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Persistent ventilation inhomogeneity after an acute exacerbation in preschool children with recurrent wheezing

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Abstract

Background: Preschool children with recurrent wheezing suffer high morbidity. It is unclear whether objective measures of asthma control, such as pulmonary function tests (PFTs), provide additional information to the clinical assessment.

Methods: We recruited children between 3 and 6 years old, with a history of recurrent wheezing in the preceding year and treated for acute wheezing exacerbation in the emergency department (ED) into an observational cohort study. Children attended two outpatient visits: the first study visit within five days of discharge from the ED and the second study visit 12 weeks after the ED visit. We performed standardized symptom score (test for respiratory and asthma control in kids (TRACK)), multiple breath washout (MBW), spirometry, and clinical assessment at both visits.

Results: Seventy-four children, mean (standard deviation (SD)) age of 4.32 years (0.84), attended both visits. Paired FEV_{0.75} and lung clearance index (LCI) measurements at both time points were obtained in 37 and 34 subjects, respectively. Feasibility for all tests improved at visit 2 and was not age-dependent. At the second study visit, a third had controlled asthma based on the TRACK score, and the mean

Abbreviations: MBW, multiple breath washout; LCI, lung clearance index; TRACK, test for respiratory and asthma control in kids.

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lung clearance index (LCI) improved from 9.86 to 8.31 ($P = .003$); however, 46% had an LCI in the abnormal range. $FEV_{0.75}$ z-score improved from -1.66 to -1.17 ($P = .05$) but remained in the abnormal range in 24%. LCI was abnormal in more than half of the children with “well-controlled” asthma based on the TRACK score. There was no correlation between PFT measures and TRACK scores at either visit.

Conclusions: Lung clearance index demonstrates a persistent deficit post-exacerbation in a large proportion of preschoolers with recurrent wheezing, highlighting that symptom scores alone may not suffice for monitoring these children.

KEYWORDS

asthma, lung clearance index, multiple breath washout, preschool children, pulmonary function test, symptom assessment, test for respiratory and asthma control in kids, wheeze

1 | INTRODUCTION

Asthma is the most common chronic disease in children, imposing a high burden on the health system through frequent emergency department (ED) visits, hospital admissions, and repeated treatment bursts.¹

Despite a decline in asthma hospitalization rates in children and youth by 50% over the past decade in Canada, preschoolers under the age of five continue to experience significantly higher rates of hospitalization than children over the age of 5 years.² Diagnosis of asthma in preschoolers is challenging, leading to delays in treatment. Yet, it is well known that 75% of all asthmatics trace their onset of wheeze to the first three years of life^{3–5} and persistence of wheeze symptoms is the strongest preschool risk factor for asthma. Furthermore, persistent wheezing in preschool children is associated with significant morbidity, high levels of atopy, bronchial hyper-responsiveness, and impaired lung function.³

Preschool children suffering from recurrent wheezing exacerbations and who have persistence of symptoms suffer a significant loss of pulmonary function between preschool and mid-school age.^{6,7} Few studies have examined the utility of pulmonary function test (PFT) measures for monitoring preschool children with wheezing disorders.^{8,9} Spirometry-derived forced expiratory volume in one second (FEV_1) is the most commonly reported PFT measure in asthma.¹⁰ Reduced FEV_1 is associated with asthma severity and predictive of exacerbations in older children and persistence of symptoms into adulthood.¹¹ Multiple breath washout (MBW) has gained attention due to its relative ease of use in preschool children. Lung clearance index (LCI), the primary outcome measure of MBW, provides a sensitive estimate of ventilation heterogeneity.

The clinical value of LCI in preschool children with wheezing disorders is not clearly established in the existing literature. A British cross-sectional study of preschoolers with wheeze reported that LCI was more sensitive than spirometry at detecting abnormal pulmonary function, and could differentiate between viral wheeze and multi-trigger wheeze.⁸ However, a Danish cross-sectional study reported that LCI did not discriminate between preschool children in the community with wheezing symptoms and healthy controls.⁹

Key Message

Lung clearance index (LCI) revealed persistent pulmonary function abnormalities in preschool children after recovery from acute wheeze exacerbations, thus providing additional insight into preschool asthma control beyond mere symptom assessment measures.

Most recently, another Danish study suggested that preschool LCI may detect children with wheezing syndromes who experience more severe exacerbations.¹²

Given the discrepancy between symptom scores and clinical outcomes and the potential role of PFTs, we designed an observational cohort study, the WheezyER study, to evaluate preschool pulmonary function changes over a 12-week period among children identified during an acute wheezing exacerbation and to evaluate its added value to clinical assessment of symptoms. Our research group has also studied changes in LCI in both healthy controls and preschool patients with cystic fibrosis (CF) to understand its role in monitoring CF lung disease.¹³ We compared changes in LCI measures and $FEV_{0.75}$ z-scores (a more sensitive measure of airflow obstruction and disease control in preschool children compared to FEV_1)¹⁴ to similarly timed measurements from our published healthy control data.¹³

2 | METHODS

The study was approved by the Hospital for Sick Children Research Ethics Board (REB 1000041089, ClinicalTrials.gov ID: NCT02743663), and informed consent was obtained from a parent or legal guardian. This was a prospective single-center observational cohort study. The primary objective was to evaluate changes in PFT outcome measures, namely $FEV_{0.75}$ z-scores and nitrogen washout-based LCI, during acute wheezing exacerbations, and to determine whether they provided additional clinical information

about preschool wheezing exacerbations not captured by symptom assessment alone. Please refer to Appendix S1 for a detailed account of the Methods.

3 | RESULTS

3.1 | Study population

We screened 575 patients attending the ED and enrolled 100 preschool children with recurrent wheezing in our WheezyER study, 20 of whom took part in the pilot study and 80 were assigned to the final WheezyER study. Out of the 80 enrolled, symptom data were missing for six; hence, 74 (92.5%) were included in the analysis (see Figure 1 for details). The participant demographics at the first study visit are shown in Table 1.

