Lung Function in Preschool Children in Low and Middle Income Countries: An Under-Represented Potential Tool to Strengthen Child Health

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Background: The burden of respiratory disease is high in low-middle income countries (LMIC). Pulmonary function tests are useful as an objective measure of lung health and to track progression. Spirometry is the commonest test, but its use is limited in preschool children. Other lung function methods have been developed but their use in LMIC has not been well described.

Aim: To review the use of preschool lung function testing in children in LMIC, with particular reference to feasibility and clinical applications.

Methods: Electronic databases “PubMed”, “Scopus”, “Web of Science”, and “EBSCO host” were searched for publications in low and middle income countries on preschool lung function testing, including spirometry, fractional exhaled nitric oxide (FeNO), oscillometry, interrupter technique, tidal breathing and multiple breath washout (MBW), from 1 January 2011 to 31 January 2022. Papers in English were included and those including only children ≥6 years were excluded.

Result: A total of 61 papers from LMIC in Asia, South America, Africa, Eurasia or the Middle East were included. Of these, 40 included spirometry, 7 FeNO, 15 oscillometry, 2 interrupter technique, and 2 tidal breathing. The papers covered test feasibility (19/61), clinical application (46/61) or epidemiological studies (13/61). Lung function testing was successful in preschool children from LMIC. Spirometry was the most technically demanding and success gradually increased with age.

Conclusion: Preschool lung function testing is under-represented in LMIC for the burden of respiratory disease. These tests have the potential to strengthen respiratory care in LMIC, however access needs to be improved.

Keywords: spirometry, fractional exhaled nitric oxide, oscillometry, interrupter technique, tidal breathing, multiple breath washout

INTRODUCTION

Childhood respiratory disease is a common cause of morbidity and mortality globally (1). The burden of acute and chronic respiratory disease is especially high in low-middle income countries (LMIC) (2), may result in impaired lung function and set a trajectory for chronic illness into adulthood (3, 4). However, access to respiratory diagnostic and management tools such as lung function are limited in many LMIC (5).
Lung function attained in early life is important for respiratory health, with low lung function associated with subsequent risk of respiratory disease (6). Pulmonary function tests are an objective measure of lung health which can be used to diagnose and track lung disease and assess response to treatment. In recent years non-invasive tests have been developed and guidelines produced for preschool children, facilitating its use in assessing respiratory health in early life (7, 8).

Lung function tests used in preschool children include spirometry, bronchial response testing, multiple breath washout (MBW), fractional exhaled nitric oxide (FeNO), oscillometry and other tests which measure resistance, including the interrupter technique (Rint), and plethysmography. With increased recognition of the importance of maximizing early life respiratory health and the growing availability of tools to do so, their use in LMIC is of particular interest.

Of the preschool lung function tests, spirometry is the most commonly used and most widely available. Even though use is limited in very young or uncooperative children, it is feasible in children as young as 3 years (9). Spirometry measures lung volumes at maximal expiration and is able to assess airflow obstruction, response to bronchodilator therapy and lung volumes on forced expiration. The commonly reported measures are the forced expiratory volume in the first second (FEV₁), forced vital capacity (FVC), FEV₁/FVC and forced expiratory flow between 25 and 75% of FVC (FEF₂₅₋₇₅). (10). Spirometry predominantly reflects airflow in large and medium sized airways, and is a poor measure of peripheral small airways or early lung disease (11). Current international recommendations for spirometry collection and interpretation in young children are available (10, 12).

Oscillometry (or the forced oscillation technique, FOT) is a simple, non-invasive technique which is performed during tidal breathing. Minimal co-operation is required thereby making this a popular measurement in preschool children. This measures the impedance of the respiratory system, which includes resistance and reactance across a range of frequencies reflecting the entire respiratory system including the small airways (13). The novel intra-breath measurement may be a more sensitive measure of small airway disease, thus allowing early detection of disease (14, 15). Recent international recommendations for oscillometry have been published on methodology, technical standards and future developments for use in children (7, 16, 17).

The interrupter technique measures the resistance of the respiratory system requiring minimal cooperation. The technique involves a sudden interruption of flow during tidal breathing, this allows for alveolar and pressure at the mouth to equilibrate therefore alveolar pressure can be estimated (18, 19). Different methods have been used to perform the test making the comparison of results difficult thus highlighting the need for test standardization. Furthermore, research is still required to determine the best algorithm to calculate pressure at the mouth during occlusion and the cut-off value for Rint post bronchodilator needs to be established (7).

Multiple breath washout (MBW) is used to assess ventilation homogeneity. It measures the functional residual capacity (FRC) and the lung clearance index (LCI) in preschool children (8). It is more sensitive than spirometry for the detection of peripheral airway disease and has been successfully used in the monitoring of children with cystic fibrosis (CF) and primary ciliary dyskinesia (PCD) (7, 20). It correlates with high resolution CT scan in CF patients as well as in children with asthma, bronchiolitis obliterans or chronic lung disease of prematurity (8, 21).

