

Reference equations for the interpretation of forced expiratory and plethysmographic measurements in infants

Zihang Lu PhD(c)^{1,2} | Rachel E. Foong PhD^{1,3} | Krzysztof Kowalik MSc¹ |
Theo J. Moraes MD, PhD¹ | Aimee Dubeau BSc¹ | Diana Lefebvre PhD⁴ |
Stephanie D. Davis MD⁵ | Susan Balkovec BSc¹ | Allan Becker MD⁶ |
Piush Mandhane MD, PhD⁷ | Stuart E. Turvey MBBS, DPhil⁸ | Wendy Lou PhD² |
Malcolm R. Sears MB, ChB⁴ | Felix Ratjen MD, PhD¹ | Padmaja Subbarao MD, MSc¹ 

¹ Division of Respiratory Medicine, Department of Pediatrics, and Program in Translational Medicine, SickKids Research Institute, The Hospital for Sick Children, University of Toronto, Toronto, Canada

² Dalla Lana School of Public Health, University of Toronto, Toronto, Canada

³ Curtin University of Technology, Perth, Western Australia

⁴ Department of Medicine, McMaster University, Hamilton, Canada

⁵ Division of Pediatric Pulmonology, Allergy and Sleep Medicine; Department of Pediatrics; Riley Hospital for Children, Indiana University School of Medicine, Indianapolis, Indiana

⁶ Department of Pediatrics and Child Health, University of Manitoba, Children's Hospital Research Institute of Manitoba, Winnipeg, Manitoba, Canada

⁷ Department of Pediatrics, University of Alberta, Edmonton, Alberta, Canada

⁸ Department of Pediatrics, Child & Family Research Institute, BC Children's Hospital, University of British Columbia, Vancouver, British Columbia, Canada

Correspondence

Padmaja Subbarao, MD, MSc, The Hospital for Sick Children, 555 University Avenue, Toronto, Ontario M5G 1X8, Canada.
Email: padmaja.subbarao@sickkids.ca

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Abstract

Background: Pulmonary function testing is commonly performed for diagnosis and clinical management of respiratory diseases. It is important to use appropriate reference equations from healthy subjects for interpretation of data from infants with lung disease. This study aimed to determine if published reference equations were similar to forced flow measures and plethysmographic infant pulmonary function testing data collected in the Canadian Healthy Infant Longitudinal Development (CHILD) Study.

Methods: Reference equations for five pulmonary function variables ($FEV_{0.5}$, FVC, FEF_{25-75} , $FEV_{0.5}/FVC$ ratio and plethysmography (FRC_{pleth})) were developed using data from the nSpire system. New reference equations developed using healthy data from the CHILD Study were compared to previously published reference equations for forced flow and plethysmographic measures.

Results: The current analysis included 131 infants (on 181 test occasions) with forced flow measures and 161 infants (on 246 test occasions) with plethysmography measures, aged 3–24 months. Age and length were major determinants of both forced flow and plethysmography measures. In addition, ethnicity (Caucasian vs non-Caucasian) was significantly associated with $FEV_{0.5}/FVC$ and FEF_{25-75} measures. We found that the published reference equations based on custom-built equipment or commercially available systems provided poor fit to our current pulmonary function

testing data, resulting in placing a large proportion of our healthy population outside the normal ranges.

Conclusions: Our current data support the need for population and device specific reference data for infant pulmonary function studies. By deriving new equipment-specific reference equations for our healthy population, we provide normative data to other centers utilizing this equipment.

KEYWORDS

infant pulmonary function testing, forced flow measures, plethysmography, reference equations, CHILD Study

1 | INTRODUCTION

Pulmonary function testing is commonly performed for diagnosis and clinical management of respiratory diseases. Infant pulmonary function testing (IPFT) was first developed in the early 1960s and advances over the last 20 years have produced commercially available systems that can ascertain forced flow measures using the raised-volume rapid thoracoabdominal compression (RVRTC)¹ technique and plethysmography². The RVRTC technique allows for generation of forced expiratory flow-volume (FEFV) curves similar to spirometry. Studies using this technique have shown that forced expiratory volume at 0.5 s (FEV_{0.5}), forced vital capacity (FVC) and average forced expired flow over the mid 50% of FVC (FEF₂₅₋₇₅) were significantly reduced in infants with wheeze and cystic fibrosis (CF).³⁻⁵ Plethysmography measures lung volumes and functional residual capacity (FRC_{pleth}) which has been found to be elevated in infants with CF and bronchopulmonary dysplasia.^{6,7} Besides being able to discriminate between health and disease, deficits in pulmonary function in early life predict wheezing disorders and asthma in childhood and into adulthood.⁸⁻¹¹ Longitudinal studies also show that low pulmonary function tracks throughout life.^{12,13} Given that reduced lung function in early life may be a risk factor for chronic respiratory disease, it is important to understand causes of reduced pulmonary function and identify windows of opportunity for interventions in early life.

In line with the Developmental Origins of Health and Disease (DoHaD) hypothesis, environmental exposures in early life may influence lung development and function, and subsequent risk of developing chronic respiratory diseases.¹⁴ Understanding the role of environmental exposures and environment-gene interactions on the development of asthma is a primary aim of the Canadian Healthy Infant Longitudinal Development (CHILD) Study.¹⁵ The CHILD Study is a longitudinal birth cohort study that recruited participants from the general population and incorporated IPFTs in its study design for early identification of risk factors that impact pulmonary function in infancy. However, in order to accurately define normal lung growth, it is important to use appropriate reference equations from healthy subjects for interpretation of data from infants with lung disease.

