The Impact of Gender and Age on Lung Function in Children with Sickle Cell Disease

Abstract

Background: Sickle Cell Disease (SCD) is a genetic blood disorder that results in sickle-shaped red blood cells, which can obstruct blood flow and lead to elevated risk of pulmonary issues. Impulse oscillometry (IOS) is a commonly used tool to measure lung function, primarily airway resistance and reactance, in children with SCD. This study aims to explore the influence of age and gender on lung function in children with SCD.

Methods: The data was taken from a Data Mendeley dataset that collected information on children with SCD and asthma, including gender, age, Body Mass Index (BMI), and concurrent medication use, across five yearly observations (2015-2020). 55 children with SCD were assessed using Impulse Oscillometry (IOS) measures of lung function, including upper (R20) and total (R5) airway resistance as well as reactance (X5) and resonant frequency (Fres). We conducted general linear mixed-effects analyses to measure the relationship between age and gender with respiratory function in children with SCD over time. Secondary analyses looked at the effects of BMI and use of hydroxyurea on IOS measures of lung function.

Results: This study investigates the impact of age and gender on respiratory function changes in children with sickle cell disease as reflected by impulse oscillometry measures. Over 5 observations, males showed a gradual increase in upper airway resistance in contrast to females. Additionally, males showed an increase in total airway resistance whereas females showed stability over the points. Both genders shared similar trajectories in airway reactance. Older age was significantly correlated with increases in airway resistance and resonant frequency across genders ($p < 0.05$). Secondary analyses, accounting for BMI and hydroxyurea usage, indicated no substantial associations with lung function measures. Higher BMI significantly correlated with lower resonant frequency values in females, but not males ($p < 0.05$).

Conclusions: Overall, no gender-related differences in lung function were found. There were no significant gender differences in lung function over time. Older age was significantly associated with a greater decline in overall lung function, particularly airway resistance, regardless of gender. The use of hydroxyurea was not a significant predictor of lung function in children with SCD. Further studies should look into how puberty and medication dosage may play a role in differential lung function between childhood and teenage years in patients with SCD.

Background:

Sickle cell disease is a genetic blood disorder created from an aminoacidic replacement in the beta-globin gene, leading to the production of abnormal hemoglobin, HbS. The structural variation of the hemoglobin surface causes red blood cells to assume a sickle shape when deoxygenated (Ceglie, 2019). The disease is particularly common in tropical regions, including sub-Saharan Africa, India, South America, and the Mediterranean. Sickle cell disease (SCD) can result in serious health complications, including chronic pain from organ damage, severe anemia, fever, stroke, and dactylitis (NIH). A significant complication of the disease is that the mutated cells can obstruct blood flow, leading to increased risk of health complications, particularly pulmonary issues.

To gain insight into respiratory function in pediatric patients with SCD, Impulse Oscillometry (IOS) is a valuable tool in pediatric medicine that assesses lung function, particularly measuring airway resistance and reactance. Airway reactance reflects the ability of the lungs to respond to changes in airflow during breathing, with higher reactance values reflecting normal lung function while lower reactance reflects airway resistance and a decline in lung function. IOS measures this as the change in pressure relative to flow in response to an oscillatory airflow signal. On the other hand, airway resistance represents the obstruction of airflow, measured as the ratio of pressure to airflow in the airways during normal breathing (Agrawal, 2016). Higher values of airway resistance thus represent suppressed lung function, as increased airway resistance in children with SCD is often a result of vaso-occlusion from the blood cells or pulmonary infarction.

Even if there are no obvious clinical signs of disease manifestation or symptoms of SCD, the constant circulation of abnormal sickle erythrocytes can cause repeated tissue injury at early stages of the disease from insufficient oxygenation (hypoxia) due to sickling of the blood cells. Thus it is recommended to start disease-modifying treatments as early as possible, particularly in children. Common medications used to treat SCD include hydroxyurea, which helps prevent the formation of sickle cells, inhaled corticosteroids (ICS), which is an anti-inflammatory lung medication, and long-acting beta 2 agonists (LABA), which is a lung muscle relaxant. Hydroxyurea is most often prescribed, as it is a well-tolerated medication and correlated with increased survival for both adults and children with SCD (McGann, 2015).

While SCD is an autosomal recessive disorder and thus not inherently sex-related, reported differences in lung function and risk of pulmonary embolisms in adult patients suggest potential gender- and age- related disparities. Older age and female sex have been independently associated with an increased risk of pulmonary issues and venous thromboembolisms (Kumar, 2018; Arigliani, 2019; Ceglie, 2019). However, limited data have been collected on the influence of sex and age on the course of SCD in pediatric populations. Additionally, certain patient characteristics, such as higher body mass index (BMI), have been linked to increased risk of SCD and of respiratory disease, although results have been inconclusive and limited in pediatric populations (Chiuve, 2015; Hall, 2018; Yang, 2023).