Fractional exhaled nitric oxide (FeNO) is a non-invasive marker of T-helper cell type 2 (TH2), eosinophilic airway inflammation. Tests can be performed with high repeatability and accuracy (22–24). Its main use is an adjunct to the diagnosis of TH2 type asthma and guiding the use of inhaled corticosteroid (ICS) treatment. In addition, FeNO can also assist in the differential diagnosis of other conditions such as cystic fibrosis (CF), PCD, scleroderma, obstructive sleep apnoea syndrome and hepatopulmonary syndrome. Fractional exhaled nitric oxide levels are low in PCD; however measurement of nasal NO improves the diagnostic accuracy and is a useful screening tool for PCD (23, 25). Normal values for FeNO are published for children from 4 years of age (24), as well as international applications and the use of FeNO (23, 24, 26). However, there are limited data on the use and feasibility of such measures in LMIC, despite the high burden of lung disease and need for objective tools to diagnose and monitor these.

We aimed to review the use of preschool lung function testing in children in LMIC, with reference to feasibility and clinical applications, to identify opportunities for optimizing diagnosis and management of childhood respiratory disease in these settings.

METHODS

We reviewed published literature of preschool lung function testing in LMIC, which included children between the ages of 3 to 5 years. We included published papers from 1 January 2011 to 31 January 2022 that included lung function testing in the preschool age group from a World Bank defined LMIC.

The search was conducted on the following electronic databases: PubMed, Scopus, EBSCOhost (Cinahl, Africa wide information, Health source- Nursing/Academic Edition), and Web of Science including the search terms: Respiratory Function Test† OR “Lung function test”† OR “pulmonary function test”† OR “respiratory function test”† OR “multiple-breath washout” OR “Forced oscillation technique” OR tidal breathing” OR “fractional excretion of nitric oxide” OR Spirometry OR Oscillometry OR “impulse oscillometry” OR “interrupter technique” OR “interrupter resistance” AND “preschool child”†. Full search strategy can be seen in Supplementary Table S1. Reviews, editorials, case reports and conference proceedings were excluded. Any papers including only children ≥ 6 years were excluded. Abstracts of identified documents were reviewed and screened by SC, with second author DG assisting with inclusion queries. All included papers were reviewed by SC.

RESULTS

A total of 626 papers were screened of which 61 were eligible for inclusion, Supplementary Figure S1. They included papers from
Spirometry

The majority (40, 68%) of papers included spirometry, (Table 1). Spirometry was used to develop reference equations, diagnose and manage respiratory diseases including asthma or CF; assess the impact of air pollution, electronic exposures (e-exposures) or socioeconomic status on lung function. Twenty (50%) studies were from Asia, 9 (22.5%) from South America, 7 (17.5%) from Africa and 4 (10%) from Europe and the Middle East.

Success rates for spirometry in preschool children increased with age (29). Children between 4–6 years of age achieved a success rate between 82–85%, (30–32), while children between 3–5 years and 3–6 years of age, success rates were 68.4% and 42% respectively (29, 33).

A number of reference ranges were generated for individual population groups in LMIC, which were compared to either local reference ranges and/or The Global Lung Function Initiative (GLI) 2012 equation (32–39). Many resulted in an over estimation/underestimation of lung function for the population assessed, highlighting the complexity of population differences in lung function. A Nigerian study determined reference equations for children with sickle cell anemia (40). Published international equations also used arm span to determine height for spirometry (41). The GLI 2012 “Caucasian” provided a reasonable fit for Jordanian children (29). When assessing spirometry in two groups of healthy children with Indian ancestry, one living in UK and the other in India, the GLI equations for best fit differed: the “GLI-Black” equation was most useful for interpreting the South-Asian data and “GLI-Other” for North Indian data (42). Similarly in a South Africa population the GLI 2012 “GLI-Caucasian” provided a good fit for the Caucasian population, “GLI-Black “ and “GLI-Southeast Asian” was a good fit for the Indian population and “GLI-Other” fit the Black African and Mixed ancestry populations well (43). These findings highlight the importance of multiple factors, including environment and socioeconomic exposures that impact population differences (42, 43).

Numerous environmental factors were reported to impact on lung function. Children living in rural areas or exposed to poorer socio-economic circumstances had lower lung function compared to those in urban areas (42, 44). Exposures to volatile organic compounds, particulate matter 10 (PM_{10}) or carbon monoxide (CO) were associated with a decrease in FEV\(_1\) and FVC in exposed preschool children (45–47).

In a study in Guatemala, where CO was used as a proxy for PM\(_{2.5}\), timing of chimney stove installation was compared to cooking over open fires, and showed a decrease in PEF of 173 ml/min/year (95% CI −341 to −7), with chimney stove installation at 18 months compared to installation at birth (48). A Chinese study failed to demonstrate any significant association between PM\(_{2.5}\) exposure and any of the spirometry lung function measures, however an increase in oscillometry resistance was noted suggesting that oscillometry may be a more sensitive measure (49). In addition to air pollution, e-waste is a growing concern. Chinese children living in e-waste exposed areas had significantly lower birth weight, chest circumference and spirometry lung function compared to those in unexposed areas (27, 28).

The majority of included papers used spirometry in the clinical diagnosis and management of pediatric obstructive lung disease including asthma and CF. The studies investigated genetic predisposition to asthma, and management of acute, poorly controlled and cough-variant asthma (CVA), and the impact of obesity (50–53). Genes associated with increased susceptibility to asthma and lower spirometry indices were identified in Chinese and Egyptian children (54, 55). One study assessed current definitions of BDR, suggesting that a BDR of >7.5% may be more valuable in young children rather than the adult defined 12% (56).

