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The significance of early recurrent wheeze for asthma outcomes in late childhood

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ABSTRACT: Recurrent early life wheeze is not always asthma, and up to 50% of children are reported to remit. With reports of adult asthma symptom relapse, we assessed the prognosis of recurrent bronchial obstruction (rBO) through adolescence in the Environment and Childhood Asthma (ECA) prospective birth cohort study.

The present study is based on data from investigations at ages 2, 10 and 16 years of 550 young people (52% males) attending at 16 years of age. Based on the presence of rBO from 0–2 years, defined as recurrent (at least two episodes) doctor-diagnosed wheeze, and asthma from 2–10 years and 10–16 years, defined as at least two episodes of doctor-diagnosed asthma, symptoms and medication use, prognosis of rBO was assessed. Bronchial hyperresponsiveness (BHR) was diagnosed by a metacholine provocation dose $\leqslant$8 μmol that caused 20% reduction in the forced expiratory volume in 1 s.

At 10–16 years, 34% of the 143 rBO children had asthma. All children with rBO had reduced lung function compared with the never asthmatics. Of the rBO children in remission, 48.4% had asthma symptoms, medication use and/or BHR compared with 26.7% with never asthma ($p<0.001$).

Only 34.3% of rBO children were without asthma symptoms, medication use or BHR by 16 years, possibly indicating future asthma risk.

KEYWORDS: Adolescence, bronchial hyperreactivity, paediatric asthma, wheeze

Wheezing in the first few years of life is a common [1] but complex condition with several causes and outcomes [2]. The long-term prognosis and variable presentation of asthma-like symptoms is highlighted in many prospective studies from birth to school age [3–5], and from childhood into adulthood [2, 6–10]. The observed natural course of wheeze in the first years of life varies, with reports of up to 50–70% of children ''out-growing'' their symptoms during school age [9, 11, 12].

However, early childhood respiratory disease increases the risk of adult asthma [13, 14] and chronic obstructive pulmonary disease (COPD) [15, 16]. Most cases of asthma start in the first few years of life [17], and the clinical presentation of asthma varies by a remitting and relapsing pattern [18, 19]. It is not clear at what age (if any) it can be said that asthma (-like) symptoms are ''outgrown'', as it is possible that benign wheeze is a different condition to early asthma presentation. Although wheeze is a hallmark of asthma, it may represent other disease entities. Thus, using wheeze as a proxy for asthma is insufficient for understanding disease prevalence and progression [20]. Other surrogate measures of asthma, such as reduced lung function and bronchial hyperresponsiveness (BHR) are important characteristics of asthma that support, but do not define, asthma.

Based on the heterogeneity of asthma in childhood, some authors suggest that asthma should not be used to describe wheezing illness in preschool children [21]. However, failing to do so might impair or delay appropriate treatment and management, and is clearly erroneous for many children. To date, we are largely unable to identify those with benign wheeze (not to recur later in childhood or adulthood) from those with an early asthma debut.

In the Environment and Childhood Asthma (ECA) prospective birth cohort study in Oslo, Norway, we aimed to assess the prognosis through adolescence of recurrent bronchial obstruction in early life, focusing on disease remission and recurrence.

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SUBJECTS AND METHODS

Study design

The present study includes data from the 0–2-, 2–10- and 10–16-year intervals obtained at the 2-, 10- and 16-year follow-up investigations that were part of the ECA study in Oslo. This population-based prospective birth-cohort study included 3754 healthy newborns born during 1 year (1992–1993), of whom 802 had lung function at birth measured by tidal breathing flow–volume loops (time to peak expiratory flow/total expiratory time) [22]. Follow-up investigations were performed at 2 years (a nested case–control study of 516 out of 612 identified children with recurrent physician-diagnosed wheeze and healthy controls), 10 years (1019 out of 1215 invited children who had lung function measured at birth or included in the 2-year case–control study) and at 16 years of age (550 of the same 1215 children) (fig. 1).