Understanding these factors' impact on lung function could aid in tailoring effective treatments for managing SCD in younger populations. Hence, the present study aims to explore gender- and age-related differences in respiratory function in a pediatric population of SCD, while also considering the potential influence of BMI and use of hydroxyurea. We hypothesize that older and female children with SCD will exhibit worse IOS measures of airway reactance and resistance compared to younger or male children.

Methods

Settings and participants:

The data used in this study was for a longitudinal retrospective study, with data collected across five yearly visits between 2015-2020. There are 90 total participants, with two cohorts in this nonrandomized, observational study: children with sickle cell disease (C-SCD) and African-American children with asthma (C-Asthma). The dataset is taken from Data Mendeley, but does not have information on recruitment methods or inclusion/exclusion criteria. For this study, we are conducting a longitudinal retrospective study, particularly on children with sickle cell disease (*N* = 55). There are 23 females and 32 males, with a mean baseline age of 148.7 months (~12.4 years) and a baseline BMI of 18.7 (**Table 1, 2**). Variables collected include SCD diagnosis, asthma diagnosis, number of visits per patient, IOS measures, BMI, age, gender, use of hydroxyurea, use of ICS, and use of LABA. IOS measures of lung function include upper (R20) and total (R5) airway resistance, airway reactance (X5), and resonant frequency (FRES).

Outcomes:

The primary endpoints of our study are the changes in IOS measures of airway resistance and reactance over time.
The covariates available of interest are gender and age, with secondary analyses that adjust for BMI and concurrent use of hydroxyurea.

Statistical Analysis:
The statistical analysis will be conducted in R Studio 4.3.2, with significance set at $p < .05$. General linear mixed-effects model for continuous outcomes will be used to test the relationship between age and gender with lung function. Age and BMI will be utilized as a continuous fixed effect, gender will be utilized as a categorical fixed effect and use of hydroxyurea will be utilized as a binary fixed effect. This study will include a stratified analysis by gender to determine the impact gender, age, BMI, and hydroxyurea have on the IOS measures. We will compare the demographics and baseline characteristics of the patients.

Our statistical analyses were completed in sections by the lung function measure of interest. We completed our analysis in the following order: IOS total airway resistance at 5 Hz (R5Hz_PP), IOS upper airway resistance at 20 Hz (R20Hz_PP), IOS airway reactance at 5 Hz (X5Hz_PP), and IOS resonant frequency (Fres_PP). To begin the statistical analysis we first looked over the means and confidence intervals of the lung function measure. We fit a linear mixed effects model to account for the influence of gender and age. We then adjusted this model for BMI and the concurrent use of hydroxyurea. We conducted a t-test to compare the means and confidence interval of the lung function measures by gender. We then fit new models stratified by gender to explore how age, BMI, and hydroxyurea treatment affect lung function in each gender group. To determine if there is an effect of age on lung function by gender, we fit a linear mixed effects model with an interaction term between age and gender. We split age into three continuous age groups (4-9, 10-14, and 15-19 years old) and conducted an ANOVA test to evaluate whether there are significant differences in the means of lung function measures that are explained by the different predictors. Then we explored if certain ages were more strongly associated with worse lung function, and if that was reflected differently in male vs female children when stratified by gender. We then investigated if there were any interaction effects of time on lung function by fitting separate linear mixed effects models with interaction terms between the observation year and gender, age, BMI, and hydroxyurea use.

Results

The study aimed to investigate the gender- and age-related changes in respiratory function in children with sickle cell disease, focusing on changes in Impulse Oscillometry (IOS) and changes in reactance over time. Our analysis elucidates the significant associations between age, sex, and respiratory outcomes. We observed different patterns of IOS measures in total airway resistance and upper airway resistance. Based on visual exploration, there is an observed increase in total airway resistance in males in each of the first 4 years then a decline in the 5th year. However, the female group does not vary much from observation 1 to observation 5 (**Figure 1**). The male group had a gradual increase in upper airway resistance from observation 1 to 4 and then it slightly declined in the last observation. Females showed a range of 80 to 100 Hz variation from observation 2 to 4 in upper airway resistance (**Figure 2**). In the airway reactance measure, both males and females started from a similar range of IOS measure and ended at 120 Hz in the last observation (**Figure 3**). While checking for resonant frequency, females only slightly increased over time, however, males showed first an increase until observation 4 and then declined from observation 4 to 5 **(Figure 4)**.

We performed a t-test to evaluate the significant mean difference of IOS measures in males and females. There was no significant difference in total airway resistance (p = 0.0573) or airway reactance (0.471), while there were significant sex-related differences in mean upper airway resistance (p = .0.03062) and resonant frequency (p = 0.02596).

