Childhood lung function is associated with adolescent-onset and persistent asthma

Hans Jacob L. Koefoed [1,2,3], Anhar Ullah[4], Jenny Hallberg[3,5], Simon Kebede Merid[3], Maura M. Kere [3], Lesley Lowe[6,7], Angela Simpson[6,7], Clare S. Murray[6,7], Ulrike Gehring [8], Roel Vermeulen[8], Inger Kull[3], Anna Bergström[9,10], Judith M. Vonk [2,11], Adnan Custovic[4], Erik Melén [3,5] and Gerard H. Koppelman [1,2]

[1]University of Groningen, University Medical Center Groningen, Beatrix Children's Hospital, Department of Pediatric Pulmonology and Pediatric Allergology, Groningen, the Netherlands. [2]University of Groningen, University Medical Center Groningen, Groningen Research Institute for Asthma and COPD, Groningen, the Netherlands. [3]Karolinska Institutet, Department of Clinical Science and Education, Södersjukhuset, Stockholm, Sweden. [4]National Heart and Lung Institute, Imperial College London, London, UK. [5]Sachs' Children and Youth Hospital, Södersjukhuset, Stockholm, Sweden. [6]Division of Immunology, Immunity to infection and Respiratory Medicine, School of Biological Sciences, The University of Manchester, Manchester Academic Health Science Centre, Manchester, UK. [7]Manchester University NHS Foundation Trust, Manchester, UK. [8]Institute of Risk Assessment Sciences, Utrecht University, Utrecht, The Netherlands. [9]Karolinska Institutet, Institute of Environmental Medicine, Stockholm, Sweden. [10]Centre for Occupational and Environmental Medicine, Region Stockholm, Stockholm, Sweden. [11]University of Groningen, University Medical Center Groningen, Department of Epidemiology, Groningen, the Netherlands.

Corresponding author: Hans Jacob L. Koefoed (h.j.l.koefoed@umcg.nl)

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Subjects who develop asthma during adolescence have a lower FEV_1 and FEV_1/FVC at age 8 years. A lower lung function in childhood may either be a risk factor or an early manifestation of "subclinical" adolescent-onset asthma. https://bit.ly/3zkQKB1

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Abstract

Background Asthma is associated with impaired lung function; however, it is uncertain if a lower childhood lung function is associated with asthma onset and persistence during adolescence. The aims of the present study were to investigate the association between childhood lung function and onset and persistence of asthma during adolescence.

Methods In the population-based BAMSE (Sweden), PIAMA (Netherlands) and MAAS (UK) birth cohorts, we analysed the association of forced expiratory volume in 1 s (FEV_1), forced vital capacity (FVC), FEV_1/FVC and forced expiratory volume at 75% of FVC at age 8 years with asthma onset and persistence in adolescence (age 12–16 years) using cohort-specific logistic regression analysis followed by meta-analysis.

Results In the BAMSE, PIAMA and MAAS cohorts, asthma incidence in adolescence was 6.1% (112/1824), 3.4% (36/1050) and 5.0% (39/779), respectively. Persistent asthma from childhood to adolescence was observed in 8.2%, 6.4% and 7.7% of all subjects within the respective cohorts. A higher FEV_1 % predicted and FEV_1/FVC at age 8 years was associated with a lower odds for adolescent-onset asthma: OR 0.98 (95% CI 0.97–1.00) and 0.97 (0.94–0.99). These associations remained significant also when restricting the analyses to subjects with no wheezing or asthma treatment in childhood. A higher FEV_1/FVC at age 8 years was associated with a lower odds for asthma persistence in adolescence (0.96 (0.93–0.99)). Sex by lung function interaction analysis was not significant.

Conclusions A higher lung function at school age was associated with a lower risk of adolescent-onset asthma, predominantly in males. This indicates that a lower lung function in childhood may precede and or potentially contribute to asthma incidence and persistence.

Introduction

Children with asthma are at risk of having a low peak lung function in early adulthood [1, 2]. This association is likely influenced by early and late childhood factors, including obesity, respiratory tract infections, shared genetic susceptibility, air pollution exposure and socioeconomic status [3]. It has been

proposed that deficits in lung function growth in individuals with asthma are a consequence of airway remodelling, such as subepithelial airway fibrosis and increased smooth muscle mass [4]. As a consequence, children with asthma may have lower lung function compared to their peers.