IPFTs have largely been standardized with the development of commercial equipment, international guidelines and published reference equations. However, published reference equations may not be applicable to all populations. Lum et al reported that reference equations derived from older "in-house" systems were inappropriate for the commercially available Jaeger system,¹⁶ and that reference equations are equipment-specific. They further suggested that users of the nSpire system, the system used in the CHILD Study, should examine the validity of reference equations for their population. The nSpire system has been used widely in North American cystic fibrosis centers for the assessment of infant lung function.^{6,17} Although no longer available commercially, it remains in clinical use in North American centers. This study aimed to determine if published reference equations are similar to RVRTC and plethysmography IPFT data collected in healthy infants using the nSpire system in the CHILD Study.

2 | METHODS

2.1 | Study population

Healthy infants aged 3–24 months enrolled in the Toronto site of the Canadian Healthy Infant Longitudinal Development (CHILD) Study were recruited for this study. Study families were invited to participate in a study visit for IPFT starting at 3 months of age, and for two additional follow-up visits 6 months apart to obtain longitudinal IPFT measurements. Infants who demonstrated prior respiratory distress, had a history of wheezing, or were exposed to maternal smoking during pregnancy were excluded from this analysis. This study was approved by the Research Ethics Board of the Hospital for Sick Children. Informed and written consent was given by the parents of the subjects.

2.2 | Pulmonary function testing

IPFTs were performed in infants during quiet sleep in the supine position, after oral sedation with chloral hydrate (60–80 mg/kg). Forced expiratory volumes and flows were measured using the RVRTC

technique, while FRC_{pleth} was measured by body plethysmography according to ATS/ERS guidelines.^{2,18} Both tests were performed using the Infant Pulmonary Lab System (nSpire Health Inc., Longmont, CO). Outcomes measured included forced expiratory volume in the first half second (FEV_{0.5}), FVC, and FEF₂₅₋₇₅. Lung function outcomes were reported as the single best maneuver with the highest sum of FVC and FEF₂₅₋₇₅. All curves used for analysis had FVC measurements within 10% of the highest FVC. FRC_{pleth} was calculated from the average of three acceptable measurements, each containing a minimum of three efforts, with each measurement within 20% of the highest FRC_{pleth} value.

2.3 | Statistical analysis

Five lung function variables (FEV_{0.5}, FVC, FEF₂₅₋₇₅, FEV_{0.5}/FVC ratio, and FRC_{pleth}) and five anthropometric variables (age, length, weight, sex, and ethnicity (Caucasian vs non-Caucasian)) were considered for the current analysis. Descriptive statistics for participants included in the analysis were reported as mean (standard deviation and range) for continuous variables and frequency (%) for categorical variables. Graphical tools were used to investigate the relationship (eg, functional form) between lung function outcomes and continuous predictors (age, length, and weight). Natural log transformations on lung function outcomes and predictors were considered to reduce the heterogeneity, and the impact of extreme values. In order to properly account for repeated measurements for subjects and to perform statistical inference, random intercepts models were used for investigating the best fit model for each lung function outcome.¹⁹ Reference equations for lung function outcomes were then constructed using the LMS (lambda-mu-sigma) method.²⁰ This is an approach that estimates the skewness (L), median (M), and coefficient of variation (S) simultaneously. Then the z-scores (standardized residual) for the lung function outcomes can be constructed by the equations: $z\text{-score} = ((\text{measurement}/M)^L - 1)/(L \times S)$. Lower and upper limits of normal (ie, LLN and ULN) were defined as the 5th (ie, -1.64) and 95th (ie, 1.64) percentile of the standard normal distribution, respectively. Goodness of fit for each model was assessed by testing the normality assumption of the residuals. The final decision on choosing one set of equations versus others depends on their clinical usefulness. New reference equations developed using data from healthy children participating in the CHILD Study were compared to reference equations published by Jones et al in 2000²¹ and Lum et al in 2016¹⁶ for RVRTC. FRC_{pleth} measures were compared with equations from Castile et al. published in 2000,²² Stocks et al in 2001² and Nguyen et al in 2013.²³ All statistical analyses were conducted using R software version 3.3.2 (<http://www.r-project.org>) or SAS 9.4 (Cary, NC) where appropriate.

3 | RESULTS

3.1 | Demographics

Of the 230 infants enrolled in the infant pulmonary function testing (IPFT) sub-cohort at the Toronto site of the CHILD Study, 162 (162/

230; 70%) completed RVRTC, while 204 (204/230; 89%) completed plethysmography (Figure 1). The current analysis included 131 infants (131/162; 81%) with RVRTC data and 161 infants (161/204; 79%) with plethysmography data. Reasons for exclusion are shown in Figure 1. Subject characteristics are shown in Table 1. For those with RVRTC data, 77 (77/131; 59%) were male and 71 (71/131; 54%) were Caucasian, with a mean (standard deviation, range) age, length and weight of 12.4 (4.8, 3.4–24) months, 74.1 (6.2, 60–89.5) cm and 9.5 (1.7, 5.9–14) kg, respectively. Similar characteristics were found for those with plethysmography data.

Relationships between the lung function variables and the anthropometric variables considered in the current study are presented in the online supplement (Figure E1–E5). In linear mixed effect models, age and length were the two major determinants for both RVRTC and plethysmography parameters (Table E1). In addition, we found that ethnicity (Caucasian vs non-Caucasian) was significantly associated with FEV_{0.5}/FVC ($P = 0.03$) and FEF₂₅₋₇₅ ($P = 0.05$) parameters.