Another study included assessing impact of ABPA on spirometry of asthmatic children (57). In a Chinese study acute asthma did not respond to adding montelukast to the regular regimen (58), however it was noted that in children with CVA, cough associated with chronic airway allergic inflammation without wheeze, had a significant improvement in FEV\(_1\), FVC, and PEF (p < 0.001). with montelukast and budesonide compared to budesonide alone, while another study noted that FEV\(_1\)/FVC was normal in CVA compared to patients with asthma (p < 0.001) (51, 52).

Spirometry was also used in South American, Turkish and South African children to monitor lung function in cystic fibrosis (59), and showed good correlation between CT scan Bhalla score and FEV\(_1\), FVC, FEF\(_{25–75}\) (60).

Fractional Exhaled Nitric Oxide

Of the 7 papers using FeNO, 4 (57%) clinical studies measured FeNO to assess risk and treatment response of asthma or recurrent wheeze; and 3 epidemiological studies assessed the impact of IAP on airway inflammation in children. These included studies mainly from Asia (5 from China, 1 from Thailand) and 1 from Ecuador, South America. There were no
TABLE 1 | Details of included studies using spirometry (n = 40).

| Authors, Year | Country | Age | No. of patients | Study type | Theme | Main finding |
|---------------|---------|-----|----------------|------------|-------|--------------|
| Zhu et al. (63) | China | 5–12yr; little group-divided into groups 5–7 years | 121 | asthma, allergic rhinitis | Spirometry was used to assess factors associated with FeNO. A greater peak expiratory flow in addition to a greater age, height/weight and level of total IgE are related to higher FeNO levels |
| He et al. (49) | China | 5–13 years | 43 | air pollution | No significant associations were noted between personal PM2.5 exposure and spirometry. |
| Kang et al. (56) | China | 4–12 years | 286-asthma, 301-control | asthma | A BDR threshold of ≥ 7.5% may be more valuable compared to ≥ 12% in childhood asthma |
| Leung et al. (55) | China | 2–7 years | 1341 | asthma | The minor allele SNP (rs408223) of CDHR3 was associated with lower FEV0.5 (β = −2.411, P = 0.004), and FEV0.5/FVC (β = −1.292, P = 0.015) |
| Sun et al. (52) | China | 3–10 years | 112 | experimental study asthma | Pulmonary function indices (FVC, FEV1 and PEF), were significantly higher (p < 0.001), in the observational group (treated with montelukast and budesonide), than the control group (budesonide alone). Treating cough variant asthma with montelukast combined with budesonide is more effective than budesonide alone. |
| Wang et al. (58) | China | 2–5 years | 120 | randomized, double-blind placebo-controlled trial | Treating acute asthma exacerbation with montelukast compared to placebo demonstrated no significant difference in the PEF and FEV1. |
| Zeng et al. (28) | China | 5–7 years | 206 | e-waste exposure | Taken together, birth weight and chest circumference may be good predictors for lung function levels in preschool children |
| Zeng et al. (27) | China | 5–7 years | 206 | e-waste exposure | Children living in the exposed area have lower lung function (FVC and FEV1). Levels compared to unexposed children. Haemoglobin levels may be a good predictor for lung function- one unit of haemoglobin (1 g/L). Decline was associated with 5 mL decrease in FVC and 4 mL decrease in FEV1. |
| Jian et al. (35) | China | 4–80 years | 7115 | cross-sectional study | This study established new reference values for the Chinese population 4 to 80 years. The “South East Asian” and “North East Asian” GLI reference equations under or overestimated the FEV1, FVC, and FEV1/FVC. Local Chinese equations underestimated FVC and FEV1. |
| Sonnappa et al. (44) | India and UK | 5–12 years | 1039 | prospective cross-sectional study | Spirometry differences were assessed between children from urban, semiurban, and rural schools. There were significant reductions in FEV1 and FVC in Indian-semiurban and Indian-rural children when compared with Indian-urban children. |
| Kumar et al. (57) | India | 5–15 years | 106 | cross-sectional asthma, ABPA | Percentage predicted values of FEV1 and FEF25–75 were lower in asthmatic children with allergic bronchopulmonary aspergillosis (ABPA). Compared to no ABPA, but this did not reach statistical significance. PEF that was significantly higher in children with aspergillus sensitization (AS). Compared to those without AS (P = 0.046). |
| Kumar et al. (50) | India | 5–18 years | 620 | cross-sectional asthma, obesity | Obese children with asthma (Group 1). Had significantly lower lung function compared to non-obese asthmatic children (Group 2). FEV1, |