This study examines the possibility that lower lung function in childhood may precede asthma in adolescence, offering an alternative perspective. Previous studies suggest an association between low lung function and subsequent respiratory health outcomes during childhood and adolescence. In the Danish Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) study, low lung function in the first month of life predicted childhood asthma at age 6 years [5]. The Isle of Wight Birth cohort (IOW) reported that non-asthmatic males who developed asthma in adolescence had greater airflow obstruction at the age of 10 years [6]. Furthermore, in the Childhood Asthma Management Program (CAMP) cohort, comprised of individuals with mild to moderate asthma followed from age 8 years, a higher forced expiratory volume in 1 s/forced vital capacity (FEV_1/FVC) during childhood was associated with a lower likelihood of asthma persistence during early adulthood (age 18–23 years) [7, 8]. However, the association between childhood lung function and asthma outcomes during adolescence in population-based cohorts has not been extensively investigated. This knowledge gap can be attributed to a sparsity of cohorts with adequate follow-up and lung function data, and the infrequent occurrence of adolescent-onset asthma [9]. Furthermore, differences in airway calibre and lung size growth between males and females warrant a sex-stratified investigation.

Therefore, we designed a study investigating the association between childhood lung function and the onset and persistence of asthma during adolescence. Our aim was to reveal the temporal relationship between childhood lung function and asthma outcomes in adolescence, addressing the possibility of sex-specific effects. This knowledge may have implications for our interpretation of how lung function parameters reflect disease development, possibly aiding early disease detection and prevention.

Methods

Study population

This study investigated data from the BAMSE (Barn/Child, Allergy, Milieu, Stockholm, Epidemiology, n=4089) (Sweden) [9, 10], PIAMA (Prevention and Incidence of Asthma and Mite Allergy, n=3963) (The Netherlands) [11, 12] and MAAS (Manchester Asthma and Allergy Study, n=1084) [13] (UK) population-based birth cohorts. For cohort-specific information, see supplementary material S1.

Clinical assessment

Lung function testing (FEV_1, FVC) was conducted in the three cohorts: BAMSE, PIAMA and MAAS according to American Thoracic Society (ATS)/European Respiratory Society (ERS) criteria (supplementary material S2) [14]. Forced expiratory volume at 75% of FVC ($FEF_{75\%}$) was also recorded in the BAMSE and PIAMA cohorts. Reference equations from the Global Lung Function Initiative (GLI) were used to calculate per cent predicted values according to age, height and sex for all cohorts [14], except for FEV_1/FVC which is presented as the unadjusted ratio [15]. The technical specifications of lung function testing for all cohorts are provided in supplementary material S2.

Definition of adolescent asthma outcomes

Asthma was defined according to the MeDALL definition as agreed by international experts, requiring subjects to meet two out of the following three criteria: ever doctor diagnosis of asthma, wheeze within the last 12 months and use of asthma medication for respiratory problems in the last 12 months [16]. Adolescent-onset asthma was defined as asthma at ages 12–16 years with no history of asthma from birth up to age 8 years (table 1, supplementary material S3). Furthermore, we investigated the association

TABLE 1 Definition of adolescent asthma outcomes

Adolescent-onset asthma	Asthma at ages 12–16 years with no history of asthma from birth up to age 8 years
Never-asthma	No history of asthma from birth and up until age 16 years
Persistent asthma	Asthma at age 8 years and at the last available measurement point between the ages of 12 and 16 years
Asthma remission	Asthma at age 8 years and no asthma at the last available measurement point between the ages of 12 and 16 years

Asthma was defined according to the MeDALL definition as agreed by international experts, requiring subjects to meet two out of the following three criteria: ever-doctor diagnosis of asthma, wheeze within the last 12 months and use of asthma medication for respiratory problems in the last 12 months [16].

between childhood lung function and adolescent-onset asthma excluding subjects who report any component of the MeDALL asthma definition between the ages of 2 and 8 years (age 3, 5 and 8 years in MAAS). Missing asthma data points were imputed using asthma status before and after the missing value. In cases where a preceding and subsequent value were both missing or inconsistent, asthma status was left blank. Analyses were otherwise performed on available data.

Inclusion criteria

To be included, subjects should have lung function data at age 8 years, known asthma status at age 8 and at least once at ages 12 or 16 years. Subjects with adolescent-onset asthma were required to have complete asthma status until age 8 years (see supplementary material S2 for cohort measurement points). For subjects with "never asthma", data on asthma status from birth up until and including the age of 16 years was required. Subjects excluded due to the study design (*e.g.* intermittent asthma in childhood) were not included in the final analyses.