Most children (58%, 39/67) had at least one parent with a diagnosis of asthma (Table 1). Almost 80% of the children (57/74) had a diagnosis of food allergy, allergic rhinitis, or atopic dermatitis, and more than half (40/68) had positive allergy skin tests (Table 1).

A third of the children (31%, 23/74) had an additional presentation to the ED for acute wheezing between the first and second study visits. Standard medical therapy for acute exacerbation of asthma¹⁵ (salbutamol and ipratropium bromide) was administered to all children at the additional ED visit; furthermore, all but one child were treated with an additional course of oral corticosteroids (OCS) at the ED visit. These children had atopic characteristics similar to the rest of the preschool wheeze cohort. There were no significant

differences in clinical parameters among those who had exacerbations between the two visits and those who did not (Table S1).

3.2 | TRACK score

Most children (88%, 65/74) had parent-reported TRACK scores suggestive of uncontrolled symptoms at the first study visit [mean (SD) score of 52.64 (22.10)] (Table 2). Twelve percent (9/74) of parents reported TRACK scores in the “controlled” symptom range at their first study visit despite their child’s recent visit to the ED (Table 1). At the second study visit (12 ± 2 weeks after the ED visit), most children (66%, 49/74) had TRACK scores that remained in the uncontrolled symptom range [mean (SD) score of 65.00 (20.34)]. Treatment with inhaled corticosteroids (ICS) did not impact this outcome: 44% (11/25) of children with “controlled” symptoms and 55% (27/49) of those with “uncontrolled” symptoms received ICS treatment ($P = .51$).

Between the two study visits, the mean TRACK score improved by a mean (SD) score of 12.4 (22.4), $P < .001$. The majority of children (58%, 43/74) experienced an improvement in symptoms.

3.3 | Pulmonary function tests

The feasibility of the preschool PFTs is shown in Table 2. Feasibility was not age-dependent and was similar for spirometry and MBW at the first study visit and improved at the second study visit. Paired

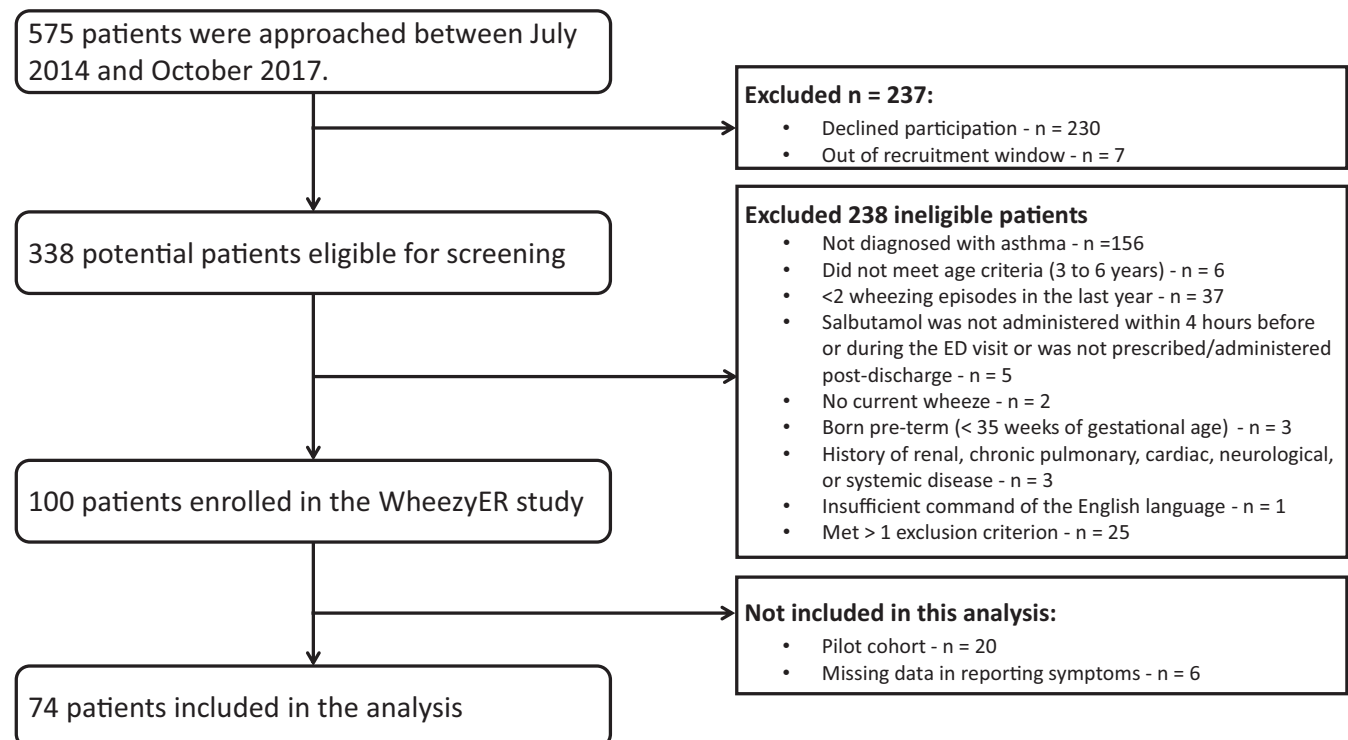


FIGURE 1 Consort diagram of patients enrolled in the WheezyER study

TABLE 1 Participant demographics at presentation to the emergency department

Demographics ^a	Preschooler with recurrent wheezing
Ethnicity, n/N (%)	
Caucasian	33/74 (45%)
Multiracial	17/74 (23%)
Black	7/74 (9%)
Other	17/74 (23%)
Sex, N (%)	
Male: Female	46 (62%): 28 (38%)
Age ^b in years	4.32 (0.84)
Height z-score ^c	-0.11 (0.97)
Weight z-score ^c	0.20 (1.00)
BMI z-score ^c	0.38 (1.06)
Maternal history of asthma n/N (%)	24/70 (34%)
Paternal history of asthma, n/N (%)	21/68 (31%)
Environmental tobacco smoke exposure, n/N (%) ^d	20/73 (27%)
Atopic sensitization, n/N (%)	40/68 (59%)
Food allergy, n/N (%)	27/73 (37%)
Aeroallergen sensitization, n/N (%)	35/68 (51%)
Oral corticosteroids in the past year, n/N (% ≥2 courses)	41/74 (55%)
ED visits for wheezing in the past year, n/N (%)	61/74 (82%)
Continuous inhaled corticosteroids use in the past year, n/N (%)	24/74 (32%)
TRACK ≥80 at acute exacerbation, n/N (%)	9/74 (12%)

^aUnless otherwise specified, all values are expressed as mean with standard deviation. Denominators in categorical values represent the number of children without missing data.

