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Asthma, bronchial hyperresponsiveness, allergy and lung function development until early adulthood: A systematic literature review

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Abstract

Background: It is unclear in which periods of life lung function deficits develop, and whether these are affected by risk factors such as asthma, bronchial hyperresponsiveness (BHR) and allergic comorbidity. The goal of this systematic review was to identify temporal associations of asthma, BHR and allergic comorbidity with large and small lung function development from birth until peak function in early adulthood.

Methods: We searched MEDLINE, EMBASE, Web of Science and CINAHL for papers published before 01.01.2020 on risk factors and lung function measurements of large and small airways. Studies were required to report lung function at any time point or interval from birth until peak lung function (age 21-26) and include at least one candidate risk factor.

Results: Of the 45 papers identified, 44 investigated cohorts and one was a clinical trial with follow-up. Asthma, wheezing, BHR and allergic sensitization early in life and to multiple allergens were associated with a lower lung function growth of large and small airways during early childhood compared with the control populations. Lung function development after childhood in subjects with asthma or persistent wheeze, although continuing to grow at a lower level, largely tracked parallel to non-affected individuals until peak function was attained.

Clinical implications and future research: Deficits in lung function growth develop in early childhood, and children with asthma, BHR and early-life IgE (poly)sensitization are at risk. This period is possibly a critical window of opportunity to identify at-risk subjects and provide treatment aimed at preventing long-term sequelae of lung function.

KEYWORDS
asthma, allergy, bronchial hyperresponsiveness, growth, lung function, small airways

1 | INTRODUCTION

Peak lung function is normally attained around the age of 22 for males and slightly earlier for females,[1] after which lung function remains stable for some years during a plateau phase before beginning to decline.[2,3] Children with asthma may reach a lower maximum lung function in adulthood,[3-6] putting them at risk for development of future COPD. Different patterns of impaired lung function development from childhood to adulthood have been described in children with asthma, such as 'normal growth', 'normal growth and early decline', 'reduced growth' and 'reduced growth and early decline'.[3] Growth of the lungs may not only be impaired during early childhood, but also throughout adolescence and early adulthood. Next to the growth of the large airways, growth of the small airways may be important, as accumulating evidence suggests that many lung diseases, including asthma and COPD, start in the small airways.[7] Therefore, better knowledge on the predictors, place (small versus large airways) and timing of the development of low lung function may set the stage for future preventative measures aimed at improving lung function growth.

So far, conflicting results have been reported on lung growth in asthmatic children. Some studies suggested no association of mild or transient asthma with reduced lung growth in the first years of life,[5,8] whereas in another study, more severe asthma and persistent wheeze were associated with reduced lung growth throughout childhood and adolescence.[4] The presence of asthma, the timing of asthma onset, persistence and severity of symptoms and the presence of allergic comorbidity may be important determinants of the maximally attained FEV_1 in early adulthood (Figure 1).[5,8-12] Moreover, it has not been systematically assessed whether these risk factors also relate to measures of small airway function growth. Thus, an important question remains when and where the lung function deficits develop: in the first years of life, in childhood, adolescence or early adulthood?

To identify the factors associated with lung function growth and their significance during different periods of development, this systematic literature review investigated current literature on the temporal associations of asthma and allergy with lung function growth of small and large airways during childhood and adolescence up to the maximum lung function in early adulthood. Asthma is heterogeneous disease with varying degrees of symptoms, comorbidities and clinical biomarkers. Candidate risk factors were therefore selected with the aim of capturing a valid representation of potential factors associated with lung function growth in subjects with asthma or allergy. In addition to asthma and wheezing in early life, bronchial hyper-responsiveness (BHR), a hallmark of asthma, was included. Furthermore, we included allergic sensitization, rhinitis and blood eosinophils as candidate risk factors for a lower lung function growth from infancy until peak lung function in early adulthood.

Key Message

Asthma, wheezing, BHR and allergic sensitization are associated with a lower lung function growth of large and small airways during early childhood. Lung function development after childhood largely tracks parallel to non-asthmatic individuals.

2 | METHODS

This systematic review (PROSPERO registration number: CRD42020172531) was conducted in accordance with guidelines reported in the Preferred Reporting Items for Systematic reviews and Meta-Analysis (PRISMA).[13]

2.1 | Search strategy

We searched MEDLINE using the PubMed search engine, EMBASE, Web of Science (Clarivate) and CINAHL (EBSCO) for papers published before 01.01.2020 with search terms as outlined in Table 1 and Appendix S1. In addition to papers screened in MEDLINE, 52 papers, retrieved from backward citation searching, were reviewed for eligibility of which 2 studies were selected for inclusion (Figure 2).

2.2 | Study selection

Abstracts of all papers were screened independently by two researchers (HJLK and AMZ). Subsequently, full-text papers were assessed for eligibility. In case of disagreement, the study was assessed by a third independent researcher (GHK). Papers were required to contain relevant primary data on studies performed in humans (inclusion criteria; see Table 2). We included longitudinal studies that provided data on temporal associations between candidate risk factors and lung function. This entails that in studies with lung function measured at one time point, the ascertainment of candidate risk factors (eg asthma diagnosis) had to precede the measurement of lung function. In studies with multiple measurements of lung function, concurrent ascertainment of a candidate risk factor and lung function testing was permitted. We investigated the following candidate risk factors: asthma diagnosis, wheezing, BHR, markers related to allergy (rhinitis, specific IgE, skin prick tests) and blood eosinophils within asthmatic populations, non-asthmatic patients or in general population-based cohorts. These studies needed to report lung function at a point between infancy until maximum lung function was attained (age 21-26). Studies presenting a mean lung function of subjects that had an age range >2 years were excluded to avoid aggregating lung function data from subjects at different stages of development. In studies reporting findings from two or more cohorts, in which not all cohorts matched the inclusion criteria, relevant data were extracted only from cohorts that matched our inclusion criteria. Letters to editors were not included in this systematic review as this format would not allow us to verify the extensive inclusion criteria or perform a complete quality analysis. Backward

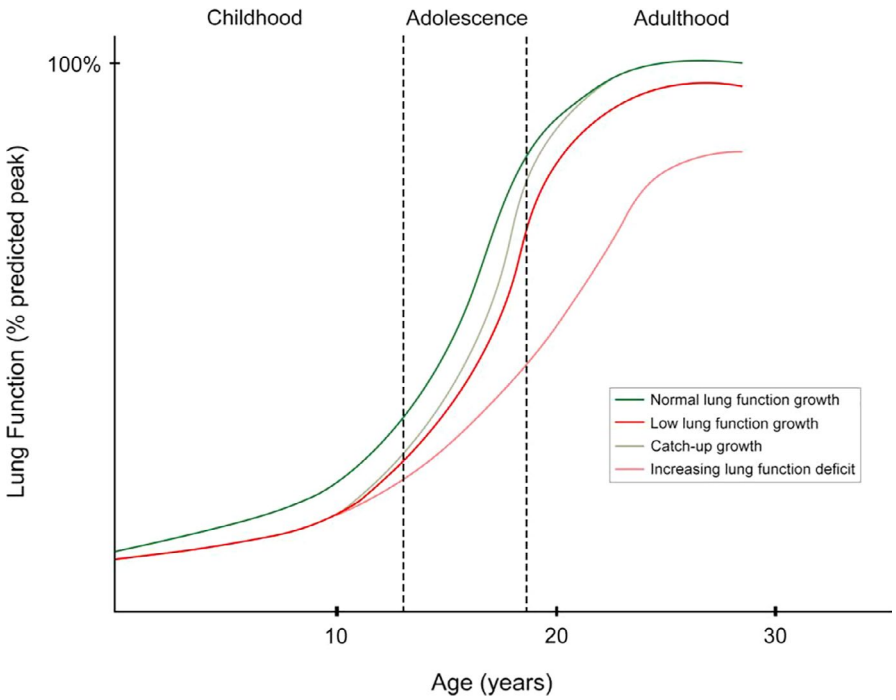

FIGURE 1 Lung function growth from childhood to adulthood. The green line represents normal lung function growth and levels. The red line represents low lung function growth and levels. The light green represents subjects with low lung function levels in early childhood and catch-up growth in adolescence and early adulthood. The pink line represents children with lower lung function levels in childhood and reduced growth until early adulthood. Figure 1 is a conceptual illustration based on Agustí et al[70]