Overall, without stratifying for gender, age was significantly associated with IOS measures of airway resistance and resonant frequency, but not X5 measures of airway reactance (**Table 4**). Age was correlated with a significant increase in measures of total and upper airway resistance by 0.27 and 0.02, respectively, as well as resonant frequency by 0.51. When stratifying the analysis by gender, age was not significantly associated with X5 measures of airway reactance in males (p = 0.4) or females (p = 0.1). However, age was significantly associated with an increase in resonant frequency in both sexes, with males having an increase in reactance by 0.3886 (p < 0.01) and females having an increase by 0.5138 (p < 0.01) per month of age. Age was significantly associated with increases in upper airway resistance for both genders, 0.22 increase in males (p = 0.0083) and 0.226 (p = 0.005) and in total airway resistance, 0.2762 increase in males (p = 0.0077) and 0.0309 increase in females (p = 0.0123). To evaluate the interaction between gender and age on lung function, we performed ANOVA and found a

significant result in resonant frequency with p = 0.039; all other measures of lung function did not have a significant interaction between gender and age.

Additionally, the effects of the interactions of observation year between variables age, BMI, and hydroxyurea use were also investigated. We performed ANOVA for each interaction term. For all measures of lung function, the interaction between observation year and age did not have a significant interaction. We found significant results for the interaction between observation year and BMI for total airway resistance (p = 0.004901), airway reactance (p = 0.004901), and resonant frequency (p = 0.001149). For all measures of lung function, the interaction between observation year and hydroxyurea use did not have a significant interaction (Table 11).

While overall age was significantly associated with changes in lung function, further analyses were done using F-tests to look at lung function in different age groups: young (4-9 years), tweens/youth (10-14 years), and teenagers (15-19 years). The younger age (group 1) had a significant association in males with total airway resistance (R5Hz_PP, F-stat = 11.7358*) and airway reactance (X5Hz_PP, Fstat = 8.1296*) **(Table 9, Figure 9a, g).** Being a male teenager (group 3) was significantly associated with total airway resistance (R5Hz_PP, Fstat = 11.5150*), upper airway resistance (R20Hz_PP, F-stat = 5.1797*), and resonant frequency (Fres_PP, F-stat = 10.3621*) (**Table 10, Figure 9c, f, l**). In females, the youngest group (group 1) was significantly associated with total airway resistance values (R5Hz_PP, F-stat = 9.5764*) (T**able 9, Figure 9a**). Airway reactance values were significantly associated with being in the youngest and teenage group as a female, as well (X5Hz_PP, F-stat = 9.0101*, 13.8207*) (**Table 10, Figure 9g, i**). The middle tween/youth age group (group 2) was not significantly associated with any of the IOS measures of lung function in either male or female children with SCD. This is visually reflected in the scatterplots from **Figure 9 (b, e, h, k),** as age group 2 seems to have very slight differences in all measures of lung function across both genders.

For our secondary analyses, we conducted general linear mixed models stratified by gender and adjusted for the potential confounders, BMI and use of hydroxyurea. BMI and use of hydroxyurea, when not stratified by gender, was not correlated with any significant change in lung function (**Table 4**). After stratification, when adjusting for BMI, we observed an insignificant decrease in airway reactance by -13.0798 (p = 0.12) in males and -6.541 (p = 0.57) in females. Per unit of BMI, there was an insignificant decrease in resonant frequency by -1.04604 (p = 0.25) in males, but a significant decrease of -2.4876 (p = 0.017) in females. BMI was not

significantly associated with changes in upper (1.48822, p = 0.3259) or total airway resistance (1.0435, 0.57364) in males. BMI also had no effect on upper (1.11597, p = 0.073721) or total airway resistance (0.7755, 0.4402) in females (**Table 7, 8**).

Since BMI was only significantly correlated with resonant frequency out of all IOS measures (**Table 8**), we chose to visually explore if there were any gender- or age-group-related differences in resonant frequency (an indicator of airway reactance) (**Figure 10**). It looks like there is a decrease in resonant frequency in young and teenage females as BMI increases (**Figure 10a, c**), while there is a general increase in resonant frequency across all age groups in males with higher BMI (**Figure 10**). This seems to visually match the quantitative findings in **Tables 7** and **8**, which indicate that females with higher BMI have significantly lower resonant frequency values ($p < 0.05$), while the increase seen in males is insignificant ($p > 0.05$). Lower resonant frequency values indicate worse lung function, meaning higher BMI is significantly correlated with the decline in lung function in females with SCD. However, the mixed effects model analyses demonstrate that older age is correlated with increased resonant frequency values, and thus a slight improvement in lung function in both genders (**Table 7, 8**). There was also a significant *interaction between observation (time) and BMI for upper airway resistance (R20Hz_PP, F-stat = 4.6325*), airway reactance (X5Hz_PP, F-stat = 8.2386*), resonant frequency (Fres_PP, F-stat = 11.1500*)* (**Table 11**). Hydroxyurea use and age did not have any significant interactions with time on IOS measures of airway resistance or reactance ($p > 0.05$, **Table 11**).