(Continued)
| Authors, Year       | Country        | Age                      | No. of patients | Study type          | Theme                          | Main finding                                                                                                                                                                                                 |
|---------------------|----------------|--------------------------|-----------------|---------------------|--------------------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Gulla et al. (92)   | India          | 138–120 months          | 46              | retrospective control study | cystic fibrosis               | Children with viral infection (Group I). Had adverse outcome in form of greater worsening of Shwachman clinical scores, number of pulmonary exacerbations requiring antibiotic usage, need for intravenous antibiotics, hospitalization rates and mortality. Spirometry decreased in both groups but was not significant. |
| Bolla et al. (37)   | India          | 5–15 years              | 790             | cross-sectional study | reference equation             | Separate equations in males and females were generated with age, weight and height as predictors. No comparison to other reference equations were made.                                                                 |
| Lum et al. (42)     | India and UK   | 5–17 years              | 8124            | observational       | reference equation             | “GLI-Black” equations were most useful for interpreting South-Asian data and “GLI-Other” for North Indian data. When using GLI-predicted values from White Europeans, FEV₁ and FVC in South-Asian children were approximately 15% lower. There was an association between socio-economic circumstances (SEC), and lung function. Lung volumes were significantly lower in those living in rural areas or exposed to poorer SEC. |
| Asrul et al. (45)   | Malaysia       | 5 and 6 years           | 120             | cross-sectional comparative study | air pollution                 | There was a significant difference in indoor air quality between urban and suburban preschools. FVC and FEV₁ among urban children were significantly lower compared to the suburban children. Exposures to indoor air pollutants, especially PM₁₀ and PM₃.₅ increases the risk of getting lung function abnormalities. |
| Choo et al. (46)    | Malaysia       | 4–6 years               | 630             | cross-sectional comparative study | air pollution                 | Urban area preschools have higher CO, PM₁₀ and PM₃.₅ concentration compared to from suburban and rural areas. FVC, FEV₁, FVC% predicted and FEV₁% predicted values were significantly lower among children from urban and suburban area preschools compared to rural preschools. |
| Kamaruddin et al.   | Malaysia       | 5–6 years               | 100             | cross-sectional comparative study | air pollution                 | Significant associations between PM₁₀ and VOCs with FEV₁ % were noted (PR = 5.55, 95% CI = 2.189–14.07), (PR = 6.15, 95% CI = 2.565–14.73), respectively in exposed compared to unexposed children. |
| Rawi et al. (47)    | Malaysia       | 5–6 years               | 11              | cross sectional study | air pollution                 | Studied preschools had a significantly higher PM and CO concentration compared to the comparative preschools. FVC, FEV₁, FVC% and FEV₁% predicted values were significantly lower among children from urban and suburban area preschools compared to rural preschools. |
| Asif et al. (39)    | Pakistan       | 5–14 years              | 3275            | cross-sectional study | reference equation             | Reference range equations were developed with predictors that included age, height, and weight. Separate equations for males and females were generated. No comparisons made to other studies. |
| Ventura et al. (59) | Brazil         | 1–15 years (median age 3.75 years) | 38 with CF,51 control | longitudinal study | cystic fibrosis               | Pasclerotic participants with higher C-reactive protein/albumin ratio at the baseline had higher odds of FEV₁ ≤ 70% after three years of follow-up. |

(Continued)
| Authors, Year | Country          | Age Description            | No. of patients | Study Type                | Theme                  | Main Finding                                                                                                                                                                                                 |
|---------------|------------------|-----------------------------|----------------|---------------------------|------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Veras et al.  | Brazil           | 6 years and younger         | 74             | Cross-sectional descriptive | feasibility           | The spirometry success rate was 82%. Performance improved with age.                                                                                                                                     |
| França et al. | Brazil           | 4–6 years                   | 195            | Reference equation         |                        | Reference range generated using height as a predictor. One equation for males and females. No comparison to GLI 2012                                                                                       |
| Jones et al.  | Brazil           | 3–12 years                  | 1990           | Cross-sectional observational study | Reference equation     | Equation generated significantly from those currently in use in Brazil-Underestimate FVC and FEV1 values.                                                                                                 |
| Burity et al. | Brazil           | 3–6 years                   | 425            | Prospective study          | Reference equation     | Full expiratory curves are more difficult to obtain in preschool children. In addition to height, gender also influenced the measures of FVC and FEV1                                                   |
| Matos et al.  | Brazil           | 4–12 years                  | 1129           | Cross-sectional study      | Asthma                 | Overweight children have less respiratory capacity, and was associated with lower FEV1/FVC ratios (PR = 1.37; 95% CI 1.14, 1.64)                          |
| França et al. | Brazil           | 4–6 years                   | 47             | Reference equation         | Asthma                 | 83% success rate for performing spirometry                                                                                                                                                            |
| Ardura-Garcia et al. (64) | Ecuador | 5–15 years                  | 264            | Cohort study               | Asthma                 | Spirometry did not predict asthma recurrence.                                                                                                                                                             |
| Heinzerling et al. (48) | Guatemala | 5–8 years                   | 506            | Prospective cohort study   | Air pollution          | A significant decrease in PEF [173 mL/min/year (95% CI −341 to −7)], and a non-significant decrease in FEV1 growth were observed with later stove installation at 18 months compared with stove installation at birth |
| Bougrida et al. | Algeria         | 5–16 years                  | 208            | Reference equation         |                       | Several predictors in the reference range and these include height, weight, age, gender BSA, BMI. Separate equations for males and females. There were significant differences in FeV1 between the measured and predicted values from published reference equations except for a USA reference equation. |
| Jiffri et al. | Egypt            | 1–15 years                  | 120 asthma, 120 controls | Reference equation         | Asthma                 | There is an association between the TNFA −308G>A polymorphism and susceptibility to asthma. Spirometry used to classify patients into asthma severity namely mild intermittent asthma, mild persistent asthma, moderate persistent asthma, or severe persistent asthma. Preferred proxy for spirometry indices in children with sickle cell anaemia may be arm span. |
| Akodui et al. | Nigeria          | 5–12 years                  | 100            | Cross-sectional study      | Sickle cell anaemia, reference equation | The relationship between smoke exposure and airway obstruction in households that did and did not use firewood daily was not significant (mean FEV1/FEV6 of 0.96 and 0.97, respectively; P = 0.41). There was a significant decline in predicted FEV1 with age (p < 0.001) |
| Thacher et al. | Nigeria          | 5–11 years                  | 299            | Cross-sectional study      | Asthma, air pollution  | There were significant correlations between PEF and manual dexterity and between FVC % predicted and balance scores Poorer lung function may affect motor development.                                                    |
| Corten et al. | South Africa     | 5–8 years                   | 12             | Cross-sectional study      | Cystic fibrosis        | GLI2012 “Other” had the best fit for Black African individuals and Mixed Ethnicity group when using z-scores. The Caucasian individuals demonstrated a good fit with the GLI2012 “Caucasian” equation and participants of Asian ancestry demonstrated a good fit to the “Southeast Asian” and “Black” equation. |
| Smith et al.  | South Africa     | 5–95 years                  | 4223           | Cross-sectional population-based study | Reference equation | The mean FEV1/FVC ratio for all the patients combined was Significantly higher than predicted for age, gender, ethnicity, and BMI                                                                             |
| Sibanda et al. | Zimbabwe         | 1–94 years                  | 240 (49 between 1-16 years of age) | Observational study       | Systemic sclerosis     |                                                                                                                                                                                                             |
TABLE 1 | Continued