3.2 | Comparisons of reference equations for RVRTC data

Previously published reference equations are shown in Table 2. When the Jones et al equations²¹ for RVRTC data were applied to healthy subjects in the CHILD Study, mean (SD) z-scores for FEV_{0.5}, FVC, FEV_{0.5}/FVC and FEF₂₅₋₇₅ were -0.31 (1.16), -0.12 (1.09), -0.17 (0.6), and -0.34 (1.06), respectively (Figure 2A–D and Table E2). In addition, z-scores for FEV_{0.5} and FVC were highly dependent on age. We found a mean (SD) 0.62 (0.16) difference in FEV_{0.5} z-scores ($P < 0.001$) and 0.47 (0.15) difference in FVC z-score ($P = 0.003$) between those below and above 12 months of age (Figures 2A and 2B). The Lum et al equations¹⁶ provided a mean (SD) of 0.22 (1.19), 0.11 (1.02), and 0.19 (0.79) for FEV_{0.5}, FVC and FEV_{0.5}/FVC, respectively (Figure 2E–G & Table E2). However, FEF₂₅₋₇₅ z-score from the Lum et al equation¹⁶ was higher than expected by 0.85 (1.17) z-scores (Figure 2H and Table E2). When using the recommended 5th and 95th centile to define the limits of normal such that 90% of the healthy population would be within the normal range,²⁴ we found that 23.2% of CHILD Study infants fell outside the normal ranges when using the Lum et al equations¹⁶ for FEF₂₅₋₇₅ (Table E2).

3.3 | Comparisons of reference equations for FRC_{pleth}

With regards to FRC_{pleth} , z-scores calculated from Castile et al equations²² had a mean (SD) of -0.04 (1.43). While the mean z-score fit our population well, the variation was quite large and thus a large proportion (22%) of observations fell outside of the normal range (Table E2). This proportion increased with age. The z-scores calculated using Stocks et al equations² were systematically lower than 0, with a mean (SD) of -0.72 (1.17) (Figure 3B and Table E2). Nguyen et al equation²³ gave significantly higher z-scores, 1.79 (1.39). Using Nguyen equation, 52.8% of our population fell outside the normal range (Figure 3C and Table E2).

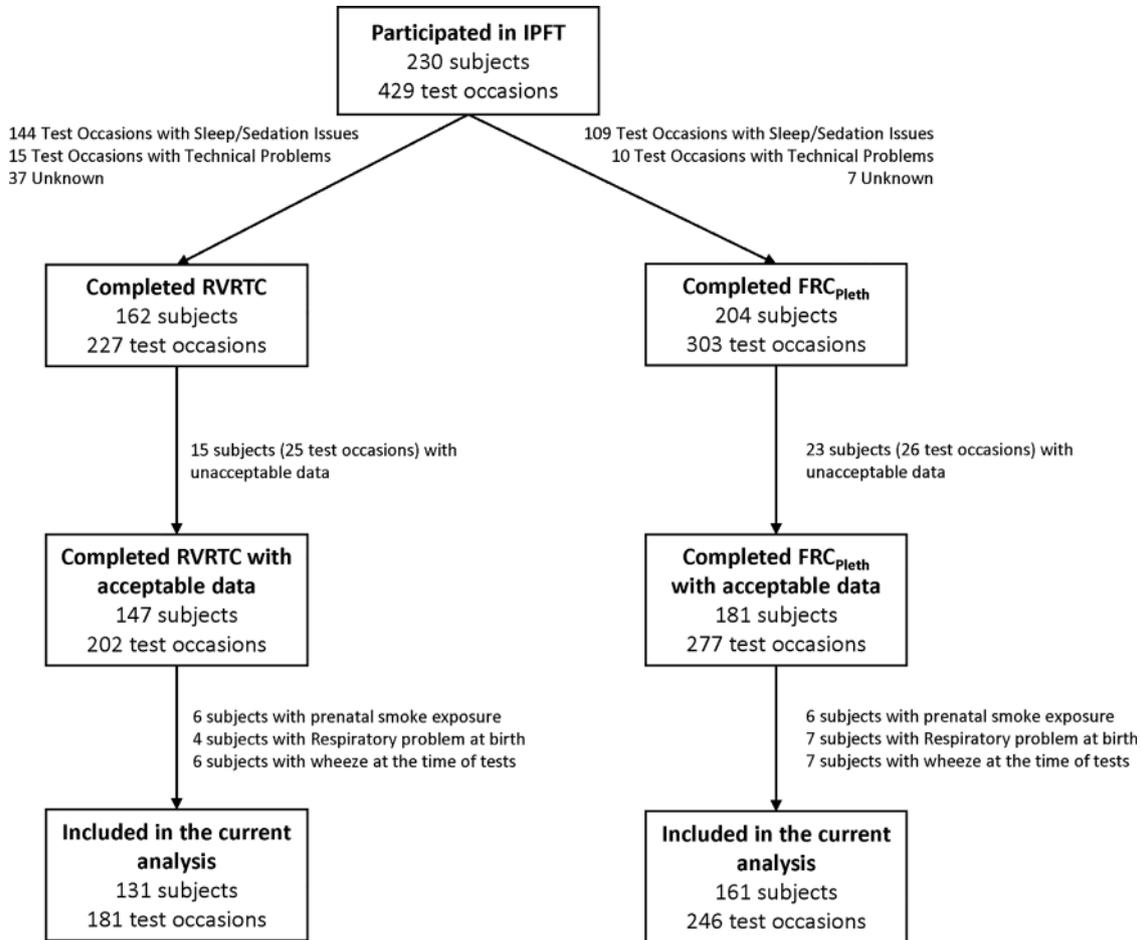


FIGURE 1 Flow chart of subjects included in study with reasons for exclusion. IPFT = infant pulmonary function testing; RVRTC = raised volume rapid thoracoabdominal compression test; FRC_{pleth} = functional residual capacity measured from plethysmography