Statistical analysis

We provide cohort-specific characteristics for adolescent asthma outcomes, reporting mean±SD for continuous variables and percentages for categorical variables. We compared included *versus* excluded subjects in all cohorts for the association between adolescent asthma outcomes and lung function at age 8 years. Logistic regression was used to analyse the association between per cent predicted lung function at age 8 (FEV_1, FVC, $FEF_{75\%}$) and adolescent-onset asthma *versus* never-asthma and asthma persistence *versus* remission, respectively. We present the odds ratios for asthma outcomes in adolescence for a 1-unit increase in lung function at age 8 years. FEV_1/FVC was included as a percentage in the regression models, and the models were adjusted for height, age and sex [15]. Analyses were performed separately in each cohort, followed by a meta-analysis using inverse-variance weighted averages with the "meta" package (version 4.15.1) in R (version 4.0.5) [17]. Heterogeneity was assessed using the Q and I^2 statistic. In case of substantial heterogeneity (I^2 > 50% or p<0.1 for Q statistic), a random-effects model was used; fixed effects models were used otherwise. Analyses were performed on all subjects and stratified by sex. Interaction analysis was performed to formally assess differences between males and females. Confounding variables (socioeconomic status, body mass index and allergic sensitisation to inhalant allergens) were selected by a review of theoretical and observed associations within the BAMSE and PIAMA cohort (supplementary material S4 and S5) [18–20].

Results

Study population

The association between lung function levels at age 8 years and adolescent asthma outcomes was analysed in 1824, 1050 and 778 subjects from the BAMSE, PIAMA and MAAS cohorts, respectively (table 1, supplementary material S6). Included subjects from the BAMSE and PIAMA cohorts had a higher prevalence of asthma at age 8 years and a higher rate of allergic sensitisation to common inhalant allergens in childhood (BAMSE age 4 years, PIAMA age 8 years) compared to excluded participants (supplementary material S7). Maternal asthma at enrolment was more prevalent for the included subjects compared to the excluded subjects in the PIAMA cohort.

Prevalence of adolescent asthma phenotypes

The majority of subjects in all cohorts (between 59.2% and 63.3%) had no history of asthma from birth until age 16 years, and between 3.4% and 6.1% of subjects developed asthma during adolescence (table 2). Persistent asthma was observed in 6.4% to 8.2% of the included subjects, while remission was seen in

TABLE 2 Prevalence of asthma phenotypes in the BAMSE, PIAMA and MAAS birth cohorts

Asthma phenotypes	BAMSE	PIAMA	MAAS
Subjects, n	1824	1050	778
Never-asthma, n (%)	1153 (63.2)	622 (59.2)	418 (53.7)
Adolescent-onset asthma, n (%)	112 (6.1)	36 (3.4)	39 (5.0)
Persistent asthma, n (%)	150 (8.2)	67 (6.4)	60 (7.7)
Asthma remission, n (%)	79 (4.3)	45 (4.3)	47 (6.0)
Subjects excluded due to study design, n (%)	330 (18.1)	280 (26.7)	214 (27.6)

For definitions of asthma phenotypes see table 1.

4.3% to 6.0%. Between 18.1% and 27.6% of subjects across all cohorts were excluded from final analyses as they did not meet the research criteria design (supplementary material S8).

Characteristics of adolescent asthma phenotypes

Adolescent-onset asthma

Adolescent-onset asthma was associated with a higher prevalence of allergic sensitisation to common inhalant allergens at age 4 years in the BAMSE cohort compared to the never-asthma group (29.3% *versus* 9.8%, p<0.01), as well as in all cohorts at age 8 years. Allergic rhinitis at age 8 years was more prevalent in subjects with adolescent-onset asthma compared to never-asthma in the BAMSE (14.0% *versus* 5.1%, p<0.01) and MAAS (25.6% *versus* 9.6%, p<0.01) cohorts (table 3). By age 16 years, this association was observed in all cohorts, with allergic rhinitis in adolescent-onset asthma ranging from 31.6% to 54.0%. In contrast, the prevalence of allergic rhinitis in the never-asthma group ranged from 13.0% to 22.0%.