0–2 years

Questionnaires at birth, and at 6, 12, 18, and 24 months, included detailed family and personal history of allergic diseases, health-related factors, and socioeconomic and environmental factors [1].

Registration cards documenting the presence of the following respiratory symptoms were completed at any doctor contact: tachypnoea, wheezing, expiratory stridor, respiratory chest retractions and sibilations/whistles. If $\geqslant$3 respiratory symptoms were documented $\geqslant$2 times, or if such an episode lasted $\geqslant$4 weeks, the subject was classified as suffering from recurrent bronchial obstruction (rBO).

At 2 years of age

The study paediatrician conducted a parental interview and clinical investigation including measuring tidal flow–volume loops before and after inhaled nebulised salbutamol [23, 24].

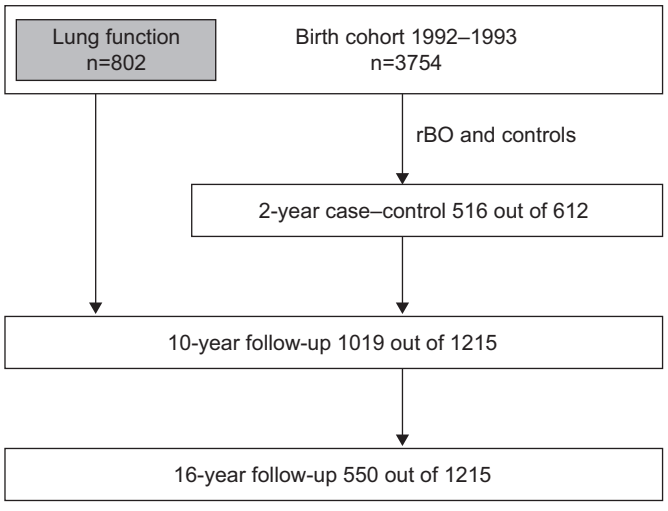

FIGURE 1. Flow chart of the children included in the Environment and Childhood Asthma study in Oslo, Norway. The overall attendance rate at the 10-year follow-up was 84%, while it was 45% at the 16-year follow-up. rBO: recurrent bronchial obstruction.

At 10 years of age

A clinical investigation included parental interview, skin prick test (SPT) for allergic sensitisation, forced expiratory flow–volume loops for lung function measures, and metacholine challenge test for BHR [1].

At 16 years of age

A clinical investigation included an interview with the subject, SPT, lung function measurements and a metacholine challenge.

All investigations required at least 4 weeks without symptoms of respiratory tract infection, no use of antihistamines for 120 h, leukotriene antagonists for 72 h, short- or long-acting β_2 agonists for 12 or 48 h or inhaled corticosteroids (ICS) for 12 h.

Written informed consent forms were obtained from parents at all phases, as well as from the subjects at 16 years of age. The study was approved by the Regional Medical Ethics Committee (Oslo, Norway) and the Norwegian Data Inspectorate and reported to the Norwegian Biobank Registry (Oslo, Norway).

Subjects and representability

The present study comprises all 550 subjects (52% males) attending the 16-year follow-up study, giving an attendance rate of 53% of the 10-year participants. The included study population was largely comparable to the entire cohort at birth, with a few exceptions. Study participants more often had older siblings, the family income was higher, and parental rhinitis was reported with borderline significance, whereas the subjects were similar in terms of parental atopic dermatitis, asthma, smoking habits and pet keeping (table 1).

In the entire cohort, 306 children were identified with rBO giving a prevalence of 8.3%. The children with rBO included in the nested case–control study at 2 years had significantly lower tidal lung function and a greater bronchodilator response than the healthy controls, as previously reported [23].

The children attending both the 10- and 16-year investigations were, at 10 years, slightly younger, slightly shorter, weighed less and were less often sensitised to at least one allergen than those who did not attend the 16-year investigation. However, they were similar in terms of personal or parental asthma, allergic rhinitis, atopic dermatitis and measured lung function (see table S1).

