Clinical implications of airway obstruction with normal or low FEV₁ 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 (FEV₁) to forced vital capacity (FVC) ratio. This impaired ratio may originate from a low FEV₁ (classic) or a normal FEV₁ 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 FEV₁, 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 (FEV₁:FVC ratio less than the lower limit of normal, LLN) at ages 8, 12 (PIAMA only) or 16 years was classified as classic (FEV₁ < LLN) or dysanaptic (FEV₁ ≥ 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 FEV₁, 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 FEV₁ 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 (FEV₁) 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 FEV₁ or a normal FEV₁, in combination with a large FVC.

WHAT THIS STUDY ADDS
⇒ Children and adolescents with airway obstruction, defined by low FEV₁ to FVC ratio, have higher risks of asthma, wheezing, use of inhaled corticosteroids and bronchial hyperresponsiveness independent of their FEV₁ levels.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY
⇒ We recommend a careful evaluation of the FEV₁ to FVC ratio in the diagnostic workup of children, similar to its application in the diagnosis of chronic obstructive pulmonary disease in adults.

Consequently, FEV₁, as a marker of airway calibre, is frequently low in subjects with obstruction. Airway obstruction with normal FEV₁ 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 FEV₁ to FVC ratio less than the lower limit of normal (LLN) originating from a low FEV₁ have a greater risk of asthma and wheezing in comparison with subjects with an FEV₁ to FVC ratio less than the LLN originating from a normal FEV₁ with a relatively larger FVC.

Dysanapsis was first described by Green et al4 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...
faster than FEV₁ in childhood, the opposite trend is observed in adolescence. Additionally, the interpretation of differing growth rates in FEV₁ 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. However, the clinical implications of airway factor for the development of chronic obstructive pulmonary disease (COPD).

Definitions for BHR, allergic sensitisation and allergic rhinitis for both cohorts are provided in online supplemental file S2. 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.

**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. 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. 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. 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 FEV₁, FVC and FEV₁:FVC using the Global Lung Function Initiative (GLI) reference equations.** 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 (FEV₁, FVC and FEV₁: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. 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. 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 FEV₁:FVC (zFEV₁: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 zFEV₁ :FVC < LLN and zFEV₁ < LLN were classified as classic obstructive, whereas those with zFEV₁ :FVC < LLN and zFEV₁ ≥ LLN were classified as

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

<table>
<thead>
<tr>
<th>Age</th>
<th>Normal</th>
<th>Classic obstruction</th>
<th>Dysanaptic obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>96.1 (1668)</td>
<td>1.0 (18)</td>
<td>2.9 (50)</td>
</tr>
<tr>
<td>Age 8</td>
<td>PIAMA, % (n)</td>
<td>92.3 (935)</td>
<td>2.2 (22)</td>
</tr>
<tr>
<td></td>
<td>Total, % (n)</td>
<td>94.7 (2603)</td>
<td>1.5 (40)</td>
</tr>
<tr>
<td></td>
<td>96.4 (1178)</td>
<td>1.1 (13)</td>
<td>2.5 (31)</td>
</tr>
<tr>
<td>Age 12</td>
<td>PIAMA, % (n)</td>
<td>93.6 (1830)</td>
<td>1.5 (29)</td>
</tr>
<tr>
<td></td>
<td>Total, % (n)</td>
<td>94.9 (658)</td>
<td>1.4 (10)</td>
</tr>
<tr>
<td></td>
<td>93.9 (2488)</td>
<td>1.5 (39)</td>
<td>4.6 (122)</td>
</tr>
</tbody>
</table>

** zFEV₁/FVC < LLN**

** zFEV₁ ≥ LLN**

** zFEV₁ < LLN**

** zFVC < LLN**

** zFVC ≥ LLN**

** Excluded**

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**Figure 1** Definition of airway obstruction groups. LLN, lower limit of normal; zFEV₁, z-score for forced expiratory volume in 1 s; zFEV₁: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 zFEV₁:FVC ≥ LLN and both zFEV₁ and zFVC ≥ LLN. Subjects with zFEV₁:FVC ≥ LLN and zFEV₁ 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 χ² 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 mediation use at age 16 by means of logistic regression using subjects

![Table 2](http://thorax.bmj.com/Thorax: first published as 10.1136/thorax-2023-220952 on 21 March 2024. Downloaded from http://thorax.bmj.com/ Thorax: first published as 10.1136/thorax-2023-220952 on 21 March 2024. Downloaded from http://thorax.bmj.com/)
Respiratory epidemiology

with normal lung function as the reference group. For subjects with two lung function 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 zFEV1: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...
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)