3.4 | nSpire equipment-specific reference equations

Given that the recently published reference equations (Lum et al¹⁶) were not suitable for our healthy population, we developed new equipment-specific reference equations. Log-transformation on both

pulmonary function outcomes from our population and predictors improved the linear trends and the normality of the residuals. Mixed effect models with random intercepts showed that age (after transformation) and length (after transformation) were major determinants of pulmonary function growth. Sex was a significant factor for

TABLE 1 Demographics of infants who successfully completed the raised volume rapid thoracoabdominal compression test (RVRTC) and plethysmography

Variable ^a	RVRTC data	Plethysmography data
Subjects, N	131	161
Test occasions, N	181	246
Sex, Male (%)	77 (58.8%)	93 (57.8%)
Ethnicity, Caucasian (%)	71 (54.2%)	87 (54.0%)
Age (months) ^b	12.4 (4.8, 3.4–24)	12.3 (4.8, 2.8–24)
Length (cm) ^b	74.1 (6.2, 60–89.5)	74 (6.4, 60–89.5)
Length z-score ^b	−0.4 (1.1, −3.2 to 2.8)	−0.3 (1.1, −3.9 to 2.8)
Weight (kg) ^b	9.5 (1.7, 5.9–14)	9.4 (1.7, 5.4–14)
Weight z-score ^b	0.1 (1.0, −2.4 to 3.4)	0 (1.0, −2.4 to 3.4)
Weight for length z-score ^b	0.4 (1.1, −2.8 to 3.8)	0.3 (1.1, −2.8 to 3.8)

^aSummary statistics are presented as mean (standard deviation, range), unless otherwise stated.

^bSummary statistics are calculated for all test occasions.

TABLE 2 Summary of currently available reference equations for RVRTC and FRC_{pleth}

Author	Year	Parameters	N	Age range	Caucasian	Equipment
Jones et al ²⁰	2000	RVRTC	155	3 to 149 weeks	69%	Custom-built system
Lum et al ¹⁶	2016	RVRTC	429 (639 tests)	4 to 118 weeks	84%	Jaeger system
Castile et al ²¹	2000	FRC _{pleth}	22 (35 tests)	3 to 120 weeks	86%	Custom-built system
Stocks et al ²	2001	FRC _{pleth}	Unknown	up to 15 months	Not applicable	Custom-built system
Nguyen et al ²²	2013	FRC _{pleth}	153 (232 tests)	2.6 to 104.7 weeks	100%	Jaeger system

FEV_{0.5} and FVC, and ethnicity or race was an important factor for FEF₂₅₋₇₅. While sex and race did not show significant associations with other lung function outcomes (e.g. FRC_{pleth}), we kept these two factors in the model for each pulmonary function outcome because they improved the normality of the residuals. Table 3 presents the new reference equations for FEV_{0.5}, FVC, FEV_{0.5}/FVC, FEF₂₅₋₇₅ and FRC_{pleth}. We compared our developed equations to published reference equations for RVRTC data (Figure 2I–L) and FRC_{pleth} data (Figure 4D). Our developed equations for RVRTC data and FRC_{pleth} data accounted for age effects appropriately, and produced standard normal distributed z-scores (ie, approximately with mean 0 and SD 1).

We calculated the difference between the z-scores derived from the published reference equations and our developed equations

(Figure 4 and Table E3). The spirometry results were underestimated for all the parameters considered, when using Jones et al reference equations (mean (SD) z-score differences for FEV_{0.5}, FVC, FEV_{0.5}/FVC and FEF₂₅₋₇₅: -0.31 (0.46), -0.12 (0.46), -0.18 (0.46), -0.34(0.84), respectively). This underestimation progressed as age increased, and it was more obvious for FEV_{0.5} and FVC, resulting in an overestimation of the number of abnormalities with age. In contrast, when using Lum et al reference equations,¹⁶ minimal overestimation was observed for FEV_{0.5}, FVC and FEV_{0.5}/FVC (mean (SD) z-score differences: 0.22 (0.24), 0.11 (0.25), and 0.18 (0.29), respectively). The overestimation was more striking and unrelated to age for FEF₂₅₋₇₅ with a mean z-score (SD) difference of 0.84 (0.25).