TABLE 1 Search strategy using PubMed

Search strategy
We searched PubMed using the following key terms:
PubMed (MESH terms)
Lung Volume Measurements/Respiratory Function Tests/Spirometry/Lung/growth and development/Allergy and Immunology/Hypersensitivity/Eosinophils/Eosinophilia/Immunoglobulin E/Asthma/Respiratory Hypersensitivity/Rhinitis, Allergic/Predictive Value of Tests/Cohort Studies/Case-Control Studies/Child/Infant/Adolescent/Young Adult/Age Distribution
Title and abstract search
lung growth/pulmonary growth/lung function meas*/spiromet*/plethysmography/forced oscillation technique*/lung clearance index/multiple breath washout/lung function*/allerg*/asthma*/hypersensit*/hypperresponsiv*/eosinophil/follow-up/followup/longitudinal/cohort/case-control/trajector*/pattern*/child*/infan*/prenatal*/fetal/pediatr*/paediatr*/school/preschool/adolscen*/teenager*/young adult*/younger adult*/young people/younger people / early life/early age/young age*/younger age*
For the full strategy and searches performed in EMBASE, CINAHL and Web of Science, please see Appendix S1

citation search was performed by screening references (using title and abstract) in all full-text assessed papers for possible inclusion.

2.3 | Study population

The aim of this systematic review was to study the development of lung function in subjects with asthma or allergy compared with a non-affected population. We investigated lung function development between the ages of 0 and 26 as this period comprises lung growth from birth until peak lung function in early adulthood. Subjects could be derived from both hospital and population-based cohorts. As asthma and allergies are highly heterogeneous conditions, different candidate risk factors were chosen that characterize these. These risk factors could be defined at a specific point in time (eg asthma at age 6) or could be based on longitudinal phenotype modelling. Comparison of lung function between affected and non-affected subjects could be performed within the same population, within a separate general population-based cohort or by utilizing standard reference values. Studies with outcome parameters derived from spirometry, forced oscillation technique (FOT), multiple-breath washout (MBW) and body plethysmography were included. Separate analyses were performed for outcome parameters reflecting the large airways (eg FEV_1: forced expiratory volume in one second, FVC: forced vital capacity, FEV_1/FVC) and the small airways (eg FEF_{25-75}: forced expiratory flow at 25%-75% of FVC, sRaw: specific airway resistance, MMEF: maximal mid-expiratory flow, R_5: resistance at 5 Hz, f_{res}: resonance frequency). We classified sRaw and

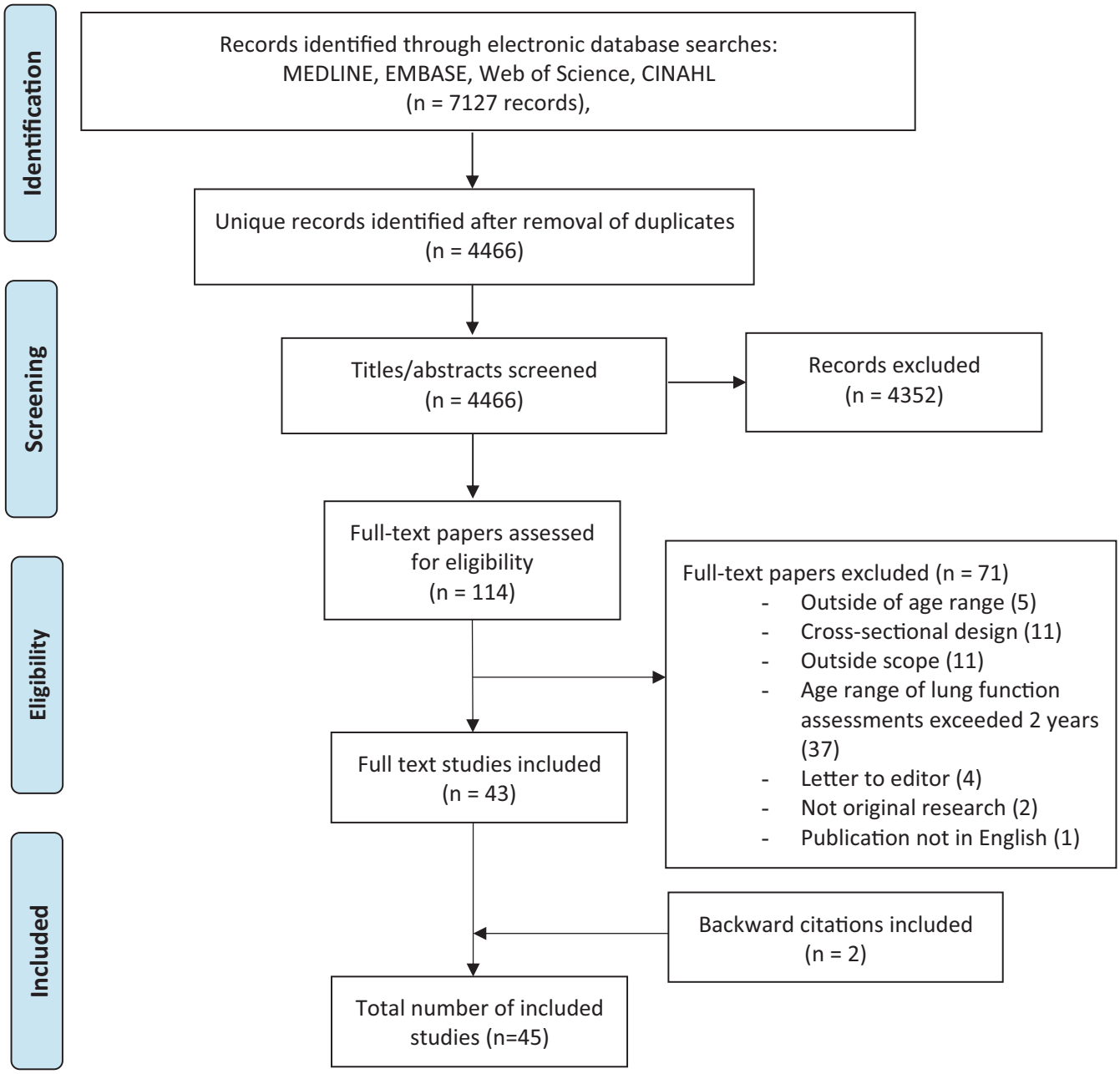

FIGURE 2 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram

MMEF as small airway parameters, although large airway obstruction could also affect this outcome, thereby making it a mixed parameter. VmaxFRC (maximum forced expiratory flow at functional residual capacity) derived from rapid chest compression in infancy was reported if the study met requirements of lung function testing later during development.