Over the course of the study, there were changes in hydroxyurea use, with 38 counts of hydroxyurea usage and 122 counts of no hydroxyurea use over five observations (**Table 3**). Adjusting for hydroxyurea use corresponded with decreases in total airway resistance (-4.6113, p = 0.65), upper airway resistance (-5.2108, p = 0.53), airway reactance (-4.5795, p = 0.9113) and resonant frequency (-10.1211, p = 0.2550) in males, although none were significant. Hydroxyurea use in females was also associated with insignificant increases in total airway resistance (3.1780, p = 0.7791), reactance (30.222, p = 0.8215), and resonant frequency (10.4950, p = 0.3121), and insignificant decrease in upper airway resistance (-12.3907, p = 0.09) (**Table 7, 8**). There were no significant interactions between time and gender across any IOS measure of lung function (**Table 6**).

Discussion

This study investigates the significant association between gender, age, and respiratory outcomes in children with sickle cell disease. We investigated different IOS measures and found varying patterns in total airway resistance and upper airway resistance between males and females. Most males exhibit a decline in total airway resistance and resonant frequency during observation year 5. Whereas females did not vary that much when comparing the first to the fifth observation year. We conducted a t-test to find if there were any gender differences in IOS measures of lung function and found significant correlations with upper airway resistance and resonant frequency. Additionally, age exhibits a positive significant association with resonant frequency in both sexes, negative associations with total and upper airway resistance in males, and a positive association with airway resistance in females. Age did not significantly affect airway reactance in either gender based on the airway reactance (X5) measurements. However resonant frequency significantly increased as age increased in both males and females, suggesting slight improvement in respiratory function. Nevertheless, older age was also significantly associated with increased total and upper airway resistance, which seems to demonstrate that overall lung function in children with SCD does decline as age increases regardless of sex, which supports published literature. The interaction between age and gender showed a significant association in airway reactance (**Table 5)**. However, unlike what we hypothesized, there were no significant gender differences in lung function over time, with an insignificant interaction between observations and gender across all IOS measures ($p > 0.05$).

We also did a visual exploration of how different age groups (young, youths, teenagers) are correlated with lung function in patients with SCD over time without stratification by gender (**Figure 5-8**). It looks like resonant frequency stays relatively stable over time in the young group (ages 4-9 yrs) and is significantly lower compared to the other age groups. This suggests that younger children have worse airway reactance and increased obstruction to airflow, meaning an increased risk for respiratory issues. This seems to support McGann's (2015) statement that starting disease-mediating medication at a young age is an important preventative measure against injury and hypoxia, since the sickling of cells already begins to affect lung function and oxygenation to other parts of the body at earlier stages of the disease. Group 2 (ages 10-14 yrs, tweens) seems to have the most irregular changes in all IOS measures of airway resistance and reactance over time, with many of the trajectories significantly different from other age groups. With extremely staggered paths across all IOS measures, Group 2 seems to slightly increase in total and upper airway resistance over time, while they decline in both measures of airway

reactance, indicating an overall trend of poor lung function, even if not statistically significant. These fluctuations in respiratory function may be due to changes in hormones or lung function growth that is associated with puberty around this time frame in both genders (Li, 2020; NICHD). Further quantitative analyses that take into account changes due to puberty may be necessary to understand why group 2 does not seem to have significant associations with lung function when stratified by gender (**Figure 9**), yet has extreme variability in all measures of lung function over time when not comparing males to females (**Figures 5-8**). Our small sample size further limits the reliability of any associations found between lung function and age groups.

Teenagers (15-19 yrs, group 3) seem to have relatively stable and high values for both measures of airway resistance (R5 and R20 Hz) and resonant frequency (Fres), although there is a slight increase over time in airway reactance values (X5 Hz). This is initially contradictory, since higher values of airway resistance indicate poor lung function, while higher values of airway reactance and resonant frequency indicate improved lung function. However, our quantitative analysis suggests that airway reactance is not significantly influenced by age (**Table 4**). However, once we stratified for gender and adjusted for BMI for each age group, it seems that while older age may be associated with improved resonant frequency measures of lung function, lung function in females with SCD is significantly more negatively impacted by BMI than males, perhaps particularly as teenagers (**Table 8, Figure 10c**).

