Prematurity-associated lung disease: is it asthma?

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To the Editor:

Survivors of very preterm birth (<32 weeks gestation) experience lung health deficits that may be progressive over time [1]. Respiratory symptoms are frequently diagnosed as asthma in this population, with studies reporting that children born preterm (<37 weeks gestation) are up to five times more at risk of developing wheezing disorders than their term-born counterparts [2], and that up to 50% of children born very preterm are diagnosed with asthma by mid-childhood [3]. Contrary to the childhood asthma paradigm, this patient population is typically nonatopic [4] with low fractional exhaled nitric oxide (F_{ENO}) [5]. Furthermore, studies of inhaled corticosteroids (ICS), which are commonly used to treat asthma, report only modest improvements in lung function for those born very preterm [6]. Indeed, some have argued that the term "asthma" should be avoided when describing prematurity-associated lung disease, especially since the underpinning mechanisms remain unclear [7]. It is highly important to distinguish between asthma and prematurity-associated lung disease in this population to guide appropriate treatment and follow-up for these individuals.

The recent European Respiratory Society (ERS) clinical practice guidelines for the diagnosis of asthma in children aged 5–16 years [8] advocates the use of two positive, evidence-based tests to confirm the diagnosis of asthma. We used the new guidelines to objectively determine the rates of asthma in a population of children and young people born very preterm, and report the agreement between the objective diagnosis and a prior physician diagnosis of asthma.

Children and young people, from two previously published studies [6, 9], attended Perth Children's Hospital between 2018 and 2022 for pulmonary function testing by trained staff members [6, 9]. Both studies had the same inclusion criteria, born ⩽32 weeks gestation, at Western Australia's only neonatal intensive care unit at the time: King Edward Memorial Hospital in Perth, Western Australia. Participants were born between 1997 and 2015, with no significant congenital abnormalities or neurodevelopmental delays likely to limit successful lung function testing. Comprehensive details about each cohort, and their representation of the wider Western Australian preterm population, can be obtained in our previous publications [6, 9].

Briefly, F_{ENO} was measured using the Medisoft Hypair FeNO (Medisoft Corporation, Sorinnes, Belgium) or NIOX Vero (Circassia, Oxford, UK). Spirometry was performed before and after administration of 400 µg salbutamol *via* spacer, using the Medisoft Hypair or BodyBox 5500 (Medisoft Corporation, Sorinnes, Belgium) and outcomes were expressed as z-scores according to the Global Lung Function Initiative equations [10]. All tests were carried out according to American Thoracic Society (ATS)/ERS guidelines [11, 12]. A bronchodilator response (BDR) by spirometry was defined according to ATS/ERS guidelines as an increase of 12% and 200 mL in forced expiratory volume 1 s (FEV_1) (the 200-mL rule was omitted for children ⩽12 years) [13]. A modified International Study of Asthma and Allergies in Childhood questionnaire [14] was completed by parents or guardians, or self-reported where appropriate, to obtain respiratory symptom history, prior clinical asthma diagnosis and asthma medication usage.

Participants met the 2021 ERS asthma diagnostic criteria [8] if they had abnormal spirometry (FEV_1 z-score and/or FEV_1/forced vital capacity (FVC) z-score < −1.645) and a positive BDR with or without elevated F_{ENO} (⩾25 ppb). We did not perform challenge testing, peak expiratory flow rate (PEFR) variability testing or trials of asthma medications on this population. Participants were only included if they had valid spirometry pre- and post-bronchodilator and matched F_{ENO}. Respiratory symptoms in the past 3 months

Shareable abstract (@ERSpublications)
Not all wheeze is "asthma" in those born very preterm. Further work is needed to better understand the aetiology of prematurity-associated lung disease and the best treatments for this population. https://bit.ly/3Tko3vi

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were defined as wheeze, rattle and/or shortness of breath at rest or during exercise. As per the asthma guidelines, those with cough as the only symptom were not included in the symptoms positive group.

Data was analysed using IBM SPSS Statistics for Windows, version 27.0. Data are presented as mean±SD or median (interquartile range (IQR)), with differences between groups measured using independent samples t-test or Mann–Whitney U-test depending on data distribution. A Chi-squared test was used for categorical data. Agreement between clinical diagnosis for asthma and diagnosis using ERS diagnostic criteria was assessed using κ-statistics.