Methods

Questions used at each time-point for the questionnaires, interviews and reported information are given in table S2.

At 10 and 16 years

The physician conducted parental and study subject interview (at 10 and 16 years, respectively) focused on the child's symptoms of asthma and other allergic disease and their respective management during the last 12 months, as well as in the period since the previous investigation.

Investigations at 16 years

Clinical investigations were performed by experienced paediatricians at every follow-up visit.

TABLE 1 Demography at birth for the subjects completing the 16-year follow-up compared with the remainder of the birth cohort (total included at birth n=3754)

	Included at 16 years	Not included at 16 years	p-value included *versus* not included
Subjects n	550	3204	
Males	285 (51.8)	1658 (51.7)	0.98
Parental asthma	69 (12.5)	387 (12.1)	0.78
Parental rhinoconjunctivitis	171 (31.1)	865 (27.0)	0.050
Parental atopic eczema	164 (29.8)	906 (28.3)	0.47
Maternal smoking during pregnancy	133 (24.2)	782 (24.4)	0.89
Number of siblings	0.6±0.7	0.5±0.7	0.009
Having older siblings	269 (50.9)[#]	1334 (43.8)[¶]	0.003
Dog in the house	44 (8.0)	300 (9.4)	0.34
Cat in the house	39 (7.1)	243 (7.6)	0.73
Paternal permanent employment	502 (93.1)[+]	2877 (92)[§]	0.37
Family gross income category	3.9±0.9	3.7±1.0	0.007
Maternal year of birth	1962 (1947–1972)	1962 (1946–1972)	
Paternal year of birth	1960 (1937–1971)	1960 (1935–1976)	
Maternal education category	4.5±1.2	4.4±1.3	0.10
Paternal education category	4.6±1.3	4.6±1.4	0.94
Years parents have lived together	5.4±3.4	5.3±3.6	0.35
Parents living together	522 (95.3)[ƒ]	2995 (93.8)[##]	0.18
rBO at 2 years	143 (26.0)[¶¶]	159 (5.1)[++]	<0.001

Data are presented as n (%), mean±SD or median (minimum–maximum), unless otherwise stated. 1250 subjects were invited for follow-up at 10 and 16 years (those with lung function measured at birth and/or who participated in the nested case–control study of recurrent bronchial obstruction (rBO) at 2 years). Parental disease is reported as the presence of disease in at least one of the parents. Family income is given in five categories: from 1 (<100 000 NOK) to 5 (>500 000 NOK). Parental education is given in six categories from 1 (maximum 9 years at elementary school) to 6 (university degree). [#]: n=529; [¶]: n=3044; [+]: n=539; [§]:n=3126; [ƒ]: n=548; [##]: n=319; [¶¶]: n=550; [++]: n=3117.

SPTs, performed according to European standards, tested for common inhalant and food allergens, which included house dust mites, pets, grass, tree and mugwort pollens and moulds, as well as cow's milk, wheat, peanut and cod, using allergens from Alyostal® (Stallergenes, Antony, France), ALK prick SQ (ALK Scherax, Wedel, Germany) and Allergopharma® (Hørsholm, Denmark) (see online supplementary material for details).

Lung function (at 10 and 16 years of age) was measured by maximally forced expiratory lung function loops with a Sensormedics V-max (Sensormedics Diagnostics, Yorba Linda, CA, USA) spirometer. The results are reported as % predicted (% pred) values of forced expiratory volume in 1 s (FEV_1) and forced expiratory flow at 25–75% of the forced vital capacity (FVC) ($FEF_{25-75\%}$) according to reference algorithms by STANOJEVIC *et al.* [25]. The ratio between FEV_1 and FVC (FEV_1/FVC) is reported as a crude ratio.