Asthma remission and persistence

In subjects who would later experience persistent asthma in adolescence, the prevalence of allergic sensitisation to common inhalant allergens ranged from 57.8% to 68.3% at age 4 years in the BAMSE and PIAMA cohort and 3 years in MAAS (supplementary material S9). This association became even more pronounced at age 8 years, with 66.7% to 83.3% of subjects with persistent asthma in adolescence being sensitised to common inhalant allergens, compared to 45.9% to 54.1% in subjects with asthma remission in adolescence. Similarly, the prevalence of allergic rhinitis at age 8 years was higher in individuals with persistent asthma compared to remission in the BAMSE (44.8% *versus* 23.0%, p<0.01) and PIAMA cohort (40.9% *versus* 20.0%, p=0.047). The prevalence of allergic rhinitis at age 16 years was higher in individuals with persistent asthma in the BAMSE and MAAS cohorts. No significant associations between sex and adolescent asthma outcomes were observed.

Childhood lung function in adolescent asthma phenotypes

Adolescent-onset asthma

In the adjusted meta-analysis of the BAMSE, PIAMA and MAAS cohorts, a 1-unit higher FEV_1 % predicted (OR 0.98 (95% CI 0.97–1.00), p=0.033) and FEV_1/FVC (0.97 (0.94–0.99), p=0.020) were associated with a lower odds for adolescent-onset asthma (figure 1, supplementary material S10, S11 and S17). In the sex-stratified analysis, a higher FEV_1 % predicted (0.97 (0.95–0.99), p=0.003) and FEV_1/FVC (0.95 (0.91–0.99), p=0.007) were associated with a lower odds for adolescent-onset asthma in males, but not in females.

We investigated the extent to which subjects with adolescent-onset asthma and never-asthma had any component of the MeDALL asthma definition (ever-doctor diagnosis of asthma, wheeze within the last 12 months and use of asthma medication in the last 12 months) at ages 2, 4 and 8 years (supplementary material S12). Although these subjects did not meet the MeDALL definition of asthma at any of these ages, we observed that some reported one of the three components.

After exclusion of subjects with any component of the MeDALL asthma definition at age 8 years, a higher FEV_1/FVC was associated with lower odds of adolescent-asthma onset for the males and females combined (OR 0.96 (0.93–1.00), p=0.026) (figure 2). Additionally, a higher FEV_1 % predicted (OR 0.97 (0.95–1.00), p=0.032) and FEV_1/FVC (OR 0.93 (0.90–0.98), p=0.004) at age 8 years were associated with a lower odds of adolescent-onset asthma for the male population. After exclusion of subjects with any MeDALL asthma components at ages 2, 4 and 8 years, similar estimates for FEV_1/FVC at age 8 years and adolescent-onset asthma were observed for the male population (non-adjusted OR 0.93 (0.89–0.99), p=0.028) (supplementary material S17). The meta-analysis of the interaction of sex with lung function at age 8 years and adolescent-onset asthma was not significant (supplementary material S18).

Asthma persistence and remission

In the adjusted meta-analysis of the BAMSE, PIAMA and MAAS cohorts, a higher FEV_1/FVC at the age of 8 years was associated with a lower odds of asthma persistence during adolescence (OR 0.96 (0.93–0.99), 0.014) (supplementary material S19 and S20). Lung function at age 8 years was not associated with persistent asthma in the adjusted sex-stratified meta-analysis.

Discussion

Using three population-based birth cohorts, we report that subjects who develop asthma during adolescence have a lower FEV_1 and FEV_1/FVC at age 8 years. Furthermore, these associations remained significant when restricting the analyses to subjects without wheezing or asthma medication use in childhood. Additionally, a higher FEV_1/FVC was associated with a lower risk of asthma persistence in

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TABLE 3 Key characteristics of subjects with adolescent-onset asthma and subjects who never had asthma