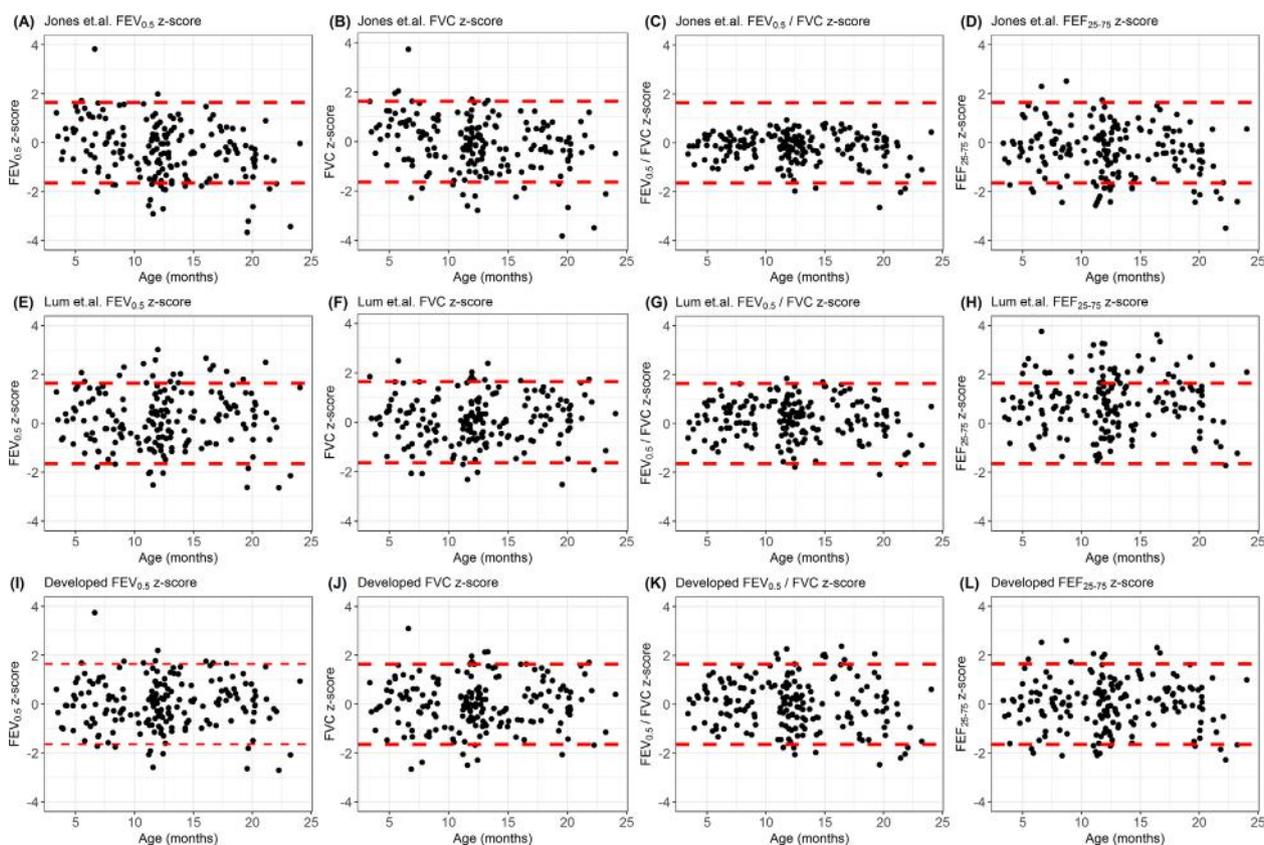


FIGURE 2 Comparisons of reference equations (A–D, Jones et al 2000 equations²¹; E–H, Lum et al 2016 equations¹⁶; I–L, Developed equations) for pulmonary function outcomes derived from the raised volume rapid thoracic compression (RVRTC) technique. (A,E, and I) FEV_{0.5} = forced expiratory volume in the first half second; (B, F, and J) FVC = forced vital capacity; (C,G,K) FEV_{0.5}/FVC; (D,H,L) FEF₂₅₋₇₅ = forced expiratory flow between 25% and 75% FVC. Dash lines represented ULN (ie, 1.64) and LLN (ie, -1.64)