^bN = 74.

^cValues did not have missing data (n = 74) and were calculated based on WHO growth charts.²³

^dEnvironmental tobacco smoke (ETS) exposure is defined as positive if a parent is currently smoking or one or more smokers currently live in the same home as the child.

longitudinal measures were achieved in 50% (37/74) and 46% (34/74) of children for FEV_{0.75} and LCI measures, respectively. The characteristics of this subcohort were similar to the overall cohort (Table S2).

3.4 | Spirometry—FEV_{0.75} z-score

FEV_{0.75} z-scores improved between the two visits (Table 2). Almost 40% (17/44) had an abnormally low FEV_{0.75} z-score (≤ -1.96) at the first study visit, and FEV_{0.75} z-score was low in a quarter (13/53) at the second study visit.

The generalized linear mixed-effect model with repeated measure was used to compare the changes in FEV_{0.75} between preschool children with wheeze and healthy controls; the difference between the two groups was statistically significant ($P = .02$).

3.5 | Multiple breath washout (MBW)

Lung clearance index measures improved from the first study visit to the second study visit in the 34 children with paired measures (Table 2). At the first study visit, the mean (SD) LCI was 9.86 (1.89) and 80% (32/40) of children had an LCI value greater than the upper limit of normal (ULN = 8), as defined in our published healthy control data.¹³ At the second study visit, the mean (SD) LCI was 8.31 (1.19); however, 46% (23/50) had an LCI in the abnormal range. The group of children with an abnormal LCI at the second study visit had a greater number of ED visits in the year preceding recruitment compared to those with LCI within the normal range (median 5 vs 3, $P = .02$). No other differences in clinical characteristics, including ICS use, atopy, family history, or ED visits within the study period, were noted between the groups.

Among the subcohort of 34 children with valid LCI measures at both visits, LCI improved significantly by a mean of 1.09 (SD 1.98, $P = .003$) (Table 2). Using a generalized linear mixed-effect model with repeated measures, the change in LCI over the two visits in preschool children with wheeze was significantly different from that seen in the healthy controls ($P < .001$). Moment ratios (M_0/M_1

TABLE 2 Symptom scores and pulmonary function testing outcomes^a in WheezyER participants from the first to second study visits

Variable	First study visit (Acute)		Second study visit (Recovery)		Changes between two visits		
	Feasibility	Measure	Feasibility	Measure	N paired	Raw changes	P-value
TRACK	74/74 (100%)	52.64 (22.10)	74/74 (100%)	65.00 (20.34)	74	12.36 (22.38)	<.001
FEV _{0.75} z-score	44/74 (59%)	-1.66 (1.24)	53/74 (72%)	-1.17 (1.18)	37	0.45 (1.34)	.05
LCI	40/74 (54%)	9.86 (1.89)	50/74 (68%)	8.31 (1.19)	34	-1.09 (1.98)	.003
FRC	40/74 (54%)	0.68 (0.15)	50/74 (68%)	0.71 (0.14)	34	0.01 (0.12)	.49
M_0/M_1	40/74 (54%)	2.14 (0.38)	50/74 (68%)	1.85 (0.22)	34	-0.19 (0.37)	.004
M_0/M_2	40/74 (54%)	10.38 (4.03)	50/74 (68%)	7.41 (2.26)	34	-1.97 (3.85)	.004

^aValues are presented as mean and standard deviation. A generalized linear mixed-effect model with repeated measure was applied to test the raw changes in pulmonary function in those children with both measures available.

and M_0/M_2) were less sensitive to airway disease than LCI and did not add any additional information to LCI (see Appendix S1).

3.6 | TRACK score and PFT outcome measures

Lung clearance index, $FEV_{0.75}$ z-scores, and TRACK scores all improved significantly between the two visits (Table 2). However,

there were no significant correlations between TRACK scores and either LCI ($\rho = 0.26$, $P = .11$) or $FEV_{0.75}$ z-score ($\rho = 0.04$, $P = .82$; Figure 2). There was also no correlation between LCI and $FEV_{0.75}$ z-scores ($\rho = -0.24$, $P = .05$). This finding is illustrated in Figure 3. At the second study visit, 25 (66%, 25/38) children had “controlled” symptoms on the TRACK score (≥ 80). Among this group, LCI was abnormal in 40% (10 children) and $FEV_{0.75}$ z-score was abnormal in 8% (2 children).

FIGURE 2 Correlation between lung function outcomes at both visits and symptom scores. Horizontal hatched lines represent the cutoffs of abnormal lung clearance index (LCI) (≥ 8) or abnormal $FEV_{0.75}$ z-score (≤ -1.96). Vertical hatched lines represent TRACK scores of 80, with scores ≥ 80 indicative of controlled symptoms: A, TRACK score and LCI at the first study visit; B, TRACK score and LCI at the second study visit; C, TRACK score and $FEV_{0.75}$ z-score at the first study visit; D, TRACK score and $FEV_{0.75}$ z-score at the second study visit

