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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 3-6 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 4.32 years (0.84), attended both visits. Paired $FEV_{0.75}$ and 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 lung clearance index (LCI) improved from 9.86 to 8.31 ($p = 0.003$); however, 46% had an LCI in the abnormal range. $FEV_{0.75}$ z-score improved from -1.66 to -1.17 ($p = 0.05$) 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: LCI 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.

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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 from a significant loss of pulmonary function between preschool and mid-school age.[6,7] Few studies have examined the utility of pulmonary function tests (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] Most recently, another Danish study suggested that preschool LCI may detect children with wheezing syndromes who experiencing more severe exacerbations.[12]

Given the discrepancy between symptoms 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 amongst 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 also compared changes in LCI measures and $FEV_{0.75}$ z-score (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]

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-centre 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 the Online Supplement for a detailed account of the Methods.

RESULTS

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, symptoms data was 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 visit. Standard medical therapy for acute exacerbation of asthma[15] (salbutamol, ipratropium bromide) was administered to all children at the additional ED visit, furthermore all but one child was treated with an additional course of 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 E1).

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" symptoms 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 symptoms range [mean (SD) score 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 ($p = 0.51$).

Between the two study visits, the mean TRACK score improved by a mean (SD) score of 12.4 (22.4), $p<0.001$. The majority of children (58%, 43/74) experienced an improvement in symptoms.

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 by the second study visit. Paired 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 E2).

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 ($\leq$ -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 ($p=0.02$).

MBW

LCI 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 (1.88) 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=0.02). No other differences in clinical characteristics, including ICS use, atopy, family history, or ED visits within the study period was noted between the groups.

Among the subcohort of 34 children with valid LCI measures at both visits, LCI improved significantly by a mean of 1.11 (SD 1.99, p = 0.002) (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 ($p<0.001$). Moment ratios (M_0/M_1, and M_0/M_2) were less sensitive to airway disease than LCI and therefore, did not add any additional information to LCI alone (See supplemental material).

TRACK score & PFT Outcome Measures

LCI, $FEV_{0.75}$ 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 ($\rho = 0.26$, $p = 0.11$) or $FEV_{0.75}$ z-scores ($\rho = 0.04$, $p = 0.82$) (Figure 2). There was also no correlation between LCI and $FEV_{0.75}$ z-scores ($\rho = -0.24$, $p = 0.05$). This finding is illustrated in Figure 3. At the second study visit, 25 (66%, 25/38) children had "controlled symptoms on TRACK score ($\geq$ 80). Among this group, LCI was abnormal in 40% (10 children) and $FEV_{0.75}$ z-score was abnormal in 8% (2 children).

Paired Spirometry & 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 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 FEV0.75 measures. Nineteen children had paired LCI and FEV0.75 measures at baseline and follow-up, but only one (5%) subject had persistently abnormal LCI and FEV0.75, at both visits. There were no evident patterns in MBW measures on those subjects with persistently abnormal FEV0.75 and vice versa (Figure 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 oral corticosteroids 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 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 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 managements 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 second study visit period was relatively short. A longer interval between study visits 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.

LCI 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 paediatric 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 are 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 multi-centre 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 paediatric 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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REFERENCES