A methacholine challenge to assess BHR was performed according to international guidelines [26], using a SPIRA dosimeter (Spira Respiratory Care Center Ltd, Hemeenlinna, Finland). The metacholine challenge is reported as positive if the provocative dose of methacholine causing a 20% fall in FEV_1 from baseline (PD_{20}) was ⩽8 μmol (further details are given in the online supplementary material).

Definitions

rBO (at 2 years) was defined as two or more physician-diagnosed episodes or at least one episode lasting ⩾4 weeks. Asthma was defined within each time period (2–10 and 10–16 years) in subjects with a positive response to two or more of the following: doctor-diagnosed asthma, asthma symptoms, and the use of anti-asthmatic medication. BHR was defined as PD_{20} ⩽8 μmol methacholine. Allergic sensitisation was defined as one or more positive SPT ⩾3 mm when compared to the negative control (0.9% NaCl), and asthma symptoms as reporting any episode with heavy breathing, wheezing, chest tightness or dry night-time cough without current cold or lower airway infection.

Determinants and outcomes

The main determinant made at 2 years of age was rBO *versus* no rBO. Based on the main determinant combined with the presence of asthma criteria at 10–16 years, the following outcomes were defined. Never rBO/asthma: subjects never fulfilling either rBO or asthma criteria; rBO-asthma: rBO subjects fulfilling asthma criteria from 10–16 years; and rBO-remission: rBO subjects not fulfilling asthma criteria from 10–16 years.

Statistical analyses

Continuous variables are presented as mean±SD for demographic purposes, and otherwise as mean (95% confidence intervals). Categorical variables are presented as counts and percentages. To assess possible differences, Pearson's Chi-squared test was used for categorical variables and t-test for continuous variables. Odds ratios were estimated by binary logistic regression, and effect modification was assessed,

defining >20% change as significant. For statistical analyses SPSS version 15.0 (SPSS, Chicago, IL, USA) was used. Statistical significance was assumed at a level of 5%.

RESULTS

The mean age (minimum–maximum) of the 550 subjects was 10.8 (8.8–12.5) years and 16.7 (15.7–17.5) years at the 10- and 16-year follow-up studies, respectively, with demographic data and family history of allergic disease given in table 1.

Prognosis by asthma classification

The prognosis for the 143 children with rBO at 2 years of age demonstrated that 34% were classified as having asthma in the last period (10–16 years), the majority with asthma presentation in all three periods (23% of all rBO children) whereas 10% had relapsing asthma after 10 years. Remission in terms of asthma definition was observed in 66% of the rBO children, dominated by children going into remission after the 2–10-year period (73%) (fig. 2).

Prognosis by symptoms and signs of asthma activity 10–16 years

Although classified without asthma after 10 years, the rBO-remission group had significantly more frequent use of asthma medication (6.3% *versus* 0.6%; $p<0.001$), although few reported use during the last 12 months compared with the never rBO/asthma, whereas asthma symptoms tended, although not statistically significantly, to be more common (27.4% *versus* 19.3%; $p=0.09$, respectively). Of the adolescents in the rBO-remission group, 32.6% had either symptoms or medication use as opposed to the 19.9% amongst the never rBO/asthma group ($p=0.009$).

BHR was also more frequent in the rBO-remission subjects (20.7% *versus* 10.2%; $p=0.008$) and, combining these reported and objective findings, 48.4% of the rBO-remission children had at least one of the reported asthma symptoms, asthma medication use or BHR compared with 26.7% of children with never asthma/rBO ($p<0.001$) (table 2).

Lung function values (FEV_1 % pred, $FEF_{25–75\%}$ % pred and FEV_1/FVC) were significantly reduced in the rBO remission group as well as the rBO asthma group compared with the never asthma groups, but were similar in the rBO groups regardless of asthma status during 10–16 years, both at 10 and 16 years of age (fig. 3 and table 3).

Allergic sensitisation was similar in all three groups at 16 years of age, whereas at 10 years rBO-asthma subjects were more often sensitised to allergens (table 3).