2.4 | Data extraction

Information on study design, candidate risk factors and lung function outcomes was collected from included papers. Results were grouped according to which type of lung function outcome was presented: estimated lung function trajectories using, for example, latent class analysis (LCA), calculated change in lung function over time (growth) and lung function levels at specific time points. If included studies provided sex-stratified associations, findings were included in the same manner in review. Definitions used for periods of development and phenotype development are provided in Appendix S3. Quality assessment of included studies was performed using a modified Newcastle-Ottawa Quality Assessment Scale for cohort studies [14,15] (see Appendix S2). Information relating to quality assessment was collected from the included paper, the supplementary data or the official cohort profile. All studies with 6 or more stars were classified as high quality, while studies with 4-5 stars were classified as moderate. In the quality assessment, the following criteria were reviewed:

TABLE 2 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
Longitudinal cohort studies and clinical trials with observational follow-up	Letter to editors, meeting abstracts, case reports and literature reviews
Age of subjects 0-26 y	>2-yr age range for mean lung function measurement
Subjects from population-based cohorts or hospital-based cohorts	Ascertainment of risk factor not preceding lung function measurement (cross-sectional studies only)
Papers published before 01.01.2020	
Publications written in English	
Predictors of outcome: • Asthma/Wheezing • BHR • Allergic sensitization (IgE and SPT) • Rhinitis • Blood eosinophils	
Lung function derived from: • Spirometry • Forced oscillation technique • Multiple-breath washout • Body plethysmography	

Abbreviations: BHR, bronchial hyper-responsiveness; IgE, immunoglobulin E; SPT, skin prick test.

1. Representativeness of the exposed cohort (eg non-selected general population-based birth cohorts)
2. Selection of the non-exposed cohort (selection from the same cohort as exposed subjects or a separate cohort).
3. Ascertainment of exposure/candidate risk factor (eg structured interview vs. self-reported observations).
4. Comparability of cohorts (degree of study control for the following confounders: age, height and sex)
5. Duration of follow-up (studies with more than 2-year follow-up were awarded a star)
6. Adequacy of follow-up (degree of follow-up and description of subjects lost to follow-up)

3 | RESULTS

3.1 | Search results

The literature search strategy identified 7127 records (Figure 2). After removal of duplicate records, 4466 records were reviewed using title and abstract. Of these, 114 full-text papers were assessed for eligibility resulting in 43 included studies. Backward citations from selected papers yielded an additional 2 studies bringing the total number of papers in the final analysis to 45.

3.2 | Characteristics of studies

Of the 45 selected papers, 38 were population-based,[4,5,16-51] 6 were clinical/hospital-based or high-risk cohorts,[52-57] and one was a clinical trial with observational follow-up.[3] In total, 23 different cohorts were identified (Figure S1), of which 15 were birth cohorts (Tables 3,4,S1). Seven studies reported lung function trajectories (Table 3). These studies mainly captured differences in lung function levels that remained stable throughout development. Next, 14 studies reported associations with lung function growth during a defined period until early adulthood (Table 4), while 33 papers reported associations with lung function levels (Table S1).

Separate lung function trajectories that capture differences in growth in an affected population relative to a control group were identified in two studies.[3,47] Small airway parameters were included in 22 studies,[5,17,21,22,25-29,31,33,35-38,41,44,48,49,52,53,56] of which $FEF_{25\%-75\%}$ was the most frequently used. Of the 45 included studies, one had a moderate level of quality, while the remaining had a high level (Appendix S2). Due to the overall high quality, differences in quality were not considered when reporting or interpreting findings from included studies. Different strategies in ascertainment of exposure, that is candidate risk factor, contributed to the greatest variation in quality amongst selected studies. The most frequent biases were use of parental questionnaires and observations to ascertain the presence of a risk factor.

3.3 | Asthma and wheezing

3.3.1 | Lung function trajectories

Asthma and wheezing

Asthma and/or wheezing were associated with a lower-than-normal lung function trajectory from childhood until adolescence [45,46] and until early adulthood.[43,45,47,48] The trajectories identified differences in lung function level over time but not growth rate during development. Asthma in childhood was associated with lower lung function trajectories for both small and large airways until early adulthood.[48]

TABLE 3 Studies on lung function trajectories

First author	Cohort	Type and age lung function measurement(s)	End-points	Predictors of outcome	Main findings (S: significant, NS: non-significant)
Schultz[46]	BAMSE (n = 1425) Population-based birth cohort	Spirometry at 8 and 16 y	Lung function trajectory: Low Normal/high Large airways: FEV_1	Asthma/wheeze	S: early wheeze and asthma ever till age 8 were associated with a low FEV_1 trajectory (<25th percentile at 8 and 16 y of age). Prevalence of early wheeze: 25% in low trajectory and 12% in normal/high trajectory. Prevalence of asthma: 23% in low trajectory and 14% in normal/high trajectory. NS: Current wheeze at age 8 was not associated with a low FEV_1 trajectory
				Allergic sensitization (IgE)	NS: allergic sensitization at age 8 was not associated with a low FEV_1 trajectory (<25th percentile at 8 and 16 y of age).
Belgrave[45]	MAAS (n = 1046) Population-based birth cohort ALSPAC (n = 1390) Population-based birth cohort	MAAS: spirometry at 5, 8, 11 and 16 y ALSPAC: Spirometry at 8, 15 and 24 yars	Lung function trajectory: Persistently high Normal Below average Persistently low Large airways: FEV_1	Asthma, wheeze	S: asthma and wheeze throughout the follow-up period were associated with a persistently low FEV_1 trajectory (see appendix of original paper for exact data)
				BHR (yes/no)	S: BHR (ALSPAC at ages 15 and 24 and MAAS at ages 5, 8, 11 and 16) was associated with a persistently low FEV_1 trajectory.
				Allergic sensitization (skin prick test)	S: allergic sensitization in early childhood in MAAS was associated with a persistently low FEV_1 trajectory. NS: allergic sensitization in adolescence (MAAS) or at age 7 (ALSPAC) was not associated with a persistently low FEV_1 trajectory
McGeachie[3]	CAMP (n = 684) Randomized controlled trial with extended follow-up in asthmatic patients	Spirometry (age 5/12-26/30)	Lung function trajectory: Normal growth Reduced growth Normal growth, early decline Reduced growth, early decline Large airways: FEV_1	BHR severity	S: more severe BHR (at inclusion) was associated with a reduced FEV_1 growth pattern (OR for reduced growth compared with normal growth: 0.61 per unit change in log-transformed mg per mL)
				Allergic sensitization (skin prick test)	S: subjects with a 'reduced growth and early decline' trajectory had a greater number of positive skin prick tests at enrolment compared with subjects with a 'normal growth' trajectory (OR for ≥3 positive skin tests vs. <3:2.42)
Rasmussen[23]	Dunedin, New Zealand (n = 788) Population-based birth cohort	Spirometry at 18 and 26 y	Lung function trajectory: Consistently normal Variable Consistently low Large airway: (FEV_1/VC)	Asthma	S: asthma reported at any time during the study (between age 9 and 26) was associated with a consistently low FEV_1/VC trajectory between ages 18 and 26. Prevalence of asthma: males: 68% in consistently low and 30% in consistently normal, females: 82% in consistently low and 30% in consistently normal
				BHR (yes/no)	S: BHR at age 9 was associated with a consistently low FEV_1/VC trajectory. Prevalence of BHR: males: 55% in consistently low and 17% in consistently normal, females: 57% in consistently low and 14% in consistently normal
				Allergic sensitization (skin prick test): House dust mite Cat Atopy IgE	S: allergic sensitization to house dust mite or to cat at age 21 was associated with a consistently low FEV_1/VC trajectory. Prevalence of house dust mite sensitization: males: 57% in consistently normal and 78% in consistently low, females: 51% in consistently normal and 90% in consistently low. Prevalence of sensitization to cat: males: 28% in consistently normal and 48% in consistently low, females: 25% in consistently normal and 50% in consistently low. Higher levels of IgE at ages 11 and 21 were also associated with a consistently low trajectory in females. Age 11 IgE: consistently normal 4.6 (ln), consistently low 5.6 (ln). Age 21 IgE: consistently normal 3.7 (ln), consistently low 5.0 (ln). NS: atopy at age 13 or 21 (at least one SPT ≥2 mm) was not associated with a consistently low FEV_1/VC trajectory. Sensitization to house dust mite and cat at age 13 was not associated with a consistently low FEV_1/VC trajectory