1. Ferrante G, La Grutta S. The Burden of Pediatric Asthma. *Front Pediatr.* 2018;6:186.
2. Information CIfH. *Asthma Hospitalizations Among Children and Youth in Canada: Trends and Inequalities.* Ottawa, ON: CIHI;2018.
3. Kurukulaaratchy RJ, Fenn MH, Waterhouse LM, Matthews SM, Holgate ST, Arshad SH. Characterization of wheezing phenotypes in the first 10 years of life. *Clin Exp Allergy.* 2003;33(5):573-578.
4. Martinez FD, Wright AL, Taussig LM, Holberg CJ, Halonen M, Morgan WJ. Asthma and wheezing in the first six years of life. The Group Health Medical Associates. *N Engl J Med.* 1995;332(3):133-138.
5. Brand PLP, Baraldi E, Bisgaard H, et al. Definition, assessment and treatment of wheezing disorders in preschool children: An evidence-based approach. *Eur Respir J.* 2008;32(4):1096-1110.
6. Belgrave DCM, Simpson A, Semic-Jusufagic A, et al. Joint modeling of parentally reported and physician-confirmed wheeze identifies children with persistent troublesome wheezing. *J Allergy Clin Immunol.* 2013;132(3):575-583.e512.
7. Belgrave DC, Buchan I, Bishop C, Lowe L, Simpson A, Custovic A. Trajectories of lung function during childhood. *Am J Respir Crit Care Med.* 2014;189(9):1101-1109.
8. Sonnappa S, Bastardo CM, Wade A, et al. Symptom-pattern phenotype and pulmonary function in preschool wheezers. *J Allergy Clin Immunol.* 2010;126(3):519-526.
9. Vilmann L, Buchvald F, Green K, Nielsen KG. Fractional exhaled nitric oxide and multiple breath nitrogen washout in preschool healthy and asthmatic children. *Respir Med.* 2017;133:42-47.
10. Tepper RS, Wise RS, Covar R, et al. Asthma outcomes: pulmonary physiology. J *Allergy Clin Immunol.* 2012;129(3 Suppl):S65-87.
11. Fuhlbrigge AL, Kitch BT, Paltiel AD, et al. FEV1 is associated with risk of asthma attacks in a pediatric population. *J Allergy Clin Immunol.* 2001;107(1):61-67.
12. Arianto L, Hallas H, Stokholm J, Bønnelykke K, Bisgaard H, Chawes BL. Multiple Breath Washout for Diagnosing Asthma and Persistent Wheeze in Young Children. *Ann Am Thorac Soc.* 2018.
13. Stanojevic S, Davis SD, Retsch-Bogart G, et al. Progression of Lung Disease in Preschool Patients with Cystic Fibrosis. *Am J Respir Crit Care Med .* 2016;195(9):1216-1225.
14. Nève V, Hulo S, Edmé J-L, et al. Utility of measuring FEV0.75/FVC ratio in preschoolers with uncontrolled wheezing disorder. *Eur Respir J.* 2016;48(2):420-427.

15. Ducharme FM, Dell SD, Radhakrishnan D, et al. Diagnosis and management of asthma in preschoolers: A Canadian Thoracic Society and Canadian Paediatric Society position paper. *Paediatr Child Health.* 2015;20(7):353-371.
16. Carroll WD, Wildhaber J, Brand PL. Parent misperception of control in childhood/adolescent asthma: the Room to Breathe survey. *Eur Respir J.* 2012;39(1):90-96.
17. Fuhlbrigge AL, Guilbert T, Spahn J, Peden D, Davis K. The Influence of Variation in Type and Pattern of Symptoms on Assessment in Pediatric Asthma. *Pediatrics.* 2006;118(2):619.
18. Downing B, Irving S, Bingham Y, Fleming L, Bush A, Saglani S. Feasibility of lung clearance index in a clinical setting in pre-school children. *Eur Respir Jl.* 2016;48(4):1074.
19. Bacharier LB, Strunk RC, Mauger D, White D, Lemanske RF, Jr., Sorkness CA. Classifying asthma severity in children: mismatch between symptoms, medication use, and lung function. *Am J Respir Crit Care Med.* 2004;170(4):426-432.
20. Stahl M, Wielputz MO, Graeber SY, et al. Comparison of Lung Clearance Index and Magnetic Resonance Imaging for Assessment of Lung Disease in Children with Cystic Fibrosis. *Am J Respir Crit Care Med.* 2017;195(3):349-359.
21. Pennati F, Salito C, Borzani I, et al. Quantitative multivolume magnetic resonance imaging (1H-MRI) in patients with cystic fibrosis (CF) lung disease:comparison with FEV1 and lung clearance index (LCI). *Eur Respir J.* 2017;50(suppl 61):OA4398.
22. Svenningsen S, Nair P, Guo F, McCormack DG, Parraga G. Is ventilation heterogeneity related to asthma control? *Eur Respir J.* 2016;48(2):370-379.
23. Organization WH. WHO child growth standards: length/height-for-age, weight-for-age, weight-for-length, weight-for-height and body mass index-for-age: methods and development. 2006.

