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Clinical implications of airway obstruction with normal or low FEV_1 in childhood and adolescence

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ABSTRACT

Background Airway obstruction is defined by spirometry as a low forced expiratory volume in 1 s (FEV_1) to forced vital capacity (FVC) ratio. This impaired ratio may originate from a low FEV_1 (classic) or a normal FEV_1 in combination with a large FVC (dysanaptic). The clinical implications of dysanaptic obstruction during childhood and adolescence in the general population remain unclear.

Aims To investigate the association between airway obstruction with a low or normal FEV_1 in childhood and adolescence, and asthma, wheezing and bronchial hyperresponsiveness (BHR).

Methods In the BAMSE (Barn/Child, Allergy, Milieu, Stockholm, Epidemiology; Sweden) and PIAMA (Prevention and Incidence of Asthma and Mite Allergy; the Netherlands) birth cohorts, obstruction (FEV_1:FVC ratio less than the lower limit of normal, LLN) at ages 8, 12 (PIAMA only) or 16 years was classified as classic (FEV_1 <LLN) or dysanaptic (FEV_1 ≥LLN) obstruction. Cross-sectional and longitudinal associations between these two types of obstruction and respiratory health outcomes were estimated by cohort-adjusted logistic regression on pooled data.

Results The prevalence of classic obstruction at ages 8, 12 and 16 in the two cohorts was 1.5%, 1.1% and 1.5%, respectively. Dysanaptic obstruction was slightly more prevalent: 3.9%, 2.5% and 4.6%, respectively. Obstruction, regardless of FEV_1, was consistently associated with higher odds of asthma (dysanaptic obstruction: OR 2.29, 95% CI 1.40 to 3.74), wheezing, asthma medication use and BHR compared with the normal lung function group. Approximately one-third of the subjects with dysanaptic obstruction in childhood remained dysanaptic during adolescence.

Clinical implications Children and adolescents with airway obstruction had, regardless of their FEV_1 level, a higher prevalence of asthma and wheezing. Follow-up and treatment at these ages should be guided by the presence of airway obstruction.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Airway obstruction (forced expiratory volume in 1 second (FEV_1) to forced vital capacity (FVC) ratio less than the lower limit of normal) is widely recognised as a key characteristic of childhood asthma.

⇒ The obstructive ratio may originate from a low FEV_1 or a normal FEV_1 in combination with a large FVC.

WHAT THIS STUDY ADDS

⇒ Children and adolescents with airway obstruction, defined by low FEV_1 to FVC ratio, have higher risks of asthma, wheezing, use of inhaled corticosteroids and bronchial hyperresponsiveness independent of their FEV_1 levels.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ We recommend a careful evaluation of the FEV_1 to FVC ratio in the diagnostic workup of children, similar to its application in the diagnosis of chronic obstructive pulmonary disease in adults.

INTRODUCTION

Airway obstruction is widely recognised as a key characteristic and prognostic marker of childhood wheezing and asthma.[1–3] Obstruction is defined as a low ratio of forced expiratory volume in 1 s (FEV_1) over forced vital capacity (FVC) and is generally considered to be the result of airway narrowing.[4] Consequently, FEV_1, as a marker of airway calibre, is frequently low in subjects with obstruction. Airway obstruction with normal FEV_1 could be a sign of physiological variability (ie fluctuations) in lung function resulting from airway hyperresponsiveness, or could be the result of anatomical unequal growth of the airways and lung parenchyma, also referred to as dysanapsis.[4 5] Regardless, it has not been well established if subjects who fulfil the criteria of an FEV_1 to FVC ratio less than the lower limit of normal (LLN) originating from a low FEV_1 have a greater risk of asthma and wheezing in comparison with subjects with an FEV_1 to FVC ratio less than the LLN originating from a normal FEV_1 with a relatively larger FVC.

Dysanapsis was first described by Green *et al*[5] in 1974 and refers to within and between-individual differences in the growth of airway calibre and lung size. To a certain extent, dysanapsis is normal during development as lung function parameters reflecting flow and volume grow at different rates during childhood and adolescence.[6] While FVC grows

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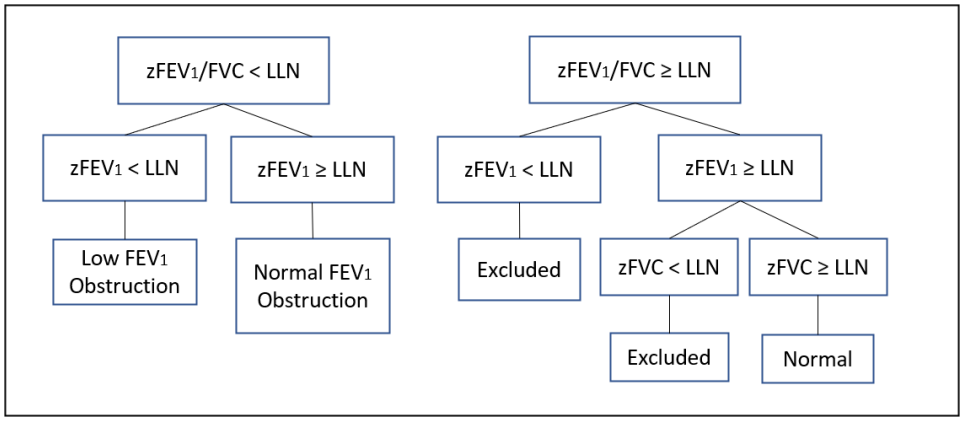