<table>
<thead>
<tr>
<th>Age 8</th>
<th>Normal</th>
<th>Classic obstruction</th>
<th>Dysanaptic obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>OR (95% CI)</td>
<td>n/N</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>218/2326</td>
<td>Ref</td>
<td>7/34</td>
</tr>
<tr>
<td>Allergic sensitisation to food</td>
<td>471/2331</td>
<td>Ref</td>
<td>10/34</td>
</tr>
<tr>
<td>Allergic inhalant sensitisation</td>
<td>682/2332</td>
<td>Ref</td>
<td>12/33</td>
</tr>
<tr>
<td>Allergic sensitisation: food or inhalant</td>
<td>900/2329</td>
<td>Ref</td>
<td>14/33</td>
</tr>
<tr>
<td>Allergic polysensitisation</td>
<td>491/2329</td>
<td>Ref</td>
<td>11/33</td>
</tr>
<tr>
<td>BHR (PIAMA only)</td>
<td>339/839</td>
<td>Ref</td>
<td>14/17</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age 12 (PIAMA only)</th>
<th>Normal</th>
<th>Classic obstruction</th>
<th>Dysanaptic obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>OR (95% CI)</td>
<td>n/N</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>96802</td>
<td>Ref</td>
<td>2/12</td>
</tr>
<tr>
<td>Allergic sensitisation to food</td>
<td>2861011</td>
<td>Ref</td>
<td>3/13</td>
</tr>
<tr>
<td>Allergic inhalant sensitisation</td>
<td>4231018</td>
<td>Ref</td>
<td>6/13</td>
</tr>
<tr>
<td>Allergic sensitisation: food or inhalant</td>
<td>5251015</td>
<td>Ref</td>
<td>6/13</td>
</tr>
<tr>
<td>Allergic polysensitisation</td>
<td>2951011</td>
<td>Ref</td>
<td>4/13</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age 16</th>
<th>Normal</th>
<th>Classic obstruction</th>
<th>Dysanaptic obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>OR (95% CI)</td>
<td>n/N</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>4661868</td>
<td>Ref</td>
<td>10/33</td>
</tr>
<tr>
<td>Allergic inhalant sensitisation</td>
<td>10682412</td>
<td>Ref</td>
<td>19/38</td>
</tr>
<tr>
<td>Allergic polysensitisation</td>
<td>7072412</td>
<td>Ref</td>
<td>11/38</td>
</tr>
</tbody>
</table>

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.

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 (online supplemental files S8 and S9).

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.

**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 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.

**Branchial 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=39) 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 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 compared with subjects with dysanaptic obstruction (online supplemental file S12).

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Respiratory epidemiology
mediation 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; 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 (zFEV1 and zFEV1:FVC) for each cohort is presented in online supplemental file S18.

### DISCUSSION

In this study, we show that airway obstruction in childhood and adolescence, defined by low FEV1, to FVC ratio, with either a low or a normal FEV1 was associated with a higher prevalence of asthma, wheezing, use of ICS and BHR. Furthermore, obstructive lung function in childhood was, regardless of FEV1, 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. Dysanaptic obstruction at age 8 remained in this group in adolescence (ie, at age 16). Most subjects with classical and dysanaptic obstructions were associated with a higher prevalence of normal versus low FEV1 in obstruction during childhood and adolescence. In our study, subjects with a low FEV1 to FVC ratio carried a similar prevalence of wheezing, asthma and ICS use regardless of their FEV1 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.

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 6 to 11 years. However, low FEV1 is often not observed in childhood asthma. Our findings support this observation, showing that airway obstruction, defined by low FEV1 to FVC ratio, with a normal FEV1, was two to three times more frequent than the combination of a low ratio with a low FEV1 at the ages of 8, 12 and 16 years. Growth of FEV1 and FVC during development is non-parallel. This divergence is attributed to differences in body composition during growth, timing of growth spurt and dimensions and muscular strength of the thoracic cage.

Ongoing growth may account for the relatively higher prevalence of normal versus low FEV1 in obstruction during childhood and adolescence. In our study, subjects with a low FEV1 to FVC ratio carried a similar prevalence of wheezing, asthma and ICS use regardless of their FEV1 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. Based on our findings, we recommend a careful evaluation of the FEV1 to FVC ratio, even if FEV1 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

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**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)