There were no differences in sex within the recurrent bronchial obstruction (rBO)-asthma or -remission groups in reported symptoms or medication use. However, among rBO-remission subjects, more females than males had a positive BHR (30.8% *versus* 13.2%; $p=0.04$).

Exposure to tobacco smoke (*in utero* as well as parental indoor smoking until 2 years of age) was not a significant risk factor or confounder of the association of rBO between asthma during 10–16 years (table S3). Even though lung function at birth was not an independent risk factor for asthma outcomes, it significantly modified the association between rBO and later asthma (table S3). The risk estimate of rBO for asthma outcomes during 10–16 years was reduced by 28% by adjusting for lung function at birth.

DISCUSSION

The prognosis of early recurrent bronchial obstruction in our birth cohort study demonstrated that only one-third had persistent asthma throughout childhood and adolescence. However, children with rBO, irrespective of asthma status from 10 to 16 years, had similarly reduced lung function and more frequent BHR at 16 years compared with those with never rBO or asthma. The rBO-remission group more often reported asthma symptoms or use of asthma medication compared with

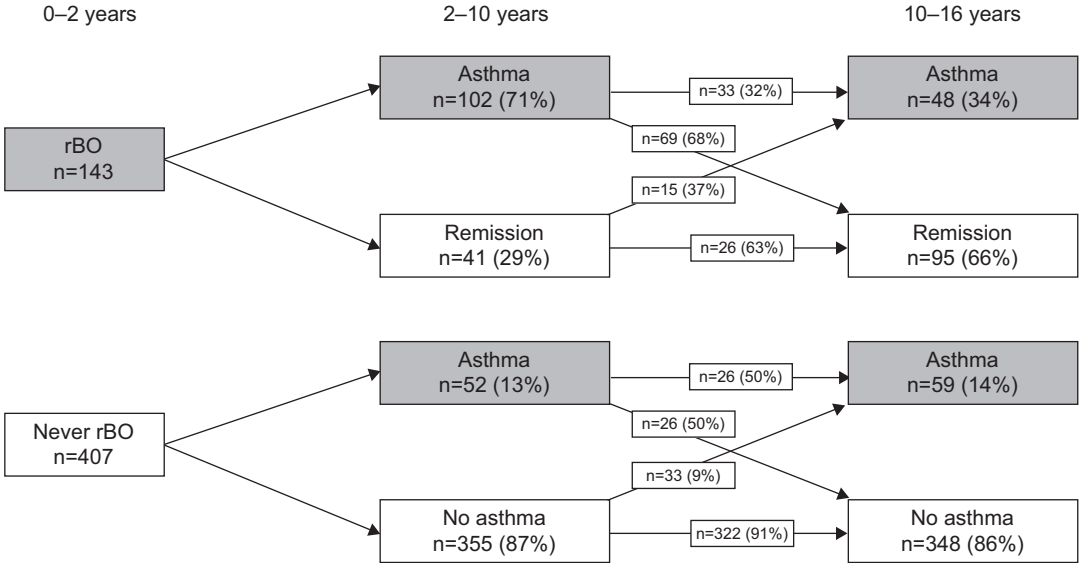

FIGURE 2. Flow chart describing the remission and relapse rates for recurrent bronchial obstruction (rBO) and never rBO subjects with regards to asthma diagnosis through the periods 2–10 years and 10–16 years. Percentages describe the rate either changing or maintaining status concerning asthma between the given periods.