Very preterm-born participants (N=234, median (IQR) age 12.9 (10.7–18.9) years) with valid F_{ENO} and pre- and post-bronchodilator spirometry measurements were included in this study. Physician diagnosed asthma was reported in 33% (77 out of 232) of the population, with a median age at diagnosis of 4.0 (2.0–6.0) years. More than half (n=133) of the participants had previously used asthma medications; 51% (119 out of 234) had used an inhaled short-acting bronchodilator, 26% (61 out of 234) had used an ICS and 15% (36 out of 234) had used an oral corticosteroid. In the 3 months prior to testing, 30 individuals had used asthma medication; 28 used an inhaled short-acting bronchodilator and 12 an ICS or oral corticosteroid. Lung function was reduced in preterm participants; mean±SD FEV_1 z-score was −0.65±1.23 and FEV_1/FVC z-score was −1.07±1.09, with 19% of the population with FEV_1 z-scores and 33% with FEV_1/FVC z-scores below the lower limit of normal. A positive bronchodilator response was observed in 25% of the participants. Median (IQR) F_{ENO} was 12.5 (9.0–20.0) ppb with 21% >25 ppb. There was no significant difference in any lung function measures between those participants with recent respiratory symptoms when compared to those without recent respiratory symptoms (table 1).

Over 60% (144 out of 234) of those born very preterm reported respiratory symptoms in the 3 months prior to testing. Of those with respiratory symptoms (the starting base for a diagnosis of asthma), 33% (47 out of 144) had only one positive diagnostic measure, therefore not meeting the ERS criteria for asthma (22 with only abnormal spirometry, seven with only a positive BDR and 18 only had elevated F_{ENO}). Using the ERS diagnostic criteria for asthma (abnormal results from two objective measures), asthma was confirmed in 21% (30 out of 144) of those with recent symptoms. However, a further 16% (23 out of 144) fell into the “asthma highly probable” group and clinically should be referred for challenge test, PEFR variability testing or asthma medication trial. There were seven individuals with abnormal results from all three measures. In those children born preterm who did not report symptoms, we saw a similar proportion satisfying the ERS diagnostic criteria for asthma (p=0.567) (table 1). Overall, 20% (46 out of 234) of those born very preterm had abnormal results and would meet the ERS diagnostic criteria for asthma regardless of symptoms, and 13% (30 out of 234) in the highly probable group.

Very poor agreement was observed between the ERS diagnostic criteria for asthma, and physician diagnosis of asthma in preterm-born children and young people (κ=0.102, 95% CI −0.107–1.215; p=0.098). We identified 30 participants who met the ERS diagnostic criteria for asthma (from the starting point of respiratory symptoms) and a total of 77 had received a doctor diagnosis of asthma. There was agreement in only 20 (21%) out of 93 cases.

Asthma is the most common childhood respiratory condition worldwide [15]; however, the misdiagnosis of asthma is widespread [16] and conjecture about its relevance after prematurity remains. This study found that ∼20% of children and young people born very preterm fulfilled the ERS criteria for an asthma diagnosis regardless of their recent symptom burden. Asthma was “highly probable” in a further 13%, who clinically would have been referred for further lung function testing or a trial of asthma medication to confirm a diagnosis.

There was poor agreement between those meeting the ERS criteria for asthma and those reporting a physician diagnosis of asthma in this population. This disagreement likely stems from prematurity-associated lung disease displaying phenotypic traits that mimic other respiratory conditions, including asthma and COPD. Airway obstruction, structural abnormalities (including gas trapping and bronchial wall thickening), peripheral lung disease, upper airway abnormalities [17] and pulmonary vascular disease are all evident at increased rates in the preterm population [3, 18]. Such complexity and individual variation in the pathophysiology have led to the recent proposal of multiple potential phenotypes of prematurity-associated lung disease [19] and acknowledgement that perhaps a treatable traits model is more appropriate than disease labels in this group. Future studies deeply phenotyping this population would offer valuable insight. However, studies have also reported poor agreement between physician diagnosis of asthma and objective measures, even in the general non-preterm population [20].

TABLE 1 Study population: children and young people born very preterm with and without respiratory symptoms in the past 3 months