	Cohort								
	BAMSE[#]			PIAMA[¶]			MAAS[+]		
	Adolescent-onset asthma	Never-asthma	p-value	Adolescent-onset asthma	Never-asthma	p-value	Adolescent-onset asthma	Never-asthma	p-value
Subjects, % (n)	6.1% (112)	63.2% (1153)		3.4% (36)	59.2% (622)		5.0% (39)	53.7% (418)	
Male, % (n/N)	38.4% (43/112)	45.6% (526/1153)	0.14	52.8% (19/36)	48.4% (301/622)	0.61	51.3% (20/39)	49.3% (206/418)	0.81
FEV_1 % pred age 8 years, mean±SD	104.2±10.5	105.6±11.0	0.20	103.5±8.5	106.8±10.5	0.07	99.2±12.1	101.7±11.1	0.19
FEV_1/FVC age 8 years, mean±SD	0.86±0.06	0.87±0.05	0.10	0.90±0.07	0.91±0.06	0.80	**0.85±0.06**	**0.87±0.05**	**0.035**
Allergic sensitisation (inhalant) age 4 years (3 years in MAAS), % (n/N)	**29.3% (27/92)**	**9.8% (93/945)**	**<0.01**	15.8% (3/19)	13.5% (42/312)	0.77	22.6% (7/31)	16.2% (61/377)	0.87
Allergic sensitisation (inhalant) age 8 years, % (n/N)	**52.3% (56/107)**	**18.2% (196/1075)**	**<0.01**	**46.7% (14/30)**	**28.0% (145/518)**	**0.03**	**46.2% (18/39)**	**23.0 (93/404)**	**<0.01**
Allergic rhinitis[§] age 8 years, % (n/N)	**14.0% (15/107)**	**5.1% (55/1071)**	**<0.01**	4.5% (1/22)	3.4% (15/436)	0.78	**25.6% (10/39)**	**9.6% (40/418)**	**<0.01**
Allergic rhinitis[§] age 16 years, % (n/N)	**54.0% (54/100)**	**16.2% (152/941)**	**<0.01**	**31.6% (6/19)**	**13.0% (33/254)**	**0.03**	**53.8% (21/39)**	**22.0% (92/418)**	**<0.01**
Maternal asthma, % (n/N)	**18.8% (21/112)**	**6.4% (74/1153)**	**<0.01**	16.7% (6/36)	14.1% (87/619)	0.66	**28.2% (11/39)**	**17.5% (73/418)**	**0.01**
BMI age 8 years, $kg \cdot m^{-2}$, mean±SD	17.1±2.2	17.1±2.2	0.86	16.1±1.6	16.2±1.8	0.81	17.4±2.3	16.9±2.3	0.18
BMI age 16 years, $kg \cdot m^{-2}$, mean±SD	21.9±2.9	21.5±2.9	0.20	21.1±3.0	20.6±2.6	0.42	22.8±4.1	21.8±3.7	0.15
Premature birth, % (n/N)	5.4% (6/112)	4.8% (55/1153)	0.78	2.8% (1/36)	3.5% (22/620)	0.81	2.9% (1/35)	2.6% (10/391)	0.92
Early life LRTI, % (n/N)	10.8% (12/111)	14.3% (161/1129)	0.32	13.9% (5/36)	12.7% (79/622)	0.84	14.3% (5/35)	8.3% (31/373)	0.23
Smoking during pregnancy, % (n/N)	8.9% (10/112)	10.9% (126/1153)	0.51	14.3% (5/35)	12.6% (78/620)	0.77	12.8% (5/39)	9.6% (40/418)	0.52
Parental smoking age 8 years, % (n/N)	19.6% (22/112)	20.8% (238/1142)	0.77	14.3% (5/35)	18.9% (113/599)	0.50	32.4% (12/37)	30.3% (125/413)	0.78
Smoking at age 16 years, % (n/N)	9.4% (10/106)	13.0% (139/1073)	0.30	0% (0/19)	8.9% (22/246)	0.17			
SES (university/other), % (n/N)	53.6% (60/112)	56.1% (647/1153)	0.61	47.2% (17/36)	59.1% (367/621)	0.16	51.3% (20/39)	49.9% (202/405)	0.87
$PM_{2.5}$ (annual average), $\mu g \cdot m^{-3}$, mean±SD	**7.2±1.3**	**7.4±1.3**	**0.043**	16.4±0.7	16.3±0.7	0.80	9.4±0.1	9.4±0.1	0.95
NO_2 (annual average), $\mu g \cdot m^{-3}$, mean±SD	11.5±4.9	12.1±5.2	0.12	22.9±6.3	23.2±6.6	0.81	22.3±2.1	22.6±2.0	0.44

n/N: number of subjects with positive response/total number with data available from all cohorts; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; BMI: body mass index; LRTI: lower respiratory tract infection; SES: socioeconomic status based on highest attained educational level of father or mother – low: primary school, lower vocational or lower secondary education; intermediate: vocational education or intermediate/higher secondary education; high: higher vocational education and university. [#]: n=1824; [¶]: n=1050; [+]: n=778; [§]: allergic rhinitis was defined as sneezing or a runny/blocked nose without having a cold combined with allergic sensitisation (see supplementary material S3 cohort-specific definition). Bold font indicates statistical significance.