| Authors, Year | Country | Age       | No. of patients | Study type | Theme            | Main finding                                                                 |
|---------------|---------|-----------|----------------|------------|------------------|-----------------------------------------------------------------------------|
| Ghasempour, M. et al. (51) | Iran    | 5–15 years | 73             | description-observation | asthma | suggesting a restrictive pattern. The severity of the restrictive changes varied with the types of autoantibodies detected. The average FEV1/FVC parameter in the cough variant asthma group was 89.44 ± 13.07, and 72.38 ± 8.47 in the classic asthma group, with a significant difference between the two groups (p < 0.05). Patients with cough variant asthma FEV25–75% were lower than expected. Spirometry can be used in the diagnosis of cough variant asthma. |
| Tabatabaie et al. (36) | Iran    | 4–10 years | 495            | reference equation   | Reference range equations were generated for both males and females using height and age as predictors. When compared to previous published international equations significant differences were noted. |
| Al-Qerem et al. (29) | Jordan  | 3–5 years  | 765            | random sampling     | reference equation   | The GLI 2012 for Caucasians is a reasonable fit for Jordanian preschool aged children. |
| Sasihuseynoglu et al. (61) | Turkey  | mean age 7.83 years | 80             | retrospective study  | cystic fibrosis | There were significant correlations between the Bhalia score and FEV1, FVC, and FEF25–75%. |

PR, Prevalence Ratio; CI : Confidence Interval; PM, particulate matter; PM2.5, particulate matter 2.5; PM10, particulate matter 10; PEF, peak expiratory flow; SNP, single-nucleotide polymorphism; FEV0.5, forced expiratory volume in 0.5-second; FVC, forced vital capacity.

published preschool studies from Africa. Included studies are summarized in Table 2.

The success rate for performing FeNO in preschool children ranged between 86–99%. Thai children living in a metropolitan area attending day care, average age of 50.1 months (range 29–72 months), achieved a success rate between 86–93% with data collected over 3 time points (61). A cohort of 507 Chinese children aged 5 years achieved a success rate of 99% (62). Over half of studies (57%) used a Niox Mino analyzer (Aerocrine, Solna, Sweden), to measure FeNO using the single breath technique. Most studies used the recommended normal standards (26). No studies have explored population differences in FeNO.

All 3 studies assessing impact of air quality on respiratory health found that environmental pollution, including benzene and PM2.5, were associated with high FeNO (49, 61, 62).

Studies from China and one from South America, used FeNO measurement in the management of preschool asthma (63–65), noting the strong association with IgE mediated inflammation and ICS efficacy (63). However, it was also suggested that FeNO may be less useful in the preschool age group for detecting ICS response, as the mean FeNO level was significantly higher only in the “older” age group than the cut off values reported in other studies for the diagnosis of asthma (63). FeNO was not able to predict recurrence (64).

**Oscillometry and Interrupter Technique**

Oscillometry has been successfully used in LMIC to assess the impact of early life exposures and for clinical management of children with respiratory disease. These include: 6 studies from Asia, 6 from South America, 2 from West Africa and 1 from the Middle East summarized in Table 2. The studies used a range of commercially available equipment including both impulse oscillometry (IOS). and airwave oscillometry (AOS).

Oscillometry has proven to be effective in assessing the impact of early life exposures on preschool lung function (49, 66). An increase in household PM2.5 exposure increased airway reactivity in Nigerian children, similarly high personal exposure to PM2.5 was associated with an increase in small airway resistance (R5–20), total airway resistance (R5), and resistance frequency dependence (R5–20), representing small airway disease, in asthmatic Chinese children living outside Shanghai (49, 66).