Tables

Table 1. Participant demographics at presentation to the Emergency Department.

Demographics*	**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[+] in years	4.32 (0.84)
Height z-score ‡	-0.11 (0.97)
Weight z-score ‡	0.20 (1.00)
BMI z-score ‡	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 (%) [#]	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%)

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

[+] N=74

‡ Values did not have missing data (n=74) and were calculated based on WHO growth charts. [23]

[#] Environmental 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.

Table 2. Symptom scores and pulmonary function testing outcomes in WheezyER participants from First to Second study visits.*

	First study visit (Acute)		Second study visit (Recovery)		Changes between Two Visits		
Variable	**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)	<0.001
$FEV_{0.75}$ z-score	44/74 (59%)	-1.66 (1.24)	53/74 (72%)	-1.17 (1.18)	37	0.45 (1.34)	0.05
LCI	40/74 (54%)	9.86 (1.89)	50/74 (68%)	8.31 (1.19)	34	-1.09 (1.98)	0.003
FRC	40/74 (54%)	0.68 (0.15)	50/74 (68%)	0.71 (0.14)	34	0.01 (0.12)	0.49
M_0/M_1	40/74 (54%)	2.14 (0.38)	50/74 (68%)	1.85 (0.22)	34	-0.19 (0.37)	0.004
M_0/M_2	40/74 (54%)	10.38 (4.03)	50/74 (68%)	7.41 (2.26)	34	-1.97 (3.85)	0.004

* Values 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.

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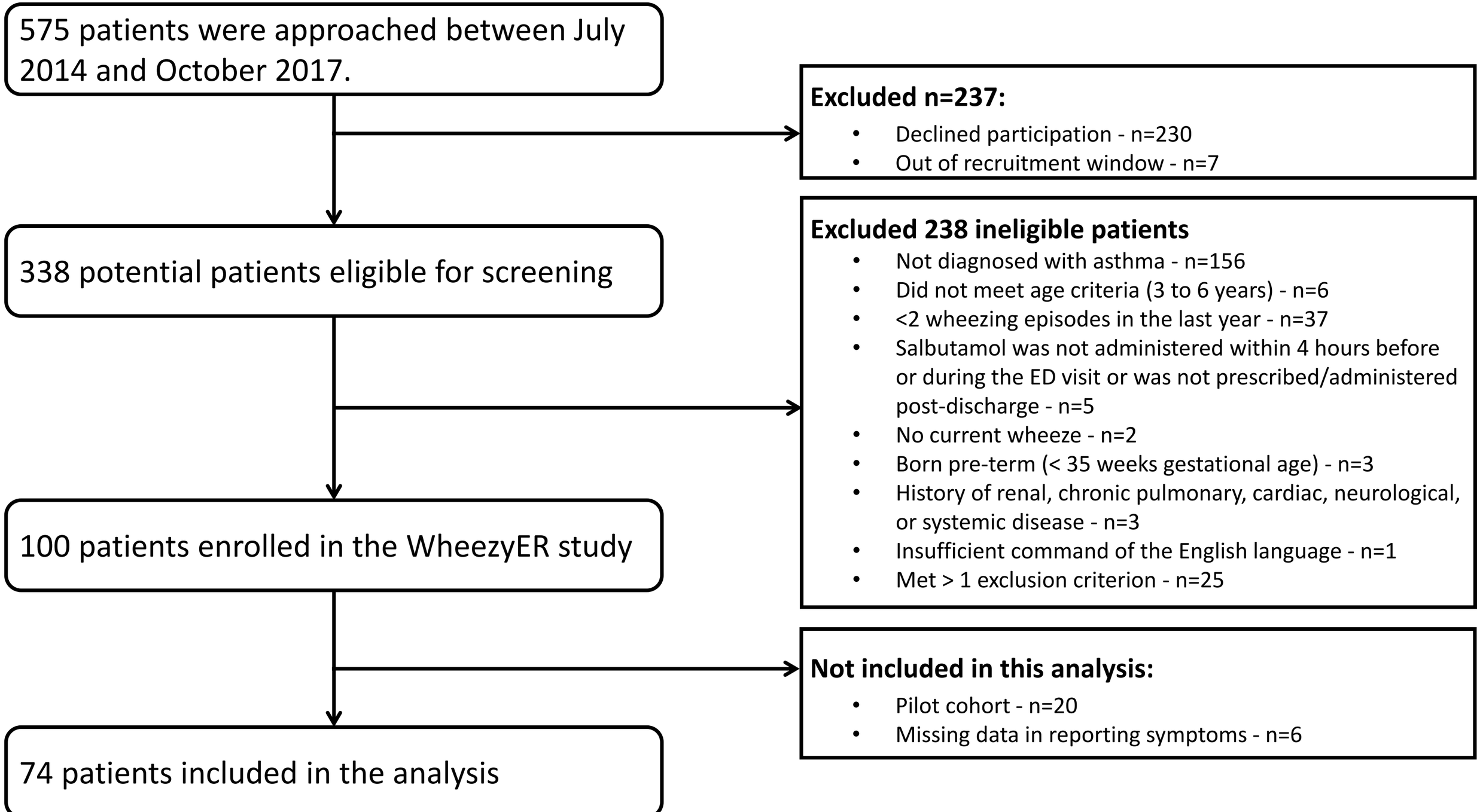
Figure Legends