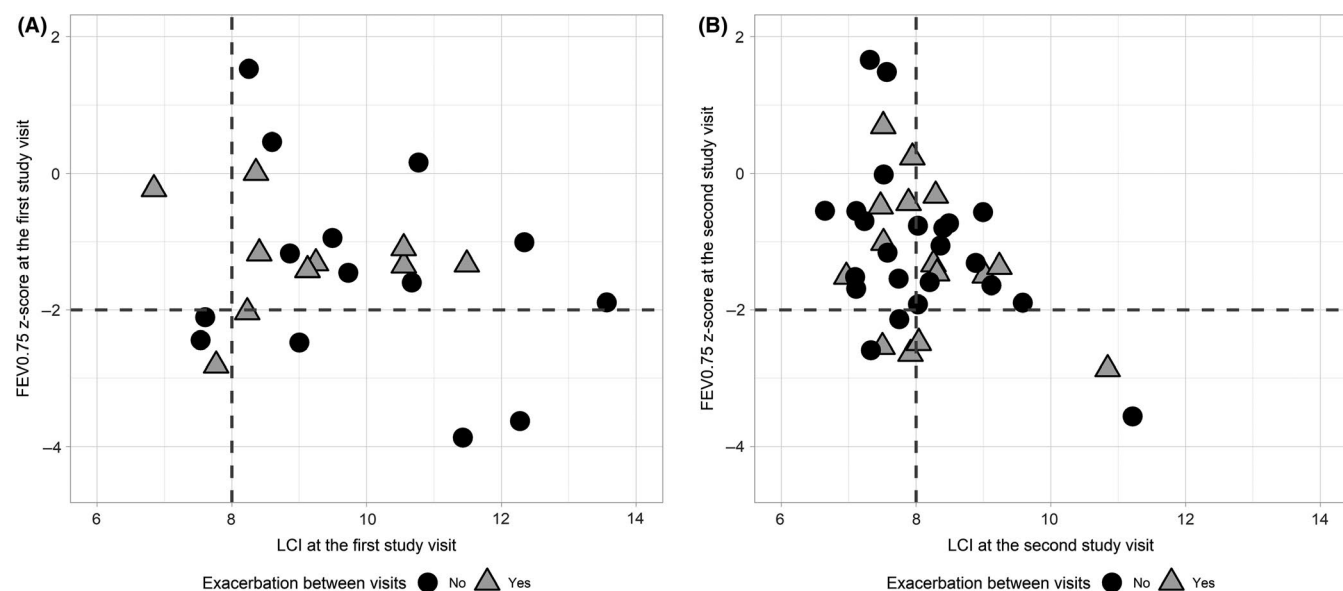
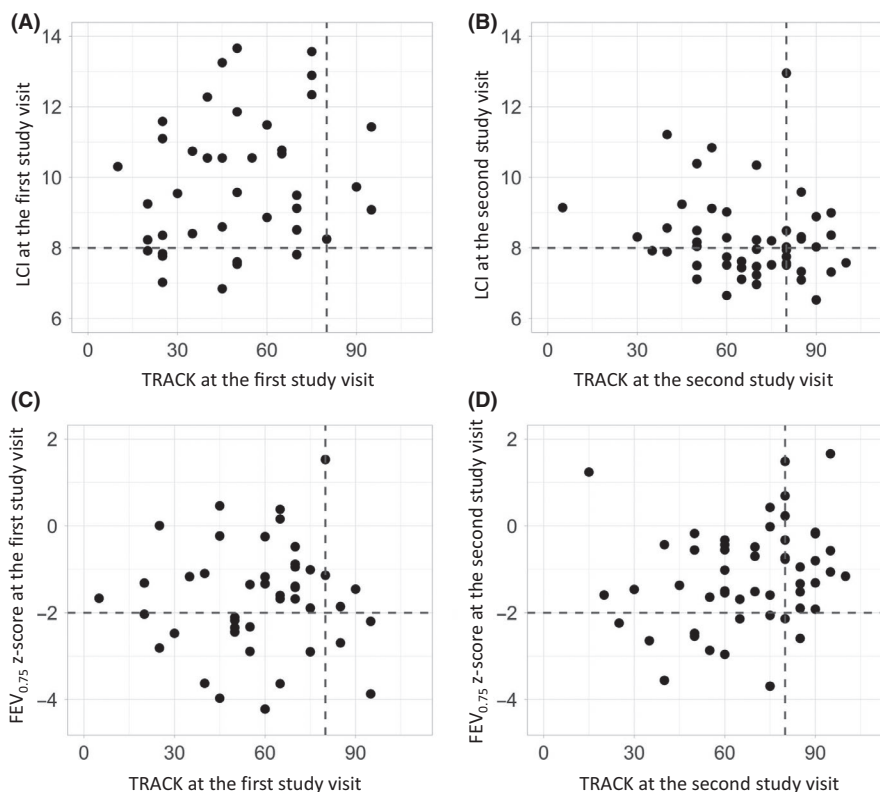


FIGURE 3 Correlation between: A, lung clearance index (LCI) and $FEV_{0.75}$ z-score at the first study visit within 5 d of ED presentation, and B, LCI and $FEV_{0.75}$ z-score at the second study visit

3.7 | Paired spirometry and MBW measures

At the first study visit, 24 children had paired $FEV_{0.75}$ and LCI measurements (Figure 3A). Twenty-three (96%) had abnormal PFT results, defined as LCI greater than the ULN and/or $FEV_{0.75}$ z-score below the lower limit of normal ($\leq LLN$). Abnormal LCI measures were recorded in 83% (20/24), and abnormal $FEV_{0.75}$ z-scores in 29% (7/24), and 17% (4/24) showed abnormalities in both measures (Figure 3A).

At the second study visit, 38 children had paired $FEV_{0.75}$ and LCI measurements. Twenty-one (55%) had abnormal PFT results. Abnormal LCI measures were recorded in 45% (17/38), and abnormal $FEV_{0.75}$ z-scores in 18% (7/38), and 8% (3/38) showed abnormalities in both measures (Figure 3B).

Of the 34 children with LCI measures at both visits, 16 (47%) had persistently abnormal LCI values. Of the 37 children who had spirometry measures at both visits, five (14%) had persistently abnormal $FEV_{0.75}$ measures. Nineteen children had paired LCI and $FEV_{0.75}$ measures at the first and second study visits, but only one (5%) subject had persistently abnormal LCI and $FEV_{0.75}$ at both visits. There was no evident correlation in MBW measures in those subjects with persistently abnormal $FEV_{0.75}$ and vice versa (Figure 4).

