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# Spirometry Versus Forced Oscillation to Assess Lung Function Outcome at 5 Years of Age

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## ABSTRACT

**Background:** Spirometry is the gold standard for assessing airway function for clinical studies; however, obtaining high-quality data in young children remains challenging. Since the forced oscillation technique (FOT) requires less subject cooperations, there has been increasing interest in FOT, particularly in young children. We evaluated whether spirometry and FOT in young children provides comparable ability to detect a treatment effect.

**Methods:** We recently reported in a randomized controlled trial that vitamin C compared to placebo treatment of mothers who smoked during pregnancy (MSDP) results in the offspring having significantly higher forced expiratory flows (FEFs) at 5-years of age, as well as significantly less wheeze at 4–6 years of age. In these same offspring, we also measured respiratory impedance using FOT at 8-Hz impedance at 3, 4, and 5 years of age.

**Results:** Although spirometry demonstrated significantly increased FEFs in vitamin C compared to placebo-treatment group at 5 years of age ($p < 0.001$), we were not able to detect a similar treatment effect using FOT impedance.

**Conclusions:** It may be challenging to obtain technically successful spirometry in preschool children; however, FEFs may provide a better outcome than single-frequency FOT impedance to assess improvements in airway function in these young subjects.

## 1 | Introduction

Assessment of airway function outcomes of young children is becoming more important as there is increasing evidence that many respiratory diseases begin very early in life and may even be secondary to in-utero exposures, such as maternal smoking during pregnancy (MSDP). We have previously reported the results of our longitudinal study entitled "Vitamin C to Decrease Effects of Smoking in Pregnancy on Infant Lung Function" (VCSIP) and demonstrated in a double-blinded randomized controlled trial (RCT) that vitamin C compared to placebo supplementation to mothers who continue to smoke during pregnancy can improve the offspring forced expiratory flows (FEFs) from

infancy through 5 years of age [1–4]. We used spirometric measures as our primary lung function outcome to assess the potential vitamin C treatment effect at 5 years of age, as we were able to obtain FEFs during infancy, and thus have a longitudinal assessment using the same measurement from infancy to 5 years of age. As spirometry can be technically challenging to obtain quality maneuvers in young children, there has been increasing interest in the use of the forced oscillation technique (FOT), which requires less subject cooperation than spirometry [5–13]. There are now commercially available FOT equipment for evaluation of young children; however, we are not aware of any studies that compared spirometry and FOT to detect a treatment effect in an RCT in young children.

Subjects had scheduled visits at 3 and 4 years of age to practice spirometry, which was our primary outcome at 5 years of age. We also obtained FOT measurements at 3, 4, and 5 years of age, as a secondary outcome. We hypothesized that FOT measures at 5 years of age would demonstrate treatment differences similar to that shown by spirometry at 5 years of age. We also hypothesized that longitudinal FOT measurements at 3, 4, and 5 years of age would potentially provide increased power to demonstrate a treatment effect compared to cross-sectional analyses.

## 2 | Methods

### 2.1 | Subjects

Details of our study design for VCSIP have previously been published [1–4]. This study was a double-blind RCT of pregnant smokers randomized to vitamin C (500 mg/day) or placebo at three sites with institutional review board approval at each site. All participants and clinical investigators remain blinded to treatment allocation and offspring of enrolled mothers were followed longitudinally from birth into childhood. Study visits to assess lung function were performed at least 3 weeks following any respiratory illness, and respiratory medications were held for at least 24 h before testing. The study was approved by the single Institutional Review Board at Oregon Health & Science University (IRB#0691) and informed consent obtained for each enrolled participant.

### 2.2 | FOT

Forced oscillation measurements were obtained using commercially available equipment (Resmon Pro 6.1, Medical Graphics, St. Paul Minnesota) at single 8-Hz frequency (f), suggested by the manufacturer for this young age group. We attempted to obtain FOT measurements in triplicate using the technical acceptance criteria of intrameasurement coefficient of variation for resistance of 30% and an intermeasurement reproducibility of 15% for children, as suggested by the manufacturer, and current standards [6]. Inspiratory, expiratory, and total Resistance (Rinsp, Rexp, and Rtot) and Reactance (Xinsp, Xexp, and Xtot) were recorded for analysis.