Regarding secondary analyses, BMI was not significantly associated with a majority of changes in lung function for both genders. However, the significant decrease in resonant frequency, another measure of airway reactance, indicates a slight decline in lung function as BMI increases in the female group. Hydroxyurea use showed an insignificant decrease in upper airway resistance. The use of hydroxyurea as a treatment for SCD in both sexes was not significantly associated with changes in IOS measures of airway resistance or reactance. This is clinically relevant since hydroxyurea is supposed to help prevent sickle cells and potential vaso-occlusion that can cause restricted airflow and pulmonary issues. The efficacy of hydroxyurea may need to be reassessed regarding its ability to help treat patients with SCD in a younger population. However, since we do not have any information on dosage or the age they started taking hydroxyurea, this may limit the results since the efficacy of the medication is dose-dependent, with long-term clinical benefits provided after escalation to maximum tolerated dose (MTD) in children with SCD (Estepp, 2014; McGann, 2015; Zimmerman, 2004). A possible follow-up to this study would be to look at gender or age differences in the clinical efficacy of

MTD since McGann (2015) mentions that starting disease-modifying treatments as early as possible is the best way to combat sickle cell disease. Perhaps some of these children started taking hydroxyurea too late, since participants changed their status of hydroxyurea use over the course of the study.

Along with these valuable insights into gender- and age-related differential respiratory outcomes in children with SCD, this study has several limitations. We do not know the nature of data collection, including their inclusion or exclusion criteria, where the study was conducted, and the race/ethnicity of the children. This is also based on observational data, which does not give any evidence for causal inference. The sample size of the study is relatively small and may limit the generalizability of the study. The influence of BMI and the use of hydroxyurea on respiratory function in children with SCD requires further study, as we found mixed results that may be due to how the study data was collected.

Overall, this study contributes to improving respiratory healthcare in pediatric SCD patients. The study can also help researchers understand the epidemiology of the disease with a diverse population. These results underscore specialized treatment approaches needed for vulnerable populations, particularly since age seems to be a key predictor of poor lung function. Gender was not found to be a significant factor in respiratory outcomes, however, further analysis looking into how puberty may differentially affect lung function in males and females with SCD is potentially relevant. By incorporating these factors into a future study, public health practitioners can optimize lung health outcomes and improve the quality of life in these patients.

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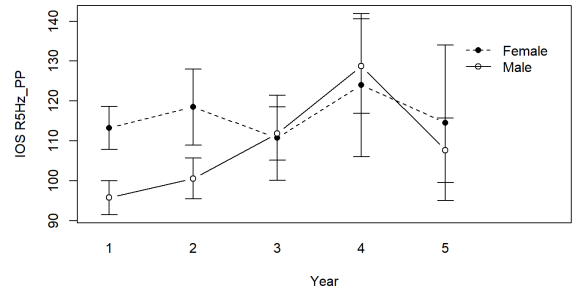
Tables and Figures:



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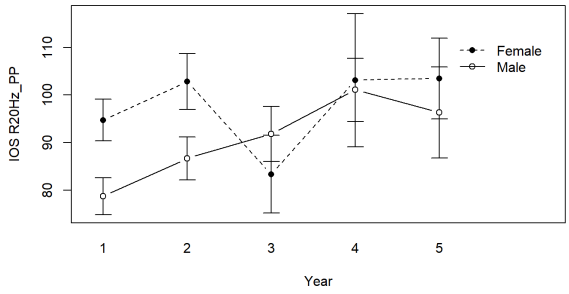

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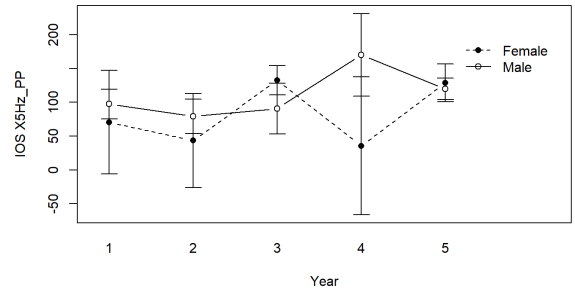

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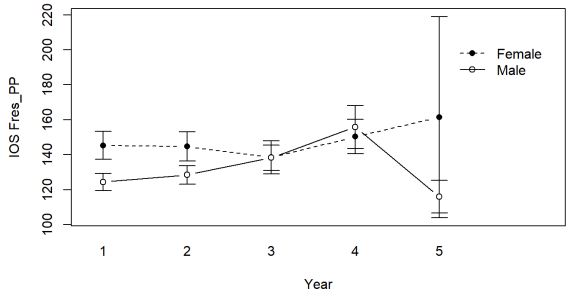

Figure 4

Figures 1-4: The figures illustrate the changes in IOS measures over 5 years (2015 to 2020).
Figure 1 shows the change in IOS airway resistance at 5Hz. Both genders exhibit overlapping confidence intervals suggesting similar variability between genders.
Figure 2 shows the change in IOS airway resistance at 20 Hz. Both genders exhibit variability in resistance with no clear pattern.
Figure 3 shows the change in IOS airway reactance at 5Hz. Both genders exhibit variability in resistance with no clear pattern.

Figure 4 shows the change in IOS resonant frequency across observation points. The data shows some variability between genders.