	No respiratory symptoms in past 3 months	Respiratory symptoms in past 3 months	p-value
Subjects	90	144	
Neonatal diagnosis of BPD	32 (35.6%)	74 (51.4%)	0.018*
Gestational age, weeks	28.28±2.34	27.72±2.57	0.088
Received surfactant	68 (75.6%)	103 (72.0%)	0.553
Maternal asthma	14 (15.6%)	26 (18.1%)	0.082
Age at diagnostic testing, years	12.7 (9.8–18.2)	18.0 (12.4–19.6)	<0.001*
Male	55 (61.1%)	71 (49.3%)	0.078
BMI, kg·m^{-2}	19.51±5.16	20.91±4.37	0.484
Lung function			
FEV_1 z-score	−0.48±1.36	−0.76±1.14	0.100
FVC z-score	0.19±1.14	0.00±1.10	0.255
FEV_1/FVC z-score	−0.90±1.14	−1.18±1.05	0.083
F_{ENO}, ppb	13.0 (10.0–20.0)	12.9 (8.5–20.3)	0.496
Abnormal spirometry	28 (31.1%)	56 (38.9%)	0.228
Bronchodilator response	20 (22.2%)	38 (26.4%)	0.473
Elevated F_{ENO}	19 (21.1%)	30 (20.8%)	0.959
Asthma medication use ever			
Inhaled bronchodilator	43/89 (48.3%)	76/142 (53.5%)	0.457
Inhaled corticosteroid	22/89 (24.7%)	39/142 (27.4%)	0.655
Oral corticosteroid	13/89 (14.6%)	23/142 (16.2%)	0.753
Montelukast	0/89 (0.0%)	2/142 (1.4%)	0.262
Asthma medication use in last 3 months			
Inhaled bronchodilator	1/88 (1.1%)	27/142 (19.0%)	<0.001*
Inhaled corticosteroid	1/88 (1.1%)	9/142 (6.3%)	0.059
Oral corticosteroid	0/88 (0.0%)	2/142 (1.4%)	0.262
Respiratory symptoms ever			
Wheeze	46/90 (51.1%)	85/140 (60.7%)	0.151
Cough	27/90 (30.0%)	75/143 (52.4%)	<0.001*
Respiratory symptoms in the last 12 months			
Wheeze	8/75 (10.7%)	39/102 (38.2%)	<0.001*
Cough	11/74 (14.9%)	50/101 (49.5%)	<0.001*
Respiratory symptoms in the last 3 months			
Wheeze	0/90 (0%)	34/143 (23.8%)	<0.001*
Cough	14/90 (15.6%)	94/144 (65.3%)	<0.001*
Rattle	0/90 (0%)	34/141 (24.1%)	<0.001*
Shortness of breath	0/90 (0%)	61/142 (43.0%)	<0.001*
Respiratory symptoms in the last 3 months on exercise	0/90 (0%)	127/142 (89.4%)	<0.001*
Asthma diagnosis			
Asthma unconfirmed	67/90 (74.4%)	91/144 (63.2%)	0.074
Asthma confirmed	16/90 (17.8%)	30/144 (20.8%)	0.567
Asthma highly probable	7/90 (7.8%)	23/144 (16.0%)	0.068
Physician diagnosed asthma ever	22/88 (25.0%)	55/144 (38.2%)	0.038*
Age diagnosed with asthma, years	2.0 (1.0–4.63)	4.0 (3.0–8.0)	0.003*
Met both ERS asthma criteria and had been diagnosed *via* a physician	5/88 (5.7%)	15/144 (10.4%)	0.212

Data are presented as mean±SD or median (interquartile range), unless otherwise stated. Subjects were classified as having bronchopulmonary dysplasia (BPD) if received 28 days of oxygen supplementation or more, as assessed at 36 weeks postmenstrual age. BMI: body mass index; FEV_1: forced expiratory volume in 1 s; FVC: forced vital capacity; F_{ENO}: fractional exhaled nitric oxide; ERS: European Respiratory Society. *: p<0.05 between no respiratory symptoms and respiratory symptoms group.

We showed that asthma diagnosis rates were not different between the symptomatic and asymptomatic groups. The ERS asthma criteria would generally not be applied to an asymptomatic patient in the clinic; however, low lung function and treatment responses are commonly observed in the asymptomatic preterm population [3, 6]. Children and their families can normalise respiratory symptoms or avoid activities that

trigger symptoms. Indeed, those born preterm are less likely to report symptoms than are individuals with asthma with the same level of lung function [21]. Although patient- and parent-reported physician diagnoses of asthma have been previously found to be a reliable source of data [22], a limitation to this study is the lack of availability to asthma diagnosis reported by physicians in medical records. This may further contribute to the poor agreement between those with a physician diagnosis of asthma and those meeting the ERS criteria in this population. Furthermore, it should be noted that four participants were regularly taking ICS at the time of lung function testing, which may account for them not meeting the "asthma confirmed" diagnosis (assuming they had achieved good asthma control). Notably, those with respiratory symptoms were older than those without symptoms. Previous studies have suggested that lung disease may be progressive over time in this population [1], which may account for increased reporting of symptoms in the older population.

There remains no evidence-based guidance on how to diagnose or manage prematurity-associated lung disease and no targeted treatments are available. Indeed, this patient population is often excluded from therapeutic trials aimed at benefiting patients with asthma and COPD. A recent trial of ICS in this population demonstrated a clinical benefit (improved FEV_1 z-score of >0.5) in ∼25%, regardless of the presence of respiratory symptoms or previous asthma diagnosis [6]. A well-powered study to assess the effectiveness of ICS in those meeting the ERS asthma criteria would be a welcome addition to the knowledge base elucidating which preterm born children might benefit from ICS.

Our findings suggest that not all wheeze is "asthma" in this population and a thorough diagnostic work up should be considered prior to the commencement of asthma pharmacotherapy.

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