4 | DISCUSSION

This study showed that almost half of preschool children with recurrent wheezing who had parent-reported “well-controlled” asthma symptoms using the TRACK score demonstrated an abnormal LCI measure, which is consistent with existing literature.^{16,17} In contrast to the literature,^{9,12,18} we observed significant differences in LCI between preschool children with recurrent wheezing

and healthy controls. Notably, previous studies focused on children from the general population or in asthma clinics, where the preschool wheezing phenotype may have been milder or well controlled. A recent publication, using a similar LCI methodology, supports the observation that LCI may be more discriminative in children with more severe or symptomatic disease.¹² Our population had a greater proportion of children who had received OCS or suffered from repeated exacerbations, which represents a more severe preschool wheeze phenotype. We also found an association between abnormal LCI and ED visits for an acute wheezing exacerbation in the previous 12 months, which is suggestive of a correlation with disease severity.¹⁹ Finally, LCI was feasible in the majority (68%) of our children at the second study visit and improved with training and age, a finding previously reported in the literature.¹⁸ Taken together, preschool LCI measurement is feasible during monitoring visits and offers complementary insights into the control of recurrent wheezing disorder in preschool children that are not available using symptom scores alone.

The management of preschool recurrent wheezing is controversial and has been the subject of four separate guidelines. Most of the controversy surrounds the diagnosis of asthma due to the heterogeneity in wheeze phenotypes as well as response to treatment. However, despite these controversies, all guidelines consistently urge close monitoring between exacerbations. In this age-group, symptom monitoring through standardized symptom assessment is promoted. However, our study offers some insights into the limitations of this approach. We found that at their second visit, after recovery from an exacerbation, 16/50 (40%) children had abnormal LCI values despite reporting good symptom control. Overall, our study demonstrates that markers of abnormal lung physiology are present despite parental assessment of good

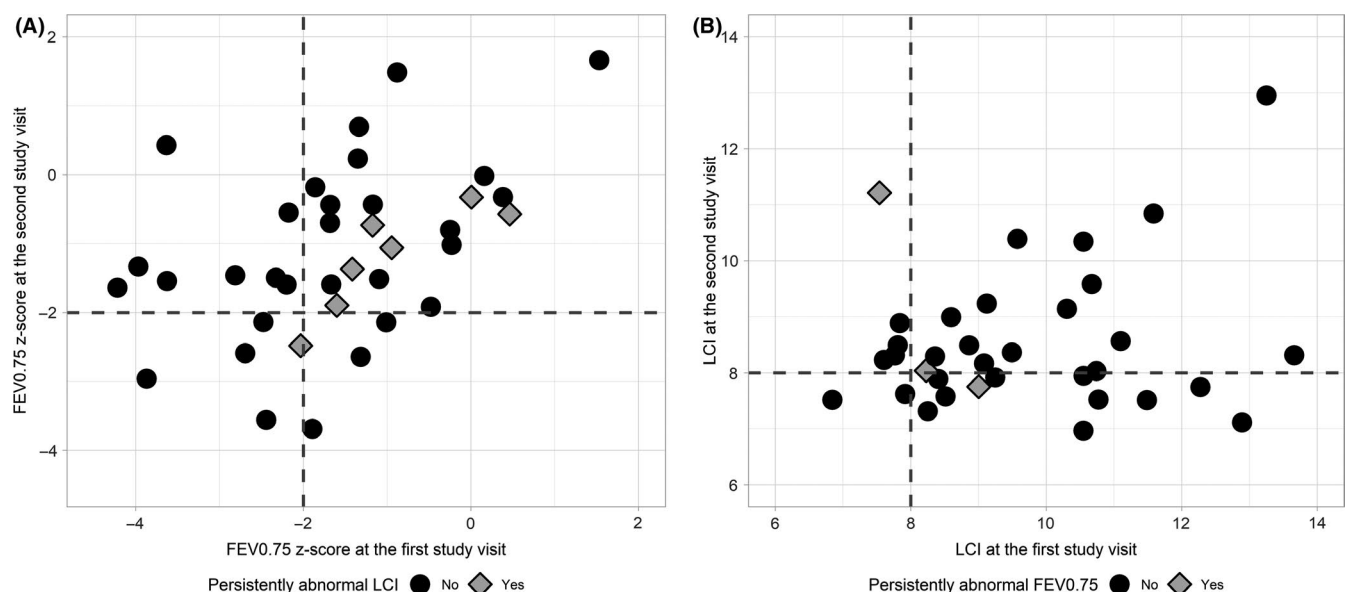


FIGURE 4 Paired longitudinal measures (LCI and $FEV_{0.75}$ z-score) at visits 1 and 2: A, $FEV_{0.75}$ z-score at the first and second study visits and B, LCI at the first and second study visits. Vertical lines represent the cutoffs of abnormal LCI (≥ 8), and horizontal lines are abnormal $FEV_{0.75}$ z-score (≤ -1.96)

control, suggesting that incorporation of physiologic outcomes may provide a more comprehensive assessment of preschool recurrent wheezing. Whether these additional measures are modifiable with treatment and the resultant impact on clinical outcomes should be the focus of future studies. We are unable to comment on the nature of the relationship between abnormal lung function and exacerbations.

In our study, more abnormalities were detected using LCI measurements compared to $FEV_{0.75}$; a quarter (13/53) of children had abnormal $FEV_{0.75}$ and 52% had an abnormal LCI at the second study visit. In those with “well-controlled” asthma symptoms on the TRACK score at the second study visit, half (53%) had an abnormal LCI measure and 10% an abnormal $FEV_{0.75}$ z-score. It is unclear whether abnormalities in MBW are of clinical significance, and given the size of the pilot study, no clinical recommendations may be made. However, it does highlight the need for further assessment of the role of MBW at detecting patients who may benefit from more aggressive management strategies, including preventative interventions, such as immunization and public health measures to reduce environmental tobacco smoke exposure.