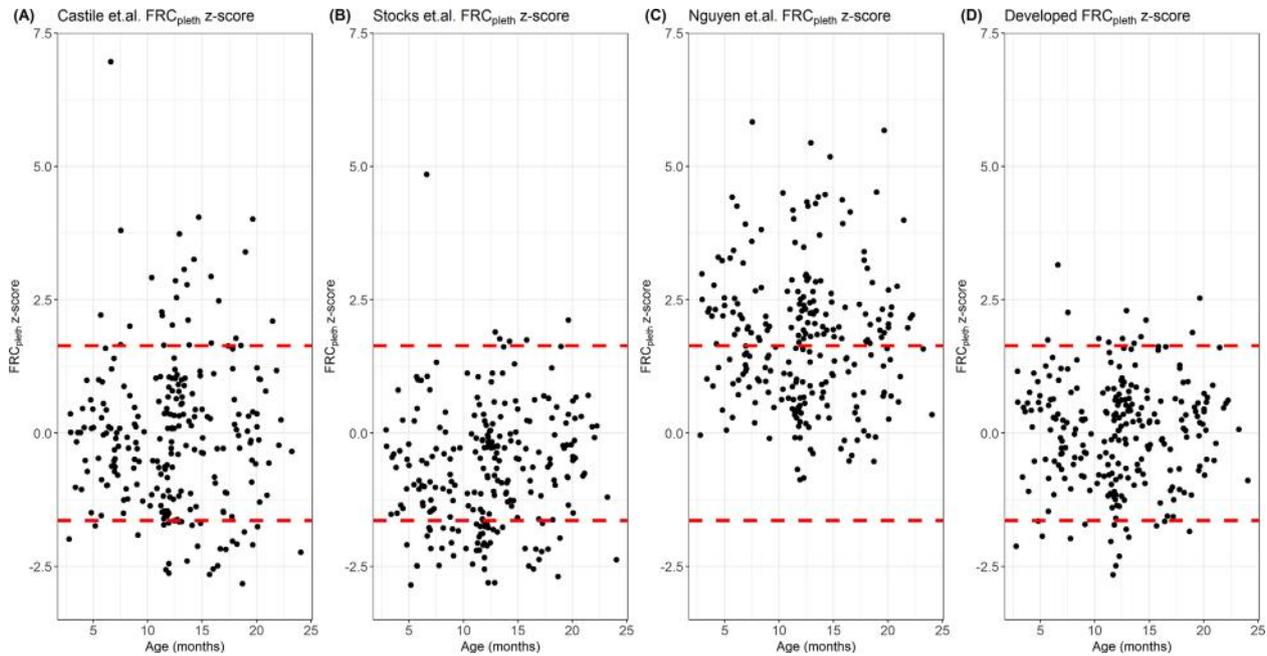


FIGURE 3 Comparisons of reference equations for functional residual capacity from plethysmography (FRC_{pleth}). (A) Castile et al 2000 equations²²; (B) Stocks et al 2001 equations²; (C) Nguyen et al 2013 equations²³; (D) Developed equations. Dash lines represented ULN (ie, 1.64) and LLN (ie, -1.64)

With respect to FRC_{pleth} , we found that the variance of the difference between the Castile et al²² and our developed z-score increased in the older age group (>12 months) compared to the younger age group (≤ 12 months), $P=0.007$ (Figure 5A). The significant differences seen using the other equations were unrelated to age (Figures 5B and 5C). This led to a mean (SD) difference of -0.72 (0.48) between Stock's 2001 z-score and our developed z-score, and 1.78 (0.52) between Nguyen 2013 z-score and our developed z-score, respectively (Table E3). Interpretation of our PFT function based on these equations would result in placing a large proportion of our healthy population outside the normal ranges.

4 | DISCUSSION

In this study, we show that published reference equations are not appropriate for interpretation of IPFT data from the healthy reference population in the CHILD Study. In this Canadian general population study, IPFT data were collected using the nSpire IPL system, for which there are currently no published reference equations. As previously shown, reference equations for IPFT outcomes are equipment specific and published equations based on custom-built equipment are inappropriate for commercially available systems.¹⁶ We confirm these findings in this study, showing that reference equations derived from the commercially available Jaeger system and a custom-built "in-house" system provided results that placed a large proportion of our healthy population outside of the normal range. We therefore developed and present new equipment-specific reference equations for the nSpire IPL system in this study.

Published equations of FRC_{pleth} from Lum et al¹⁶ and Nguyen et al²³ were based on data collected using the Jaeger Bodybox system, while Castile et al²² used custom made equipment which may have served as a prototype for the nSpire system. Published equations of RVRTC data from Jones et al and Stocks et al used custom-built systems for data collection. Previous studies show that FEFV healthy reference data from the Jaeger System are lower than that from the custom-built system used by Jones et al²¹ possibly due to BTPS (body temperature, pressure, and saturated) or volume-drift corrections.²⁵ Similar results were seen in our study, where we found that when applying Jones et al²¹ equations to our healthy subjects, z-scores were highly dependent on age, which would result in an overestimation of abnormal $FEV_{0.5}$ and FVC with increasing age. Lum et al¹⁶ equations using the Jaeger system provided a reasonably good fit for our $FEV_{0.5}$ and FVC reference data with minimal bias, however these equations were inappropriate for $FEV_{0.5}/FVC$ ratio and FEF data. The difference in the FRC reference equations can mainly be attributed to the differences in deadspace of the equipment. Stocks et al² used custom-made equipment with a larger deadspace (total >30 mL) which may have influenced the respiratory pattern, contributing to lower than zero FRC z-scores when their reference equations were applied to our data. In contrast, Nguyen et al²³ used the Jaeger system in which dead space was minimized, hence contributing to higher than zero FRC z-scores when applying their reference equation to our data. Castile et al²² used custom made equipment, in which deadspace was subtracted based on the mask size, and therefore their equation provided a relatively better fit to our current FRC_{pleth} data. However their equation was based on a much smaller sample size (Table 2), and larger variances were seen when applied to CHILD data.

TABLE 3 Newly developed reference equations for nSpiire equipment specific raised volume rapid thoracic compression (RVRTC) technique and plethysmography pulmonary function outcomes

Lung function	Equations
log (FEV _{0.5})	
M	$-0.4585 + 0.1386 * \log(\text{age}) + 1.3658 * \log(\text{length}) - 0.0239 * \text{sex} - 0.0204 * \text{race}$
S	0.0261
L	2.0356
log (FVC)	
M	$-1.775 + 0.2090 * \log(\text{age}) + 1.7009 * \log(\text{length}) - 0.0489 * \text{sex} + 0.0226 * \text{race}$
S	0.0241
L	$-35.61147 + 17.07892 * \log(\text{age})$
log(FEV _{0.5} /FVC)	
M	$5.4284 - 0.0336 * \log(\text{age}) - 0.2378 * \log(\text{length}) + 0.0205 * \text{sex} - 0.0179 * \text{race}$
S	0.0177
L	20.026
log (FEF ₂₅₋₇₅)	
M	$1.2903 + 0.0621 * \log(\text{age}) + 1.1478 * \log(\text{length}) + 0.0263 * \text{sex} - 0.0597 * \text{race}$
S	0.033
L	2.3084
log (FRC _{pleth})	
M	$-0.8166 + 0.1453 * \log(\text{age}) + 1.3704 * \log(\text{length}) - 0.0354 * \text{sex} - 0.0062 * \text{race}$
S	0.0279
L	$-141.7082 + 32.27446 * \log(\text{age})$

L, skewness; M, predicted median; S, coefficient of variation.