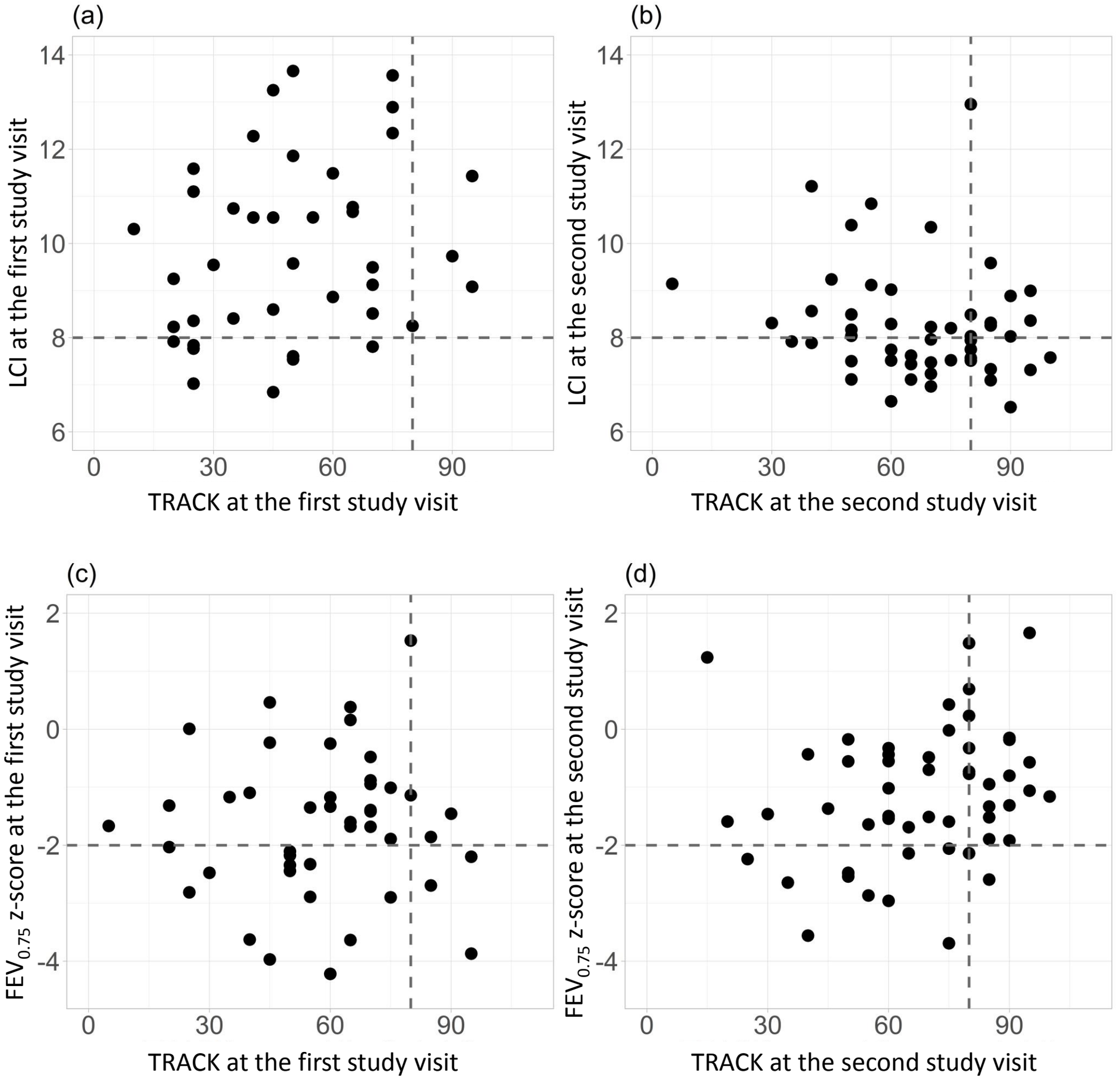
Figure 1. Consort diagram of patients enrolled in the WheezyER study.