TABLE 2 Symptoms and anti-asthmatic medication usage reported during the interval 10–16 years of age and bronchial hyperresponsiveness (BHR) assessed at 16 years of age

	Never rBO/asthma[#]	rBO-remission 10–16 years	rBO-asthma 10–16 years
Subjects	322	95	48
Asthma symptoms	62 (19.3)	26 (27.4)	48 (100)***
Use of any asthma medication	2 (0.6)	6 (6.3)***	47 (97.9)***
Current[¶] β_2-agonist	0	1 (1.1)	26 (54.2)
Current[¶] ICS/LTRA	1 (0.3)	0	27 (56.3)
β_2-agonist 10–16 years	1 (0.3)	5 (5.3)	15 (31.3)
ICS/LTRA 10–16 years	0	2 (2.1)	10 (20.8)
BHR	32 (10.2)[+]	19 (20.7)[§]**	11 (24.4)[f]**
At least one of asthma symptoms or medication	64 (19.9)	31 (32.6)**	48 (100)***
At least one of asthma symptoms, medication or BHR	86 (26.7)	46 (48.4)***	48 (100)***

Data are presented as n or n (%). Asthma symptoms: any reported episode with heavy breathing, wheezing, chest tightness or dry night-time cough without current cold or lower airway infection. BHR is defined as a provocative dose of $\leqslant$8 μmol methacholine causing a 20% fall in forced expiratory volume of 1 s from baseline. rBO: recurrent bronchial obstruction; ICS: inhaled costicosteroid; LTRA: leukotriene receptor antagonist. [#]: reference group; [¶]: within the last 12 months; [+]: n=314; [§]: n=92; [f]: n=45. All p-values are given compared with children who never fulfilled the rBO or asthma definition. **: p<0.01; ***: p<0.001.

the never rBO/asthma group, and 48.4% of the children in apparent remission still had asthma symptoms, use of asthma medication and/or BHR after 10 years of age. Thus, only one-third of the children with rBO by 2 years of age were found to be without asthma medication, asthma symptoms or BHR by 16 years of age.

Using asthma classification, the 34% of the children with persistent or relapsed disease after rBO at 16 years in the present study is in line with wheeze outcomes in comparable studies; 40% at 10 years from the Isle of Wight, UK [9], 30% at 16 years in the Tucson Respiratory Study [2] and 37% at 13 years in the German Multicenter Allergy study (MAS) [27]. In birth cohorts with a shorter follow-up time (to 5–8 years), persistence of early wheeze varied from about 20% [3, 5] to 40% [28]. Our temporal rBO-asthma phenotypes thus resemble the persistent and early transient wheeze phenotypes in other studies [12], but differ in terms of their using wheeze [2–5, 9, 28] rather than asthma as outcomes.

Exchanging asthma classification with ''wheeze'', 47% of our rBO children had persistent wheeze up to 16 years of age (see online supplementary material), whereas at 10 years ''wheeze ever'' and ''early transient wheeze'' were reported by 30.6% and 8.8%, respectively [1]. The corresponding figures were 40.3% and 20.4%, respectively, in the Isle of Wight study [9]. Approximately one-third of the early wheezers in Oslo were ''transient'' compared with ~50% in the UK study (at 10 years), whereas it is not known what the corresponding results for 16 years would be in the UK study. We required at least two doctor-confirmed episodes of obstructive airway disease where wheeze alone was insufficient to classify the episode as bronchial obstruction. Thus, not only are our classification criteria more conservative than in comparable studies, but we also determined the presence of rBO at 2 years rather than at 3 and 4 years of age [9, 12, 27, 28], highlighting the importance of early-life respiratory events.

All rBO subjects in the present study had reduced lung function at 10 and 16 years of age. The reduced lung function in rBO subjects with persistent or remitting asthma in the present study is in line with findings from the Tucson study at 16 years [2], and the Avon Longitudinal Study of Parents and Children (ALSPAC) [3] and Prevention and Incidence of Asthma and Mite Allergy (PIAMA) [5] studies at 6 years, whereas lung function at 10 years was not impaired among the 139 transient wheezers in the Isle of Wight, UK cohort [9].

