 2014 Obase et al., 2001
Sputum neutrophils			Boulet, Turcotte, Plante, et al., 2012[ComR] Broekema et al., 2011 Volbeda et al., 2010			Boulet, Turcotte, Plante, et al., 2012[ComR] Broekema et al., 2011 Waserman et al., 2012 Volbeda et al., 2010 Arshad et al., 2014
Sputum histamine			-		Broekema et al., 2011	
Sputum macrophages			Waserman et al., 2012 Volbeda et al., 2010			Waserman et al., 2012 Volbeda et al., 2010
Sputum lymphocytes			Waserman et al., 2012 Volbeda et al., 2010	Broekema et al., 2011[ClinR]		Waserman et al., 2012 Volbeda et al., 2010 Broekema et al., 2011[ComR]
Sputum TNF-α	Obase et al., 2001		Waserman et al., 2012		Waserman et al., 2012	Obase et al., 2001
Sputum IL-5			Waserman et al., 2012			Waserman et al., 2012
Sputum IL-10			Waserman et al., 2012			Waserman et al., 2012
Sputum IL-12			Waserman et al., 2012		Waserman et al., 2012	
BAL eosinophils	Warke et al., 2002					-
BAL neutrophils			Warke et al., 2002			-
BAL mast cells			Warke et al., 2002			-
BAL macrophages			Warke et al., 2002			-
BAL lymphocytes			Warke et al., 2002			-
Subepithelial eosinophils			van Den Toorn et al., 2001			Broekema et al., 2011
Epithelial eosinophils			van Den Toorn et al., 2001			van Den Toorn et al., 2001
EPX immunopositivity			-		Broekema et al., 2011[ComR]	Broekema et al., 2011[ClinR]
Subepithelial neutrophils			-			Broekema et al., 2011
Subepithelial tryptase	van Den Toorn et al., 2001			van Den Toorn et al., 2001		
Epithelial tryptase			van Den Toorn et al., 2001	van Den Toorn et al., 2001		Broekema et al., 2011
Subepithelial chymase			van Den Toorn et al., 2001	van Den Toorn et al., 2001		
Epithelial chymase			van Den Toorn et al., 2001	van Den Toorn et al., 2001		
Subepithelial macrophages			van Den Toorn et al., 2001			van Den Toorn et al., 2001 Broekema et al., 2011
Epithelial macrophages			van Den Toorn et al., 2001			van Den Toorn et al., 2001
Subepithelial CD^{4+} T-cells			van Den Toorn et al., 2001			Broekema et al., 2011 van Den Toorn et al., 2001
Epithelial CD^{4+} T-cells			van Den Toorn et al., 2001			van Den Toorn et al., 2001
Subepithelial CD^{8+} T-cells			van Den Toorn et al., 2001			Broekema et al., 2011 van Den Toorn et al., 2001
Epithelial CD^{8+} T-cells			van Den Toorn et al., 2001			van Den Toorn et al., 2001
Subepithelial CD^{25+} T-cells			van Den Toorn et al., 2001			van Den Toorn et al., 2001
Epithelial CD^{25+} T-cells			van Den Toorn et al., 2001			van Den Toorn et al., 2001
Subepithelial CD^{69+} T-cells			van Den Toorn et al., 2001			van Den Toorn et al., 2001
Epithelial CD^{69+} T-cells			van Den Toorn et al., 2001			van Den Toorn et al., 2001
Subepithelial CD^{20+} B-cells			-			Broekema et al., 2011
Subepithelial IL-5	van Den Toorn et al., 2001					van Den Toorn et al., 2001

Table 2 (*continued*)

Markers in asthma remission	Significantly higher/lower than in healthy controls (P < 0.05)			Significantly higher/lower than in persistent asthmatics (P < 0.05)		
	Higher (+)	Lower (-)	Non-significance	Higher (+)	Lower (-)	Non-significance
Epithelial IL-5			van Den Toorn et al., 2001			van Den Toorn et al., 2001
Subepithelial INOS			van Den Toorn et al., 2001	van Den Toorn et al., 2001		
Epithelial INOS	van Den Toorn et al., 2001					van Den Toorn et al., 2001

Study groups (number of asthma/remission/control)
Arshad et al., 2014: n = 108/45/0, mean age 18, Andersson et al., 2013: n = 84/43/0, age range 16–17, Boulet, Turcotte, Plante, et al., 2012: n = 29/42/15 mean age 32, Broekema et al., 2011: n = 103/62/0, mean age 49, range 18–75, Kim et al., 2014: n = 31/30/31, mean age 8, Noma et al., 1999: n = 6/7/7, age range 6–35, Obase et al., 2001: n = 20/20/80, mean age, range 20–29, Panhuysen et al., 1997: n = 161/201/0 mean age 48, range 35-71, Tomiita et al., 2015: n = 18/15/14, mean age 21, van Den Toorn et al., 2001, 2000: n = 19/18/17, mean age 22, range 18–25, Volbeda et al. 2010: n = 46/7/0 mean age 49, range 18–70, Warke et al., 2002: n = 0/25/35, mean age 7, Waserman et al., 2012: n = 15/15/15, mean age 14, range 12–18, Xu et al., 2000: n = 0/20/30, age range >18.