(Continues)

TABLE 3 (Continued)

First author	Cohort	Type and age lung function measurement(s)	End-points	Predictors of outcome	Main findings (S: significant, NS: non-significant)
Berry[43]	TCRS (n = 599) Population-based birth cohort	Spirometry at 11, 16, 22, 26 and 32 y	Lung function trajectory: Persistently low Normal Large airways: FEV_1/FVC	Asthma	S: asthma between the ages of 6 and 32 (survey age 6, 11, 22, 26 and 32) was associated with a persistently low FEV_1/FVC trajectory. Prevalence of asthma ranged from 7.7% to 18.0% in the normal trajectory and from 26.4% to 43.9% in the persistently low trajectory
Karmaus[48]	IoW birth cohort (n = 1157) Population-based birth cohort	Spirometry at 10, 18 and 26 y	Lung function trajectory: low high Large airways: FVC, FEV_1, FEV1/FVC: low high Lung function trajectory: low medium high Small airways: FEF_{25-75}	Asthma	Males S: asthma at ages 4, 10, 18 and 26 was associated with a low FEV_1/FVC and FEF_{25-75} trajectory. Asthma at ages 4, 10 and 26 was associated with a low FEV_1 trajectory. NS: asthma at ages 4, 10, 18 and 26 was not associated with a low FVC trajectory. Asthma at age 16 was not associated with a low FEV_1 trajectory Females S: asthma at ages 10, 18 and 26 was associated with a low FEV_1/FVC and FEF_{25-75} trajectory. Asthma at age 18 was associated with a low FEV_1 trajectory (see appendix of original paper for exact data). NS: asthma at age 4 was not associated with a low FEV_1/FVC or FEF_{25-75} trajectory. Asthma at ages 4, 10 or 26 was not associated with a low FEV_1 trajectory
				Allergic sensitization (skin prick test)	Males S: allergic sensitization at age 4 was associated with a low FEV_1/FVC trajectory (RR 1.64). Females S: Allergic sensitization at age 4 was associated with a low FEV_1, FVC and FEF_{25-75} trajectory (RR 1.32)
Bui[47]	TAHS (n = 2438) Population-based birth cohort	Spirometry at 7, 13, 18, 45, 50 and 53 y	Lung function trajectory: Persistently high Average Below average Persistently low Early below average, accelerated decline Early low, accelerated growth, normal decline Large airways: FEV_1	Asthma	S: childhood asthma (during the first 7 y of life) was associated with the persistently low (OR 1.7 compared with the average trajectory) and the early below average, accelerated decline (OR 3.1 compared with the average trajectory) FEV_1 trajectory. NS: Childhood asthma was not associated with early low, accelerated growth, normal decline or persistently high FEV_1 trajectory
				Allergic rhinitis	S: allergic rhinitis (during the first 7 y of life) was associated with the early below average, accelerated decline FEV_1 trajectory (OR 2.0 compared with the average trajectory). NS: allergic rhinitis was not associated with the other lung function trajectories.
				Food allergy	NS: food allergy (during the first 7 y of life) was not associated with a lung function trajectory

Note: In papers reporting significant associations without providing estimates, these estimates were recorded as missing in the results. All lung function outcomes are pre-salbutamol unless otherwise specified.

Abbreviations: BHR, bronchial hyper-responsiveness; FEF_{25-75}, forced expiratory flow at 25%-75% of FVC; FEV_1, forced expiratory volume in 1 s; FVC, forced vital capacity; IgE, immunoglobulin G; n, based on number of subjects with lung function measurement relevant to analysis; NS, not significant; OR, odds ratio; RR, risk ratio; S, significant; VC, vital capacity.

TABLE 4 Studies on lung function growth

First author	Cohort	Age lung function measurement(s)	End-points	Predictors of outcome	Main findings (S: significant, NS: non-significant)
Hallberg[30]	BAMSE (n = 1957) Population-based birth cohort	Spirometry at 4 and 8 y	Lung function growth (4-8 y) Large airways: PEF	Asthma phenotypes: Never Transient Persistent Late onset	S: Transient asthma (−5.8 L/min) had a lower growth in PEF compared with never asthma. NS: persistent or late-onset asthma was not associated with growth in PEF
Hallberg[41]	BAMSE (n = 2355) Population-based birth cohort	Spirometry at 8 and 16 y	Lung function growth (8-16 y) Large airways: FEV_1, FVC, FEV_1/FVC Small airways: FEF_{50}	Asthma phenotypes: Never Early transient Early persistent Late onset	S: early persistent (FEV_1 −262 mL, FEF_{50} −668 mL) and late-onset asthma (FEV_1 −124 mL, FEF_{50} −350 mL) had lower growth in FEV_1 and $FEF_{50,}$ compared with never asthma. Early transient asthma had lower growth in FEF_{50} (−221 mL) NS: early transient asthma was not associated with growth in FEV_1. No asthma phenotypes were associated with growth in FEV_1/FVC
Bisgaard[53]	$COPSAC_{2000}$ (n = 336) High-risk birth cohort (children from asthmatic mothers)	Raised volume rapid thoracic compression in neonatal period. Spirometry at age 7	Lung function growth (0-7 y) Large airways: FEV_1, FVC, FEV_1/FVC Small airways: FEF_{50}	Asthma Blood eosinophils	S: asthma at the age of 7 was associated with a lower growth in $FEV_{1\ (Z\text{-score }-0.62)}$ and FEF50 (Z-score −0.69) from infancy until the age of 7 compared with no asthma NS: blood eosinophils (at age 6) were not associated with lung function growth between the ages of 0 and 7
Hallas[56]	$COPSAC_{2000}$ (n = 367) High-risk birth cohort (children from asthmatic mothers)	Raised volume rapid thoracic compression in neonatal period. Spirometry half-yearly between 5 and 7 y and at 13 y. Whole-body plethysmography half-yearly between 3 and 7 and at 13 y	Lung function growth (0-13 y) Large airways: FEV_1 Small airways: MMEF, sRaw	Asthma phenotypes: Ever asthma, Never asthma Asthma remission Asthma and allergic sensitization (skin prick test, IgE)	NS: asthma during the first 13 y of life was not associated with a lower lung function growth compared with never asthma. Asthma remission was not associated with catch-up growth up until the age of 13 NS: asthma and concurrent allergic sensitization (at age 13) was not associated with a lower lung function growth ($FEV_{1,}$ MMEF or sRaw) from 1 month until age 13 compared with asthma and no allergic sensitization
Duijts[44]	ALSPAC (n = 7278) Population-based birth cohort	Spirometry at ages 9 and 15	Lung function growth (9-15 y) Large airways: FEV_1, FEV_1/FVC Small airways: FEF_{25-75}	Wheezing phenotypes: Transient early Prolonged early Intermediate onset Late onset Persistent Never/infrequent	S: Prolonged early (FEV_1/FVC −0.23 SDU, FEF_{25-75} − 0.10 SDU) and persistent (FEV_1/FVC −0.27 SDU, FEV_1 −0.13 SDU) wheezing had lower growth in FEV_1/FVC and FEF_{25-75} compared with never/infrequent wheezing NS: transient, intermediate-onset or late-onset wheezing was not associated with a different growth in FEV_1/FVC and FEF_{25-75} compared with never/infrequent wheezing. No association between wheezing phenotypes and growth in FEV_1 was found