BHR was found more frequently in both rBO groups in the present study, in line with findings of the ALSPAC and PIAMA studies [5], and in children with persistent wheeze in other studies [3, 5, 9]. BHR in children with rBO may indicate chronic airway inflammation [29], regardless of active asthma symptoms at the age of 16 years [30], and increases the risk of adulthood disease relapse [31]. The female preponderance for positive BHR amongst rBO-remission subjects has, to our knowledge, not been described previously. However, more BHR in pubertal [32] and adult females compared with males has been reported [33, 34].

Reduced lung function and BHR and in childhood have been associated with adult asthma [8, 13, 14, 31]. Reduced lung function at birth in our study significantly modified the association between rBO and later asthma in the present study. Reduced lung function at birth and at 10 years, as well as BHR at 10 years, all influenced asthma outcomes and may thus suggest an increased risk of adult asthma and possibly also COPD [15, 16]. We found no effect of tobacco smoke exposure *in utero* and up to 2 years of life, which is in line with findings of the MAS study at 13 years [27], but in contrast to results from both the Isle of Wight and the MAS studies at 10 years of age [35, 36] and also into adult age [37], both intrauterine and environmental childhood smoking was associated with reduced lung function and respiratory symptoms.

The rBO-remission children reported more use of asthma medication, although these were small numbers and only a minority reporting current use. The reports of asthma symptoms were not more frequent amongst the rBO-remission children.

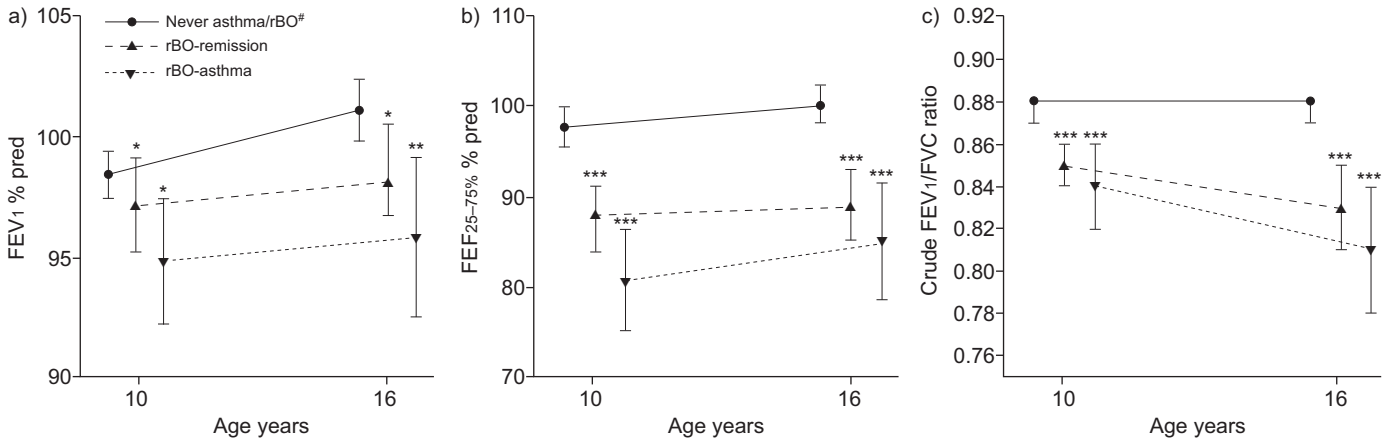

FIGURE 3. Prognosis of recurrent bronchial obstruction (rBO) in terms of lung function. Lung function values are given for a) forced expiratory volume in 1 s (FEV_1), b) forced expiratory flow at 25–75% of the forced vital capacity (FVC) ($FEF_{25–75\%}$), and c) the FEV_1/FVC ratio, given as a crude ratio. All values are given as mean (95% CI). % pred: % predicted. #: reference group. *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$.

Although wheeze symptoms were also reported among never/infrequent wheezers in the statistically derived phenotypes (up to 8 years of age) in the ALSPAC and PIAMA studies [5], it is unclear whether or not this will be associated with asthma in later childhood.