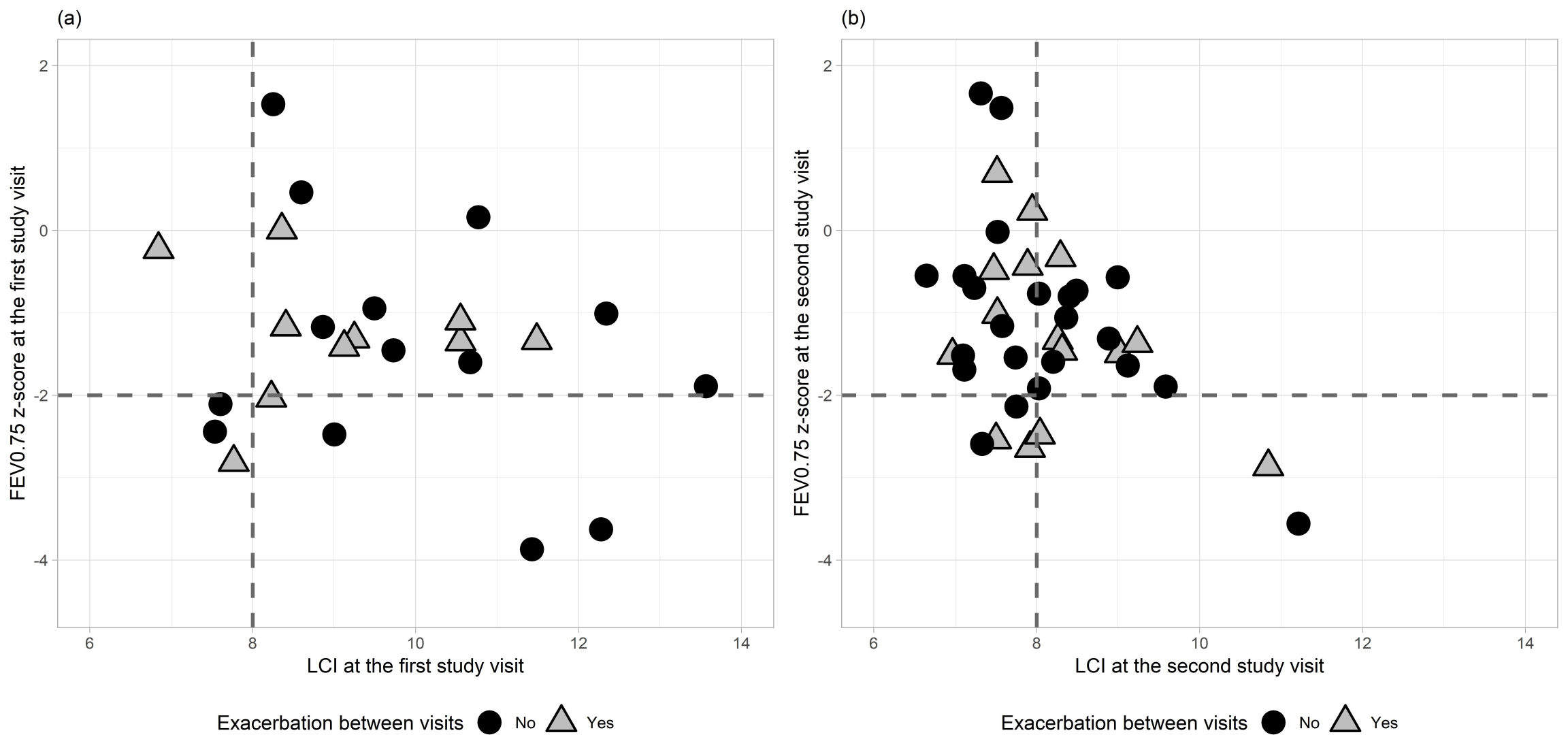
Figure 2. Correlation between lung function outcomes at both visits and symptom scores. Horizontal hatched lines represent the cut offs of abnormal LCI (≥ 8) or abnormal $FEV_{0.75}$ z-score (≤-1.96). Vertical hatched lines represent TRACK scores at 80, with scores ≥ 80 indicative of controlled symptoms: (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.