(Continues)

TABLE 4 (Continued)

First author	Cohort	Age lung function measurement(s)	End-points	Predictors of outcome	Main findings (S: significant, NS: non-significant)
Belgrave[38]	MAAS (n = 1051) Population-based birth cohort	Whole-body plethysmography at ages 3, 5, 8 and 11	Lung function growth (3-11 y) Small airways: sRaw	Wheezing phenotypes: No wheezing Transient early Late onset Persistent	S: Persistent wheezing had a larger increase in sRaw (0.011 kPa/s^{-1} /y) over time compared with no wheezing. NS: transient and late-onset wheezing were not associated with change in sRaw between ages 3 and 11
				Allergic sensitization phenotypes (skin prick test and IgE): Non-atopic Dust mite Non-dust mite Multiple early Multiple late	S: The multiple early (0.011 kPa/s^{-1} /y) and multiple late (0.008 kPa/s^{-1} /y) trajectories had a larger increase in sRaw compared with non-atopic
Sherrill[16]	Dunedin, New Zealand (n = 696) Population-based birth cohort	Spirometry at 9, 11, 13 and 15 y	Lung function growth (9-15 y) Large airways: FEV_1, VC, FEV_1/VC	Wheezing phenotypes: Severe wheezing Moderate wheezing Occasional wheezing Non-wheezing	S: moderate wheezing (between the ages of 3 and 15) (−0.053 L/y) had a lower FEV_1 growth compared with non-wheezing. Occasional wheezing (0.031 L/y) had a greater VC growth compared with non-wheezing. Severe (0.499%/y) and moderate wheezing (0.303% /y) had a higher growth in FEV_1/VC compared with non-wheezing. NS: severe and occasional wheezing were not associated with FEV_1 growth. Severe and moderate wheezing were not associated with VC growth
				BHR severity: Hyper-responsive Mildly responsive Non-responsive Consistently responsive Remission New responders Consistently non-responsive	S: mild (−0.032 L/y) and hyper-responsive (−0.045 L/y) BHR were associated with a lower FEV_1 growth compared to non-responders. Mildly responsive BHR (−0.023 L/y) was associated with a lower VC growth. Hyper-responsive BHR (−0.394%/y) was associated with a lower growth in FEV_1/VC. Consistent responders and new responders had a lower FEV_1 and FEV_1/VC growth compared with never responders (means not provided). NS: hyper-responsive BHR was not associated with a VC growth. Mildly responsive BHR was not associated with FEV_1/VC growth. Subjects who went into remission did not have a different lung function growth compared with consistently non-responsive BHR
Sears[4]	Dunedin, New Zealand (n = 613) Population-based birth cohort	Spirometry at 9, 11, 13, 15, 18, 21 and 26 y	Lung function growth (9-26 y) Large airways: FEV_1/FVC	Wheezing phenotypes: Persistent from onset Relapse Remission Intermittent Transient Never wheeze	NS: Growth in FEV_1/FVC was not different for any wheezing phenotypes compared with never wheezing

(Continues)

TABLE 4 (Continued)

First author	Cohort	Age lung function measurement(s)	End-points	Predictors of outcome	Main findings (S: significant, NS: non-significant)
Arshad[37]	IoW birth cohort (n = 181 at age 18) Population-based birth cohort	Spirometry at 10 and 18 y	Lung function growth (10-18 y) Large airways: FEV_1, FVC Small airways: FEF_{25-75}	Asthma groups: Persistent Remission	Males S: Remission of asthma (2.6 L) was associated with a higher growth in FEV_1 (between 10 and 18 y) compared with persistent asthma (2.4 L). Remission of asthma (2.7 L) was associated with a higher growth in FEF_{25-75} compared with persistent asthma (2.1 L). NS: No asthma groups were associated with growth in FVC. Females NS: Remission of asthma was not associated with a difference in lung function growth compared to subjects with persistent asthma
Kurukulaaratchy[33]	IoW birth cohort (n = 418, male 186, female 232) Population-based birth cohort	Spirometry at 10 and 18 y	Lung function growth (10-18 y) Large airways: FEV_1, FVC, FEV_1/FVC Small airways: FEF_{25-75}	Asthma groups: Adolescent-onset Never-asthma	Males NS: subjects with adolescent-onset asthma did not have a different growth in lung function compared with never asthma. Females S: subjects with adolescent-onset asthma (1.36 L) had a lower growth in FEV_1 (between 10 and 18 y compared with never asthma (1.52 L). NS: asthma groups were not associated with growth of FVC, FEV_1/FVC and FEF_{25-75}
Morgan [5]	TCRS (n = 826) Population-based birth cohort	Partial expiratory flow volume manoeuvre at age 6. Spirometry at ages 11 and 16	Lung function growth (6-16 y) Large airways: VmaxFRC Small airways: FEF_{25-75}	Wheezing phenotypes: Never Transient early Late onset Persistent	NS: None of the wheezing phenotypes had a different lung function growth compared with never wheezing
Jędrychowski[21]	Krakow, Poland (n = 1001) Population-based cohort	Spirometry at 9 and 11	Lung function growth (9-11 y) (binary: slow lung function growth (SLFG)=lowest quintile of growth) Large airways: FEV_1, FVC Small airways: FEF_{25-75}	Asthma/wheezing phenotypes: Healthy New cases Continued Remission	S: Continued asthma between the age of 9 and 11 was associated with a higher prevalence of SLFG (FEV_1 OR 3.46, FVC OR 3.40 and FEF_{25-75} OR 5.84) compared with healthy subjects. New symptoms of asthma between the age of 9 and 11 were associated with SLFG for FEV_1 (OR 1.46) between the age of 9 and 11. Remission of asthma symptoms was associated with SLFG for FEF_{25-75} (OR 2.63). NS: remission of asthma symptoms was not associated with SLFG for FEV_1 or FVC
Nakadate[18]	Ibaraki, Japan (n = 325) Population-based cohort	Spirometry at 10 and 14	Lung function growth (10-14 y) Large airways: FEV_1, FVC Small airways: FEF_{50}, FEF_{25}	Asthma categories: Category A: asthma at first survey (10 y) Category B: bronchitis or pneumonia at first survey (10 y) Category C: no asthma, bronchitis or pneumonia at any time during follow-up	S: Category A (–79 mL/s year) was associated with a lower annual growth in FEF_{25} compared with Category C (8 mL/s/y). NS: category A was not associated with a different growth in FEV_1, FVC or FEF_{50} compared with Category C