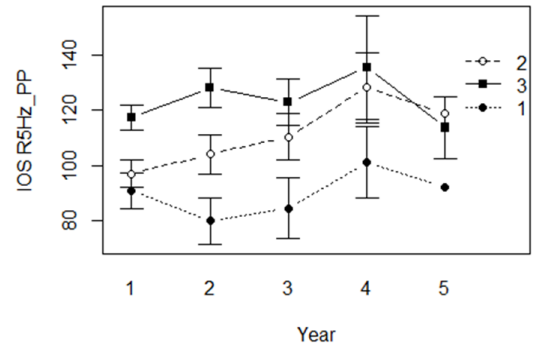

Figure 5

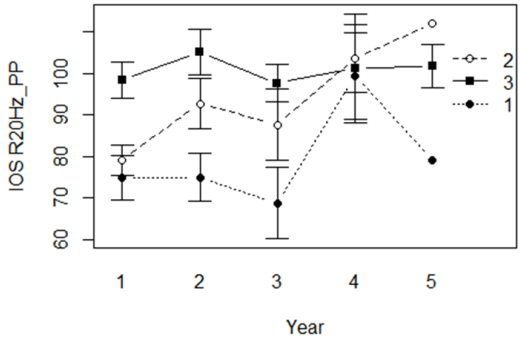

Figure 6

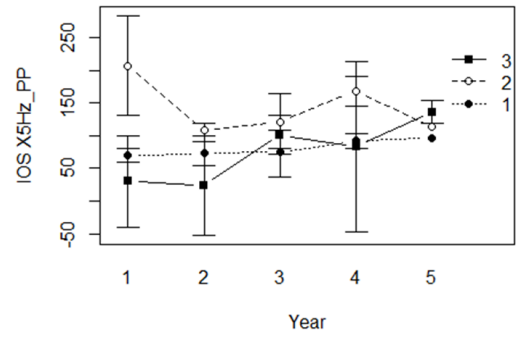

Figure 7

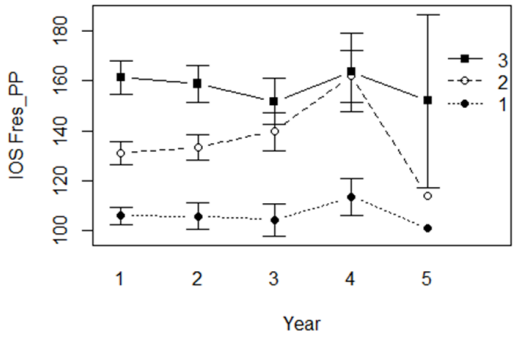

Figure 8

Figures 5-8 demonstrate the change in IOS measures of lung function over 5 years with 95% confidence intervals, stratified by three age groups: 4-9 years (young - group 1) , 10-14 years (youth/tween - group 2), 15-19 years old (teenagers - group 3).

Figure 5 shows the change in IOS airway resistance at 5 Hz over time, stratified by the three age groups.

Figure 6 shows the change in IOS airway resistance at 20 Hz over time, stratified by the 3 age groups.

Figure 7 shows the change in IOS airway reactance at 5 Hz over time, stratified by the three age groups.

Figure 8 shows the change in IOS resonant frequency (a marker of reactance) over the 5 yearly points of observation, stratified by the three age groups.