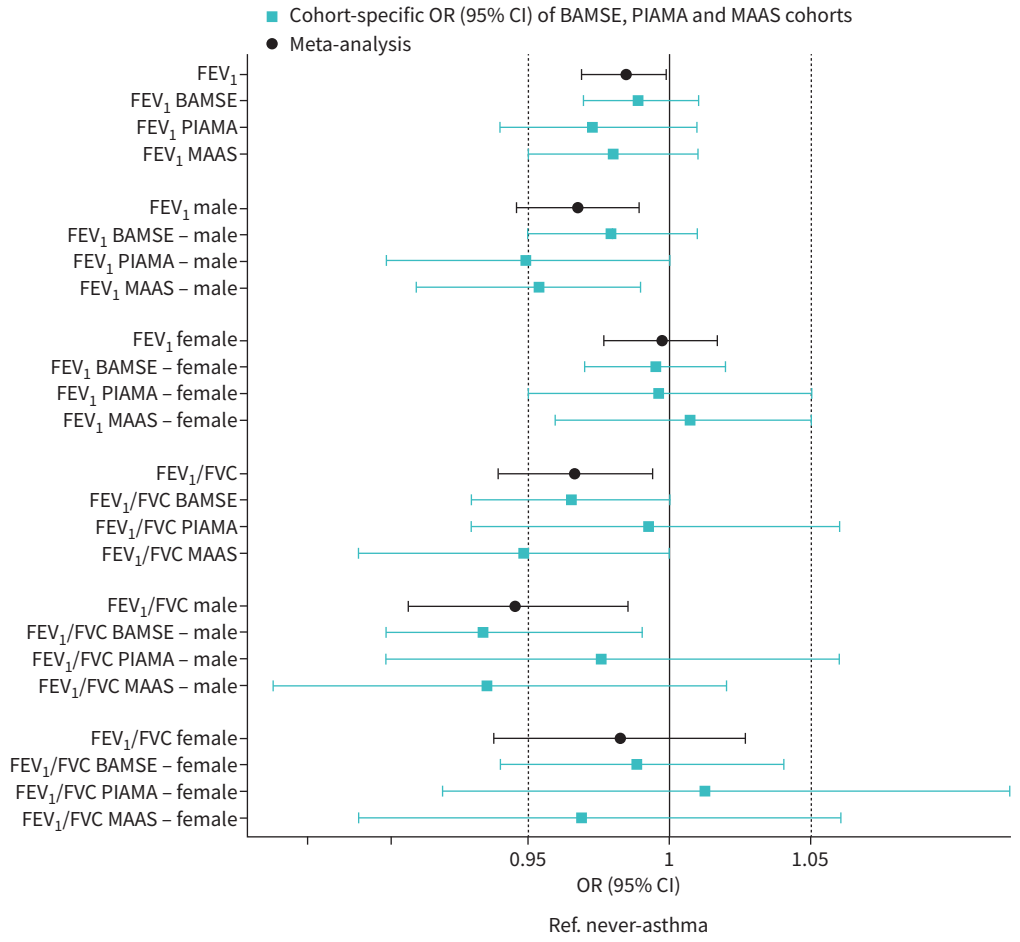

FIGURE 1 Meta-analysis and cohort-specific OR (95% CI) of BAMSE, PIAMA and MAAS cohorts on the association between lung function at age 8 years and adolescent-onset asthma *versus* never-asthma (adjusted for BMI at age 8 years, SES and allergic sensitisation to common inhalant allergens at age 8 years). FEV_1 is investigated using % predicted (Global Lung Function Initiative) while FEV_1/FVC is investigated as a percentage and adjusted for age, sex and height. BMI: body mass index; SES: socioeconomic status; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity.

adolescence. Differences between sexes were not significant. We propose that a lower lung function in childhood can either be a risk factor or an early manifestation of adolescent-onset asthma. To our knowledge, our study is the first to report the association between childhood lung function and adolescent asthma outcomes across multiple cohorts.

We found that subjects developing asthma during adolescence had a lower FEV_1/FVC during childhood. Our data suggest that a lower FEV_1/FVC in childhood is a risk factor for adolescent-onset asthma [21]. Alternatively, a lower FEV_1/FVC at age 8 years could also serve as an early manifestation of "subclinical" asthma. After stratification based on sex, significant findings were observed in males only. These findings align with observations from the IOW cohort, where males who developed asthma in adolescence had a lower FEV_1/FVC at age 10 years [6]. This suggests that airway obstruction may precede asthma development, at least in males. The different observations done in males compared to females may relate to the shift in the presence and severity of asthma between the sexes from childhood to adolescence. Prepubescent females tend to have larger airways relative to lung size in comparison to males [22]. As the pubertal growth spurt occurs, males experience a relatively greater growth in airway calibre in proportion to lung size, leading to an increase in FEV_1/FVC compared to females [23]. The changing relationship between flow *versus* volume could partially explain the transition in asthma prevalence and severity between the sexes from childhood to adolescence [22]. The association between a lower lung function and adolescent-onset asthma was primarily observed in males, with non-significant findings in sex-interaction