<table>
<thead>
<tr>
<th>Age 16</th>
<th>Normal</th>
<th>Classic obstruction</th>
<th>Dysanaptic obstruction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Asthma (MedDALL)</td>
<td>284/2061 Ref</td>
<td>13/32 4.72 (2.29 to 9.74)**</td>
<td>25/85 2.86 (1.75 to 4.67)**</td>
</tr>
<tr>
<td>Asthma doctor diagnosis</td>
<td>373/2156 Ref</td>
<td>18/32 6.44 (3.16 to 13.10)**</td>
<td>31/86 2.81 (1.78 to 4.44)**</td>
</tr>
<tr>
<td>Wheezing in the past 12 months</td>
<td>199/2130 Ref</td>
<td>8/35 2.78 (1.25 to 6.24)**</td>
<td>20/87 2.31 (1.64 to 4.77)**</td>
</tr>
<tr>
<td>Asthma medication use in the past 12 months</td>
<td>282/2136 Ref</td>
<td>12/33 3.88 (1.88 to 7.98)**</td>
<td>24/86 2.63 (1.61 to 4.30)**</td>
</tr>
<tr>
<td>ICS use in the past 12 months</td>
<td>182/2158 Ref</td>
<td>9/32 4.45 (2.02 to 9.80)**</td>
<td>21/87 3.62 (2.16 to 6.08)**</td>
</tr>
<tr>
<td>Allergic rhinitis</td>
<td>387/1351 Ref</td>
<td>5/23 0.82 (0.30 to 2.26)</td>
<td>17/56 1.15 (0.64 to 2.07)</td>
</tr>
</tbody>
</table>

n/N: number of subjects with positive response/total number with data available from both cohorts.

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

<table>
<thead>
<tr>
<th>Age 16</th>
<th>Normal (n=1368)</th>
<th>Classic obstruction (n=18)</th>
<th>Dysanaptic obstruction (n=53)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normal (n=1344), % (n)</td>
<td>95.2 (1303)</td>
<td>66.7 (12)</td>
<td>54.7 (29)</td>
</tr>
<tr>
<td>Classic obstruction (n=17), % (n)</td>
<td>0.7 (9)</td>
<td>11.1 (2)</td>
<td>11.3 (6)</td>
</tr>
<tr>
<td>Dysanaptic obstruction (n=78), % (n)</td>
<td>4.1 (56)</td>
<td>22.2 (4)</td>
<td>34.0 (18)</td>
</tr>
</tbody>
</table>

BAMSE, Barn/Child, Allergy, Milieu, Stockholm, Epidemiology; ICS, inhaled corticosteroids; MedDALL, Mechanisms of the Development of ALLergy; PIAMA, Prevention and Incidence of Asthma and Mite Allergy; ref, reference.
childhood BMI and relatively higher growth of FVC compared with FEV.\textsuperscript{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.\textsuperscript{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, \textit{at} age 8.5 years.\textsuperscript{30} Alternatively, a higher BMI could be a proxy for a greater muscle mass.

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, and FVC.

In lung development, dysanapsis has been suggested to be caused by differential airway and lung growth velocities during childhood and adolescence.\textsuperscript{4} While FVC grows faster than FEV, in childhood, the opposite trend is observed in adolescence. Additionally, prepubescent girls have larger airway size relative to lung size than boys.\textsuperscript{31, 32} Conversely, growth of airways relative to volume is enhanced in adolescent boys. These differences in lung development may partially explain the 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, 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, and FVC between the sexes.\textsuperscript{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.\textsuperscript{33} In contrast, 34% remained dysanaptic obstructive during adolescence, while only 11.1% remained classic obstructive, suggesting an early childhood origin of dysanaptic obstruction.\textsuperscript{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.\textsuperscript{34} As the GLI fit differs between cohorts,\textsuperscript{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, and FVC; however, this was done in clinical cohorts enriched with patients with asthma.\textsuperscript{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, 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, and FVC could be classified as dysanaptic obstructive if FEV, is lowered (due to increased variability) while FVC remains high. Consequently, subjects with both high FEV, 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, parameters exists.\textsuperscript{35, 36} A normal FEV, 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, and a higher prevalence of asthma, wheezing and ICS use led us to conclude that the ratio between FEV, and FVC is more important than FEV, when evaluating the risk of adverse respiratory health outcomes in childhood and adolescence. Therefore, we recommend a careful evaluation of the FEV, to FVC ratio in the diagnostic workup of children with wheezing, similar to its application in COPD diagnosis in adults.\textsuperscript{37} Future research should address if dysanaptic obstruction during childhood and adolescence is associated with subsequent development of COPD.
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Patient consent for publication Not required.

Ethics approval This study involves human participants. BAMSE received ethical approval from the Stockholm Ethical Review Board (ref 2016/1380-31/2), and all participants and/or their parents provided consent. The PIAMA study was approved by the medical ethics committee at each respective measurement point, and informed (parental) consent was obtained as summarised in Wigia et al. (METC protocol number 07-3377k). Participants gave informed consent to participate in the study before taking part.

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