Figure 9

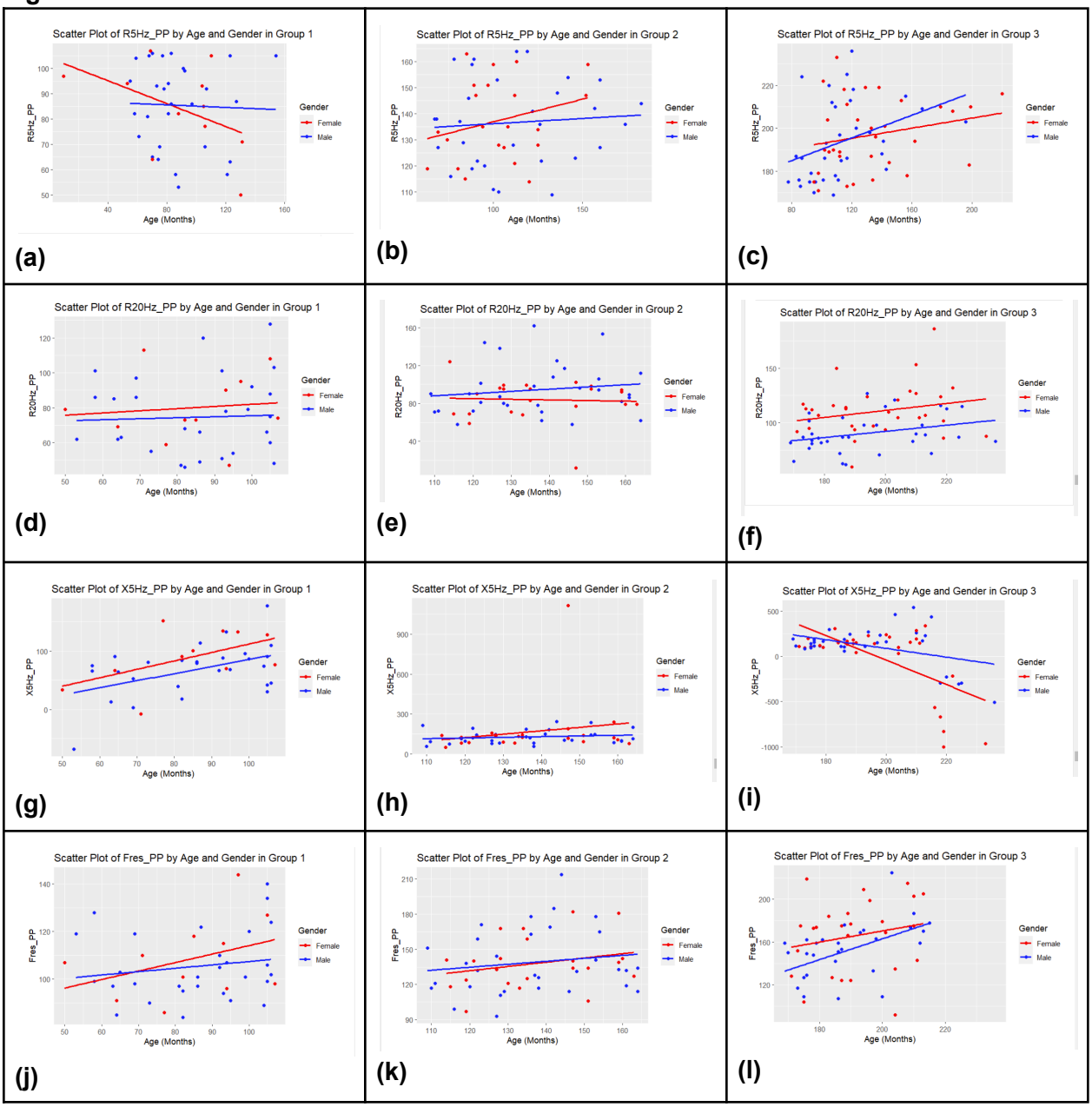

Figure 9: Scatterplots demonstrate the association between IOS measures of lung function and the different age groups (1-3), stratified by gender.

(a-f): total (5 Hz) and upper (20 Hz) airway resistance across young children (group 1), tween/youths (group 2), and teenagers (group 3) stratified by gender.

(g-i): airway reactance (X5 Hz) across young children (1), tween/youth (2), and teenagers (3) stratified by gender.

(j-l): resonant frequency (another measure of airway reactance) across young children (1), tween/youth (2), and teenagers (3) stratified by gender.

Figure 10

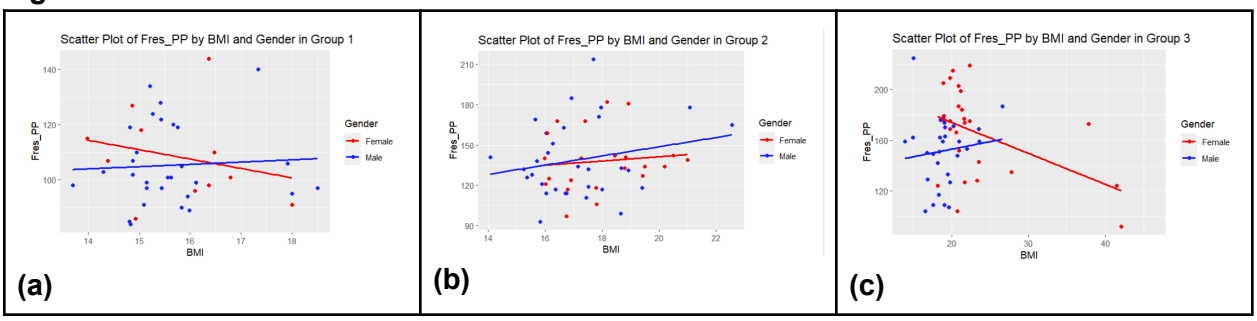

Figure 10 *(a-c)*: Demonstrates association between BMI and resonant frequency per age group, stratified by gender.