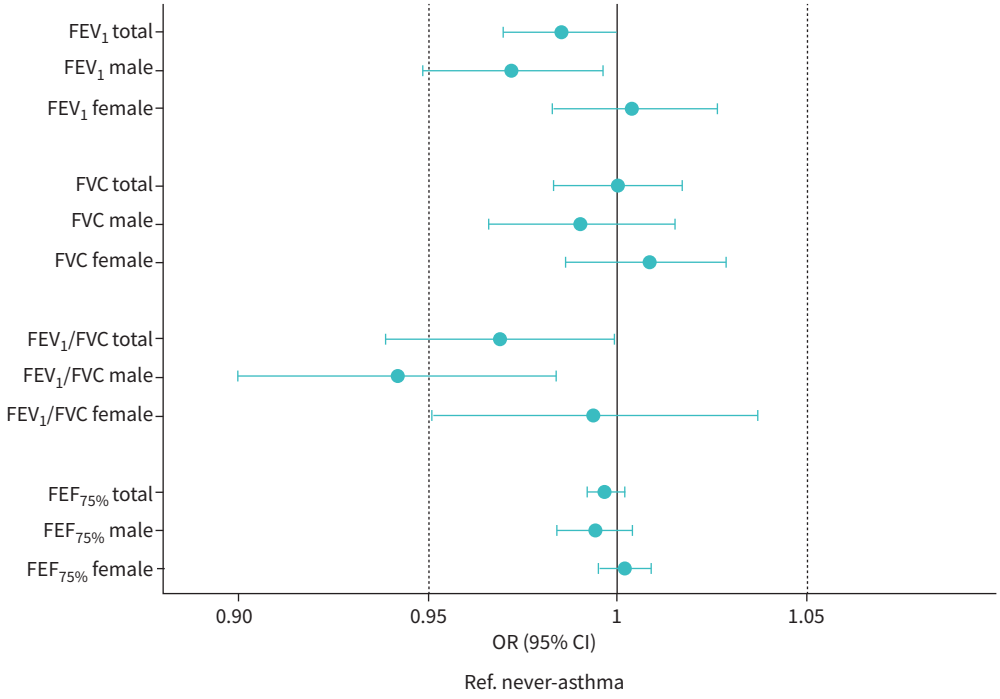

FIGURE 2 Meta-analysis of BAMSE, PIAMA and MAAS on the association between lung function at age 8 years and adolescent-onset asthma *versus* never-asthma (adjusted for BMI at age 8 years, SES and allergic sensitisation to common inhalant allergens at age 8 years). Subjects with any component of the MeDALL asthma definition at age 8 years were excluded. BMI: body mass index; SES: socioeconomic status; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; $FEF_{75\%}$: forced expiratory volume at 75% of FVC.

analyses. Consequently, we cannot ascertain differences between sexes. However, the limited power in the sex-interaction analysis of relatively infrequent phenotypes may contribute to this uncertainty.

Previously considered a late hallmark of asthma, airway remodelling is likely to occur early in asthma disease progression [24, 25]. In a retrospective investigation of endobronchial biopsy material of 27 children (median age 8.7 years), Pohunek *et al.* [26] found that children subsequently diagnosed with asthma had more local eosinophilic inflammation and greater subepithelial lamina reticularis thickening compared to those who did not receive an asthma diagnosis. Greater lamina reticularis thickness has also been linked to asthma in young adult subjects, though not correlating with disease duration [27]. Evidence for the association between airway remodelling in paediatric asthma and loss of lung function is compelling, yet not definitive [28]. Our findings show that a lower lung function may predate the onset of asthma during adolescence. We considered the possibility that the lower FEV_1 and FEV_1/FVC at age 8 years was due to active asthmatic symptoms, not meeting the MeDALL definition. Indeed, subjects with adolescent asthma had more often a doctor's diagnosis, history of wheeze or use of asthma medication in childhood. However, when we limited our analysis to subjects without any of the MeDALL definition criteria throughout childhood, we still observed the association of lower FEV_1/FVC in male children with adolescent-onset asthma. This supports the hypothesis of a more obstructive lung function being an early characteristic or predictor of adolescent-onset asthma in males. The observed associations of FEV_1 and FEV_1/FVC and not FVC with adolescent-onset asthma support the idea of lower FEV_1 being a reflection of airway obstruction as opposed to having small lungs. The reduced number of subjects in the sensitivity analysis likely contributes to lower significance (male FEV1/FVC: p=0.002 *versus* p=0.026).