The proportion of children with allergic sensitisation at 16 years was similar in children with rBO and never asthma in the present study, which is in contrast to other articles [2, 3, 5, 9, 27] reporting more often allergic sensitisation in persistent compared with never-wheeze subjects and early transient wheeze [9]. At 10 years, with 26% *versus* 25.2% of the never asthma and never wheezers, allergic sensitisation was comparable in the ECA and Isle of Wight studies, respectively [1, 9]. The high sensitisation rate at 16 years in the present study also in nonasthmatics, although being remarkable, may obscure the effect of atopy on these subjects.

Strengths and limitations

The prospective design, close follow-up during the first 2 years of life, and thorough characterisation at 10 and 16 years of age are the main strengths of our study, as well as reducing the risk of recall bias. We have chosen to report the findings by relevant period rather than the last year only for each period, as we believe this better reflects the development of the disease. Loss to follow-up between 10 and 16 years of age is unfortunately a common feature of long-term cohort studies of this age [2]. In such cohorts running for a long period of time, there is a risk of overestimating respiratory outcomes. There can be a selection towards those with a previous respiratory diagnosis and also an increased in awareness of symptoms and secondarily increased reporting of symptoms. However, the effect of this potential bias is somewhat reduced by the fact the children attending the 16-year follow-up study were similar in terms of allergic disease or rBO at 10 years compared with those who did not attend the 16-year investigation. Furthermore, the objective documentation is important in a group (adolescents) who often underreport symptoms of disease [38]. With the comparability of asthma phenotypes to other birth cohort studies, we therefore believe that the results of the present cohort are likely to reflect the natural progression of recurrent early wheeze through puberty in a general population.

TABLE 3 Lung function, bronchial hyperresponsiveness and allergic sensitisation at 10 and 16 years of age

	10 years of age			16 years of age		
	Never asthma/rBO	rBO-remission	rBO-asthma	Never asthma/rBO	rBO-remission	rBO-asthma
Subjects n	322	95	48	322	95	48
FEV_1 % pred	98.4 (97.4–99.4)	97.1 (95.2–99.1)*	94.8 (92.2–97.4)*	101.1 (99.8–102.3)	98.1 (96.7–100.5)*	95.8 (92.5–99.1)**
FEV_1/FVC	0.88 (0.87–0.88)	0.85 (0.84–0.86)***	0.84 (0.82–0.86)***	0.88 (0.87–0.88)	0.83 (0.81–0.85)***	0.81 (0.78–0.84)***
$FEF_{25–75\%}$ % pred	97.7 (95.5–99.9)	87.9 (83.9–91.9)***	80.7 (75.3–86.31)***	100.2 (98.2–102.3)	89.0 (85.1–93.0)***	85.1 (78.6–91.5)***
PD_{20} $\leqslant$8 μmol	24.2	37.9*	54.2***	10.2	20.7**	24.4**
Allergic sensitisation	26.4	36.8	41.7*	50.2	55.8	52.1

Data are presented as mean (95% CI) or % unless otherwise stated. The reference is never recurrent bronchial obstruction (rBO)/asthma. FEV_1: forced expiratory volume in 1 s; % pred: % predicted; FVC: forced vital capacity; $FEF_{25–75\%}$: forced expiratory flow at 25–75% of the FVC; PD_{20}: provocative dose of methacholine causing a 20% fall in FEV_1. *: $p<0.05$; **: $p<0.01$; ***: $p<0.001$.

Conclusion

The prognosis of recurrent bronchial obstruction in the first 2 years of life appears to be good, with only one-third having asthma at 16 years of age. However, children with rBO in remission had reduced lung function, as well as more frequent BHR and use of asthma medication, possibly indicating increased risk of subsequent respiratory disease in adulthood.

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STATEMENT OF INTEREST

Conflict of interest information can be found alongside the online version of this article at www.erj.ersjournals.com

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