This study has limitations that warrant consideration. Firstly, the interval between the two study visits was relatively short. A longer interval is needed to assess whether the abnormal LCI values are predictive of a severe asthma phenotype or if the resolution of abnormalities requires a more extended period. Furthermore, this study was not designed to assess response to a trial of standardized therapy. Therefore, we cannot comment on the responsiveness of LCI to standardized treatment. In addition, information regarding exacerbations between the two study visits was only available for those children who attended the ED; hence, unreported milder exacerbations may have been missed. Finally, we did not perform sputum, exhaled nitric oxide, or urinary analyses of inflammatory markers. Hence, we cannot comment on the relationship between PFT outcomes and inflammation in preschoolers with wheeze.

Lung clearance index and $FEV_{0.75}$ are the PFT measures evaluated in this study. The former is a marker of global ventilation inhomogeneity, including peripheral airways, end-bronchioles, and alveolar spaces, whereas the latter measure is primarily derived from the central airways. This difference is highlighted in the current study by the findings of persistently abnormal LCI measures in a higher portion of children compared to $FEV_{0.75}$ (47% vs 14%). The use of spirometry is well-established in the management of asthma. MBW-derived LCI is being increasingly used in the clinical settings for the management of patients with CF, and as discussed previously, there is an increasing interest in its use in the pediatric asthma population, particularly given the evidence suggesting that MBW is a more sensitive marker of disease activity than FEV_1 in CF. The pathophysiology of CF and asthma is very different. Whereas the former affects both airways and the parenchyma due to inflammatory and infective process, the latter is primarily a disease of the airways. Hence, findings in CF are not directly applicable to asthma. Nevertheless, there is increasing evidence of the utility of MBW in asthma, particularly as LCI is also a

marker of inhomogeneity within the peripheral airways, data about which is not available from $FEV_{0.75}$.

Larger multicenter studies are needed to assess the role of MBW in the clinical management of preschool children with asthma. Magnetic resonance imaging (MRI) of the lungs is a rapidly advancing imaging modality, which can provide regional functional and anatomical lung data. Recently, a number of small studies have shown correlation between quantitative and enhanced functional MRI biomarkers and MBW and spirometry abnormalities in pediatric and adult patients with CF^{20,21} and adults with asthma.²² Insight derived from the combination of these complementary multi-modality techniques is greater than the sum of individual modalities. This is an exciting avenue for future clinical trials as multi-modality biomarkers of disease will facilitate personalized precision medicine and individualized targeted therapy.

In conclusion, we have demonstrated that PFT outcomes are abnormal in a significant number of preschool children with wheezing three months post-ED visit for acute wheeze exacerbation. This indicates that symptom scores alone are insufficient for monitoring recovery from severe exacerbations in a select cohort of preschoolers with asthma, and PFT outcomes could provide additional insight into preschool asthma control beyond symptom assessment alone. Further studies utilizing multi-modality biomarkers that characterize both the lung physiology and inflammation are necessary to improve our understanding of the heterogeneity of wheezing phenotypes in this age-group.

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CONFLICT OF INTERESTS

TE is involved in a sponsored trial by DBV, receives grants from Innovation Fund Denmark, and is the Co-I or scientific lead in three investigator-initiated oral immunotherapy trials supported by the Allergy and Anaphylaxis Program SickKids and serves as associate editor for Allergy and on an advisory board of ALK. The rest of the authors declare no relevant conflicts of interest associated with this publication and no financial support for the work that could have influenced its outcome.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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Persistent ventilation inhomogeneity after an acute exacerbation in preschool children with recurrent wheezing

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SUPPLEMENTARY MATERIALS

METHODS

Study Design and Setting

We conducted a prospective cohort, single center study that recruited preschool subjects who presented during an acute wheezing exacerbation to the ED between July 2014 and October 2017 at the Hospital for Sick Children, Toronto, Ontario, Canada and were discharged with a diagnosis of “acute asthma exacerbation”. Visits were conducted at the first study visit within 5 days of the ED visit and at the second study visit 12 ± 2 weeks later. Standardized pulmonary function testing (MBW and spirometry), questionnaires and clinical assessments were conducted in an outpatient setting at each visit. Raw data from a previously published study of preschool healthy control subjects (of similar age) with repeated spirometry and MBW measurements were used as a control group.¹

Definition of ED Asthma discharge

Any of the following Emergency Department discharge diagnoses were deemed eligible for recruitment purposes: asthma, asthma exacerbation, asthma exacerbation (mild), asthma exacerbation secondary to viral infection, bronchospasm, cough (possible asthma or reactive airways, or variant asthma), reactive airways disease (with or without possible asthma), viral upper respiratory infection with wheezing, wheezing, wheezing (first episode), or wheezing (query reactive airways disease).

Study Populations

Persistent Wheeze (PW): Children aged 3-6 years who presented to the ED at The Hospital for Sick Children for a wheezing exacerbation between July 2014 and October 2017 were screened for study participation. Children were eligible if they received a physician diagnosis of “acute asthma/wheeze exacerbation” at discharge from ED, had at least two wheezing episodes in the previous 12 months, and received salbutamol during the current wheezing episode. Children were excluded if they had co-

morbidities (e.g. renal, cardiac, neurological, or systemic conditions), were born prematurely (before 35 weeks gestational age), or had insufficient command of the English language. Children were included if they were assessed by clinicians at both visits and had no missing data in reporting symptoms.

Healthy Controls (HC): We have previously published results on a healthy control group on 72 children aged 2.5-6 years of age with data available on LCI and spirometry measurements.¹ These children were recruited as part of a preschool CF study at our centre and underwent PFTs at the enrollment visit, and 1, 3, 6 and 12 months post-enrollment.

Study Measures

We collated the following measures at each clinical visit for preschool wheezing subjects.

The parents of preschool children with asthma completed a standardized asthma symptom questionnaire (Test for Respiratory and Asthma Control in Kids - TRACK) that assesses the functional aspects of asthma control (wheezing, coughing, and shortness of breath, and the use of quick-relief medications and oral corticosteroids).² A TRACK score of ≥ 80 suggests that asthma is controlled and a change in score of > 10 represents a clinically meaningful change in respiratory control.³ Medication use and parental medical history of asthma and allergies were also documented.