In a Ghanaian longitudinal cohort, infants exposed to a less diverse nasopharyngeal microbiome had a higher small airway resistance compared to a more diverse microbiome at 4 years of age (67). Further, in a Mexican birth cohort study, prenatal omega 3 fatty acid supplementation in pregnancy did not influence preschool lung function at 36, 48 or 60 months (68).

Oscillometry was easily performed by preschool children with the overall success rate ranging between 74–98% in studies making it a particularly attractive option (69–73). As a clinical tool oscillometry for preschool children is supported by studies that are able to detect differences in prebronchodilator lung function of preschool children with respiratory symptoms compared to those without respiratory symptoms (74).

Reference data for Mexican, Thai, Turkish and Colombian children have been collected (70–72, 75–77), facilitating the use in diagnosis of respiratory disease. It is also a useful tool to assess airway reversibility in asthmatic children and cut off values for bronchodilator response were proposed (69, 73). A Chinese study in children with obstructive sleep apnea hypopnea syndrome (OSAHS) demonstrated an increase in total airway resistance in children with...
TABLE 2 | Detail of included studies that assessed fractional exhaled nitric oxide (n = 7), oscillometry (n = 15), interrupter technique (n = 2), and tidal breathing (n = 2).

| Authors, Year | Country | Age | No. of patients | Study type | Theme | Main finding |
|---------------|---------|-----|----------------|------------|-------|-------------|
| **Fractional exhaled nitric oxide** | | | | | | |
| Zhang et.al (62) | China | 5 years | 507 | cross-sectional study | air pollution | Indoor and outdoor PM2.5 levels in day care centres were associated with higher levels of FeNO. FeNO levels were also associated with current wheeze and physician diagnosed pneumonia. |
| Han et.al (65) | China | 4–11 years (4–6 and 7–11 years) | 142 | cross-sectional descriptive study | asthma | Family management (FM), describes how family members cooperate and integrate the management of childhood chronic disease into their daily family life. FM was closely related to asthma control and could significantly predict FeNO value and C- ACT score. |
| Li et al. (22) | China | 32–48.7 months | 88 | | recurrent wheeze | sRAGE may be a novel biomarker of inflammation of the respiratory tract. There was a significant negative correlation between serum sRAGE and FeNO (p < 0.001). In the high-risk asthma group, sRAGE levels increased significantly while FeNO decreased significantly after Pulmicort therapy |
| Zhu et al. (63) | China | 5–12 yr; little group classified as 5–7 years. | 121 | | asthma, allergic rhinitis | Height and total lgE are well correlated with FeNO in asthmatic children greater age, height/weight, peak expiratory flow (PEF), and higher level of total lgE (p < 0.001) are associated with higher FeNO levels |
| He et al. (49) | China | 5–13 years | 43 | | air pollution | An increase in 24-h personal PM2.5 exposure one day prior to the clinic visit was associated with a significant increase in FeNO (airway inflammation), of 9.6% |
| Siwarom et.al (61) | Thailand | 29–72 months | 436 | randomised control study | air pollution | The mean FeNO levels were statistically different in each season (p < 0.001). FENO levels had a strong association with high benzene levels (OR 5.9, 95%CI 1.5–22.9; p-value = 0.01). |
| Ardura-Garcia, C.et al. (64) | Ecuador | 5–15 years | 264 | cohort study | asthma | FeNO level did not predict asthma recurrence. |
| **Oscillometry** | | | | | | |
| Zhang et.al (78) | China | 3–14 years | 120 | retrospective study | upper airway obstruction | R2 in the OSAHS group was significantly higher than that in the non-OSAHS group (p = 0.0025) |
| He et al. (49) | China | 5–13 years | 43 | | air pollution | An increase in 24-h personal PM2.5 exposure one day prior to the clinic visits was associated with a significant increase in total airway resistance (R2) of 6.3%, small airway resistance (R8–R20) of 15.8% |
| Li et al. (82) | China | <14 years | 42 | case review | bronchiolitis obliterans | In children with bronchiolitis obliterans impulse oscillometry showed an increase in Z4 (147.5 ± 19.3% of the predicted value, normal: less than 120% of the predicted value), R4 (140.4 ± 12.8% of the predicted value, normal: less than 120% of the predicted value), and X4 (226.5 ± 13.4% of the predicted value, normal: less than 120% of the predicted value). This suggested increasing peripheral airway resistance. |
| Udomittipong et al. (70) | Thailand | 3–7 years | 291 | cross-sectional study | reference equation | Reference values for respiratory impedance using FOT were generated using height and arm span were generated. |
| Udomittipong et al. (73) | Thailand | 3–6 years | 150 | | asthma | Cut-off values for evaluating bronchodilator response in FOT were determined: Rrs6: −23%, Rrs8: −20%, Rrs10: −20%, Xrs6: 36%, Xrs8: 60%, and Xrs10: 43%. |