Figure 1 Definition of airway obstruction groups. LLN, lower limit of normal; $zFEV_1$, z-score for forced expiratory volume in 1 s; $zFEV_1$:FVC, z-score for forced expiratory volume in 1 s to forced vital capacity ratio.

faster than FEV_1 in childhood, the opposite trend is observed in adolescence. Additionally, the interpretation of differing growth rates in FEV_1 and FVC becomes more complex due to variations in growth between males and females at different stages of development. Dysanapsis has been associated with obesity regardless of asthma status, greater use of asthma medication and asthma disease exacerbations in children with obesity.[7] In the adult population, dysanapsis has been identified as a risk factor for the development of chronic obstructive pulmonary disease (COPD).[8] However, the clinical implications of airway obstruction with a normal FEV_1 during childhood and adolescence in the general population remain unclear.[4]

We therefore aimed to investigate the association between airway obstruction originating from either a low FEV_1 (classic obstruction) or a normal FEV_1 (dysanaptic obstruction) in childhood and adolescence, and respiratory health outcomes. Furthermore, we investigated the stability of these obstruction phenotypes from childhood to adolescence. We hypothesised that both classic and dysanaptic obstructions in childhood and adolescence were associated with a higher prevalence of asthma and wheezing compared with those without airway obstruction.

METHODS

Study population

This study uses data from the population-based BAMSE (Barn/Child, Allergy, Milieu, Stockholm, Epidemiology; Sweden) and PIAMA (Prevention and Incidence of Asthma and Mite Allergy; the Netherlands) birth cohorts. The BAMSE birth cohort consists of 4089 subjects born between 1994 and 1996 in Stockholm, Sweden.[9 10] Follow-up was performed by questionnaires at ages 1, 2, 4, 8, 12 and 16 years, and clinical assessment was performed at ages 4, 8 and 16 years. The PIAMA cohort consists of 3963 newborns from 1996/1997 in the Netherlands.[11 12] Questionnaires were completed by parents during pregnancy, at 3 months, annually until the age of 8, and at ages 11, 14 and 16 years. Clinical examinations were performed at ages 4, 8, 12 and 16 years. In the PIAMA cohort, informed (parental) consent was obtained as summarised in Wijga *et al*.[13]

Clinical assessment

Lung function testing was performed by spirometry according to the American Thoracic Society/European Respiratory Society criteria in both cohorts.[14] Additional information regarding lung function testing at each measurement point in both cohorts is provided in online supplemental file S1. We calculated the z-scores for FEV_1, FVC and FEV_1:FVC using the Global Lung Function Initiative (GLI) reference equations.[15] To improve comparability of the data, mean centring of the z-scores was performed separately for each cohort and age group. This was done by calculating the mean z-score (FEV_1, FVC and FEV_1:FVC) in healthy subjects (ie, never asthma, no wheezing in the past year and never smoking (age 16 only)) and subsequently subtracting this mean z-score from each individual z-score.[16] Bronchial hyperresponsiveness (BHR) was tested in all high-risk and in a random selection of low-risk children of the PIAMA cohort at age 8.[13] Definitions for BHR, allergic sensitisation and allergic rhinitis for both cohorts are provided in online supplemental file S2.

Definition of airway obstruction groups

Subjects with a z-score for FEV_1:FVC ($zFEV_1$:FVC) <LLN (defined as the fifth percentile of the distribution, which corresponds to a z-score of −1.645) were classified as obstructive (figure 1). Subjects with both $zFEV_1$:FVC <LLN and $zFEV_1$ <LLN were classified as classic obstructive, whereas those with $zFEV_1$:FVC <LLN and $zFEV_1$ ≥LLN were classified as

Table 1 Prevalence of obstructive groups at ages 8, 12 and 16 in the BAMSE and PIAMA birth cohorts

	Normal	Classic obstruction	Dysanaptic obstruction
Age 8			
BAMSE, % (n)	96.1 (1668)	1.0 (18)	2.9 (50)
PIAMA, % (n)	92.3 (935)	2.2 (22)	5.5 (56)
Total, % (n)	94.7 (2603)	1.5 (40)	3.9 (106)
Age 12			
PIAMA, % (n)	96.4 (1178)	1.1 (13)	2.5 (31)
Age 16			
BAMSE, % (n)	93.6 (1830)	1.5 (29)	5.0 (97)
PIAMA, % (n)	94.9 (658)	1.4 (10)	3.6 (25)
Total, % (n)	93.9 (2488)	1.5 (39)	4.6 (122)

Classic obstruction defined at each measurement point as subjects with $zFEV_1$:FVC <LLN and $zFEV_1$ <LLN. Dysanaptic obstruction defined as $zFEV_1$:FVC <LLN and $zFEV_1$ ≥LLN.
BAMSE, Barn/Child, Allergy, Milieu, Stockholm, Epidemiology; LLN, lower limit of normal; PIAMA, Prevention and Incidence of Asthma and Mite Allergy; $zFEV_1$, z-score for forced expiratory volume in 1 s; $zFEV_1$:FVC, z-score for forced expiratory volume in 1 s to forced vital capacity ratio.

dysanaptic obstructive. The normal lung function group was identified by $zFEV_1$:FVC ≥LLN and both $zFEV_1$ and zFVC ≥LLN. Subjects with $zFEV_1$:FVC ≥LLN and $zFEV_1$ and/or zFVC <LLN were excluded from subsequent analyses (online supplemental file S3).