At the second study visit, we performed allergy skin prick testing to environmental allergens (*Alternaria alternata*, *Cladosporium herbarium*, *Penicillium notatum*, *Aspergillus fumigatus*, cat pelt, dog epithelium, *Dematophagoides pteronyssinus*, *Dermatophagoides farine*, cockroach, 9-tree pollen mix, 3-grass pollen mix, 7-weed pollen mix, ragweed) and food extracts (peanut, cow's milk, egg white, soybean). Histamine and glycerin served as the positive and negative controls. Atopy was defined as a positive skin prick test (i.e. allergen wheal diameter > 2 mm greater than negative control) for a minimum of one allergen.

A clinician with expertise in preschool asthma assessed the participants clinically. A standardized medical history capturing details about cough, wheeze, wheeze triggers, allergies to both food and inhalants, allergic rhinitis, and eczema over the child's lifetime was obtained. Following assessment of history, the clinician classified the children as episodic viral wheeze if the only trigger for wheezing or cough was viruses and as multi-trigger wheeze if there was a history of wheeze or cough triggered by exercise or allergens outside of a viral illness. A standardized physical examination documented the presence of wheeze, respiratory distress, and oxygen saturation. The Paediatric Respiratory Assessment Measure (PRAM) score was recorded.⁴ Ethnicity was self-reported on the questionnaire by parents.

We obtained blood samples from the children and total IgE, CBC, and differential were measured. We measured height, weight, and BMI in clinic and these were standardized using WHO growth charts for preschoolers.⁵

We performed Nitrogen Multiple Breath Washout (N₂MBW) using the nitrogen open circuit bias flow washout system on Spiroware 3.1.6. (Exhalyzer D® EcoMedics AG, Duernten, Switzerland). Facemasks with added putty to minimize dead space were used. We observed the ATS/ERS recommendations, including the use of putty inside of facemasks to minimize deadspace, and utilizing children's movies to distract the participants during testing in order to ensure regular, tidal breathing. Two operators were performing testing to ensure adequate monitoring of the results in real-time and a full seal with the facemask⁶ A minimum of 3 trials were collected and at least two technically acceptable trials were used to report LCI. Test quality was reviewed offline after testing to ensure stable tidal volumes, end-expiratory volume, absence of leaks, and minimal sigh, swallows or pauses. Tests which did not meet these standards were not included in the analysis⁶.

We performed spirometry using the ndd Easy on-PC system (ndd Medical Technologies, Inc., Andover, MA, USA). A minimum of three trials were attempted with all subjects. Offline review of all trials for acceptability and reproducibility was based on ATS/ERS guidelines and completed by a Registered Respiratory Therapist (RRT).⁷ As per Health Canada and our IRB regulations, salbutamol could only be

106 administered to children older than 4 years; thus, post-bronchodilator spirometry was not be assessed in
107 all subjects.

108

Statistical Analysis

Participants' characteristics are presented as mean (standard deviation), or frequency (percentage), as appropriate. Comparisons of lung function outcomes between the first study visit and the second study visit were performed using paired t-tests or Wilcoxon-Mann Whitney tests. These were also confirmed by generalized linear regression models with repeated measures with random intercepts. Spirometric parameters are reported as z-scores, with a normal range of ± 1.96 .⁸ The upper limit of normal of LCI, M_1/M_0 and M_2/M_0 were defined as the mean + $1.96 \times$ standard deviation (i.e. 8.0) of the previously published healthy population.⁹ The correlations between lung function tests and TRACK score were assessed using the Spearman correlation tests.

Generalized mixed-effects models with repeated measures were used to distinguish changes in LCI, $FEV_{0.75}$ and moment ratios (M_1/M_0 and M_2/M_0) over a three months period in wheezing children and healthy controls¹. Event was used as the time-variable and an interaction between disease status (wheezing or health) and event was used to assess whether the changes in lung function tests differed between health and wheezing children.

All statistical analyses were based on available data and missing data were not imputed. All analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA), and R 3.4.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Feasibility in Lung Function Tests

The ability of wheezing subjects to perform either MBW or spirometry improved between the first study visit and the second study visit: the success rate for MBW improved from 54% to 68%, and $FEV_{0.75}$ improved similarly, from 59% to 72% (Table 2). This differs from feasibility data seen in the previously published healthy control group, which had 66% and 86% feasibility for MBW at the

Enrolment and 3 month visits, while the feasibility for spirometry was 70% and 71% respectively.¹ However, these were first and third visits for the healthy controls, compared to the first and second visits for the WheezyER participants.

We obtained paired FEV_{0.75} and LCI at both visits in 26% of the children with preschool wheeze. The characteristics of this subcohort with full, paired PFT measures were similar to the overall cohort (Table E3).

Upper Limit of Normal of LCI

The upper limit of normal (ULN) of LCI was defined as 8, as determined from the observed data for asthma subjects at their enrollment visit from a previously published healthy control group¹. We also determined the ULN from the 3-month visit (closer in age to our wheezing population), to test if our slightly different age would affect the ULN. Using data from the 3-month visit resulted in the same ULN of 8.0 (7.1+1.96×0.5). There was no relationship observed between LCI and age/ height in acute wheezing children at any visits, same as what has been observed in this healthy control group.

Sample size

The sample size calculation for LCI was based on the assumption that we would be able to observe at least 1.2 LCI units change from the first study visit to the second study visit, and that the standard deviation would be less than 2. A sample size of 24 would have 80% power to detect a significant change in LCI at a significance level of 0.05.

Variability of Lung Function Tests

The variability of LCI and FEV_{0.75} z-score in children with preschool asthma are summarized in Table E4. The intra-test repeatability (%CV) of the LCI was similar with the inter-test reproducibility. The intraclass correlation coefficient (ICC) of LCI observed in children with asthma was 0.48, which was larger than that observed in healthy subjects (0.38).¹ Higher ICC in preschool children with asthma might

156 be explained by the changes in symptoms from acute to recovery visits; similar results were observed in

157 $FEV_{0.75}$ z-score.