(Continued)
### TABLE 2 | Continued

| Authors, Year | Country            | Age                  | No. of patients | Study type                     | Theme                      | Main finding                                                                 |
|---------------|--------------------|----------------------|-----------------|--------------------------------|----------------------------|------------------------------------------------------------------------------|
| Gupta et al. (69) | North India       | 2–18 years           | 345             | prospective intervention study | asthma                     | Oscillometry is a useful tool to assess lung function and airway reversibility in asthmatic children. It can provide an objective measurement in children unable to perform spirometry. |
| Medeiros et al. (74) | Brazil           | 3–6 years            | 76              | cross-sectional study          | respiratory symptoms      | IOS in children with respiratory symptoms were higher pre-bronchodilator for R5 Hz and R5–20 Hz compared to those children without respiratory symptoms. |
| Duenas-Meza et al. (77) | Colombia        | 3–5 years            | 96              | cross-sectional study          | reference equation        | Normal IOS reference range equations were determined, and height was the only predictor. A fall in R5 Hz of 28% or an increase in X2 Hz of 36% postbronchodilator can be considered as an upper limit of normal. |
| Gutiérrez-Delgado et al. (69) | Mexico      | birth cohort until 5 years | 772             | double-blind, randomized, placebo-controlled study | Intervention with DHA | Prenatal DHA supplementation did not influence IOS values with respect to resistance and reactance at 6, 8, and 10 Hz. |
| Gochicoa-Rangel et al. (71) | Mexico       | 2.7–15.4 years       | 280             | reference equation             | reference equation        | Reference range equations were derived for impulse oscillometry. Predictors include age and height. Marked differences were noted between the derived reference equation when compared to other studies. Separate reference ranges for male and females were generated. |
| Gochicoa-Rangel et al. (75) | Mexico       | 4–15 years(mean age 8.6) | 224             | cross-sectional study          | reference equation        | Due to the robust adjustment of the equation derived from Gochicoa-Rangel et al. (71) this equation has been recommended for clinical and research purposes in a Mexican population. |
| Shackleton et al. (72) | Mexico       | 3–5.2 years          | 584             | double-blind, randomized, placebo-controlled clinical trial | reference equation        | Reference ranges for FOT were generated for Mexican children. Height was the only predictive factor and the same equation for males and females was used. An Australian reference range equation overestimate lung function in Mexican children. |
| Dubowski et al. (67) | Ghana         | 4 years              | 112             | prospective study              | infection exposure        | Infants exposed to a less diverse NPM (nasopharyngeal microbiota) had a higher small airway resistance (R5–R20 = 17.9%, 95% CI 35.6, 0.23; p = 0.047). Compared to a more diverse phenotype |
| Dutta et al. (66) | Nigeria        | 2 years (mean age 2.9 years) | 223             | randomised control trial       | air pollution              | Increase in postnatal household air pollution (PM2.5), were significantly associated with higher airway reactance at 5 Hz (X5 Hz; P= 0.04) |
| Er et al. (76) | Turkey         | 3–7 years            | 151             | reference equation             | Reference equation        | Reference values for IOS in healthy Turkish children were determined. Resistance was significantly correlated with height and reactance was significantly correlated with age (p < 0.05–). Separate equations were derived for males and females. |
| **Interrupter technique** |                |                      |                 |                                |                            |                                                                                              |
| Rocha et al. (79) | Brazil         | 5 to 18 years (mean 10.79 years) | 38              | cross-sectional study          | cystic fibrosis            | Interrupter resistance (Rint), correlates well with spirometry. There was a strong correlation between inverse Rint and FEV1 (r = 0.8; p < 0.001), and moderate correlation between inverse Rint and FEF25–75% (r = 0.74; p < 0.001). Rint was not accurate in evaluating bronchodilator response. |

(Continued)
OSAHS compared to children with snoring but without OSAHS (78).

The interrupter technique was used in 2 South American studies, one of which looked at the development of reference values for newborn, infants and preschool children, while the other measured Rint in children with cystic fibrosis and found that Rint correlated well to spirometry FeV1 and FEF25–75, but not accurate in determining bronchodilator response (79, 80).

Tidal Breathing

Tidal breathing was used in 2 studies, one an Indian birth cohort and the other a Chinese retrospective cohort study (81, 82). (Table 2). Tidal breathing measurements were in keeping with an obstructive pattern in patients with bronchiolitis obliterans (82). Indian children who had an acute respiratory tract infection in infancy had increased ratios of tidal expiratory flow (TEF) at 25 or 50% of tidal expiratory volume to peak TEF (TEF50 or TEF25/peak TEF) at 3 years suggesting increased airway resistance (81).

Table 2 | Continued

| Authors, Year | Country  | Age            | No. of patients | Study type               | Theme | Main finding                                                                 |
|---------------|----------|----------------|-----------------|--------------------------|-------|-----------------------------------------------------------------------------|
| Gochicoa et al. (80) | Mexico   | 24 days to 6.6 years | 264             | prospective, cross-sectional descriptive study | reference equation | Reference values for interrupter technique (Rint), was determined in Mexican children. There was an inverse relationship between Rint and height. Females had a higher Rint than males (P = 0.054). |
| Kumar et al. (81) | India    | 3 years         | 310             | prospective birth cohort study | acute respiratory infections | The ratio of tidal expiratory flow (TEF) at 25 or 50% of tidal expiratory volume to peak TEF (TEF50 or TEF25/peak TEF) at 3 years was significantly increased in children who had an acute respiratory infection in infancy. |
| Li et al. (82) | China    | <14 years       | 42              | case review               | bronchiolitis obliterans | The tidal breathing analysis revealed a decreased TPEF% TEF (18.2 ± 0.26%, normal: more than 40%), or VPEF%VE (21.7 ± 0.32%, normal: more than 40%). |