Asthma and wheezing

Asthma was defined as fulfilling two of the following three criteria, according to the Mechanisms of the Development of ALLergy (MeDALL) definition,[17] as agreed by international experts: ever had doctor-diagnosed asthma, wheezing within the last 12 months and use of any asthma medication within the last 12 months. All these variables were defined using data collected by questionnaires (online supplemental file S2).

Statistical analysis

Cohort-specific descriptive analyses were reported as mean and SD for normally distributed continuous variables and as percentages for categorical variables. Pearson's χ^2 and independent sample t-test were used to compare differences between the obstruction groups. We analysed the cross-sectional association between classic and dysanaptic obstruction and the prevalence of asthma according to the MeDALL definition and its components separately (ie, ever doctor-diagnosed asthma, wheezing and use of asthma medication in the past 12 months; online supplemental file S2) and use of inhaled corticosteroids (ICS) at ages 8, 12 and 16.[17] To analyse these associations, we performed a cohort-adjusted logistic regression on pooled data to estimate the OR using the normal lung function group as reference. To investigate differences between classic and dysanaptic obstruction, we repeated the analysis with the dysanaptic group as reference. We investigated the role of body mass index (BMI) as a possible confounder by means of meta-analysing cohort-specific estimates using inverse-variance weighted averages with the 'meta' package (V.4.15.1) in R (V.4.0.5) reporting fixed effects.[18] We also analysed the prospective association between obstructive groups at age 8 and the risk of asthma, wheezing and medication use at age 16 by means of logistic regression using subjects with normal lung function as the reference group. For subjects with two lung function

Table 2 Characteristics of airway obstruction groups at age 8 in the BAMSE and PIAMA cohorts

	BAMSE			PIAMA		
Cohort	Normal (ref)	Classic obstruction	Dysanaptic obstruction	Normal (ref)	Classic obstruction	Dysanaptic obstruction
Demographics						
Subjects, n	1668	18	50	935	22	56
Age, mean (SD)	8.3 (0.5)	8.1 (0.5)	8.3 (0.5)	8.1 (0.3)	8.0 (0.3)	8.2 (0.3)**†
Male, % (n)	48.9 (816)	61.1 (11)	46.0 (23)	49.1 (459)	50.0 (11)	42.9 (24)
Height (cm), mean (SD)	132.3 (6.0)	127.8 (6.2)**	131.4 (6.5)†	132.8 (5.6)	133.1 (4.6)	134.5 (5.3)*
BMI (kg/m^2), mean (SD)	17.21 (2.2)	17.40 (2.1)	18.07 (2.7)**	16.3 (1.9)	16.3 (2.7)	17.3 (2.3)**
BMI z-score, mean (SD)	0.60 (0.96)	0.75 (1.04)	0.94 (1.09)*	0.05 (0.93)	−0.05 (1.23)	0.50 (0.87)**
Maternal asthma, % (n/N)	12.1 (202/1668)	16.7 (3/18)	6.0 (3/50)	16.0 (149/932)	22.7 (5/22)	17.9 (10/56)
Environmental tobacco smoke exposure, % (n)	17.1 (283/1668)	5.6 (1/18)	38.0 (19/50)**†	22.8 (200/877)	14.3 (3/21)	24.0 (12/50)
Respiratory infections, % (n)	9.2 (153/1668)	11.1 (2/18)	12.0 (6/50)	23.3 (215/923)	45.5 (10/22)*	23.6 (13/55)
SES						
Low, % (n/N)	2.2 (37/1668)	0.0 (0/18)	0.0 (0/50)	9.8 (91/933)	9.1 (2/22)	14.3 (8/56)
Intermediate, % (n/N)	42.9 (715/1668)	55.6 (10/18)	54.0 (27/50)	35.0 (327/933)	22.7 (5/22)	44.6 (25/56)
High, % (n/N)	54.9 (916/1668)	44.4 (8/18)	46.0 (23/50)	55.2 (515/933)	68.2 (15/22)	41.1 (23/56)
Early life risk factors						
Maternal smoking during pregnancy, % (n/N)	11.8 (197/1668)	11.1 (2/18)	24.0 (12/50)**	17.6 (163/925)	13.6 (3/22)	14.3 (8/56)
Premature birth, % (n/N)	5.2 (87/1668)	11.1 (2/18)	10.0 (5/50)	4.7 (44/932)	0 (0/22)	7.3 (4/55)
Birth by caesarean section, % (n/N)	12.2 (204/1668)	22.2 (4/18)	28.0 (14/50)**	10.2 (94/926)	9.1 (2/22)	7.3 (4/55)
Birth weight (kg), mean (SD)	3.5 (0.54)	3.5 (0.51)	3.5 (0.80)	3.5 (0.54)	3.5 (0.54)	3.6 (0.55)
Breast feeding more than 16 weeks, % (n/N)	93.8 (1515/1616)	88.9 (16/18)	84.0 (42/50)**	36.6 (342/935)	40.9 (9/22)	35.7 (20/56)
Wheezing in the first year of life, % (n/N)	14.4 (235/1632)	33.3 (6/18)*	32.0 (16/50)**	22.4 (204/909)	38.1 (8/21)	26.4 (14/53)
Respiratory infections in the first year of life						
Pneumonia, % (n/N)	2.9 (47/1631)	0.0 (0/18)	6.0 (3/50)	2.7 (25/928)	4.8 (1/21)	3.8 (2/53)
Bronchitis, % (n/N)	7.1 (116/1629)	5.6 (1/18)	10.0 (5/50)	14.2 (132/927)	14.3 (3/21)	18.9 (10/53)