(Continues)

TABLE 4 (Continued)

First author	Cohort	Age lung function measurement(s)	End-points	Predictors of outcome	Main findings (S: significant, NS: non-significant)
Weiss[17]	Boston, USA (n = 602) Population-based cohort	Spirometry annually during the 13-y of follow-up starting at enrolment (age 5-9)	Lung function growth (5-9 to 18-22 y) Large airways: FEV_1, FVC Small airways FEF_{25-75}	Asthma categories: Active asthma Inactive asthma No asthma	Males S: active asthma (−4.18% /y) was associated with a lower growth in FEF_{25-75}% predicted compared with no asthma. Active asthma (2.45% /y) was associated with a higher growth in FVC % predicted compared with no asthma. NS: No association was seen for growth in FEV_1. Females S: active asthma (−2.12% /y) was associated with a lower growth in FEV_1% predicted compared with no asthma. Active asthma (−5.75% /y) was associated with a lower growth in FEF_{25-75}% predicted compared with no asthma. NS: no significant association was seen for growth in FVC. NS: inactive asthma was not associated with differences in lung function growth compared with no asthma

Note: In papers reporting significant associations without providing estimates, these estimates were recorded as missing in the results. All lung function outcomes are pre-salbutamol unless otherwise specified.

Abbreviations: BHR: bronchial hyper-responsiveness; FEF_{25-75}: forced expiratory flow at 25% and 75% of FVC; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; IgE: immunoglobulin G; MMEF: maximal mid-expiratory flow; n: based on number of subjects with lung function measurement relevant to analysis; NS: not significant; PEF: peak expiratory flow; S: significant; sRaw: specific airway resistance; VC: vital capacity; VmaxFRC: maximum forced expiratory flow at functional residual capacity.

3.3.2 | Lung function growth

Asthma and wheezing

Asthma and/or wheezing before the age of 7 [30,53] and later in childhood [21] were associated with a lower lung function growth during childhood. Asthma and/or wheezing during childhood [18,41] and during adolescence [16,17] were associated with a lower lung function growth during adolescence. Adolescent-onset asthma was associated with a lower FEV_1 growth in females between ages 10 and 18, but not in males.[33] Interestingly, remission of asthma in males during the same period of development was associated with a greater gain in FEV_1 and FEF_{25-75} from childhood to early adulthood when compared to subjects with a persistent asthma phenotype.[37] However, another study reported that remission of asthma during childhood was not associated with catch-up growth from infancy until the age of 13.[56] Asthma and/or wheezing was significantly associated with lower growth of large and small airway parameters during childhood in three out of four studies [17,21,53] ; one study did not confirm this.[33] Lower lung function growth during childhood in subjects with asthma [56] and wheezing [38] using sRaw (ie higher sRaw) and small airways expiratory flows (higher MMEF) during childhood [56] was reported in two independent studies.

Wheezing phenotypes

A persistent wheezing phenotype was associated with a larger increase in specific airway resistance (sRaw) during childhood compared with the never-wheezing subjects.[38] Early transient,[41] prolonged early,[44] persistent [41,44] and late-onset [41] wheeze were associated with a lower lung function growth from childhood until adolescence. The association for persistent wheezing was reported in studies using both LCA and a hypothesis-driven approach combined with asthma treatment records for phenotype development. In contrast, one study found that growth of FEF_{25-75} from age 6 until 16 in subjects with any of the reported wheezing phenotypes was not significantly different from non-wheezing subjects.[5] Although phenotype definition was also defined a priori, this study differed from Hallberg et al in that persistence of wheeze was based solely on reporting during the first 6 years of life. Another study that incorporated reporting of wheeze between the ages of 9 and 26 reported no difference in the change in FEV_1/FVC between the ages 9 and 26 between subjects with any wheezing phenotype compared with the never-wheeze reference group.[4]

3.3.3 | Lung function at distinct stages of development

Asthma and wheezing

A history of asthma or wheezing before the age of 7 [22,26,30,39-41,51] and later in childhood [20,28,39,52] was associated with lower lung function levels during childhood. Childhood asthma was associated with a lower lung function in adolescence, which persisted into adulthood in two studies.[20,52] Persistence of asthma from childhood to adulthood was associated with lower FEV_1 during early adulthood.[37]

Remission of asthma during adolescence was associated with higher FEV_1/FVC level in early adulthood when compared to subjects with persistent asthma.[54] We identified no studies investigating the difference in lung function levels between subjects with asthma remission and never asthma.

Wheezing phenotypes

Transient [19,36] and persistent [36] wheezing phenotypes were associated with a lower lung function in infancy. An association between wheezing phenotype and lung function for transient wheezing was observed in studies using both LCA and a hypothesis-driven approach for phenotype development, while an association for persistent wheezing was only reported in the ALSPAC cohort using LCA. At age 3, persistent wheezing was associated with a higher sRaw (ie higher resistance) when compared to non-wheezers at age 3. At age 5, both transient and persistent wheezing phenotypes were associated with a higher sRaw.[27]

Later in childhood, (early) transient,[5,19,24,25,27,29,31,32,35,36,40,49] persistent,[5,19,24,25,27,29,31,32,35,36,40,49] prolonged early [29] and late-onset wheezing [25,29,35,40] were associated with lower lung function levels when compared to non-affected control subjects. Associations with lung function for (early) transient, late-onset and persistent wheezing were observed in studies using both a hypothesis-driven approach [5,19,24,25,27,31] and LCA.[29,32,35,36,40,49] Transient (early),[5,44] prolonged early,[44] intermediate-onset,[44] late-onset [44] and persistent [5,44] wheezing phenotypes were also associated with lower lung function levels in adolescence. Transient wheezing was the only phenotype developed using both LCA and a hypothesis-driven approach to be associated with a lower lung function level in adolescence. Granell et al found that phenotypes with early childhood-onset wheezing persisting into adolescence were associated with FEV_1/FVC and FEF_{25-75}; however, no association was seen for FEV_1.[50] In one study, a persistent wheezing phenotype was associated with lower lung function levels in adulthood.[4] Ten studies included both small and large airway parameters in their analysis with asthma and/or wheezing (including longitudinal phenotypes thereof).[5,25,28,29,33,35,36,41,49,52] All these papers found that asthma and/or wheezing were associated with both reduced large and small airway parameters.

3.4 | Bronchial hyper-responsiveness

3.4.1 | Lung function trajectories

BHR, measured in childhood, adolescence and adulthood, was associated with a lower-than-normal lung function trajectory in childhood, up to early adulthood.[23,45] One study reported that more severe BHR in childhood was associated with a reduced lung function growth trajectory based on FEV_1.[3] No studies reported the association between BHR and trajectories of the small airways.

3.4.2 | Lung function growth

More severe BHR measured in childhood and adolescence was associated with a lower growth of FEV_1, FEV_1/VC and VC from age 9 to 15 until adolescence.[16] Adolescent-onset BHR was associated with a lower growth pattern of FEV_1 in adolescence compared with subjects without BHR,[16] whereas remission of BHR was not associated with lower lung function growth until adolescence compared with subjects who were never–BHR-responsive.[16] No studies analysed the association between BHR and small airway growth.