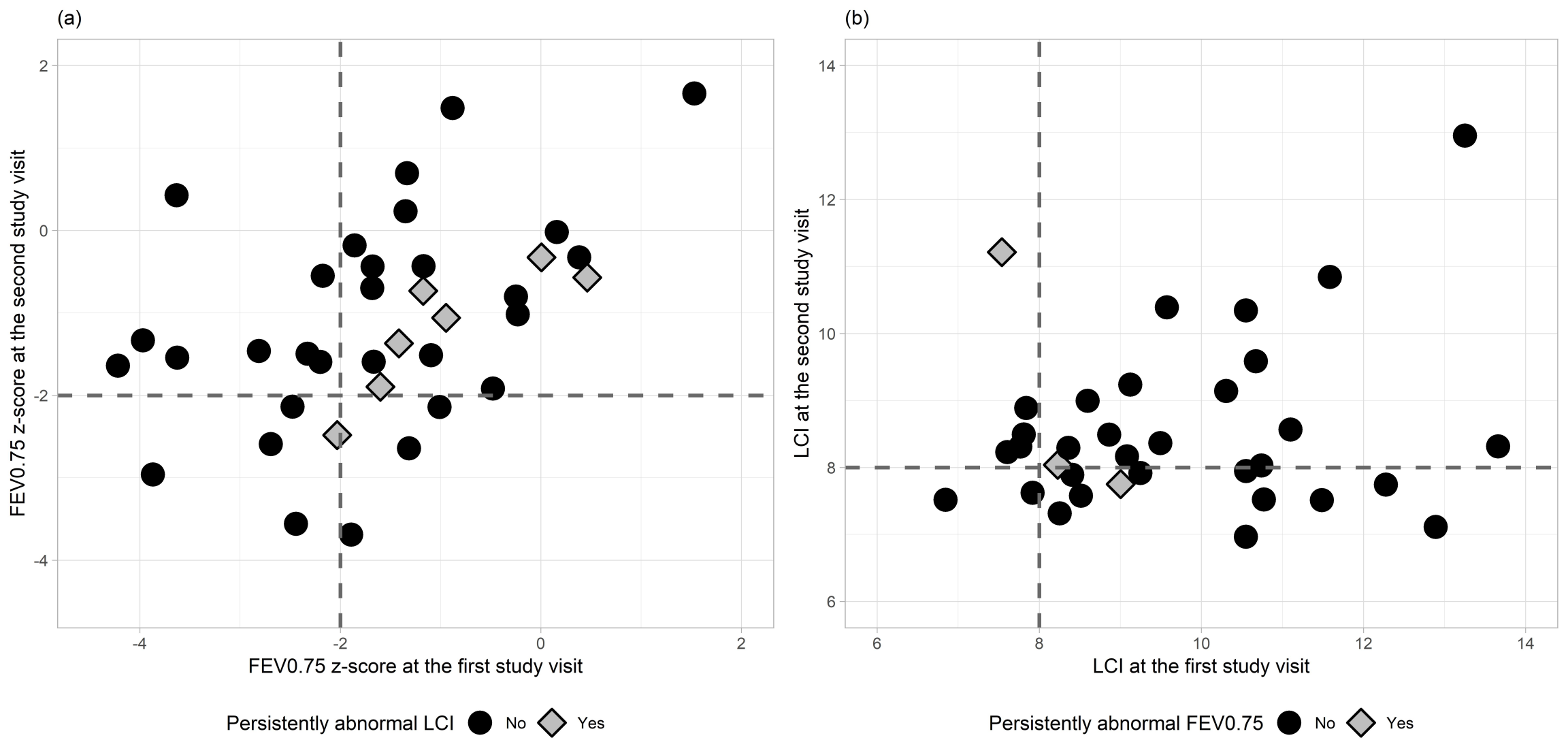
Figure 3. Correlation between: (a) LCI and $FEV_{0.75}$ z-score at the first study visit within 5 days of ED presentation, and (b) LCI and $FEV_{0.75}$ z-score the second study visit.