### 2.3 | Spirometry

After completion of FOT measurements, forced expiratory maneuvers were obtained using commercially available spirometry equipment (Vitalograph, Ennis Ireland). Adhering to the American Thoracic Society (ATS)/European Respiratory Society (ERS) acceptance criteria, we attempted to obtain three technically acceptable maneuvers [7, 14]. Forced expiratory volume (FVC) and FEFs at 75%, 50%, and between 25% and 75% FVC were recorded for analysis.

### 2.4 | Statistical Analysis

Our primary spirometric outcome was FEF25-75 and our primary FOT outcome was Rinsp. Mixed effect model, Repeated Measures ANOVA, was used for FOT at 3, 4, and 5 years of age to compare treatment effect over time. Included in these models were the treatment arm (vitamin C vs. placebo) clinical site, gestational age (GA) at randomization (≤ 18 vs > 18 weeks), sex, race, and z-score of height at each age. Bayesian Information Criterion (BIC) was employed to determine the optimal correlation structure within

**TABLE 1** | Demographics of children with technically acceptable FOT measurements by treatment group at 5 years of age.

| | Placebo ($N = 81$) | | Vitamin C ($N = 73$) | | $p$ value ($\chi^2$) |
|---|---|---|---|---|---|
| | $N$ | % | $N$ | % | |
| Sex | | | | | |
| Female | 42 | 51.9 | 39 | 53.4 | 0.8453 |
| Male | 39 | 48.1 | 34 | 46.6 | |
| Race | | | | | |
| Black | 9 | 11.1 | 10 | 13.7 | 0.5237 |
| White | 53 | 65.4 | 51 | 69.9 | |
| More than one | 19 | 23.5 | 12 | 16.4 | |
| Ethnicity | | | | | |
| Hispanic | 13 | 16.1 | 11 | 15.1 | 0.8669 |
| Non-Hispanic | 68 | 83.9 | 62 | 84.9 | |
| White | | | | | |
| Nonwhite | 28 | 34.6 | 22 | 30.1 | 0.5576 |
| White | 53 | 65.4 | 51 | 69.9 | |
| Location | | | | | |
| IU | 33 | 40.7 | 29 | 39.7 | 0.9719 |
| OHSU | 14 | 17.3 | 12 | 16.4 | |
| SWW | 34 | 42.0 | 32 | 43.8 | |
| Gestational age at randomization | | | | | |
| ≤ 18 | 38 | 46.9 | 30 | 41.1 | 0.4679 |
| > 18 | 43 | 53.1 | 43 | 58.9 | |

*Note:* Location and gestational age at randomization were stratification factors.

subjects. We also performed a cross-sectional analysis of FOT at 5 years of age using Analysis of Covariance (ANCOVA) to evaluate a vitamin C treatment effect for FOT assessment at 5 years of age with randomization GA, site, sex (white or nonwhite), adjusted height as covariates. For subjects who both have FOT and spirometric assessment at 5 years of age, we also performed ANCOVA with spirometry measurements as response variables to explore how these measurements might compare to FOT in evaluating our treatment effect. Partial correlation was used to assess the strength of the relationship between spirometric and FOT measurements at age 5 years after accounting for adjusted height. We also performed a sensitivity analysis in which we only included subjects who had FOT measurement at 3, 4, and 5 years of age. The purpose of this sensitivity analysis was to assess whether our findings were robust to missing data. Missing data were not imputed because mixed effect model using maximum likelihood estimation is known to be robust to missing data under missing at random (MAR). To check whether the data has been MAR, we investigated distribution of covariates with respect to missingness.