3.4.3 | Lung function at distinct stages of development

The presence of BHR in childhood and until adulthood was associated with a lower FEV_1 and FEV_1/FVC level in early adulthood.[20,23] No studies reported associations between BHR and small airway lung function.

3.4.4 | Atopic sensitization

Lung function trajectories

Allergic sensitization between the ages of 3 and 11 was associated with a persistently low FEV_1 trajectory until adolescence,[45,48] but this association was not seen for sensitization in adolescence.[45] Another study also reported no association between allergic sensitization at age 8 and a low lung function trajectory during adolescence.[46] A higher number of positive skin prick tests in childhood were associated with a lower FEV_1 trajectory until adulthood compared to subjects with a normal trajectory.[3] Allergic sensitization in adulthood to house dust mite or to cat in adulthood was associated with a consistently lower FEV_1/VC trajectory in adulthood,[23] whereas food allergy was not associated with any lung function trajectory.[47] Allergic rhinitis was associated with an '*early below average, accelerated decline*' trajectory.[47] Allergic sensitization in early childhood was associated with both small and large airway trajectories in females.[48] In males, allergic sensitization at age 4 was only associated with a low FEV_1/FVC trajectory but not with the trajectory of the small airway parameter (ie FEF_{25-75}).[48]

Lung function growth

Sensitization to multiple allergens early in life was associated with an increase in sRaw between the ages of 3 and 11 compared with non-atopic subjects.[38] Asthma with concurrent allergic sensitization, measured at age 13, was not associated with a lower degree of lung function growth in large and small airway parameters from infancy until the age of 13, compared to subjects with asthma without allergic sensitization.[56] None of the papers assessed the role of allergic rhinitis in lung function growth.

Lung function at distinct stages of development

At age 3, a positive skin prick test was associated with a higher sRaw in non-wheezing subjects compared with the non-atopic non-wheezing group.[22] A combined wheezing and atopic phenotype in childhood was associated with a lower FEV_1 and FEV_1/FVC at age 7.[57] In two separate cohorts, sensitivity to a wide variety of allergens, including mite, pollens, cat and dog around age 10/11, was associated with a lower FEV_1 and FEV_1/FVC.[34] Early sensitivity to mite, grass and tree pollens with later onset of sensitivity to pets was associated with a lower FEV_1 at age 11 (based on sensitivity testing at ages 1, 3, 5, 8 and 11).[34] Allergic sensitization to cat dander at age 13 was associated with a lower FEV_1 level between the ages of 9 and 15.[16] In one study, atopic wheeze was associated with lower lung function parameters of both large and small airways (FEV_1, FEV_1/FVC, FEF_{75} and FEF_{25}) at age 7 compared with no wheeze.[28] For subjects with early-onset timothy grass sensitization and a dust mite sensitization trajectory (based on sensitization profiles at ages 5, 8 and 11 years), a lower FEV_1 was reported at age 11.[42] At ages 8-9, a late-onset allergic rhinitis phenotype was associated with lower FEV_1 and FEF_{25-75} compared with the reference group.[49] Atopic wheeze was associated with lower FEV_1, FEV_1/FVC, FEF_{75} and FEF_{25} at age 7 compared with no wheezing.[28] A late-onset allergic rhinitis phenotype was associated with lower large and small airway parameters (FEV_1, FEF_{25-75} and FEV_1/FVC).[49]

Blood eosinophils

Only one study reported associations of blood eosinophils with lung function outcomes. No association between blood eosinophils at age 6 and lung function growth (FEV_1, FVC, FEV_1/FVC and FEF_{50}) between 0 and 7 years was found for either large or small airway parameters.[53]

4 | DISCUSSION

4.1 | Main findings

Asthma and different patterns of wheezing are associated with a low lung function trajectory in childhood, adolescence and up to early adulthood.[43,45-48] Additionally, BHR is a strong risk factor for low lung function in childhood up to adolescence.[3,45] Most studies report this for large airways parameters (FEV_1, FEV_1/FVC), with a paucity of studies of the small airways. In asthmatic and wheezing children, reduced lung function growth appears to occur mainly in early childhood, after which lung function often tracks at a parallel, but lower level to that of non-affected individuals.[4,5,43] Allergic sensitization [45] and allergic rhinitis [47] are also associated with lower-than-normal lung function trajectories, yet results varied. The timing of allergic sensitization (preschool age) and the level of sensitization (polysensitization) appeared to be strongly predictive of low lung function growth.[3,34,38]

4.2 | Lung function development until peak function in subjects with asthma or wheezing

Many children with asthma or wheezing have a lower lung function level and lower lung function growth, and reach a lower peak lung function in early adulthood compared with a control population,[43,45-48] possibly predisposing them to COPD.[3] This is likely attributed to a lower degree of lung function growth during early childhood [30,53] after which lung function growth tracks parallel to non-asthmatic controls.[4,5] Consequently, early childhood should be identified as a key period of development in which exposure to risk factors such as asthma and wheezing play an integral role in lung function growth. Despite this, the association of adolescent-onset BHR with a lower lung function growth pattern suggests that lung function development can change after childhood as well.[16] This is further emphasized by the improvement in lung function in early adulthood in subjects with asthma remission, relative to subjects with persistent asthma.[37,54] These observations were done in mainly population-based studies that include children with mild asthma. Thus, future studies should also address lung growth in children with persistent, moderate-to-severe asthma, since evidence suggests that lung growth up to the plateau may be limited.[3] The heterogeneity of lung function development is further increased by sex-related differences,[17,33,48] and future research should therefore incorporate sex-stratified analyses to further explore these differences.

Asthma is a highly heterogeneous condition, which can present as several phenotypes with varying degrees of severity. Based on findings presented in this systematic review, a greater disease severity, manifested by earlier onset and persistence of asthma and or wheezing, was associated with lung function deficits throughout development compared with the control population. In addition to an earlier onset and persistence of symptoms, the number of exacerbations may be important as well in subjects with asthma. In this systematic review, we did not include exacerbations as a candidate risk factor for lung function growth. However, the number of exacerbations in children with asthma and wheezing has been reported to be predictive of a lower lung function throughout childhood compared to children with asthma and no exacerbations.[38,58] As such, accurate recognition of asthma exacerbations and timely intervention to treat and prevent exacerbations may be warranted to preserve optimal lung function growth.

4.3 | Preschool asthma, wheezing phenotypes and lung function

Asthma predominantly starts in preschool life, often as recurrent wheezing episodes. Different patterns of wheeze were associated with low lung function in childhood and adolescence. After the seminal publication by Martinez et al,[19] describing transient early wheeze, late-onset wheeze and persistent wheeze in early

childhood, these patterns of wheezing onset and persistence have been confirmed in other cohorts and by machine learning approaches.[29,32,35,36,38,40,44,49,59,60] Children with an early transient wheeze had a lower lung function compared with persistent, late-onset and never-wheezing phenotypes at the age of 2 months, prior to onset of wheezing and that lung function remained at a lower level during childhood in this group,[19] with a replication study yielding conflicting results.[25] Direct comparison is made difficult by different approaches in establishing the wheezing phenotypes. Later in childhood, transient wheeze phenotypes were still associated with lower lung function levels.[5,19,24,25,27,29,31,32,35,36,40,49] This supports the hypothesis that transient wheeze early in life is likely the clinical presentation of congenitally narrow airways predisposing to wheeze, especially during viral infections. Following growth of airway calibre, wheezing resolves in most subjects; however, a lower lung function remains.