Figure 4.- Paired longitudinal measures (LCI and $FEV_{0.75}$ z-score) at visit 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 cut offs of abnormal LCI (≥ 8) and horizontal lines are abnormal $FEV_{0.75}$ z-score (≤-1.96).


575 patients were approached between July 2014 and October 2017.
Excluded n=237:
Declined participation - n=230
Out of recruitment window - n=7
338 potential patients eligible for screening
Excluded 238 ineligible patients
Not diagnosed with asthma - n=156
Did not meet age criteria (3 to 6 years) - n=6
<2 wheezing episodes in the last year - n=37
Salbutamol was not administered within 4 hours before or during the ED visit or was not prescribed/administered post-discharge - n=5
No current wheeze - n=2
Born pre-term (< 35 weeks gestational age) - n=3
History of renal, chronic pulmonary, cardiac, neurological, or systemic disease - n=3
Insufficient command of the English language - n=1
Met > 1 exclusion criterion - n=25
100 patients enrolled in the WheezyER study
Not included in this analysis:
Pilot cohort - n=20
Missing data in reporting symptoms - n=6
74 patients included in the analysis


(a)
(b)
(c)
(d)
LCI at the first study visit
LCI at the second study visit
FEV0.75 z-score at the first study visit
FEV0.75 z-score at the second study visit
TRACK at the first study visit
TRACK at the second study visit
14
12
10
8
6
2
0
-2
-4
0
30
60
90


(a)
(b)
FEV0.75 z-score at the first study visit
FEV0.75 z-score at the second study visit
LCI at the first study visit
LCI at the second study visit
2
0
-2
-4
6
8
10
12
14
Exacerbation between visits
No
Yes


(a)
FEV0.75 z-score at the second study visit
2
0
-2
-4
-4
-2
0
2
FEV0.75 z-score at the first study visit
Persistently abnormal LCI
No
Yes
(b)
LCI at the second study visit
14
12
10
8
6
6
8
10
12
14
LCI at the first study visit
Persistently abnormal FEV0.75
No
Yes