## 3 | Results

One hundred seventy-eight offspring of randomized pregnant smokers were studied with FOT at 5 years of age. There were no differences in sex, race, or age at 5 years of age between the offspring delivered to the vitamin C versus placebo-treated pregnant smokers who completed FOT measurements at 5 years of age (Table 1), as well as at 3 and 4 years of age (data not shown). The cross-sectional comparison of Resistance and Reactance data for subjects in each treatment group are summarized in Table 2. For all three ages (3, 4, and 5) there were no significant differences in Resistance (inspiratory, expiratory, total) measured at 8 Hz between the treatment groups. For cross-sectional analysis, a treatment effect was only significant for inspiratory reactance at 5 years of age. Longitudinal analysis for the 178 subjects that had technically successful measurements at one or more of the three ages (3, 4, and 5 years of age) did not find a significant treatment effect for Resistance or Reactance (Table 3). The *p* values for the cross-sectional and longitudinal computational models with the *p* values for treatment effect and covariates are used for summaries in the Supporting Information tables (Supporting Information S1: Table 1A,B). Longitudinal analysis for the 86 subjects with a

**TABLE 2** | Cross-sectional analysis of FOT resistance and reactance measurements by treatment group at 3, 4, and 5-years of age.

| | Placebo | | | Vitamin C | | | Difference | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | *N* | Mean | SE | *N* | Mean | SE | Mean | SE | % Difference | *p* value* |
| **Rinsp** | | | | | | | | | | |
| Age 3 | 56 | 9.88 | 0.25 | 51 | 10.09 | 0.27 | −0.21 | 0.34 | 2.1 | 0.5357 |
| Age 4 | 72 | 8.56 | 0.20 | 69 | 8.47 | 0.22 | 0.08 | 0.27 | −1.0 | 0.7589 |
| Age 5 | 81 | 7.28 | 0.16 | 73 | 7.50 | 0.18 | −0.22 | 0.22 | 3.0 | 0.3250 |
| **Rexp** | | | | | | | | | | |
| Age 3 | 56 | 11.12 | 0.32 | 51 | 11.53 | 0.35 | −0.40 | 0.44 | 3.6 | 0.3592 |
| Age 4 | 72 | 9.79 | 0.26 | 69 | 9.89 | 0.28 | −0.09 | 0.35 | 1.0 | 0.7886 |
| Age 5 | 81 | 8.57 | 0.19 | 73 | 8.54 | 0.21 | 0.02 | 0.25 | −0.3 | 0.9274 |
| **Rtot** | | | | | | | | | | |
| Age 3 | 56 | 10.59 | 0.29 | 51 | 10.91 | 0.32 | −0.32 | 0.39 | 3.0 | 0.4220 |
| Age 4 | 72 | 9.24 | 0.23 | 69 | 9.26 | 0.25 | −0.03 | 0.31 | 0.3 | 0.9320 |
| Age 5 | 81 | 8.03 | 0.17 | 73 | 8.09 | 0.19 | −0.06 | 0.23 | 0.7 | 0.8036 |
| **Xinsp** | | | | | | | | | | |
| Age 3 | 56 | −3.82 | 0.17 | 51 | −3.88 | 0.19 | 0.06 | 0.24 | 1.6 | 0.7967 |
| Age 4 | 72 | −3.14 | 0.15 | 69 | −3.21 | 0.16 | 0.07 | 0.19 | 2.2 | 0.7255 |
| Age 5 | 81 | −2.38 | 0.11 | 73 | −2.75 | 0.12 | 0.36 | 0.15 | 15.1 | 0.0143 |
| **Xexp** | | | | | | | | | | |
| Age 3 | 56 | −4.11 | 0.27 | 51 | −4.21 | 0.29 | 0.10 | 0.37 | 2.5 | 0.7790 |
| Age 4 | 72 | −3.50 | 0.21 | 69 | −3.84 | 0.22 | 0.34 | 0.27 | 9.8 | 0.2084 |
| Age 5 | 81 | −2.98 | 0.14 | 73 | −3.19 | 0.15 | 0.21 | 0.19 | 7.2 | 0.2633 |
| **Xtot** | | | | | | | | | | |
| Age 3 | 56 | −4.05 | 0.23 | 51 | −4.08 | 0.25 | 0.03 | 0.31 | 0.8 | 0.9183 |
| Age 4 | 72 | −3.34 | 0.17 | 69 | −3.58 | 0.18 | 0.25 | 0.23 | 7.3 | 0.2851 |
| Age 5 | 81 | −2.73 | 0.12 | 73 | −2.99 | 0.13 | 0.26 | 0.16 | 9.5 | 0.1110 |

Abbreviations: exp, expiratory; insp, inspiratory; R, resistance; tot, total; X, reactance.
*$p$ value were adjusted by sex, white/nonwhite, clinical site, and gestational age at randomization and the covariates of standardized height.