n/N: number of subjects with positive response/total number with data available from both cohorts.
BMI (kg/m^2) z-scores were based on WHO reference equations for the BAMSE cohort and national reference equations for the PIAMA cohort.[38 39] SES was based on the highest attained educational level of the father or the mother—low: primary school, lower vocational or lower secondary education; intermediate: vocational education or intermediate/higher secondary education; high: higher vocational education and university. Respiratory infections: in BAMSE, defined as current respiratory tract infection/cough at the time of spirometry; in PIAMA, defined as respiratory infections or colds 3 weeks prior to lung function testing.
*P<0.05, **P<0.01, for comparisons of classic or dysanaptic obstructive vs normal.
†P<0.05, ††P<0.01, for comparisons of dysanaptic vs classic obstructive.
BAMSE, Barn/Child, Allergy, Milieu, Stockholm, Epidemiology; BMI, body mass index; PIAMA, Prevention and Incidence of Asthma and Mite Allergy; ref, reference; SES, socioeconomic status.

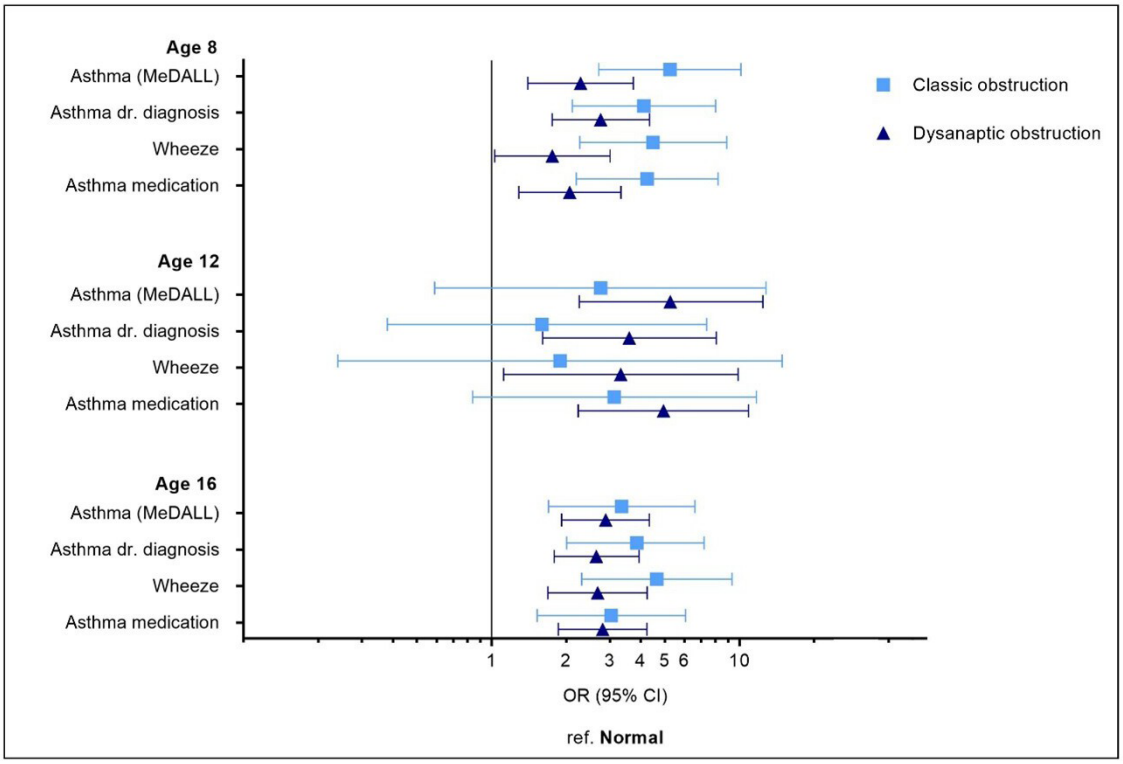

Figure 2 OR of the cross-sectional association at ages 8, 12 and 16 of the obstructive groups with asthma and wheezing in the BAMSE and PIAMA cohorts. Asthma in the last 12 months was defined as fulfilling at least two of the following three criteria: doctor (dr) diagnosis of asthma ever, wheezing in the last 12 months and/or use of asthma medication during the last 12 months (MeDALL definition). BAMSE, Barn/Child, Allergy, Milieu, Stockholm, Epidemiology; MeDALL, Mechanisms of the Development of ALLergy; PIAMA, Prevention and Incidence of Asthma and Mite Allergy; ref, reference.

measurements available, we compared obstructive group membership at ages 8 and 16 years by means of cross-tabulation. Statistical analyses were performed using SPSS (V.27.0) and R (V.4.2.2). Statistical significance was set at a 5% level.