Asthma in adolescence was associated with a higher prevalence of allergic sensitisation to common inhalant allergens at age 8 years. ~30–54% of subjects with adolescent-onset asthma and >50% of subjects with persistent asthma have allergic rhinitis as a comorbidity. Our findings are consistent with other cohorts, including CAMP, EGEA and OLIN, reporting an association between allergic sensitisation and a higher incidence and persistence of asthma in adolescence [20, 29, 30]. The interplay between allergic sensitisation, childhood lung function and adolescent asthma outcomes is complex. Allergic sensitisation and rhinitis may exacerbate airway inflammation and contribute to the development of asthma symptoms.

However, there is currently insufficient evidence to suggest that desensitisation treatment or treatment of allergic rhinitis alters the natural progression of asthma [8, 31].

This study has strengths and weaknesses that should be considered when interpreting its findings. Firstly, we employed three extensively documented population-based birth cohorts. We applied the MeDALL asthma definition, based on multiple variables [32]. Nonetheless, we acknowledge that certain participants who failed to meet two of three asthma criteria at age 8 years, despite potentially exhibiting asthmatic symptoms earlier in childhood, may have been misclassified. We therefore performed a sensitivity analysis, excluding subjects with any component of the MeDALL asthma definition throughout childhood. The sensitivity analysis reinforced the findings, particularly in the male population. Furthermore, asthma is highly heterogeneous in nature, and it is conceivable that the MeDALL definition may not fully capture asthma across in all populations. Consistent significant estimates between childhood lung function and adolescent-onset asthma were not observed across all cohorts indicating less robust associations. This may be the result of low statistical power in each cohort, with few individuals developing adolescent-onset asthma. Additionally, given stronger associations in males, overall cohort associations may be less pronounced. Furthermore, it is possible that not all individuals with adolescent-asthma onset exhibit lower childhood lung function. Future research should explore lung function trajectories leading up to symptom onset.

Our study has both clinical and methodological implications. Consequently, (early) childhood should be identified as a window of opportunity for potential medical intervention. Findings in the COPSAC cohort support this, where children developing asthma before 13 years had lower lung function at 1 month compared to non-affected peers, suggesting inadequate lung growth in utero or the first month of life [33]. Alternatively, lower lung function preceding clinical asthma onset could be attributed to a higher variability rather than chronic low lung function [34]. Future research should address the extent to which lower lung function preceding clinical asthma onset can be attributed to early or late childhood, thereby ensuring that we move towards guided prevention.

Cohorts like CAMP and PIAMA have employed predictive modelling incorporating lung function to ascertain the probability of asthma outcomes during adolescence [7, 35]. While our primary objective was not to predict asthma outcomes, our findings lend support to the prospect of using lung function as a tool for predicting health outcomes. Furthermore, the realisation that lung function could predate clinical signs of asthma highlights the need for a greater emphasis on trajectory analysis. Tracking of individual lung function trajectories could potentially identify growth failure, even before symptom onset [36, 37]. Similarly to COPD in adulthood, lower lung function during childhood and adolescence can be a risk factor for the development of asthma [38].

Multiple studies report lower lung function levels in children and adolescents with asthma [2]. This study contributes novel insights by emphasising that lower FEV_1 and FEV_1/FVC may precede the onset of asthma during adolescence. We propose that lower lung function serves as an early characteristic of asthma onset, a risk factor for the development of asthma, or both. Furthermore, our findings underscore the atopic nature of adolescent-onset and persistent asthma. Future studies should include lung function measurements prior to the onset of asthma to better understand the temporal interplay between asthma and lung function.

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Conflict of interest: H.J.L. Koefoed, A. Ullah, S.K. Merid, L. Lowe, R. Vermeulen, M.M. Kere, U. Gehring, A. Bergström, J. Hallberg and J.M. Vonk have no conflicts of interest to report. G.H. Koppelman reports grant support from Netherlands Lung Foundation, TEVA the Netherlands, GSK, Vertex, Ubbo Emmius Foundation, European Union

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