The early persistent, intermediate and late-onset wheezing phenotypes have also been associated with low lung function growth until adolescence and early adulthood.[59] Furthermore, the association of persistent,[32,59] intermediate [32,44,59] and late-onset wheezing phenotypes [32,44,59] with a later diagnosis of asthma in childhood suggests that these wheezing phenotypes have a stronger relation to asthma and reflect ongoing inflammatory airway disease. Children with persistent wheeze had a lower lung function in infancy compared with never-wheezing subjects in the SWS study,[36] but this was not replicated for persistent or late-onset wheeze phenotypes in the Tucson study.[19] A direct comparison is, however, not possible due to differences in phenotype modelling. Low lung function in early life may be a reflection of a more severe asthma phenotype with earlier onset, thereby being both causally and consequentially related to a lower lung function growth. Since almost all studies were done in general populations, it is likely that these observations reflected milder asthma, as severe asthma has a low prevalence in the general population.[61]

4.4 | Risk factors for lung function development: BHR, atopy and eosinophils

BHR is a universally recognized hallmark of asthma and has been associated with lower lung function in childhood,[62,63] adolescence [16] and adulthood,[4,20,23,64] making it a prime risk factor for adverse lung function growth. The notion of BHR as strong predictor of lower lung function growth is supported by the association of adolescent-onset BHR with a lower lung function growth pattern in that period of life.[16] In parallel, improvement in lung function growth, which may be seen as catch-up growth, was observed in adolescent subjects with BHR remission.[16] These findings suggest that lung function growth is amendable to change after childhood as well.

The use of inhaled corticosteroids (ICS) has not shown to improve lung function growth in subjects with asthma [65] ; however, a sparsity of information exists on the topic. Use of ICS amongst subjects with asthma has furthermore been associated with a lower lung function level during development in several studies.[4,23,52] However, interpretation of the association between ICS and lung function growth in a non-randomized setting is complicated as ICS use suggests a more severe asthma phenotype. There was a paucity of studies investigating the association between blood eosinophils and lung function growth. Recently published research has shown that blood eosinophils in adolescent subjects with asthma are associated with a lower lung function growth.[66] Therefore, further research should investigate the role of ICS and anti-eosinophilic treatments in the preservation of lung function development in subjects with asthma.

Allergic sensitization [45] and allergic rhinitis [47] are associated with lower-than-normal lung function trajectories, yet results varied between studies. In some studies, children sensitized to common allergens were more likely to have a lower-than-normal lung function trajectory until childhood,[45,48] adolescence [45,46,48] and early adulthood [3,48] compared to children without sensitization. The timing of allergic sensitization (preschool age) and the level of sensitization (polysensitization) appeared to be strong predictors of low lung function growth.[3,34,38] The association of early onset of sensitization or polysensitization with lower lung growth may be the result of a more atopic constitution leading to a more severe and chronic course of asthma.

Next to sensitization, allergic rhinitis was associated with a lower-than-normal lung function trajectory until adulthood.[47] The association between allergic rhinitis and adverse lung function is supported by the Norwegian ECA cohort in which lung function growth in FEV_1 and $FEF_{25\%-75\%}$ until adolescence was significantly lower in children with allergic rhinitis, atopic dermatitis and asthma compared to children with only asthma or rhinitis,[12] findings also supported by the PARIS cohort.[49] These findings suggest that there is an additive effect of allergic comorbidity on lung function deficits in children with asthma and that the contribution to airway inflammation is also present in the small airways. Consequently, allergic rhinitis should be seen as a risk factor for lower lung function growth, primarily in children with asthma. Allergic rhinitis, in addition to sharing many of the same immunologic traits of the lower airway, may also impact lung inflammation by not properly performing air humification and filtration during periods of rhinorrhoea. Given the association with lung function growth, it may be speculated that accurate recognition and treatment of allergic rhinitis in children with asthma may potentially impact long-term lung function development.

4.5 | Small airway disease

In this systematic review, we found that asthma and/or wheezing,[17,21,53] allergic sensitization [28,48,56] and allergic rhinitis [49] were associated with both large and small airway parameters. Furthermore, two studies reported lower lung function growth during childhood in subjects with asthma [56] and wheezing [38] using

sRaw and MMEF during childhood.[56] Disease of the small airways, defined as airways with a diameter of <2 mm in adults,[67] is therefore an integral part of lung function development in children with asthma and allergy. Small airway parameters should be further evaluated for their value in the clinical management of childhood respiratory disease. However, lack in definitions for small airway disease and uniform lung function testing that provides an accurate reflection of peripheral impairment complicates analysis of growth patterns.[68] We identified no papers using multiple-breath washout in this systematic literature review. Given the need to establish better methods for analysing peripheral airway damage, we recommend cohorts to analyse lung function growth until peak lung function using MBW.[68] Furthermore, impulse oscillometry (IOS) has shown to be a promising approach in assessing small airway function and future studies should develop reference values in large, population-based samples to facilitate a meaningful clinical interpretation.[69]

4.6 | Strengths and limitations

An obvious limitation of our work is that asthma definitions were highly heterogenous: asthma is difficult to define early in life, and studies defining wheezing phenotypes were therefore also addressed. Given the heterogeneity of disease definition and lung function outcomes, a formal meta-analysis was not appropriate. In addition to differences in applied definitions, international linguistic variation in the understanding of the word 'wheeze' further complicates comparison of cohorts. When establishing phenotypes, several studies used latent class analysis. This is a relatively new statistical model aimed at uncovering real-world longitudinal patterns of asthma onset and persistence. However, differences in follow-up, parental- vs. physician-confirmed wheeze and use of ICS may conceal valid representations of groups within the general population. Furthermore, small sample sizes of certain phenotypes may inhibit the ability to discern significant associations. In this review, a 2-year maximum age range for lung function data at any measurement point was an inclusion criterium, to enable analysis of lung function development in a distinct time frame. As a result, 37 studies were excluded. However, this criterion increased the validity of our findings as the association between exposure and lung function is analysed within a certain period of development. Furthermore, it improved our ability to compare the selected studies.

4.7 | Critical appraisal and directions for future research

Lung function from childhood tracks until early adulthood, especially in children with a low initial lung function. Remission or re-emergence of asthma and BHR may, however, impact lung function growth in adolescence, and catch-up growth in adolescence is a possibility. Despite this, the degree and pace of lung growth at different periods of development and age at which peak lung function is achieved is subject to individual variation. Future research should therefore aim to investigate growth using both large and small airway parameters until individual peak lung function is achieved, while stratifying for sex. This research should be performed not only in population-based studies, but also in clinical cohorts of children with asthma. Since 11% of children with moderate-to-severe asthma met the lung function criterium for COPD at age 26,[3] future studies should try to identify children at risk for COPD and develop novel therapeutic approaches to preserve and enhance lung growth in childhood.

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AUTHOR CONTRIBUTION

HJLK: Research design; database searches; screening; full-text review for eligibility; data analysis and interpretation; manuscript—drafting. AMZ: Research design; database searches; screening; and full-text review for eligibility; critical revisions of the drafted article. GHK: Research design; research supervision; data analysis and interpretation; critical revisions of the drafted article. JMV: research supervision; data analysis and interpretation; critical revisions of the drafted article.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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