Legend

A: Adenosine-'5-monophosphate provocation test induced eosinophilia, B: capacity of T-regs to suppress proliferation of effector T-cells, BAL: bronchial alveolar lavage, ClinR: only in clinical asthma remission, ComR: only in complete asthma remission, ECP: eosinophil cationic protein, EPX: eosinophilic peroxidase, FeNO: fractional exhaled nitric oxide, INOS: inducible nitric oxide synthase

of asthma (Liu, 2015). A cross-sectional cohort of 30 children with asthma remission, 31 with persistent asthma and 30 controls were studied in the KOREA study (Kim et al., 2018). DNA was extracted from nasopharyngeal swabs, to analyze the composition of microbiota among the groups and their clinical features. Genera that comprised more than 1% of the microbiota in over 50% of the samples were analyzed. The authors found a significantly higher abundance of *Staphylococcus* in the asthma-group (13%), compared to the asthma remission (8%) and controls (2%). The relative highest abundance of *Haemophilus influenzae* was seen in the healthy controls, while *Fusobacterium* was seen relatively highest in the remission-group. Additionally, there was a significant negative correlation between the separate abundance of *Staphylococcus* and *Firmicutes* with bronchial hyperresponsiveness, and a negative correlation with *Streptococcus* and lung function. This could imply that a different airway microbiome might contribute to the severity of bronchial hyperresponsiveness, resulting in a different course of asthma in children (Kim et al., 2018).

Taken all together, these three studies implicate pathophysiological pathways that have not yet been studied thoroughly in asthma remission. They found significant differences between asthma remission and both asthma and controls, strengthening the hypothesis that asthma remission is a valid pathological state, with the potential of identifying a causal pathway leading to remission. In this sense, complete asthma remission is most likely to be a more rewarding candidate state for research compared to clinical asthma remission.

9. Pharmacological potential of achieving asthma remission

As described previously, two interventions are thought to have the potential to induce long-term asthma remission: weight reduction and hormonal therapy. And by elucidating the pathways associated with the relatively new disease state called complete asthma remission (e.g. inflammatory- and gene-expression features) there is an opportunity for identifying new potential targets. As an analogy: in the last decades, understanding short-term variation as related to eosinophil numbers in asthmatics has greatly assisted the introduction of anti-IL5 therapy (Brussino, Heffler, Bucca, Nicola, & Rolla, 2018; Kips et al., 2003). Similarly, but on a much longer time scale, understanding indicators or pathways associated with complete remission could also help introducing new therapeutic targets. There are various novel therapies for asthma that are under development (Upham & Chung, 2018): Dupilumab (Zayed et al., 2018), a monoclonal antibody that blocks the common receptor for IL-4 and IL-13, Tezepelumab (Corren et al., 2017), a monoclonal antibody directed against thymic stromal lymphopoeitin which is produced by epithelial cells and affects multiple immune cells, and Fevipiprant (Kao & Parulekar, 2019), an agent that blocks the prostaglandin D2 receptor CRTH2. Unsurprisingly, these three options are predominantly tested on severe asthmatics, but in future might be used to achieve asthma remission in less severe cases.

10. Conclusions and future perspectives

Defining asthma remission is a complex issue; to date, it is poorly understood even though it has been the ultimate therapeutic goal for so long. When determining the prevalence, risk factors, and clinical correlates of remission based on ill-defined criteria, the relevance can be questioned. However, when defined properly, such as in complete asthma remission, we might find biological triggers that actually cause asthma to spontaneously remit. We believe that complete asthma remission is a more robust pathological disease state, which has more prognostic and scientific value than clinical asthma remission. Future research is needed to explore its phenotype and underlying mechanisms. To further look into the clinical features of asthma remission, it could be rewarding to assess small airways disease using novel diagnostic tools, such as measuring and analysing particles in exhaled air (Soares et al., 2018), functional CT imaging by parametric response mapping of the lungs (Bell et al., 2019), optical coherence tomography of the airway walls (Goorsenberg et al., 2018), and further characterization of the histology in endobronchial biopsies. These new techniques might give us more insight in the detection and monitoring of small airways disease and remodeling, both being proposed contributors to persistence of asthma. To disentangle underlying mechanisms, single cell RNA-sequencing of inflammatory- and epithelial cells has the potential to find targets which may induce asthma remission (Regev et al., 2017).

Conflict of interest statement

O.A. Carpaij, J.K. Burgess, H.A.M. Kerstjens, M.C. Nawijn and M. van den Berge, report no relationship/conditions/circumstances that present a potential conflict of interest for this submitted work.

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