RESULTS

Study population

From the BAMSE and PIAMA cohorts, 1736 and 1013 participants were included in the cross-sectional analysis at the age of 8 years (table 1). At the age of 16 years, the number of subjects included was 1956 (BAMSE) and 693 (PIAMA). Additionally, we included 1222 subjects at the age of 12 years from the PIAMA cohort. Based on atypical lung function patterns (figure 1), we excluded 109, 45 and 123 subjects at the ages of 8, 12 (PIAMA only) and 16 (online supplemental file S3). The longitudinal analysis of the transition between the obstructive groups from ages 8 to 16 included 1131 subjects from the BAMSE cohort and 308 subjects from the PIAMA cohort (online supplemental file S4).

The included subjects at age 16 in the BAMSE cohort and at all ages in the PIAMA cohort were more likely to be female compared with the excluded participants. Additionally, the included subjects from both cohorts were more likely to have higher socioeconomic status and to be breastfed in the first 16 weeks of life, less likely to be exposed to maternal smoking during pregnancy or have a mother who smoked at each follow-up point. Subjects included at age 8 in the PIAMA cohort more often had a mother with asthma (online supplemental file S5).

Prevalence of airway obstruction groups

Most subjects in both cohorts (between 92.3% and 96.4%) had a normal lung function at ages 8–16 years (table 1). The prevalence of classic and dysanaptic obstruction ranged from 1.0% to 2.2% and from 2.5% to 5.5%, respectively, throughout the 8–16 years age range. Lung function levels for all groups, including mean-centred z-scores, are provided in online supplemental file S6.

Characteristics of classic and dysanaptic obstruction

At the 8-year follow-up, the dysanaptic obstruction group in the PIAMA cohort was on average older and taller compared with subjects with a normal lung function. Subjects with dysanaptic obstruction had a higher BMI in both cohorts at age 8 compared with the normal group (table 2). In contrast, subjects with classic obstruction did not have a different BMI compared with the dysanaptic obstructive or normal group at any measurement point. In both cohorts at age 8, dysanaptic obstruction was associated with higher $zFEV_1$:FVC compared with classic obstruction (online supplemental file S7). This association was also seen at age 12 in PIAMA and at age 16 in BAMSE. Dysanaptic obstruction was associated with a higher prevalence of environmental tobacco smoke exposure at ages 8 and 16 in the BAMSE cohort and a higher prevalence of personal smoking at age 16 in the PIAMA cohort. There was no significant difference in the proportion of male and female subjects between the obstructive groups at ages 8, 12 and 16 (online supplemental files S8 and S9).

Table 3 OR of the cross-sectional associations at age 8, 12 (PIAMA only) and 16 of the obstructive groups with BHR, allergic rhinitis and sensitisation (pooled data)

	Normal		Classic obstruction		Dysanaptic obstruction	
	n/N	OR (95% CI)	n/N	OR (95% CI)	n/N	OR (95% CI)
Age 8						
Allergic rhinitis	218/2326	Ref	7/34	2.72 (1.16 to 6.35)*	7/86	0.90 (0.41 to 1.99)
Allergic sensitisation to food	471/2331	Ref	10/34	1.67 (0.79 to 3.51)	18/91	0.98 (0.58 to 1.66)
Allergic inhalant sensitisation	682/2332	Ref	12/33	1.30 (0.63 to 2.66)	41/92	1.86 (1.22 to 2.77)**
Allergic sensitisation: food or inhalant	900/2329	Ref	14/33	1.10 (0.55 to 2.21)	43/91	1.36 (0.89 to 2.07)
Allergic polysensitisation	491/2329	Ref	11/33	1.88 (0.90 to 3.90)	30/91	1.85 (1.18 to 2.89)**
BHR (PIAMA only)	339/839	Ref	14/17	6.88 (1.96 to 24.13)**	30/50	2.21 (1.24 to 3.96)**
Age 12 (PIAMA only)						
Allergic rhinitis	96/802	Ref	2/12	1.47 (0.32 to 6.81)	1/21	0.37 (0.05 to 2.78)
Allergic sensitisation to food	286/1011	Ref	3/13	0.76 (0.21 to 2.78)	9/26	1.34 (0.59 to 3.05)
Allergic inhalant sensitisation	423/1018	Ref	6/13	1.21 (0.40 to 3.61)	14/26	1.64 (0.75 to 3.58)
Allergic sensitisation: food or inhalant	525/1015	Ref	6/13	0.80 (0.27 to 2.40)	16/26	1.49 (0.67 to 3.32)
Allergic polysensitisation	295/1011	Ref	4/13	1.08 (0.33 to 3.53)	12/26	2.08 (0.95 to 4.55)
Age 16						
Allergic rhinitis	466/1868	Ref	10/33	1.31 (0.62 to 2.77)	26/87	1.28 (0.80 to 2.05)
Allergic inhalant sensitisation	1068/2412	Ref	19/38	1.26 (0.66 to 2.39)	55/118	1.10 (0.76 to 1.59)
Allergic polysensitisation	707/2412	Ref	11/38	0.98 (0.48 to 1.99)	37/118	1.10 (0.74 to 1.64)