Notes: Age in months, length in cm, race = 1 for Caucasian and 0 for other, sex = 1 for male and 0 for female FEV_{0.5}/FVC multiplied 100 before converted to z-scores.

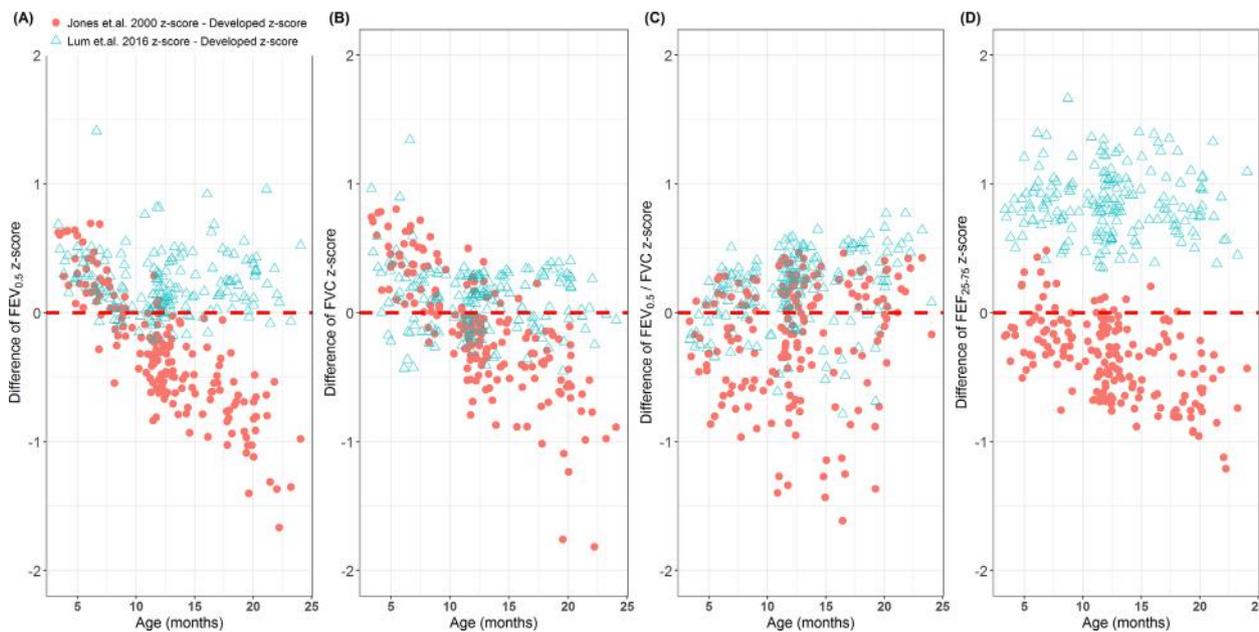


FIGURE 4 Calculated difference between developed z-scores and published z-scores for pulmonary function outcomes derived from the raised volume rapid thoracic compression (RVRTC) technique. (A) FEV_{0.5} = forced expiratory volume in the first half second; (B) FVC = forced vital capacity; (C) FEV_{0.5}/FVC; (D) FEF₂₅₋₇₅ = forced expiratory flow between 25% and 75% FVC. Dash lines represented zero