FeNO, fractional exhaled nitric oxide; OR, odds ratio; CI, 95% confidence interval; PM2.5, particulate matter 2.5; C-ACT, Childhood Asthma Control Test; sRAGE, Receptor for Advanced Glycation End products; Zs, magnitude of respiratory impedance; R5: total respiratory resistance; X5: distal capacitive reactance; obstructive sleep apnea hypopnea syndrome (OSAHS); R5Hz, total resistance at 5 Hz; R20 Hz: central resistance at 20 Hz; R5−R20 Hz, difference between resistance at 5Hz and 20 Hz; IOS, Impulse oscillometry; PM2.5:particulate matter 2.5; CI:95% confidence interval; Frs6, Frs8, Frs10, Resistance at 6 Hz, 8Hz and 10Hz; Xrs6, Xrs8, and Xrs10, Reactance at 6 Hz, 8Hz and 10Hz; DHA, docosahexaenoic acid; TPEF% TEF, ratio of time to reach peak tidal expiratory flow to total expiratory time; VPEF%VE, ratio of volume to reach peak expiratory flow to total expiratory volume.

CONCLUSION

Preschool lung function tests used in LMIC were feasible with high success rates. Success with spirometry increased with age (29), and oscillometry had higher feasibility compared to spirometry. All tests were useful for clinical application and epidemiological studies. Comprehensive preschool testing including spirometry, FeNO, oscillometry and tidal breathing were only reported from China, and only 19 countries of 137 registered LMIC (14%) were represented in the review, a large discrepancy as the majority (80%) of children live in LMIC, where the burden of early life respiratory disease and exposures known to cause illness are high. These include air pollution, maternal smoking, a high infectious load including tuberculosis, and high rates of preterm birth (2, 83–86). Lung function tests assessing these vulnerable groups are lacking. A number of studies explored the effects of air pollution; and the studies suggest that air pollutants increase airway inflammation and may in part explain the association between household air pollution and recurrent wheeze (83). Given the burden of early life exposures and the need to identify preventative measure, priority should be given to strengthening access to lung function assessment tools.

The majority of clinical studies focussed on asthma diagnosis and management, including defining BDR in young children. The prevalence of asthma in LMIC is high, with a temporal increase in severe asthma (87). Of particular concern is that up to 40% of children in LMIC with severe symptoms are undiagnosed (87, 88). Oscillometry was useful, and more sensitive than spirometry, in measuring airway resistance and cut off values for BDR response was also determined. FeNO has been identified as a useful adjunct in diagnosis and informing treatment in asthmatic patients (89). Access to these tests to improve diagnosis and management is needed for the many children living in LMIC.

Other clinical uses have included management of chronic lung conditions like CF, bronchiolitis obliterans, OSAHS, obesity and systemic sclerosis all of which are associated with respiratory complications. Lung function tests assessing vulnerable groups such as children born preterm, those living with HIV or exposed in utero and those with a history of pulmonary TB and other early life lower respiratory tract infections are lacking in children from LMIC.

The importance of reference range equations were highlighted in these studies. A healthy standard is needed for lung function tests to distinguish between health and disease in different populations. The GLI reference equations attempt to address this, however unique environmental exposures including in-utero exposures influence lung development and this needs to be
considered when developing reference equations (90). Research studies assessing impact of exposures require appropriate patient samples and statistical modeling and should include both exposed and unexposed control groups.

There are currently no published data for MBW in preschool children in LMIC settings, however data on infant testing have been published in South Africa (3, 91). There is limited data on tidal breathing and the interrupter technique. Impulse and airway oscillometry use different input signals and this may impact results especially at high impedance, which is associated with disease. Furthermore, FeNO single breath and tidal breathing measures have different interpretation of normal ranges, and the results are not interchangeable. These factors may affect the interpretation and comparison of data.

Challenges to accessing lung function testing need to be addressed, these include lack of trained personnel as each lung function test requires specialized training skills and lack of financial resources to support development and implementation of these tests. Spirometry and oscillometry are relatively inexpensive, whereas FeNO and MBW are currently more expensive further limiting access. Equipment maintenance and poor access locally to consumables and technical support incur further costs. This reduces research outputs and lack of robust data to better diagnose, prevent and manage respiratory disease in these settings (5).

In conclusion, preschool testing in LMIC is feasible, both epidemiologically and clinically. It has the potential to be useful in strengthening the diagnosis, management and prevention of respiratory diseases in younger children but is underutilized. Spirometry still remains a key clinical and epidemiological tool in LMIC, however has limitations especially in young children. Understanding and addressing the challenges for improving access to these tools is needed in order to strengthen the prevention, early diagnosis and management of childhood respiratory disease in LMIC.

AUTHOR CONTRIBUTIONS

SC, DG, and HZ conceived the idea. SC and DG reviewed the literature and drafted the manuscript. HZ provided further input into the manuscript. All authors reviewed, contributed, and approved the final manuscript.

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SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fped.2022.908607/full#supplementary-material

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