n/N: number of subjects with positive response/total number with data available from both cohorts.
*P<0.05, **P<0.01, for comparisons between classic or dysanaptic obstructive and normal lung function groups (ref).
BHR, bronchial hyperresponsiveness; PIAMA, Prevention and Incidence of Asthma and Mite Allergy; ref, reference.

In the BAMSE cohort, subjects with dysanaptic obstruction more frequently had a mother who smoked during pregnancy compared with the normal group. Also, birth by means of a caesarean section was more prevalent in the dysanaptic obstruction group at age 8 compared with normal in the BAMSE cohort. Additionally, breastfeeding for more than 16 weeks was less prevalent in BAMSE subjects with dysanaptic obstruction at age 8 compared with subjects with normal lung function.

Airway obstruction groups and cross-sectional associations with asthma and wheezing

Subjects with either classic or dysanaptic obstruction had higher odds of having asthma compared with subjects with normal lung function at ages 8 and 16 (age 8: classic, OR 5.25, 95% CI 2.71 to 10.15; dysanaptic, OR 2.29, 95% CI 1.40 to 3.74) (figure 2, online supplemental file S10). Furthermore, subjects with either form of airway obstruction were more likely to experience wheezing and use ICS in the past 12 months at ages 8 and 16 (online supplemental file S10). At age 12 years in the PIAMA cohort, dysanaptic, but not classic, obstruction was associated with higher odds of asthma, wheezing and asthma medication use. Both classic and dysanaptic obstructions were associated with higher odds of ICS use at age 12 in the PIAMA cohort (online supplemental file S10). Additional adjustment for BMI resulted in similar estimates, and all associations remained significant (online supplemental file S11).

Comparing asthma and wheezing between the two obstructive groups, subjects with classic obstruction had higher odds of asthma (OR 2.29, 95% CI 1.03 to 5.12) and wheezing in the past 12 months (OR 2.56, 95% CI 1.09 to 5.98) at the age of 8 years compared with subjects with dysanaptic obstruction (online supplemental file S12).

Bronchial hyperresponsiveness

Of the subjects with classic and dysanaptic obstruction at age 8, 82.4% (n=14) and 60.0% (n=30) were BHR-positive, compared with 40.4% (n=339) in the normal group (online supplemental files S13 and S14). Both types of airway obstruction were associated with higher odds of BHR compared with the normal group (table 3), with no significant difference between the obstructive groups.

Allergic rhinitis

At age 8, classic, but not dysanaptic, obstruction was associated with higher odds of allergic rhinitis compared with the normal group (table 3). This association was not observed at ages 12 and 16 for either obstructive group (online supplemental files S15 and S16).

Allergic sensitisation

In the cross-sectional analysis of obstructive groups and allergic sensitisation at age 8, subjects with dysanaptic obstruction showed higher odds of sensitisation to common inhalant allergens (OR 1.86, 95% CI 1.22 to 2.77) and allergic polysensitisation (OR 1.85, 95% CI 1.18 to 2.89) compared with the normal group (table 3). Allergic sensitisation did not differ between the obstructive groups (online supplemental file S13).

Obstruction groups and their longitudinal association with asthma and wheezing

Subjects with either classic or dysanaptic obstruction at age 8 had higher odds of having asthma, wheezing, asthma medication use and use of ICS in the past 12 months at age 16 compared with subjects with normal lung function (table 4). The association between airway obstruction at age 8 and wheezing and medication use at age 16 was similar between subjects with classic and dysanaptic obstruction;

Table 4 OR of the prospective association of the obstructive groups at age 8 with asthma and wheezing at age 16 in the BAMSE and PIAMA cohorts (pooled data)

	Normal		Classic obstruction		Dysanaptic obstruction	
	n/N	OR (95% CI)	n/N	OR (95% CI)	n/N	OR (95% CI)
Age 16						
Asthma (MeDALL)	284/2061	Ref	13/32	4.72 (2.29 to 9.74)**	25/85	2.86 (1.75 to 4.67)**
Asthma doctor diagnosis	373/2156	Ref	18/32	6.44 (3.16 to 13.10)**	31/86	2.81 (1.78 to 4.44)**
Wheezing in the past 12 months	199/2130	Ref	8/35	2.78 (1.25 to 6.24)*	20/87	2.83 (1.64 to 4.77)**
Asthma medication use in the past 12 months	282/2136	Ref	12/33	3.88 (1.88 to 7.98)**	24/86	2.63 (1.61 to 4.30)**
ICS use in the past 12 months	182/2158	Ref	9/32	4.45 (2.02 to 9.80)**	21/87	3.62 (2.16 to 6.087)**
Allergic rhinitis	387/1351	Ref	5/23	0.82 (0.30 to 2.26)	17/56	1.15 (0.64 to 2.07)

n/N: number of subjects with positive response/total number with data available from both cohorts.
*P<0.05, **P<0.01, for comparisons between classic or dysanaptic obstructive and normal lung function groups (ref.).
BAMSE, Barn/Child, Allergy, Milieu, Stockholm, Epidemiology; ICS, inhaled corticosteroids; MeDALL, Mechanisms of the Development of ALLergy; PIAMA, Prevention and Incidence of Asthma and Mite Allergy; ref, reference.

however, classic obstruction was associated with a higher OR of doctor-diagnosed asthma at age 16 compared with dysanaptic obstruction (online supplemental file S17).