**TABLE 3** | Longitudinal analyses of FOT measurements at 3, 4, and 5 years of age by treatment group ($N = 178$).

| | Placebo | | Vitamin C | | Difference | | | Treatment effect* | |
|---|---|---|---|---|---|---|---|---|---|
| | Mean | SE | Mean | SE | Mean | SE | % Change | *p* value at each age | Overall *p* value |
| Rinsp | | | | | | | | | |
| Age 3 | 9.71 | 0.21 | 10.03 | 0.22 | −0.32 | 0.29 | −3.25 | 0.2733 | 0.2908 |
| Age 4 | 8.40 | 0.19 | 8.53 | 0.20 | −0.12 | 0.26 | −1.47 | 0.6372 | |
| Age 5 | 7.31 | 0.18 | 7.55 | 0.19 | −0.23 | 0.25 | 3.19 | 0.3562 | |
| Rexp | | | | | | | | | |
| Age 3 | 10.96 | 0.26 | 11.46 | 0.28 | −0.50 | 0.36 | 4.56 | 0.1694 | 0.2662 |
| Age 4 | 9.63 | 0.24 | 9.95 | 0.25 | −0.31 | 0.32 | 3.27 | 0.3298 | |
| Age 5 | 8.63 | 0.23 | 8.66 | 0.24 | −0.03 | 0.31 | 0.36 | 0.9194 | |
| Rtot | | | | | | | | | |
| Age 3 | 10.43 | 0.23 | 10.86 | 0.25 | −0.43 | 0.32 | 4.08 | 0.1921 | 0.2830 |
| Age 4 | 9.08 | 0.21 | 9.31 | 0.22 | −0.23 | 0.29 | 2.58 | 0.4209 | |
| Age 5 | 8.05 | 0.21 | 8.13 | 0.22 | −0.09 | 0.28 | 1.10 | 0.7567 | |
| Xinsp | | | | | | | | | |
| Age 3 | −3.75 | 0.14 | −3.89 | 0.15 | 0.14 | 0.20 | −3.76 | 0.4765 | 0.1075 |
| Age 4 | −3.08 | 0.13 | −3.27 | 0.14 | 0.19 | 0.18 | −6.24 | 0.2870 | |
| Age 5 | −2.41 | 0.13 | −2.78 | 0.13 | 0.37 | 0.17 | −15.41 | 0.0353 | |
| Xexp | | | | | | | | | |
| Age 3 | −4.11 | 0.21 | −4.32 | 0.22 | 0.20 | 0.29 | −4.97 | 0.4783 | 0.1183 |
| Age 4 | −3.46 | 0.19 | −3.86 | 0.19 | 0.40 | 0.25 | −11.52 | 0.1167 | |
| Age 5 | −2.98 | 0.18 | −3.27 | 0.19 | 0.29 | 0.25 | −9.63 | 0.2417 | |
| Xtot | | | | | | | | | |
| Age 3 | −4.03 | 0.17 | −4.17 | 0.18 | 0.13 | 0.24 | −3.29 | 0.5812 | 0.1371 |
| Age 4 | −3.28 | 0.16 | −3.60 | 0.16 | 0.31 | 0.21 | −9.59 | 0.1413 | |
| Age 5 | −2.74 | 0.15 | −3.03 | 0.16 | 0.29 | 0.21 | −10.60 | 0.1659 | |

Abbreviations: exp, expiratory; insp, inspiratory; R, resistance; tot, total; X, reactance.
*$p$ value were adjusted by sex, white/nonwhite, clinical site, and gestational age at randomization and the covariates of standardized height.