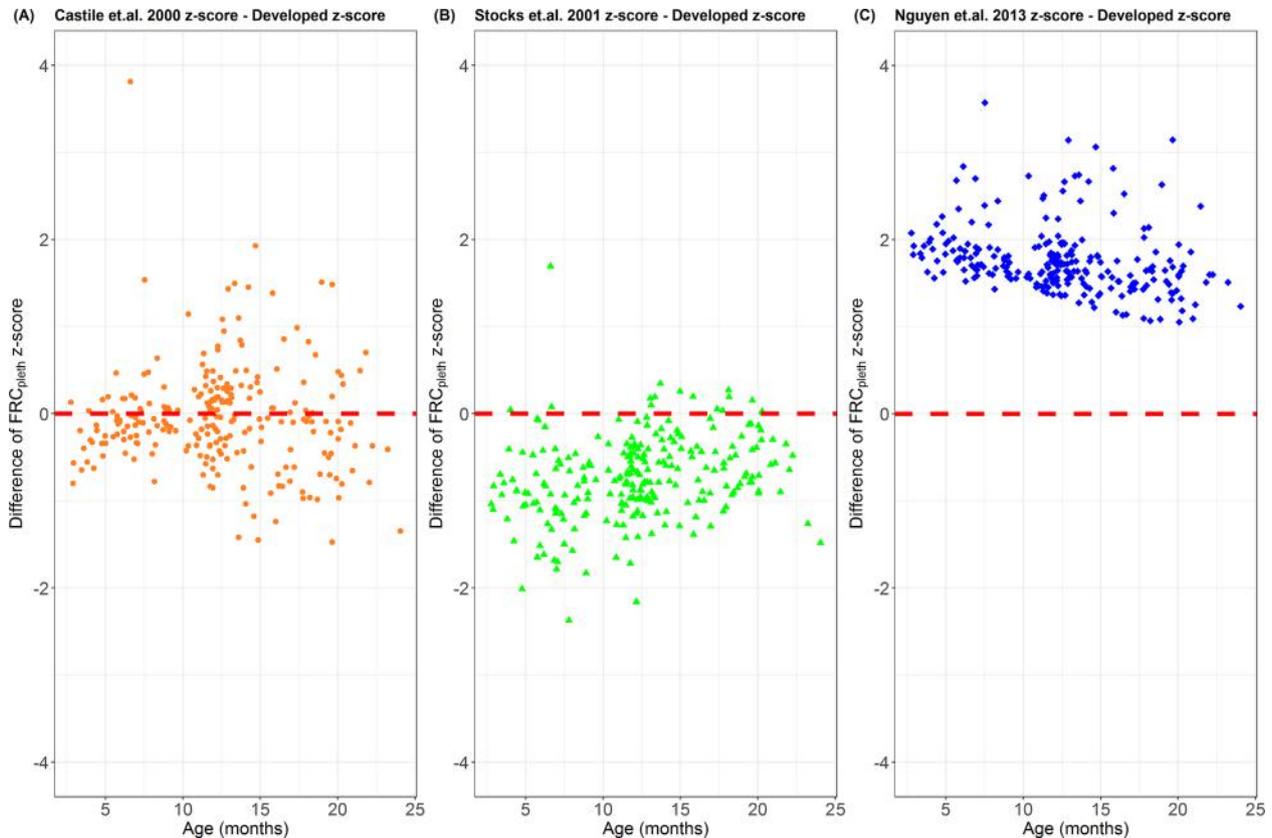


FIGURE 5 Calculated difference between developed z-scores and published z-scores for functional residual capacity from plethysmography (FRC_{pleth}). Dash lines represented zero. (A) Castile et al 2000 z-score²²-Developed z-score; (B) Stock et al 2001 z-score²-Developed z-score; (C) Nguyen et al 2013 z-score²³-Developed z-score

While equipment differences may be a major driver for the lack of fit of published reference equations, the statistical methods used to generate reference equations differed for each of the published studies. Similar to Lum et al,¹⁶ we used the LMS method. Jones et al²¹ and Stocks et al² used linear regressions with standard error of prediction, while Nguyen et al²³ also used a regression analysis and absolute residuals approach. For exploratory purpose, we also applied multiple regressions to our RVRTC data, but we achieved smaller R square values for spirometry parameters compared to Jones et al.²¹ Compared to simple multiple regressions, the LMS method allows us to model not only mean and variance but also the skewness simultaneously. This method may provide a better alternative to fitting our data particularly when the data are highly skewed. It is possible that the choice of statistical method may have influenced the reference values.

It is also important to note that the healthy infant population used in this study is markedly different from those in the published equations. Firstly, the healthy populations used to generate the previously published equations consisted of predominantly (~70%) Caucasian infants. In our cohort, Caucasians accounted for about 54% of the population. It has previously been shown that non-Caucasian infants had reduced $FEV_{0.5}$ and FVC compared with Caucasian infants.²⁶ Ethnicity plays an important role in predicting pulmonary function values.²⁴ In our equations, while we accounted for ethnic differences by indicating if subjects were Caucasian or non-Caucasian,

the non-Caucasian group consisted of multiple ethnicities, which we were unable to further sub-classify due to low numbers in individual ethnic sub-groups. Hence, we used a single classification, which may not be the best representation of the different ethnicities. In our current study, we found that $FEV_{0.5}/FVC$ and FEF_{25-75} were significantly associated with ethnicity (Table E1). This may also contribute to the poor fit of our data when using Lum et al¹⁶ equations, which were developed based on a population with a larger proportion (84%) of Caucasians (Table 2). In addition, unlike our current study, the previously published studies from Nguyen et al²³ and Lum et al¹⁶ did not exclude infants exposed to maternal smoking during pregnancy from the healthy population.^{16,23} Jones et al²¹ also included smoke exposed infants and instead corrected for smoke exposure in the published equations. We excluded six infants with confirmed prenatal smoke exposure given studies suggesting that tobacco smoke can impair lung development.²⁷⁻²⁹ We would argue that these infants have suffered some lung insult and therefore philosophically should not be included in the reference population for lung health.

A limitation of this paper is that we had a smaller sample size in our study population for RVRTC data compared with Lum et al¹⁶ who included data from multiple centres and had more than 400 subjects. The number of subjects who successfully completed plethysmography in our study was also low but is comparable to the number of subjects in the publication by Nguyen et al.²³ Also, relatively few measurements

from subjects above the age of 20 months were available and data in this age range should be interpreted with caution. Our cohort consisted of a multi-ethnic population, however, we were inadequately powered to appropriately ascertain the impact of the various specific ethnicities. Our current observational data does not allow us to determine the contribution of equipment and population to the observed differences in z-score fit. This can only be addressed by comparing data from different healthy populations using the same device—a challenging study design for infant studies. We are aware that the nSpire system is no longer commercially available; however, a recent survey of clinical infant lung function testing practices found that the nSpire system is the most commonly used equipment³⁰ and this device is currently still utilized in clinical studies and clinical care, thus the reference equations we developed in this paper will be of relevance for some time.

In this study, we present new reference equations that may be suitable for use in IPFT data collected from the nSpire IPL system. Similar to previous studies, we found that length and age are the major factors influencing IPFT measures. While the equations published here are applicable to IPFT data collected using the nSpire IPL system in a multi-ethnic infant population aged 0–24 months ideally centers should continue to generate normative data specific to their healthy population in order for us to truly understand the impact of ethnicity, gender and equipment on infant lung function data. We anticipate that by deriving new equipment-specific reference equations for our healthy population, we will enhance the interpretation of IPFT data from the CHILD Study for the investigation of the effects of environmental exposures on pulmonary function outcomes.

CONFLICT OF INTEREST

None.

ORCID

Padmaja Subbarao  <http://orcid.org/0000-0003-0394-1933>

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section at the end of the article.

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