Transition between obstructive groups in childhood and adolescence

In both the BAMSE and PIAMA cohorts, majority of the participants with a normal lung function at age 8 also had a normal lung function at follow-up in adolescence (ie, at age 16). Most subjects with classic and dysanaptic obstruction at age 8 showed normal lung function in subsequent measurements (66.7% and 54.7%, respectively). However, one-third (34.0%) of the subjects with dysanaptic obstruction at age 8 remained in this group in adolescence (table 5). Of the subjects with normal lung function at age 8, 0.7% and 4.1% developed classic and dysanaptic obstruction at age 16, respectively. Transition between lung function groups for each cohort is presented in online supplemental file S18. Lung function levels per subject (zFEV$_1$ and zFEV$_1$:FVC) for those who changed group membership are presented in online supplemental files S19 and S20.

DISCUSSION

In this study, we show that airway obstruction in childhood and adolescence, defined by low FEV$_1$ to FVC ratio, with either a low or a normal FEV$_1$ was associated with a higher prevalence of asthma, wheezing, use of ICS and BHR. Furthermore, obstructive lung function in childhood was, regardless of FEV$_1$, associated with a higher prevalence of asthma, wheezing and medication use in adolescence. Dysanaptic obstruction was associated with higher BMI in childhood in both cohorts and in adolescence in the BAMSE cohort, an association not seen in classic obstructive lung function. Of subjects with a dysanaptic obstructive lung function in childhood, one-third remained in the same group in adolescence.

A low or below-normal FEV$_1$ is widely recognised as a key characteristic and prognostic marker of childhood wheezing and asthma,[2 3 19–23] and the Global Initiative for Asthma guidelines identify low FEV$_1$ as a risk factor for asthma exacerbations and persistent airflow limitation in adolescents and children ages 6–11 years.[2] However, low FEV$_1$ is often not observed in childhood asthma.[16] Our findings support this observation, showing that airway obstruction, defined by low FEV$_1$ to FVC ratio, with a normal FEV$_1$ was two to three times more frequent than the combination of a low ratio with a low FEV$_1$ at the ages of 8, 12 and 16 years. Growth of FEV$_1$ and FVC during development is non-parallel.[6] This divergence is attributed to differences in body composition during growth, timing of growth spurt and dimensions and muscular strength of the thoracic cage.[24] Ongoing growth may account for the relatively higher prevalence of normal versus low FEV$_1$ in obstruction during childhood and adolescence. In our study, subjects with a low FEV$_1$ to FVC ratio carried a similar prevalence of wheezing, asthma and ICS use regardless of their FEV$_1$ level. Importantly, both classic and dysanaptic obstructions were associated with a higher prevalence of BHR at age 8. The precise mechanism explaining the association between a relatively narrow airway calibre to lung volume and BHR is not fully understood. This may result from abnormalities in airway smooth muscle contractility such as a myogenic contractile response to greater stretching, or the mechanisms of autonomic regulation could play a role.[25 26] Based on our findings, we recommend a careful evaluation of the FEV$_1$ to FVC ratio, even if FEV$_1$ is normal, while considering the unique characteristics of each patient, to assess the risk of current or future respiratory disease.

In both cohorts, dysanaptic obstruction was associated with higher BMI, particularly at age 8, although BMI values were generally within the normal range. This is consistent with previous studies showing a positive association between childhood BMI and relatively higher growth of FVC compared with FEV$_1$.[27] Meanwhile, in adults with obesity, the opposite pattern is seen as the physical effects of abdominal obesity reduce the chest wall compliance and obstruct the downward displacement of the diaphragm during inspiration, resulting in a lower FVC.[28 29] The precise mechanisms underlying the association between a greater FVC in children and a higher BMI are uncertain. According to a meta-analysis of 25 000 children from 24 birth cohorts, greater infant weight gain could be associated with greater FVC compared with FEV$_1$ at age 8.5 years.[30] Alternatively, a higher BMI could be a proxy for a greater muscle mass.

Table 5 Transition between obstructive groups between the ages of 8 and 16 in the BAMSE and PIAMA cohorts (pooled data)

	Age 8		
	Normal (n=1368)	Classic obstruction (n=18)	Dysanaptic obstruction (n=53)
Age 16			
Normal (n=1344), % (n)	95.2 (1303)	66.7 (12)	54.7 (29)
Classic obstruction (n=17), % (n)	0.7 (9)	11.1 (2)	11.3 (6)
Dysanaptic obstruction (n=78), % (n)	4.1 (56)	22.2 (4)	34.0 (18)

BAMSE, Barn/Child, Allergy, Milieu, Stockholm, Epidemiology; PIAMA, Prevention and Incidence of Asthma and Mite Allergy.