**TABLE 4** | Spirometry measurements at 5 years of age by treatment group in children who also had FOT measurements.

| | Placebo ($N = 81$) | | Vitamin C ($N = 72$) | | Difference | | | |
|---|---|---|---|---|---|---|---|---|
| Spirometry | Mean | SE | Mean | SE | Mean | SE | % Change | *p* value |
| FEF25_75 | 1.245 | 0.038 | 1.438 | 0.041 | −0.193 | 0.051 | 15.5 | 0.0002 |
| FVC | 1.289 | 0.020 | 1.275 | 0.022 | 0.015 | 0.027 | −1.1 | 0.5908 |
| FEV1 | 1.109 | 0.016 | 1.137 | 0.017 | −0.028 | 0.021 | 2.5 | 0.1885 |
| FEF75 | 0.615 | 0.025 | 0.762 | 0.027 | −0.147 | 0.034 | 23.9 | < 0.0001 |
| FEF50 | 1.399 | 0.040 | 1.588 | 0.044 | −0.189 | 0.055 | 13.5 | 0.0007 |

*$p$ value were adjusted by sex, white/nonwhite, clinical site, and gestational age at randomization and the covariates of standardized height.

measurement at 3, 4, and 5 years of age did not show a significant difference in Resistance or Reactance between the treatment groups (Supporting Information S1: Table 2B). We also compared the demographics of subjects with and without successful FOT data and found no differences related to vitamin C versus placebo group (data not shown).

A total of 153 children had both spirometry and FOT measurements performed at 5 years of age with the spirometry measurement shown in Table 4. FEFs of FEF25-75, our apriori primary outcome, as well as FEF50 and FEF75, were all significantly higher in vitamin C compared to placebo-treatment group. There were no significant treatment effects for FVC and FEV1. FOT measures of Resistance and Reactance correlated with spirometric measures; decreasing resistance were associated with increased FEFs, and increasing reactance correlated with increasing FEFs and FVC (Table 5).

**TABLE 5** | Correlations of FOT (resistance and reactance) with spirometry (FEFs and FVC) at 5-years of age.

| | FEF25_75 | FVC | FEV1 | FEF75 | FEF50 |
|---|---|---|---|---|---|
| **Rinsp** | | | | | |
| Correlation* | −0.285 | −0.353 | −0.414 | −0.154 | −0.310 |
| *p* value | **< 0.001** | **< 0.0001** | **< 0.0001** | **0.061** | **< 0.001** |
| **Rexp** | | | | | |
| Correlation | −0.330 | −0.235 | −0.329 | −0.212 | −0.339 |
| ***p* value** | **< 0.0001** | **0.004** | **< 0.0001** | **0.010** | **< 0.0001** |
| **Rtot** | | | | | |
| Correlation | −0.324 | −0.290 | −0.374 | −0.196 | −0.339 |
| ***p* value** | **< 0.0001** | **0.000** | **< 0.0001** | **0.017** | **< 0.0001** |
| **XInsp** | | | | | |
| Correlation | 0.269 | 0.380 | 0.448 | 0.205 | 0.275 |
| ***p* value** | **0.001** | **< 0.0001** | **< 0.0001** | **0.012** | **0.001** |
| **Xexp** | | | | | |
| Correlation | 0.244 | 0.130 | 0.208 | 0.148 | 0.261 |
| *p* value | **0.003** | **0.115** | **0.011** | **0.072** | **0.001** |
| **Xtot** | | | | | |
| Correlation | 0.277 | 0.246 | 0.327 | 0.188 | 0.290 |
| *p* value | **0.001** | **0.003** | **< 0.0001** | **0.022** | **< 0.001** |

Abbreviations: exp, expiratory; insp, inspiratory; R, resistance; tot, total; X, reactance.
*Pearsons partial correlation ($N = 150$, adjusted by height).

## 4 | Discussion

Our current RCT is the first to compare the ability of spirometry and FOT to detect a treatment effect in young children. We previously reported significant improvements in FEFs, as well as a decreased wheeze in offspring at 5 years of age whose mothers received vitamin C compared to placebo treatment for MSDP [1–4]. In contrast, our single-frequency FOT measurements did not perform as well as spirometry, either at 5 years of age, nor using longitudinal FOT data at 3, 4, and 5 years of age.