Demographics:

Table 1: Summary Statistics of Gender

Gender	Count	Percentage
Female	23	41.8
Male	32	58.1

Table 2: Summary Statistics for Baseline Age and BMI

Continuous Variables	Mean	SD
Age (In months)	148.7	47.98
BMI	18.702	4.617

Table 3: Summary Statistics for Hydroxyurea Usage

Hydroxyurea Treatment (By observations)	Count	Percentage
Yes	38	23.75
No	122	76.25

Outcomes:

Table 4: Adjusted Mixed Effects Model for BMI and Hydroxyurea Use

Lung Function	Parameter	Estimate	SE	P-val
R5Hz_PP	Age	**0.2735**	0.0726	**< .05**
	BMI	1.0716	0.8331	> .05
	Hydroxyurea	-2.5911	7.3813	> .05
R20Hz_PP	Age	**.02038**	0.0544	**< .05**
	BMI	1.4806	.61216	> .05
	Hydroxyurea	-10.240	5.4387	> .05
X5Hz_PP	Age	-0.8063	0.5789	> .05
	BMI	-6.1513	6.6705	> .05
	Hydroxyurea	16.0449	59.094	> .05
Fres_PP	Age	**0.51090**	0.0677	**< .05**
	BMI	-1.4603	0.8007	> .05
	Hydroxyurea	-2.0580	6.8105	> .05

Table 5: Interaction between age and gender

Lung Function	Parameter	P-Val
R5Hz_PP	Age:Gender	0.79881
R20Hz_PP	Age:Gender	0.98651
X5Hz_PP	**Age:Gender**	**0.03965**
Fres_PP	Age:Gender	0.65040

Table 6: Interaction between gender and observation occurrence

Lung Function	Parameter	P-Val
R5Hz_PP	Observation:Gender	0.34331

R20Hz_PP	Observation:Gender	0.23459
X5Hz_PP	Observation:Gender	0.28840
Fres_PP	Observation:Gender	0.18315

Table 7: Adjusted Mixed Effects Model Stratified by Gender - Male

Lung Function	Parameter	Estimate	SE	P-val
R5Hz_PP	Age	**0.2762**	0.1007	**< .05**
	BMI	1.0435	1.8440	> .05
	Hydroxyurea	-4.6113	10.0610	> .05
R20Hz_PP	Age	**0.2232**	0.08208	**< .05**
	BMI	1.48822	1.50141	> .05
	Hydroxyurea	-5.21080	8.17488	> .05
X5Hz_PP	Age	0.4025	0.4729	> .05
	BMI	-13.0798	8.4075	> .05
	Hydroxyurea	-4.5795	40.6995	> .05
Fres_PP	Age	**0.3886**	0.0903	**< .05**
	BMI	1.9623	1.6020	> .05
	Hydroxyurea	-10.1211	8.7249	> .05

Table 8: Adjusted Mixed Effects Model Stratified by Gender - Female

Lung Function	Parameter	Estimate	SE	P-val
R5Hz_PP	Age	**0.3090**	0.1162	**<.05**
	BMI	0.7755	0.9845	> .05
	Hydroxyurea	3.1780	11.2133	> .05
R20Hz_PP	Age	**0.22604**	0.07433	**< .05**
	BMI	1.11597	0.57857	> .05
	Hydroxyurea	-12.39065	7.05470	> .05

X5Hz_PP	Age	-2.102	1.260	> .05
	BMI	-6.541	11.621	> .05
	Hydroxyurea	30.222	132.186	> .05
Fres_PP	Age	**0.6138**	0.1079	**< .05**
	BMI	**-2.4876**	0.9668	**< .05**
	Hydroxyurea	10.4950	10.1425	> .05

Table 9: Analysis of Variance of Table - association between Male children and measures of lung function across different age groups.

	Age (F-statistic)		
Lung Function	Group 1 (4-9 yrs)	Group 2 (10-14 yrs)	Group 3 (15-19 yrs)
R5Hz_PP	**11.7358***	0.7012	**11.5150***
R20Hz_PP	0.4149	1.5796	**5.1797***
X5Hz_PP	**8.1296***	2.5936	3.8412
Fres_PP	0.0031	1.7128	**10.3621***

* p- value < 0.05

Table 10: Analysis of Variance of Table - Association between Female children with different age groups

	Age (F-statistic)		
Lung Function	Group 1 (4-9 yrs)	Group 2 (10-14 yrs)	Group 3 (15-19 yrs)
R5Hz_PP	**9.5764***	0.7231	1.6240
R20Hz_PP	0.0045	0.7262	1.2074
X5Hz_PP	**9.0101***	0.0306	**13.8207***
Fres_PP	0.7045	0.6973	0.2962

* p-value < 0.05

Table 11: Analysis of Variance Table: Interaction between Observation with Age, BMI and Hydroxy across IOS measures of lung function

Lung Function	Observation:Age (F-stat)	Observation:BMI (F-stat)	Observation:Hydroxy (F-stat)
R5Hz_PP	3.0406	1.3373	0.0771
R20Hz_PP	0.7854	**4.6325***	0.0567
X5Hz_PP	0.4205	**8.2386***	0.0059
Fres_PP	0.2786	**11.1500***	0.4934

* p- value < 0.05