Dysanaptic obstruction was found to be associated with early childhood risk factors, including birth by caesarean section and a lower prevalence of breastfeeding, although results varied across cohorts. Notably, dysanaptic obstruction was associated with a higher prevalence of wheezing in the first year of life. This suggests that factors contributing to airway obstruction in childhood may partly originate from the first years of life. Future studies should investigate the association between early life exposures and the differential development of FEV_1 and FVC.

In lung development, dysanapsis has been suggested to be caused by differential airway and lung growth velocities during childhood and adolescence.[4] While FVC grows faster than FEV_1 in childhood, the opposite trend is observed in adolescence. Additionally, prepubescent girls have larger airway size relative to lung size than boys.[31 32] Conversely, growth of airways relative to volume is enhanced in adolescent boys. These differences in lung development may partially explain the sex shift in asthma prevalence and disease severity observed in adolescence. We did not find any differences in the prevalence of dysanaptic obstruction between the sexes during childhood or adolescence. This could be due to the LLN as a cut-off not capturing longitudinal differences in FEV_1 and FVC growth between the sexes. Alternatively, we did not see these differences in our data as the reference equations adjusted for differential growth differences in FEV_1 and FVC between the sexes.[6] We did observe that approximately half of the subjects with dysanaptic obstruction transitioned to a normal state in adolescence, indicating plasticity of lung function growth during this period.[33] In contrast, 34% remained dysanaptic obstructive during adolescence, while only 11.1% remained classic obstructive, suggesting an early childhood origin of dysanaptic obstruction.[31 32]

This study has strengths and limitations that should be considered when evaluating our findings. First, we used population-based birth cohorts with multiple lung function measurements and included a validated asthma definition based on multiple variables.[34] As the GLI fit differs between cohorts,[16] we performed mean centring to improve comparability. Previous research on dysanapsis in the paediatric population has applied a more stringent definition of dysanaptic obstruction using higher cut-off levels for FEV_1 and FVC; however, this was done in clinical cohorts enriched with patients with asthma.[7] In our population-based cohorts, stricter definitions of dysanaptic obstruction yielded insufficient numbers of subjects to investigate different forms of airway obstruction and respiratory health outcomes. Regardless, we observed significant differences in the distribution of the FEV_1 to FVC ratio and FVC between these two forms of airway obstruction, indicating that they are distinct from each other.

We realise that dysanapsis in our cohorts may reflect ongoing bronchial constriction as opposed to non-reversible differences in airway calibre and volume. A subject with large FEV_1 and FVC could be classified as dysanaptic obstructive if FEV_1 is lowered (due to increased variability) while FVC remains high. Consequently, subjects with both high FEV_1 and FVC may be classified as dysanaptic obstructive, partly due to lung function variability in subjects with asthma-like symptoms. Additionally, the accuracy of spirometry reflecting airway calibre and lung size in the paediatric population remains uncertain. Further elucidation of anatomical versus physiological obstructive lung function patterns requires reversibility testing and imaging studies. Furthermore, it would be interesting to compare established biomarkers of asthma disease such as fractional exhaled nitric oxide (FeNO) and blood eosinophils between the airway obstruction groups. The prevalence of allergic sensitisation and allergic rhinitis was higher in dysanaptic obstruction compared with normal; however, this analysis was complicated by low statistical power. The prevalence of BHR at age 8 reflects the selection of high-risk children and is not applicable to the general population; however, the comparison between lung function groups is informative. Additionally, both cohorts are of primarily Caucasian descent. Future studies should investigate the generalisability of our findings to populations of other ancestries. Furthermore, although we strive to reflect the general population, the external validity of our findings may be impacted by attrition bias. Consequently, we recommend validation of our results in other population-based cohorts.

The objective of this study was to examine the co-occurrence of two respiratory phenotypes, that is, airway obstruction and asthma/wheezing/medication use/BHR, from a clinical perspective. As both phenotypes are likely to have the same underlying aetiology and/or causative agents, we did not adjust for any covariates. However, we examined BMI as a potential confounder and observed that associations remained materially unchanged in the adjusted analyses.

Previous studies have shown that in children, adolescents and young adults, a subgroup with an obstructive lung function and normal FEV_1 parameters exists.[35 36] A normal FEV_1, in the case of airway obstruction, may make physicians less inclined to pursue medical follow-up. However, our results showing associations between airway obstruction, irrespective of the level of FEV_1, and a higher prevalence of asthma, wheezing and ICS use led us to conclude that the ratio between FEV_1 and FVC is more important than FEV_1 when evaluating the risk of adverse respiratory health outcomes in childhood and adolescence. Therefore, we recommend a careful evaluation of the FEV_1 to FVC ratio in the diagnostic workup of children with wheezing, similar to its application in COPD diagnosis in adults.[37] Future research should address if dysanaptic obstruction during childhood and adolescence is associated with subsequent development of COPD.

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