Forced expiratory maneuvers, which were initially developed to assess lung function in adults have been extended for use in children for many years [15–17]. However, the technical ease of obtaining FOT measurements compared to spirometry in young children has highlighted its greater potential as a pulmonary function outcome in young children. Our FOT data is consistent with previously published studies in children; resistance decreased, and reactance increased with somatic growth, increasing height or age. While FEFs increased between 15% and 25% in the vitamin C compared to placebo group (Table 4), there was no significant treatment effect detected for FOT resistance (Table 2). The only FOT parameter that suggested a treatment effect was the inspiratory reactance measured at 5 years of age. The more negative reactance in the vitamin C compared to placebo group would suggest a smaller compliance (C) in the vitamin C group [$X = -1/(2\pi fC)$], the physiologic interpretation of this finding is unclear. FOT compliance can reflect some combination of the elastic properties of the lung parenchyma, the volume of the lung, and airways obstruction, which is most evident by a frequency dependence of compliance. We have no direct measures of lung volume in our subjects; therefore, we cannot determine whether the two groups differ in lung volume. However, we found no difference between the two treatment groups in spirometric FVC, which suggest similar lung volumes. As we found higher FEFS in the vitamin C group, we had expected the vitamin C group to have higher reactance rather than a lower reactance; however, the specific pulmonary pathophysiology related to MSDP and the mechanism for the improvement in FEFs remains unclear. We found that spirometric and FOT measurements demonstrated weak to moderate correlations, which may reflect not only that these two measurements are assessed over different lung volumes but may also reflect differing components of lung function.

There are several strengths and limitations to our study. A major strength is our cohort of young children who are part of an RCT that we have previously demonstrated that vitamin C compared to placebo treatment of their mothers who continued to smoke during pregnancy resulted in improved FEFs at 3, 12, and 60 months of age, as well as less wheeze [1–4]. Therefore, we had an established treatment effect demonstrated by spirometry for comparing to the FOT measurements. Second, this cohort was from three different centers, which illustrates the potential for these outcomes to be used in a multicenter study of this young age group. A limitation of our study is using a single 8-Hz frequency (f), which may be less sensitive than assessment of the frequency dependence of impedance [18]. Therefore, we were not able to evaluate whether using multiple frequencies and assessing frequency dependence of impedance would be better able to detect the treatment effect. It is also possible that

using a more stringent acceptance criteria might be beneficial in detecting a treatment effect for this young age group. While we did not obtain FOT measurements in the entire sample size of children who completed FEF data at 5 years of age due to our inability to perform FOT remotely, this was < 10% of the sample size and these subjects did not differ from those who had FOT measurements.

In summary, FEFs were readily able to detect a significant effect for vitamin C treatment versus placebo for MSDP, and as anticipated it was associated with higher values for all FEFs. The offspring of the vitamin C treated pregnant smokers also had significantly decreased wheeze, consistent with higher FEFs. However, using a single 8-Hz FOT signal, there was no difference in resistances, and we found only inspiratory reactance had a statistically significant difference related to treatment, which was minimal, and went in the opposite direction than anticipated. Although longitudinal data has the potential to provide greater power than cross-sectional data analysis, the longitudinal study design was still not able to detect any treatment effect with regard to FOT measurements.

### Author Contributions

**Robert S. Tepper:** conceptualization, funding acquisition, writing–original draft, writing–review and editing, formal analysis. **Kristin Milner:** investigation, writing–review and editing, supervision. **Julia Harris:** investigation, writing–review and editing. **Brianna Lee:** writing–review and editing, formal analysis, data curation. **Michelle Cunningham:** investigation, writing–review and editing. **Christina Tiller:** investigation, writing–review and editing, supervision. **Lyndsey E. Shorey-Kendrick:** writing–review and editing. **Diane Schilling:** investigation, writing–review and editing. **Julie Brownsberger:** investigation, writing–review and editing. **Kelvin MacDonald:** writing–review and editing. **Annette Vu:** writing–review and editing, formal analysis. **Byung S. Park:** writing–original draft, writing–review and editing. **Eliot R. Spindel:** conceptualization, investigation, funding acquisition, writing–original draft, writing–review and editing. **Cynthia D. Morris:** funding acquisition, writing–original draft, writing–review and editing, formal analysis. **Cindy T. McEvoy:** conceptualization, funding acquisition, writing–original draft, writing–review and editing.

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### Conflicts of Interest

The authors declare no conflicts of interest.

### Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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### Supporting Information

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