158 *MBW*

159 Moment ratios M_0/M_1 and M_0/M_2 decreased ($p = 0.004$) in mean (SD) similarly to LCI (Table 2) but were

160 less sensitive to airway disease than LCI and therefore, did not add any additional information to LCI

161 alone.

162

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Supplementary tables

Table E1. Comparison between subjects with and without an exacerbation between Visit 1 and Visit 2.

Clinical Parameters	No Exacerbations (N=51)	Exacerbations (N=23)	P ^Δ
Sex, N (%)			0.10
Male : Female	28 (54.9)	18 (78.3)	
Ethnicity, n/N (%)			0.27
African American	4/51 (7.8)	2 (8.7)	
Caucasian	19/51 (37.3)	14/23 (60.9)	
North East Asian	3/51 (5.9)	1/23 (4.3)	
Other/Mixed	19/51 (37.3)	3/23 (13.0)	
South East Asian	6/51 (11.8)	3/23 (13.0)	
Age ⁺ in years	4.29 (0.87)	4.39 (0.77)	0.65
Weight z-score ‡	16.70 [14.95, 19.00]	17.70 [15.85, 19.80]	0.31
Height z-score ‡	102.80 [98.10, 109.40]	103.40 [102.45, 111.70]	0.11
BMI z-score ‡	15.92 (1.50)	15.96 (1.85)	0.93
Food sensitization	13/47 (27.7)	5/21 (23.8)	0.97
Aeroallergen sensitization	21/47 (44.7)	14/21 (66.7)	0.16
LCI change*	-0.94 [-2.62, 0.05]	-0.52 [-1.25, 0.02]	0.52
FEV075 z-score change*	0.09 (0.17)	0.13 (0.17)	0.51
FRC change*	0.01 (0.08)	0.02 (0.16)	0.97
Abnormal LCI at Visit 2	16/30 (53.3)	11/20 (55.0)	1.00
Abnormal FEV075 z-score at Visit 2	8/36 (22.2)	5/17 (29.4)	0.82

Data presented from the first study visit, as mean (SD), median [IQR] or N (%) were appropriate.

*Difference between second and first study visit.

^Δ Fisher's exact test, t-test or Wilcoxon signed ranks test applied to categorical or continuous measures where appropriate.

‡ Values did not have missing data (n=74) and were calculated based on WHO growth charts.

⁺N=74

198 Table E2. Participant demographics of the subcohort with paired pulmonary function measures at both
199 visits

Demographics*	Preschoolers with paired pulmonary function measures	P ^Δ
Ethnicity, n/N (%)		
Caucasian	5/19 (26%)	0.19
Multiracial	7/19 (39%)	0.25
Black	4/19 (21%)	0.23
Other	3/19 (16%)	0.76
Sex, N (%)		
Male : Female	13 (68%) : 6 (32%)	0.79
Age ⁺ in years	4.50 (0.71)	0.34
Height z-score	0.34 (0.85)	0.08
Weight z-score	0.56 (0.75)	0.06
BMI z-score	0.51 (0.88)	0.55
Maternal history of asthma, n/N (%)	6/18 (33%)	1.00
Paternal history of asthma, n/N (%)	6/18 (33%)	1.00
Environmental tobacco smoke exposure, n/N (%)	6/19 (32%)	0.77
Atopic sensitization, n/N (%)	13/19 (77%)	0.60
Food allergy, n/N (%)	7/19 (37%)	1.00
Aeroallergen sensitization, n/N (%)	12/17 (71%)	0.18
Oral corticosteroids in the past year, n/N (% ≥ 2 courses)	13/19 (68)	0.44
ED visits for wheezing in the past year, n/N (%)	17/19 (89%)	0.73
Continuous inhaled corticosteroids use in the past year, n/N (%)	8/19 (42%)	0.43
TRACK ≥ 80 at acute exacerbation, n/N (% Yes)	1/19 (5%)	0.68

200 * Unless otherwise specified, all values are expressed as mean with standard deviation. Denominators in
201 categorical values represent the number of children without missing data.

202 ^Δ Fisher's exact test or Wilcoxon signed ranks test was applied to categorical or continuous measures, to
203 test the difference between full cohort (Table 1) and subcohort.

204 ⁺ N=19

Table E3. Variability of LCI and FEV_{0.75} outcome measures in preschool asthma, as represented by CV and ICC.

	CV% Median (Range) (Within-Subject Within-Test)		CV% Median (Range) (Within-Subject Between-Test)	ICC (Proportion of the Variability Explained by the Variability Between-Subjects)	
	Overall	Visit 2		Overall	Visit 2
LCI	7.73 (0.74, 31.77)	5.37 (1.02, 17.19)	7.90 (0.57, 40.86)	0.48	0.81
FEV _{0.75}	7.75 (2.01, 36.20)	4.07 (0.84, 10.37)	10.96 (0.23, 43.90)	0.71	0.96
M ₁ /M ₀	6.51 (1.44, 27.27)	4.07 (0.76, 12.33)	7.32 (0.23, 35.14)	0.52	0.84
M ₂ /M ₀	15.69 (2.41, 55.54)	8.40 (1.02, 29.94)	16.07 (0.31, 71.57)	0.53	0.86

Supplementary Figures

Figure E1. Correlation between MBW outcomes (M_1/M_0 and M_2/M_0) at both visits and symptom scores. Horizontal hatched lines represent the cut offs of abnormal M_1/M_0 (≥ 2.6) or abnormal M_2/M_0 (≥ 6.6). Vertical hatched lines represent TRACK scores at 80, with scores ≥ 80 indicative of controlled symptoms.

- (a) TRACK score and M_1/M_0 at the first study visit.
- (b) TRACK score and M_1/M_0 at the second study visit.
- (c) TRACK score and M_2/M_0 at the first study visit.
- (d) TRACK score and M_2/M_0 at the second study visit.

